HONG KONG JOURNAL of OPHTHALMOLOGY

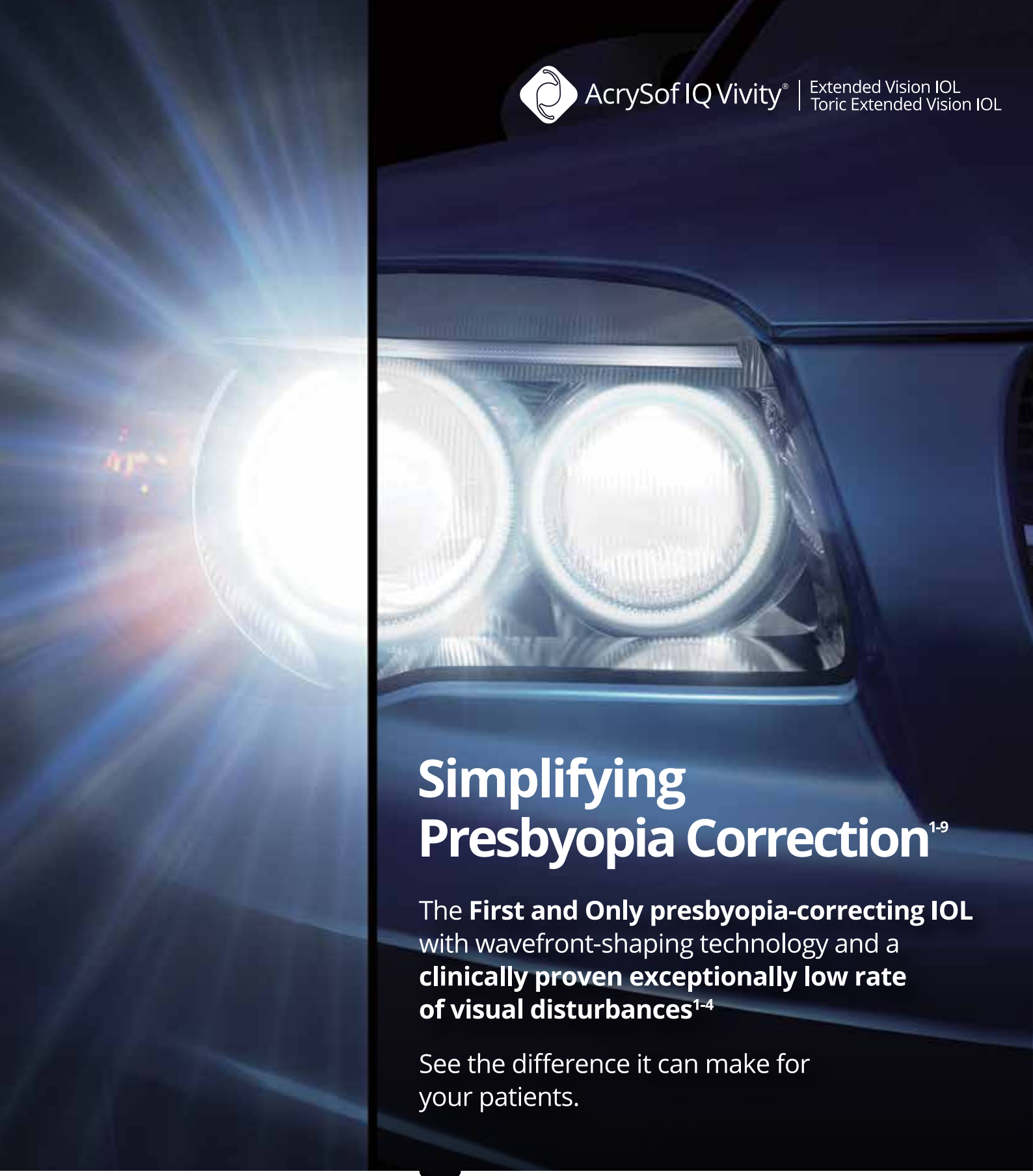
December 2022 Vol. 26 No. 2 ISSN 1027-8230

The Official Publication of
The College of Ophthalmologists of Hong Kong

香港眼科醫學院

香港眼科學刊

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS



Simplifying Presbyopia Correction[1-9]

The **First and Only presbyopia-correcting IOL** with wavefront-shaping technology and a **clinically proven exceptionally low rate of visual disturbances**[1-4]

See the difference it can make for your patients.

References: 1. AcrySof® IQ Vivity® Extended Vision IOL Directions for Use. **2.** Alcon Data on File, US Patent 9968440 B2, May 15, 2018. **3.** Alcon Data on File, TDOC-0055575. 09 Apr 2019. **4.** Alcon Data on File. TDOC-0055576. 23-Jul-2019. **5.** Alcon Data on File, TDOC-0056718. 18-Jun-2019. **6.** Ligabue E, et al. ACRYSOF IQ VIMTY: Natural vision at a range of distances provided by a novel optical technology. Cataract & Refractive Surgery Today. April 2020 // **7.** Alcon Data on file. A02062-REP-043696, Optical Evaluations of Alcon Vivity®, Symfony*, Zeiss* AT LARA* AT LISA IOLs. Feb 2020. **8.** Lawless M. Insight news. "An IOL to change the cataract surgery paradigm?" available at "https://www.insightnews.com.au/an-iol-to-change-the-cataract-surgery-paradigm/". Accessed Date 17.07.2020. **9.** Ike K. Ahmed, et al. The Vivity Extended Depth of Focus IOL: Our Clinical Experience. Cataract & Refractive Surgery Today. February 2021//

Please refer to product direction for use for complete list of indications, contraindications and warnings.

Alcon

AcrySof IQ Vivity® | Extended Vision IOL Toric Extended Vision IOL | Advancing CATARACT SURGERY

CONTENTS

香港眼科學刊

香港眼科醫學院

HONG KONG JOURNAL OF OPHTHALMOLOGY

The Official Publication of the College of Ophthalmologists of Hong Kong

December 2022

Volume 26 Number 2

ISSN 1027-8230

Editor-in-Chief
Alvin KH Kwok

Correspondence
The College of Ophthalmologists of Hong Kong
Room 802, 8/F, Hong Kong Academy of Medicine Jockey Club Building
99 Wong Chuk Hang Road
Aberdeen, Hong Kong, China.
Tel (852) 2761 9128
Fax (852) 2715 0089
E-mail: cohk@netvigator.com

Published by
HONG KONG ACADEMY OF MEDICINE PRESS

EDITORIAL BOARD

Information for Authors

Aims and Scope

- The *Hong Kong Journal of Ophthalmology* (HKJO) is the official publication of the College of Ophthalmologists of Hong Kong. The Journal aims to promote academic developments in ophthalmology, and to maintain continuing ophthalmological education of doctors of this specialty and other related disciplines. It is hoped that through achieving these aims, the quality of eyecare we offer to our patients can be lifted to new heights. The Journal will consider any submissions that fulfill these aims for publication.
- The Journal accepts high-quality submissions in the following categories: Original Article, Review, Perspective, Case Report, Photo Essay, Clinical Quiz, or Letter to the Editor. Editorials are by invitation only.
- The Journal is circulated to all members of the College of Ophthalmologists of Hong Kong and other professional societies and academic institutions in Hong Kong and internationally.

Journal Policies

- The HKJO adheres to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org) and the Core Practices of the Committee on Publication Ethics (COPE; https://publicationethics.org).
- Submitted manuscripts must be original works that have not been published elsewhere (in whole, in part, or as a preprint) and are not under consideration by another publication.
- To improve the quality and clarity of published articles, the Journal recommends the use of reporting guidelines in the preparation of manuscripts, such as those advocated by the EQUATOR Network (http://www.equator-network.org/), for example, CONSORT for randomized trials, or CARE for case reports.
- Any sponsor(s) of the research involved, along with grant number(s) should be provided.
- All authors must provide a statement reporting any conflicts of interest. Where none exist, please state 'The authors have no conflicts of interest to declare.' Authors may use the ICMJE Conflict of Interest form.
- For all research involving living humans (including studies involving human tissue, retrospective studies, and database studies), an appropriate research ethics committee must be consulted. A statement must be included in the manuscript that provides the name of the research ethics committee and approval number (or waiver)
- A statement on consent must also be included, indicating how patient(s)/guardian(s) provided informed consent (eg, written or verbal), or that the requirement for patient consent was waived by the review board.
- The authors shall make available the complete data on which the manuscript is based. A statement describing how the data can be accessed must be included in the manuscript. For clinical trials and other large datasets, the Journal recommends that data are deposited in a public repository and shared using a permanent identifier (such as a DOI).
- For details of the Journal policies on publication ethics, including authorship, plagiarism, and processes for handling appeals or complaints, please see the Journal website.

Submissions

- Manuscripts should be submitted through the HKJO online submission system at https://hkjo.hk/index.php/hkjo/about/submissions. Please register for an account with the system and upload files according to the instructions. All files must be submitted through the system.
- Please provide a blinded manuscript as a single file. Any identifying information (eg, references to past publications, name of an author's institution) should be masked or removed from the blinded manuscript.
- Manuscripts should be submitted in Word format (.doc or .docx).
- Manuscripts must be written in English (US spellings as per the Merriam-Webster Dictionary).
- In general, manuscripts should be prepared following the 'IMRaD' structure as recommended by the ICMJE (http://icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html).
- For each author, please provide the full name, professional qualifications, and affiliation (where the study was conducted)
- The full name, postal address, telephone and fax numbers, and email address of the corresponding author must be provided. The corresponding author, on behalf of the authors, is responsible for all contact with the Journal.
- A structured abstract of ≤250 words is required for Review Articles and Original Articles. The abstract should provide a complete summary of the article, including the aims/purpose, main methods, key results, and conclusions. Abbreviations and clinical or technical jargon should be avoided.
- Tables should be typed using the 'Insert Table' feature of MS Word, with one item of data per cell and minimal formatting. Large tables may be provided in MS Excel format. Tables should be numbered and concisely titled. Abbreviations should be defined in footnotes.
- The number of figures should be restricted to the minimum necessary to support the textual material. Figures should be .JPG format with a resolution of ≥350 dpi. Figures should be included in the manuscript file; large image files may be submitted separately. Legends should be provided for each figure to indicate the anatomical area and pathological condition shown. All symbols and abbreviations should be defined in the legend.
- The references should be numbered in the order in which they are first cited in the text. Each reference citation should be in superscript Arabic numerals after full-stops and commas. At the end of the article, the full list of references should be presented in Vancouver style. Include the names of all authors, title of the article, abbreviated name of journal, year of publication, volume number, and inclusive pages, in that order.
- Please refer to the latest ICMJE recommendations on Manuscript Preparation for further information on references and for general guidance on style: http://icmje.org/recommendations/browse/manuscript-preparation/

Peer Review

- HKJO operates a double-blind peer-review process. Details of the peer review process can be found on the Journal website.

Copyright

- On acceptance of an article for publication in HKJO, copyright of the article is transferred to the Journal.
- The Journal has a fully Open Access policy and publishes all articles under a Creative Commons license (CC BY-NC-ND 4.0). For any use other than that permitted by this license, written permission must be obtained from the Journal.

Correspondence

- All correspondence on editorial issues should be addressed to the Editorial Office (editorial@hkjo.hk).

香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
BEST ORIGINAL ARTICLE AWARD

Purpose

To encourage submissions to the *Hong Kong Journal of Ophthalmology* (HKJO) by trainees and fellows of the College of Ophthalmologists of Hong Kong (COHK).

Awards and Prizes

Two awards will be given out every year. Each awardee will be given a $2000 cash prize (HK dollars), which is supported generously by the Timothy KC Liu Fund.

Eligibility

- One award is open to all fellows and members of the College; another one is limited to trainees only.
- Applicants must be a paid-up member or fellow of COHK at the time of submission.
- Trainees refer to those who have not been conferred the title 'FCOphthHK' at the time of submission.
- Only the first author of the article will be eligible for the prize. If the first author is not eligible for the award, i.e. not a member or fellow of COHK, then the order of consideration of awardee will be from the second author onwards to the last author.
- Original articles (including, but not limited to, prospective or retrospective clinical studies, observational studies, epidemiological studies, basic science studies, meta-analysis, etc) published in the HKJO during the year will automatically enter the selection process.
- Case reports (with case number <3), review articles and letters to the editor will not be eligible for this award.
- Submissions pending acceptance will not be eligible for the award.
- Entries will be based on the article as a unit, but not the author. Because of this, it is possible that one single author wins both awards, given that he/she is the first author of the two best original articles published that year (but he/she has to be a trainee in this case as one award is open for trainees only).

Selection Panel

- Editor-in-Chief
- 1 representative from the University of Hong Kong
- 1 representative from the Chinese University of Hong Kong and
- President of the College

Selection Criteria

- Originality
- Scientific merit
- Methodology
- Presentation style

Award Presentation Ceremony

The awards will be given out at the following year's conferment ceremony.

Hong Kong Journal of Ophthalmology: past, present, and future

Since the establishment of our Journal website (hkjo.hk) in 2015, considerable progress has been made to enhance the editorial workflow and readership. For 2022 alone, there is a 20% increase in submission from both local and overseas authors, and there is a 15% year-on-year traffic growth to our website. Website visitors are most commonly from Hong Kong SAR, Mainland China, and United States (**Table**). The most viewed articles for the past year are "Intraocular gas in vitreoretinal surgery",[1] "Recommendations of the treat-and-extend regimen for neovascular age-related macular degeneration: 2020 updates",[2] and "Long-term outcomes of free internal limiting membrane transplant for unclosed macular holes after extensive internal limiting membrane peeling and silicone oil tamponade: a report of two cases".[3]

Table. Top 10 visitors to the *Hong Kong Journal of Ophthalmology* website in 2022 (as of 18 December 2022)

Location	No. (%) of visits
Hong Kong SAR	2236 (36.4)
Mainland China	947 (15.4)
United States	680 (11.1)
India	302 (4.9)
Singapore	120 (2.0)
United Kingdom	115 (1.9)
Japan	114 (1.9)
Indonesia	101 (1.6)
Turkey	76 (1.2)
Australia	70 (1.1)
Others	1387 (22.6)
Overall	**6148**

In this issue, readers will note an increase in the number of published articles. With the change to the continuous publication mode in September 2022, articles are published online first before they are published in print. The time from submission to publication is thus shortened, which helps to speed up the dissemination of ophthalmic knowledge.

After thorough preparation, we applied for inclusion in the Directory of Open Access Journals (DOAJ) in August 2022. To fulfil the requirements of DOAJ, enhancements were made to our Journal and editorial workflow during the terms of the last two editorial boards. This is a stepping stone towards future indexing in the PubMed, which will enhance our Journal's reputation and international exposure. We would like to take this opportunity to thank all editorial board members, authors and reviewers, the Council of the College of Ophthalmologists of Hong Kong, and the Hong Kong Academy of Medicine Press for the steadfast support and input.

Alvin Ka Hong Au,[1] *MHM (UNSW), FHKAM (Ophth)*
Alvin Kwan Ho Kwok,[2] *MD (HK), MD (CUHK), PhD (HK), FRCS (UK), FRCOphth (UK), FHKAM (Ophth), PostGrad DipEpidem & Biostat (CUHK), MBBS (HK)*
[1]*Private practice*
[2]*Department of Ophthalmology, Hong Kong Sanatorium & Hospital*

Correspondence and reprint requests:
Dr Alvin Kwan Ho Kwok, Department of Ophthalmology, 4/F, Li Shu Fan Block, Hong Kong Sanatorium & Hospital, 2 Village Road, Hong Kong.
Email: alvinkhkwok@netvigator.com

References

1. *Mohamed S, Lai TY. Intraocular gas in vitreoretinal surgery. Hong Kong J Ophthalmol 2010;14:8-13.*
2. *Kwok AKH, Lam WC, Fong AHC, et al. Recommendations of the treat-and-extend regimen for neovascular age-related macular degeneration: 2020 updates. Hong Kong J Ophthalmol 2021;25:39-46.* Crossref
3. *Kwok AKH. Long-term outcomes of free internal limiting membrane transplant for unclosed macular holes after extensive internal limiting membrane peeling and silicone oil tamponade: a report of two cases. Hong Kong J Ophthalmol 2020;24:18-21.* Crossref

ORIGINAL ARTICLE

Global survey of lacrimal surgeons on practice of nasolacrimal duct obstruction amid COVID-19 pandemic

Chun Wah Lam[1], *MBBS (Hons), MRCSEd, AFCOphthHK; Tessa Fayers*[2], *FRCOphth; Hunter Kwok Lai Yuen*[1], *FRCOphth, FRCSEd, FCOphthHK; Reynaldo Javate*[3], *FICS; Jane Olver*[4], *FRCS, FRCOphth*

[1]*Hong Kong Eye Hospital, Hong Kong*
[2]*Department of Ophthalmology, Imperial College Healthcare NHS Trust, London, UK*
[3]*Department of Ophthalmology, University of Santo Tomas Hospital, Manilla, Philippines*
[4]*Clinica London, London, UK*

Correspondence and reprint requests:
Dr Chun Wah Lam, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong. Email: matthewlam300@gmail.com

Abstract

Objective: To survey lacrimal surgeons worldwide on their practice of nasolacrimal duct obstruction amid the coronavirus disease 2019 (COVID-19) pandemic.

Methods: A 24-question survey was designed to investigate lacrimal surgeons worldwide on their practice of nasolacrimal duct obstruction before the COVID-19 outbreak, during the first wave of COVID-19 pandemic (Spring 2020), and during the study period (12 March 2021 to 12 May 2021). The survey was uploaded to a website, and the link of the survey was sent to international oculoplastic societies for further distribution to their members.

Results: A total of 570 respondents from 68 countries or regions were included in the analysis. During the study period, the preferred surgical technique for nasolacrimal duct obstruction was external dacryocystorhinostomy (DCR) [69.9%], followed by endoscopic DCR (46.0%). 95.1% of respondents performed silicone intubation. When the risk of COVID-19 infection was high, respondents preferred external DCR to endoscopic DCR. Respondents used higher levels of personal protective equipment for lacrimal irrigation and surgery during the study period than before the COVID-19 outbreak, in compliance with guidelines on aerosol-generating medical procedures.

Conclusions: Amid the COVID-19 pandemic, the preferred surgical treatment worldwide for nasolacrimal duct obstruction remains external DCR. The experience gained from the COVID-19 pandemic enables lacrimal surgeons to better prepare for future pandemics.

Key words: COVID-19; Lacrimal duct obstruction; Surveys and questionnaires

Introduction

In March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic. The viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) isolated from bodily fluids is particularly heavy in the respiratory tract (including the nasal passages).[1-6] As the lacrimal system is contiguous with the nasal mucosa, orbital and lacrimal surgeons are at risk of infection during lacrimal irrigation and dacryocystorhinostomy (DCR); the risk is increased during manipulation of nasal mucosa in nasal endoscopy.

At the start of the pandemic, most services involving lacrimal drainage were suspended, as were other aerosol-

generating medical procedures (AGMP).[7-11] Variant strains with high infectivity kept emerging even after widespread coverage of vaccination.[12-20] Lacrimal surgeons adjust their practice to limit viral spread while gradually resuming lacrimal services. This study aims to survey lacrimal surgeons worldwide on their practice of nasolacrimal duct obstruction before the COVID-19 outbreak, during the first wave of COVID-19 pandemic (Spring 2020), and during the study period (12 March 2021 to 12 May 2021).

Methods

A 24-question survey was designed to investigate lacrimal surgeons worldwide on their practice of nasolacrimal duct obstruction before the COVID-19 outbreak, during the first wave of COVID-19 pandemic (Spring 2020), and during the study period (12 March 2021 to 12 May 2021). The survey was uploaded to the website https://kwiksurveys.com, and the link of the survey was sent to British Oculoplastic Surgery Society, European Society of Ophthalmic Plastic and Reconstructive Surgery, Australian & New Zealand Society of Ophthalmic Plastic Surgeons, Asia Pacific Society of Ophthalmic Plastic and Reconstructive Surgery, and American Society of Ophthalmic Plastic and Reconstructive Surgery for further distribution to their members through emails or notice board. The survey was also sent to lacrimal surgeon networks in the Middle East and South America through emails and WhatsApp groups known by the authors. Participants were invited to leave their emails for the results of the survey and follow-up.

Results

A total of 684 responses were received during the study period from 12 March 2021 to 12 May 2021. After excluding those who were not performing lacrimal surgery and those who had incomplete responses with no useful data, 570 respondents from 68 countries or regions were included in the analysis (**Figure**). There was no duplicate response.

During the study period (from 12 March 2021 to 12 May 2021)

During the study period (which was largely pre-vaccination and before the emergence of Delta and Omicron variants), 65.9% of respondents considered their countries in an increasing phase of infection, whereas 34.1% of respondents reported low/decreasing/stable infection rates in their countries or regions (eg, Australia, New Zealand, and Taiwan).

97.4% of respondents reported resumption of part, if not all, of lacrimal services; only 2.6% of respondents were still not seeing patients needing lacrimal services. For lacrimal assessment, 86.4% of respondents resumed syringing and probing and 31.2% resumed nasal endoscopy for routine epiphora in those without COVID-19 symptoms, whereas 8.6% deferred these diagnostic tests in accordance with governmental orders or institutional guidelines or at individual discretion. For lacrimal surgery, 73.6% of respondents resumed all lacrimal surgery with no restrictions from their institutions, whereas 21.7% resumed urgent lacrimal surgery only and 4.7% were not permitted to perform lacrimal surgery.

For preoperative viral testing, 73.0% and 16.3% of respondents performed SARS-CoV-2 testing on all patients and high-risk patients, respectively, whereas 10.7% of respondents performed no testing, mainly because of

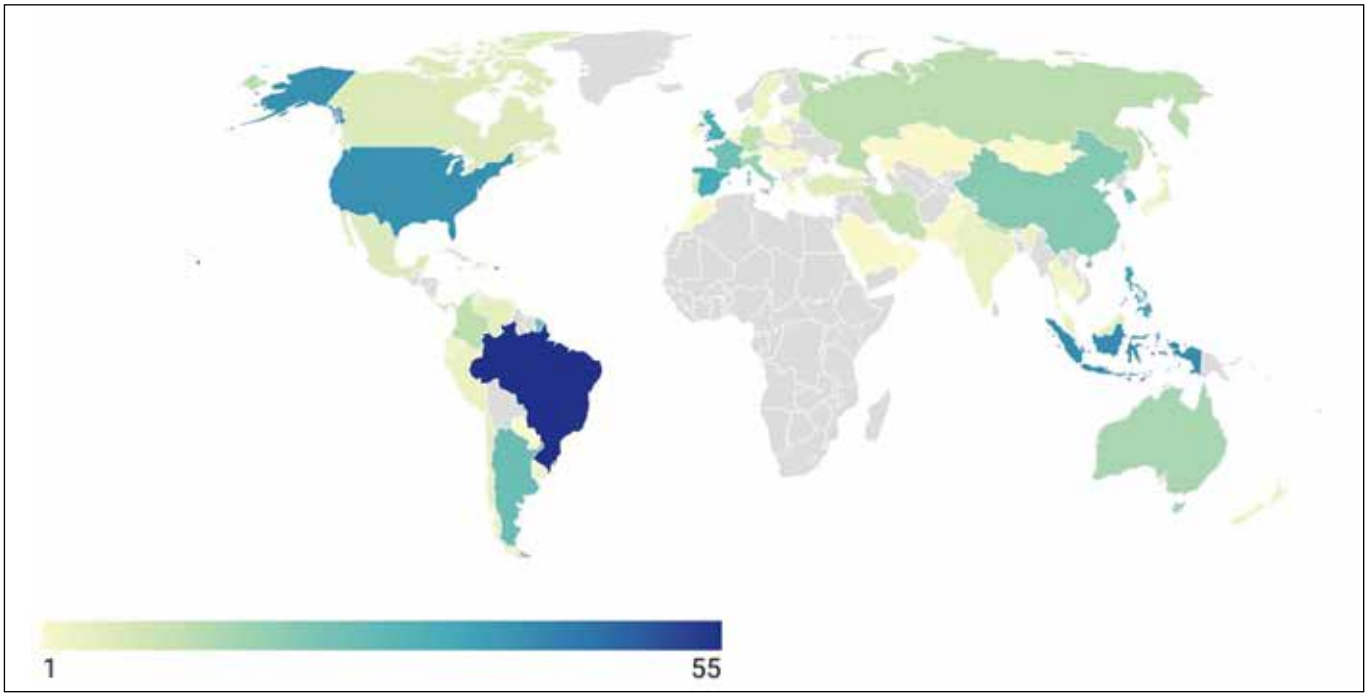


Figure. Worldwide distribution of respondents.

logistic or administrative reasons, or low infection rates in their regions. For those who performed testing, 81.3% of respondents used the nasal polymerase chain reaction test, 9.7% used the nasal rapid antigen test, 1.7% used the serum antibody test, and 3.9% used the saliva test.

For personal protective equipment (PPE), during syringing and probing, 4.7% of respondents reported not using any PPE, whereas 43.5% and 49.5% reported wearing a surgical mask and a N95 mask, respectively, with or without a face shield. During nasal endoscopy, 37.3% and 54.6% of respondents reported wearing a surgical mask and a N95 mask, respectively, with or without a face shield. During lacrimal surgery, 55.1% of respondents reported wearing a N95 mask and 24.3% reported wearing a face shield. Compared with before the COVID-19 outbreak, during the study period more respondents opted to wear a N95 mask (35.7% vs 49.5%, p<0.01) or a face shield (15.4% vs 24.9%, p<0.01) during syringing and probing, and more respondents opted to wear a N95 mask (40.6% vs 55.1%, p<0.01) or a face shield (14.2% vs 24.3%, p<0.01) during lacrimal surgery (**Table 1**).

For nasolacrimal duct obstruction, the preferred technique was external DCR (69.9%), followed by endoscopic DCR (46.0%), lacrimal recanalization (21.3%), and balloon dacryoplasty (4.7%). 15.3% of respondents preferred both endoscopic and external DCR. These proportions were comparable with those before the COVID-19 outbreak (p=0.873). Among respondents in countries with high COVID-19 infections, 62.6% preferred external DCR and 26.2% preferred endoscopic DCR, whereas among respondents in countries with low or stable COVID-19 infections, 39.5% preferred external DCR and 39.5% preferred endoscopic DCR (p<0.01).

95.1% of respondents performed silicone intubation. Of them, 37.9% chose to remove the tube by direct visualization of the nose and retrieving the cut tubes with forceps, whereas 20.9% chose to retrieve the tube by endoscopic guidance. 95.3% of respondents removed the tube in outpatient consultation rooms or minor treatment rooms and 4.5% in the operating theater (**Table 2**).

Before COVID-19 outbreak

The preferred lacrimal surgery procedure was external DCR (72.8%), followed by endoscopic endonasal DCR (46.0%), lacrimal recanalization (22.8%), and balloon

Table 1. Choice of personal protective equipment during syringing and probing, lacrimal surgery, and nasal endoscopy before the COVID-19 outbreak and during the study period (12 March 2021 to 12 May 2021)*

Personal protective equipment	Before the COVID-19 outbreak		During the study period (12 March 2021 to 12 May 2021)		
	Syringing and probing	Lacrimal surgery	Syringing and probing	Lacrimal surgery	Nasal endoscopy
No personal protective equipment	19.8	3.0	4.7	0.6	5.1
Surgical mask alone	37.9	49.1	37.1	32.7	31.9
N95 mask alone	25.4	30.4	31.8	36.6	33.2
Surgical mask and face shield	4.1	3.5	6.4	5.6	5.4
N95 mask and face shield	10.4	10.2	17.7	18.5	21.4
Face shield alone	0.9	0.5	0.9	0.2	1.0
Powered air-purifying respirator	1.6	3.3	1.5	5.8	2.0

** Data are presented as % of respondents*

Table 2. Method and setting of silicone tube removal before the COVID-19 outbreak and during the study period (12 March 2021 to 12 May 2021)*

Silicone tube removal	Before the COVID-19 outbreak	During the study period (12 March 2021 to 12 May 2021)
Method		
Removal from the eye rather than the nose	31.4	31.0
Tube cut at medial canthus and patient blowing it out	32.3	31.7
Direct visualization and retrieval with forceps	39.6	37.9
Endoscopic endonasal retrieval	22.5	20.9
Setting		
Operating theater	3.0	4.5
Minor treatment room	19.9	19.5
Outpatient consultation room	77.1	75.8

** Data are presented as % of respondents*

dacryoplasty (7%). 14.9% preferred both endoscopic and external DCR. Among respondents from developed countries/regions (high-income areas as defined by the World Bank[21]), 51.2% preferred external DCR and 36.7% preferred endoscopic DCR, whereas among respondents from non-high-income countries/regions, 64.1% preferred external DCR and 25.4% preferred endoscopic DCR ($p<0.01$).

For PPE, during syringing and probing, 42.0% of respondents wore a surgical mask and 19.8% did not wear any PPE. During lacrimal surgery, 52.6% of respondents wore a surgical mask and 40.6% wore a N95 mask; 14.2% wore a face shield (**Table 1**). 97.7% performed silicone intubation. The proportions of respondents in terms of silicone tube removal were similar to those during the study period (**Table 2**).

During the first wave of COVID-19 pandemic (Spring 2020)

For most countries, the first wave of COVID-19 pandemic was around Spring 2020. Among the respondents, 10.0% stopped all lacrimal services, 24.2% deferred all lacrimal surgery, 12.8% deferred cases at high risk of COVID-19 infection, and 36.6% provided services for acute dacryocystitis only (as an urgent indication).

Discussion

In response to the first wave of COVID-19 pandemic in 2020, many countries implemented lockdown and social distancing measures. Most elective surgeries were suspended, including lacrimal surgeries that involve nasolacrimal duct obstruction. In a survey of lacrimal practice in Asia-Pacific published in May 2020, 57.8% of the respondents were unsure when to resume elective surgeries, and 62.8% were uncertain about the preferred screening strategy or precautionary approach prior to resuming surgeries.[15]

Starting from 2021, the number of new cases and deaths had decreased owing to implementation of social distancing and quarantine measures and the gradual increase in vaccination coverage.[4,6] However, with the emergence of Delta and Omicron variants with increased infectivity, the number of cases had risen again.

Lacrimal services of syringing and probing and nasal endoscopy involve contact with tears and the nasal mucosa, where droplets or aerosolized particles of SARS-CoV-2 can be generated. External and endoscopic endonasal DCR are often performed with mechanical tools, high speed burrs, and suction, and are considered AGMP at risk of COVID-19 spread.[22]

The choice to perform external DCR or endoscopic endonasal DCR largely depends on surgeon preference based on their training, experience, and equipment. In the United Kingdom in 2008, 59% of ophthalmic surgeons had never performed endonasal DCR. In the US in 2013, 93.9% preferred external DCR, whereas in India in 2016, 86% preferred external DCR. In the Asia-Pacific region in 2017, 79.2% of surgeons preferred endoscopic DCR and 71.1% preferred external DCR.[23-27] In our survey, external DCR remains the preferred lacrimal surgery among lacrimal surgeons worldwide. Nonetheless, endoscopic DCR is more preferred by high-income countries than non-high-income countries (36.7% vs 25.4%). This may be due to differences in equipment, training, and expertise. A systematic review concluded that endonasal DCR and external DCR are comparable in terms of success rate.[28] There is no evidence to suggest whether external or endoscopic DCR is riskier in terms of spread of COVID-19. Nonetheless, endoscopic DCR involves more manipulation of the nasal mucosa than external DCR. In our survey, infection rates of countries affected the choice of DCR technique; only 26.2% preferred endoscopic DCR in countries with high infection rate, whereas 39.5% preferred so in countries with low/stable infection rate.

Lacrimal irrigation and probing are part of the basic lacrimal assessment and a potential source of aerosol generation. The presence of SARS-CoV-2 in tears and conjunctival secretion highlights the potential risk.[29] Some guidelines recommend the use of low-capacity syringes and 25 or 27 G cannulas to minimize the force generated during the procedure, and the use of adequate PPE for syringing and probing.[19] In our survey, the proportion of respondents who did not wear any PPE decreased from 19.8% before the COVID-19 outbreak to 4.7% during the study period ($p<0.01$). Similarly, for syringing and probing, the proportion of respondents who wore a N95 mask and a face shield increased from 35.7% and 15.4%, respectively, before the COVID-19 outbreak to 49.5% and 24.9%, respectively, during the study period ($p<0.01$). Syringing and probing is a potential AGMP and thus adequate protection is warranted. Wearing a surgical mask has become a basic requirement in clinics and hospitals to reduce transmission through direct inhalation in close proximity.[11,16,22]

Nasal endoscopy is useful in preoperative assessment and postoperative management of endoscopic DCR. Nasal endoscopy is an AGMP, as it involves suction and intra-nasal manipulations.[9,22] In our survey, during the study period, 37.3% and 54.6% of respondents wore a surgical mask and a N95 mask, respectively, and 27.8% also wore a face shield. Most respondents wore PPE during nasal endoscopy, consistent with guidelines on AGMPs.

For lacrimal surgery, respondents had shifted from wearing a surgical mask alone (49.1% to 32.7%) to wearing a N95 mask (40.6% to 55.1%) and a face shield (14.2% to 24.3%) [$p<0.01$] since the pandemic. Although surgical masks are good protection against droplet transmission, N95 masks are more effective in blocking infective aerosols. Face shields and goggles are recommended for additional protection.[22] During the pandemic, higher levels of PPE are necessary when performing lacrimal surgery.

During the study period, 89.3% of respondents performed preoperative testing for SARS-CoV-2 for patients. However, preoperative viral testing has limited sensitivity, especially in asymptomatic or pre-symptomatic persons. Therefore, surgeons should put on appropriate PPE, adjusting for the risk of surgery, prevalence of COVID-19 in the community, and availability of PPE. Lacrimal surgery is a potential AGMP; it is recommended to wear a N95 mask, a face shield/goggles, and a water-impermeable gown even if the patient is tested negative, especially when local infection rates are high.[9]

During the study period, 95.1% of respondents performed silicone intubation. The use of silicone stents results in a higher success rate of DCR.[30-32] 73.5% of surgeons in the Asia-Pacific region and 75% to 100% of surgeons in the United Kingdom performed silicone intubation.[25,27]

One limitation to this survey was potential recall bias, particularly with respect to questions about the early pandemic period. In addition, the effect of vaccination was not assessed (because the vaccination program had just been begun during the study period), as were preoperative application of povidone iodine on nasal mucosa, detailed surgical steps, equipment used (for suction or irrigation, bone drills, cautery), lacrimal surgical training, and telemedicine so as to keep the questionnaire brief.

Conclusion

Aerosolized spread of viral particles during AGMP should be minimized while performing lacrimal services. With the experience gained from the COVID-19 pandemic, orbital and lacrimal surgeons are better prepared to face future novel viral strains.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (Reference: KC/KE-21-0160/ER-3).

Acknowledgements

We would like to thank clinicians who took time to complete the survey and the national and international oculoplastic societies who helped distribute the survey link to their members.

References

1. *Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 transmission and pathogenesis. Trends Immunol 2020;41:1100-15.* Crossref
2. *Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021;97:312-20.* Crossref
3. *Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.* Crossref
4. *World Health Organization. Coronavirus Disease (COVID-2019) Situation Reports. 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 13 March 2022.*
5. *Tang JW, Marr LC, Li Y, Dancer SJ. Covid-19 has redefined airborne transmission. BMJ 2021;373:n913.* Crossref
6. *World Health Organization. Available at: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-how-is-it-transmitted. Accessed 13 March 2022.*
7. *Workman AD, Jafari A, Welling DB, et al. Airborne aerosol generation during endonasal procedures in the era of COVID-19: risks and recommendations. Otolaryngol Head Neck Surg 2020;163:465-70.* Crossref
8. *Mick P, Murphy R. Aerosol-generating otolaryngology procedures and the need for enhanced PPE during the COVID-19 pandemic: a literature review. J Otolaryngol Head Neck Surg 2020;49:29.* Crossref
9. *Lammers MJW, Lea J, Westerberg BD. Guidance for otolaryngology health care workers performing aerosol generating medical procedures during the COVID-19 pandemic. J Otolaryngol Head Neck Surg 2020;49:36.* Crossref
10. *Tan L, Kovoor JG, Williamson P, et al. Personal protective equipment and evidence-based advice for surgical departments during COVID-19. ANZ J Surg 2020;90:1566-72.* Crossref
11. *Revised guidelines for potential aerosol-generating procedures (AGPs) within the ENT clinic. 2021. Available at: https://www.entuk.org/_userfiles/pages/files/covid19/revised_agp_guidelines.pdf*
12. *Ali MJ. COVID-19 pandemic and lacrimal practice: multipronged resumption strategies and getting back on our feet. Indian J Ophthalmol 2020;68:1292-9.* Crossref

13. *Mak ST, Yuen HK. Oculoplastic surgery practice during the COVID-19 novel coronavirus pandemic: experience sharing from Hong Kong. Orbit 2020;39:316-8.* Crossref
14. *Lanni V, Iuliano A, Laezza MP, Uccello G, Tranfa F, Strianese D. Oculoplastic management of patients in the Covid-19 era: experience from an Italian tertiary referral center. Orbit 2020;39:391-3.* Crossref
15. *Nair AG, Narayanan N, Ali MJ. A survey on the impact of COVID-19 on lacrimal surgery: the Asia-Pacific perspective. Clin Ophthalmol 2020;14:3789-99.* Crossref
16. *Nguyen AX, Gervasio KA, Wu AY. COVID-19 recommendations from ophthalmic and plastic reconstructive surgery societies worldwide. Ophthalmic Plast Reconstr Surg 2020;36:334-45.* Crossref
17. *Quaranta-Leoni FM, Paridaens D, Verity D. European Society of Ophthalmic Plastic and Reconstructive Surgery (ESOPRS) recommendations for oculoplastic surgeons during the COVID-19 pandemic: a challenge for the future. Orbit 2020;39:460-2.* Crossref
18. *American Academy of Ophthalmology. List of urgent and emergent ophthalmic procedures. Available at: https://www.aao.org/headline/list-of-urgent-emergent-ophthalmic-procedures.*
19. *Ali MJ, Hegde R, Nair AG, et al. All India Ophthalmological Society–Oculoplastics Association of India consensus statement on preferred practices in oculoplasty and lacrimal surgery during the COVID-19 pandemic. Indian J Ophthalmol 2020;68:974-80.* Crossref
20. *Nair AG, Gandhi RA, Natarajan S. Effect of COVID-19 related lockdown on ophthalmic practice and patient care in India: results of a survey. Indian J Ophthalmol 2020;68:725-30.* Crossref
21. *The World Bank. Available at: https://www.worldbank.org/en/home*
22. *Daigle P, Leung V, Yin V, Kalin-Hajdu E, Nijhawan N. Personal protective equipment (PPE) during the COVID-19 pandemic for oculofacial plastic and orbital surgery. Orbit 2021;40:281-6.* Crossref
23. *Barmettler A, Ehrlich JR, Lelli G Jr. Current preferences and reported success rates in dacryocystorhinostomy amongst ASOPRS members. Orbit 2013;32:20-6.* Crossref
24. *Nair AG, Kamal S, Agarwal A. Indian survey on practice patterns of lacrimal and eyelid disorders (iSUPPLE): report 2: mitomycin-C and lacrimal stents in dacryocystorhinostomy. J Craniofac Surg 2016;27:2015-9.* Crossref
25. *Gauba V, Islam T, Saleh GM, Zuberbuhler B, Vize C. The practice of dacryocystorhinostomy (DCR) surgery by ophthalmologists in the United Kingdom (UK). Orbit 2008;27:279-83.* Crossref
26. *Huang J, Malek J, Chin D, et al. Systematic review and meta-analysis on outcomes for endoscopic versus external dacryocystorhinostomy. Orbit 2014;33:81-90.* Crossref
27. *Kwok T, Ali MJ, Yuen H. Preferred practice patterns in endoscopic dacryocystorhinostomy among oculoplastic surgeons in Asia-Pacific region. Orbit 2018;37:248-53.* Crossref
28. *Sobel RK, Aakalu VK, Wladis EJ, Bilyk JR, Yen MT, Mawn LA. A comparison of endonasal dacryocystorhinostomy and external dacryocystorhinostomy: a report by the American Academy of Ophthalmology. Ophthalmology 2019;126:1580-5.* Crossref
29. *Hu Y, Chen T, Liu M, et al. Positive detection of SARS-CoV-2 combined HSV1 and HHV6B virus nucleic acid in tear and conjunctival secretions of a non-conjunctivitis COVID-19 patient with obstruction of common lacrimal duct. Acta Ophthalmol 2020;98:859-63.* Crossref
30. *Kang MG, Shim WS, Shin DK, Kim JY, Lee JE, Jung HJ. A systematic review of benefit of silicone intubation in endoscopic dacryocystorhinostomy. Clin Exp Otorhinolaryngol 2018;11:81-8.* Crossref
31. *Feng YF, Cai JQ, Zhang JY, Han XH. A meta-analysis of primary dacryocystorhinostomy with and without silicone intubation. Can J Ophthalmol 2011;46:521-7.* Crossref
32. *Fayers T, Dolman PJ. Bicanalicular silicone stents in endonasal dacryocystorhinostomy: results of a randomized clinical trial. Ophthalmology 2016;123:2255-9.* Crossref

Brolucizumab and faricimab as new treatment options for diabetic macular edema: perspective

Ho Lam Wong[1]; Nicholas Siu Kay Fung[2], MBChB, MRCS (Edin), FCOphth HK, FHKAM (Ophthalmology); Alvin Kwan Ho Kwok[3], MBBS (HK), MD (HK), MD (CUHK), PhD (HK), PDip Epidemiology and Biostatistics (CUHK), FRCSEd, FCSHK, FCOphth HK, FRCOphth, FHKAM (Ophthalmology)

[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[3]Department of Ophthalmology, Hong Kong Sanatorium & Hospital, Hong Kong

Correspondence and reprint requests:
Dr Alvin Kwan Ho Kwok, 4/F, Li Shu Fan Block, Department of Ophthalmology, Hong Kong Sanatorium & Hospital, 2 Village Road, Happy Valley, Hong Kong. Email: alvinkwok@hksh.com

Abstract

Diabetic macular edema (DME) is the leading cause of blindness in the working populations, with patients requiring 10.7 intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents per year. The high rate of non-compliance of anti-VEGF injection in patients with DME and the unmet need in current regimen may result in suboptimal visual outcome. Brolucizumab, an antibody fragment anti-VEGF-A agent, has been approved to treat neovascular age-related macular degeneration, as illustrated in the HAWK and HARRIER trials. Similarly, the KESTREL and KITE DME trials have shown that brolucizumab 6 mg achieves greater improvement in best-corrected visual acuity and greater reduction in central subfield thickness at week 52, compared with aflibercept 2 mg. Fewer patients with brolucizumab have intraretinal and subretinal fluid. Careful monitoring, prompt diagnosis, and timely intervention enable early management of adverse effects including intraocular inflammation and retinal artery occlusion. Moreover, in the BOULEVARD trial, patients with DME on faricimab 1.5 and 6.0 mg have demonstrated greater gain in Early Treatment Diabetic Retinopathy Study letters and greater reduction in central subfield thickness, compared with patients on ranibizumab 0.3 mg. The YOSEMITE and RHINE trials have demonstrated greater improvement in best-corrected visual acuity and two-step Diabetic Retinopathy Severity Scale at week 52 after faricimab 6 mg than after aflibercept 2 mg. Thus, brolucizumab and faricimab are efficacious, durable, and well tolerated, with improved treatment outcome and patient compliance.

Key words: Brolucizumab; Diabetic retinopathy; Faricimab; Macular edema

Introduction

Diabetic macular edema (DME) is the leading cause of blindness in the working populations in developed countries, affecting 12% of people with type 1 diabetes and 28% of people with type 2 diabetes.[1] In 2020, the worldwide prevalence of DME was estimated to be 20 million, which is expected to rise to 30 million by 2045. This imposes an immense burden to the healthcare system.[2]

Current treatment options for DME include primary glycemic control, laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factors (VEGFs), anti-VEGF biosimilars, or corticosteroids, and pars plana vitrectomy. Novel therapies involving cytokine inhibitors, adhesion molecular inhibitors, and Kallikrein-Kinin systemic inhibitors are increasingly popular.[3] The

development of anti-VEGFs revolutionized the medical management of DME. Intravitreal injection of anti-VEGF has a favorable benefit-risk ratio and is more effective than laser photocoagulation on visual improvement and optimization.[4]

Nonetheless, the non-compliance rate of anti-VEGF treatment in patients with DME is high.[5] The most common barrier to follow-up adherence is the long waiting time in clinics, followed by the presence of other medical conditions. Patients with DME typically need to attend 34 medical appointments per year on average.[6] In a survey of European retina specialists in 2014 to 2015, patients with DME had 7.3-fold (95% confidence interval [CI]=6.3-8.6; p<0.0001) increased odds of no showing in appointments than patients with neovascular age-related macular degeneration (nAMD).[5] Missed appointment for anti-VEGF treatment is associated with decreased visual acuity and thus affects both functional and clinical outcomes.[7,8]

Anti-VEGF agents are typically administered every 1 to 3 months. Even with the treat-and-extend regimen, patients still need to receive 10.7 injections per year.[9] There is an unmet need under the current management protocol. According to a survey by the American Society of Retina Specialists in 2017, retinal specialists prefer treatments that require fewer injections and have longer duration of action for patients with DME.[10] Yet, visual outcome positively correlates with the frequency of anti-VEGF treatment; more injections result in better visual acuity.[11] To prevent undertreatment and suboptimal visual outcomes, a new treatment option for DME is needed to lessen the healthcare burden.

In patients with diabetes, hyperglycemia damages small blood vessels in the eye and promotes the release of VEGF. VEGF-A increases neoangiogenic events and vascular permeability.[12] The angiopoietin (Ang) tyrosine kinase endothelial receptor (Tie) pathway plays a role in vascular homeostasis and modulates vascular permeability, inflammation, and angiogenesis.[13] Ang-1 binds to Tie-2, which blocks vascular leakage and proinflammatory cascade in the endothelial cells. However, Ang-2 is an antagonist that destabilizes the vessels and renders them more vulnerable to VEGF. Fluid accumulation disrupts the architecture of the neurosensory unit and leads to retina dysfunction.[14] Both intraretinal fluid and subretinal fluid are associated with DME activity, with intraretinal fluid being more prevalent owing to the disruption of the inner blood-retinal barrier.[15] Over 25% of patients with untreated DME lose ≥2 lines of visual acuity within 2 year, and thus early treatment is important.[16,17] However, up to 40% of patients with anti-VEGF treatment have persistent intraretinal and subretinal fluid accumulation after 3 years.[18] A more effective treatment to dry the macula is needed.

Brolucizumab

Brolucizumab is a humanized, single-chain antibody fragment, anti-VEGF-A agent, with a molecular mass of ~26 kDa.[19] It is approved by the United States Food and Drug Administration for treatment of nAMD and DME. In the HAWK and HARRIER phase-3 clinical trials, patients treated for nAMD demonstrated improved best-corrected visual acuity at week 48 (+6.6 letters and +7.6 letters, respectively, both p<0.001).[20] Reduction in central subfield thickness at week 48 was greater after brolucizumab treatment than aflibercept treatment (-172.8 vs -143.7 μm and -193.8 vs -143.9 μm, respectively, both p<0.001), with anatomical outcome favoring brolucizumab.[20] Each 6 mg of brolucizumab results in a 10-fold higher molar dose than aflibercept in the same volume; brolucizumab has more durable efficacy and necessitates less frequent dosing.[19,21] Brolucizumab binds with high affinity to all VEGF-A isoforms and demonstrates similar potency and affinity as aflibercept does.[22,23] Preclinical studies suggest that the small molecular size of brolucizumab facilitates better retina penetration relative to larger VEGF inhibitors.[23,24] Given its longer dosing interval, better tissue penetration, and high binding affinity to VEGF, brolucizumab may help resolve the unmet needs for DME treatment.

In the KESTREL and KITE phase-3 studies that enrolled 926 patients with DME in 36 countries, brolucizumab 6 mg given at 6-week intervals was compared with aflibercept 2 mg given at the standard 4-week intervals during the loading phase.[25,26] Following the loading phase, >50% of patients with brolucizumab (55.1% in KESTREL and 50.3% in KITE) remained on a 3-month interval through year 1 as determined by disease activity assessment, whereas all patients with aflibercept were switch to a 2-month interval.[25] In patients who did not show disease activity after three loading doses of brolucizumab, the likelihood of staying on the 3-month dosing interval through year 1 was 87.6% (95% CI=78.8-93.0) in the KESTREL study and 95.1% (95% CI=87.4-98.1) in the KITE study.[25] Brolucizumab was non-inferior to aflibercept in terms of best-corrected visual acuity at week 52, with >50% of patients maintaining a 3-month dosing interval.[25] In the KITE study, reduction in central subfield thickness was greater with brolucizumab than aflibercept (-187.1 vs -157.7 μm, p=0.001). In the KESTREL and KITE studies, higher proportion of eyes with brolucizumab achieved central subfield thickness of <280 μm at week 52 (Δ13.4% [95% CI=4.9%-23.7%] and Δ16.3% [95% CI=5.7%-25.9%], respectively), and lower proportion of eyes with brolucizumab had intraretinal/subretinal fluid residue at week 52 (Δ-13.2% [95% CI= -23.2% to -3.8%] and Δ-18.4% [95% CI= -28.5% to -8.3%], respectively).[25]

Brolucizumab is well-tolerated. In the KESTREL study, the rates of intraocular inflammation (IOI) were 4.7% (n=9), 3.7% (n=7), and 0.5% (n=1) in patients with brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg, respectively. In the KITE study, the rate of IOI was similar in patients with brolucizumab 6 mg and aflibercept 2 mg (1.7% [n=3] vs 1.7% [n=3]), and the rate of IOI and retinal vasculitis was similar to that in the HAWK study and lower than

that in the HARRIER study.[26] The difference is likely due to a longer dosing interval of 6 weeks in the loading phase in the KITE study and differences in disease entity and study design. Most cases of IOI and retinal vasculitis resolved with or without treatment. Nonetheless, the United States Food and Drug Administration reports that there are 4% chance of IOI (anterior uveitis, intermediate uveitis, posterior uveitis, and retinal vasculitis) and 1% chance of retinal artery occlusion.[27] IOI most commonly occurs at 30 days after intravitreal brolucizumab injection, with affected eyes showing segmental sheathing, vascular nonperfusion, cotton wool spots, and sclerotic vessels.[28] At 25 days after brolucizumab injection, adverse effects such as decreased visual acuity, floaters, eye pain, and eye redness may occur.[29]

In management of nAMD, injection of three doses of brolucizumab at 4-week intervals is recommended.[30] Patients should be followed up at 8 weeks after the third dose (week 16) to assess the drug effect and any adverse outcomes. Subsequent follow-up should be extended to 12 weeks if the disease is stable with no intraretinal/subretinal fluid accumulated. However, treatment should maintain at an 8-week interval if the disease is active with intraretinal/subretinal fluid accumulated. Patient-centered dialogue, patient information booklet, and procedure-specific consent form should be provided to patients. Patients should understand risk factors of IOI including old age, female, history of diabetes, neutralizing antibodies, and prior IOI.[31] Regular monitoring by self and doctors is vital for early detection of IOI. Patients with symptoms of floaters and ocular discomfort for >2 days ought to be evaluated for IOI.[32] Ophthalmological examination should be performed at baseline, 3 months after the loading phase, and 6 or 9 months. Examination should include beam slit lamp assessment of the anterior chamber, dilated fundoscopy assessment of the anterior and posterior vitreous, central and peripheral retina, and pars plana, color fundus photography, and optical coherence tomography. Topical corticosteroid drops should be used for anterior uveitis, whereas systemic corticosteroids should be used for intermediate uveitis, posterior uveitis, and retinal vasculitis.[32] Careful monitoring, prompt diagnosis, and timely intervention are the key of managing adverse effects of brolucizumab.[33]

Faricimab

Faricimab is a 150 kDa-size, bispecific antibody for treatment of DME, nAMD, and retinal vein occlusion.[13] It acts by binding to both VEGF-A and Ang-2 to block vascular leakage and pathological growth of abnormal vessels. In the BOULEVARD phase-2 trial, 229 patients with DME were randomly assigned to receive intravitreal injection of faricimab or ranibizumab.[34] Patients with faricimab 6 mg and 1.5 mg had a mean improvement in visual acuity of 13.9 (80% CI=12.2-15.6) and 11.7 (80% CI=10.1-13.3) letters of ETDRS (Early Treatment Diabetic Retinopathy Study) after 24 weeks, respectively, whereas 72.1% (80% CI=62.9%-79.8%) and 60.6% (80% CI=51.6%-68.9%) of patients had improvement of ≥10 ETDRS letters, respectively. Reduction in central subfield thickness was -225.8 (80% CI= -242.5 to -209.1) μm and -217.1 (80% CI= -233.0 to -201.2) μm, respectively. In addition, 38.6% and 27.7% of patients had more than two-step improvement in Diabetic Retinopathy Severity Scale, respectively. Compared with faricimab 6 mg, ranibizumab 0.3 mg only achieved a mean improvement in visual acuity of 10.3 ETDRS letters, with a mean difference of 3.6 (80% CI=1.5-5.6, p=0.03), and the mean difference in reduction in central subfield thickness was -21.1 (80% CI= -38.7 to -3.5) μm.

In the YOSEMITE and RHINE phase-3 trials, 1891 patients with DME were randomly assigned to receive faricimab 6 mg every 8 weeks (n=315 and n=317, respectively), faricimab 6 mg at a personalized treatment interval (n=313 and n=319, respectively), or aflibercept 2 mg every 8 weeks (n=312 and n=315, respectively).[35] In the YOSEMITE study, the mean best-corrected visual acuity improvement was 10.7 and 11.6 ETDRS letters in the two faricimab groups, respectively. In the RHINE study, the mean best-corrected visual acuity improvement was 11.8 and 10.8 ETDRS letters in the two faricimab groups, respectively, compared with 10.3 ETDRS letters in the aflibercept group. In the YOSEMITE and RHINE studies, >70% of the patients in the two faricimab groups received injection every 12 weeks or longer during year 1, and 68% and 64% of patients in the respective studies showed no significant interval reduction during year 1. In the YOSEMITE study, the adjusted mean reduction in central subfield thickness was -206.6 (95% CI= -214.7 to -198.4) μm and -196.5 (95% CI= -204.7 to -188.4) μm in the two faricimab groups, respectively. In the RHINE study, the reduction in central subfield thickness was -195.8 (95% CI= -204.1 to -187.5) μm and -187.6 (95% CI= -195.8 to -179.5) μm in the two faricimab groups, respectively. In the YOSEMITE study, 46.0% (95% CI=38.8%-53.1%) and 42.5% (95% CI=35.5%-49.5%) of patients in the two faricimab groups achieved more than two-step improvement in Diabetic Retinopathy Severity Scale at week 52. In the RHINE study, the proportions of patients were 44.2% (95% CI=37.1%-51.4%) and 43.7% (95% CI=36.8%-50.7%), respectively. In the YOSEMITE and RHINE studies, 2% and 1% patients with faricimab had IOI, respectively, and two patients in each study had endophthalmitis, but no patient had retinal vasculitis (unlike cases that result from brolucizumab treatment). Overall, faricimab is well tolerated with a good safety profile.

Conclusion

Brolucizumab 6 mg and faricimab 6 mg are viable treatment options for DME; they are efficacious, durable, and well tolerated, with improved treatment outcome and patient compliance and hence decreased healthcare burden.

Contributors

All authors designed the study, acquired the data, analyzed

the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

References

1. *Romero-Aroca P. Managing diabetic macular edema: the leading cause of diabetes blindness. World J Diabetes 2011;2:98-104.* Crossref
2. *Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology 2021;128:1580-91.* Crossref
3. *Chauhan MZ, Rather PA, Samarah SM, Elhusseiny AM, Sallam AB. Current and novel therapeutic approaches for treatment of diabetic macular edema. Cells 2022;11:1950.* Crossref
4. *Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017;237:185-222.* Crossref
5. *Jansen ME, Krambeer CJ, Kermany DS, et al. Appointment compliance in patients with diabetic macular edema and exudative macular degeneration. Ophthalmic Surg Lasers Imaging Retina 2018;49:186-90.* Crossref
6. *Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. Clin Ophthalmol 2016;10:939-46.* Crossref
7. *Ramakrishnan MS, Yu Y, VanderBeek BL. Visit adherence and visual acuity outcomes in patients with diabetic macular edema: a secondary analysis of DRCRnet Protocol T. Graefes Arch Clin Exp Ophthalmol 2021;259:1419-25.* Crossref
8. *Angermann R, Rauchegger T, Nowosielski Y, et al. Systemic counterregulatory response of angiopoietin-2 after aflibercept therapy for nAMD: a potential escape mechanism. Acta Ophthalmol 2021;99:e869-e875.* Crossref
9. *Payne JF, Wykoff CC, Clark WL, et al. Randomized trial of treat and extend ranibizumab with and without navigated laser for diabetic macular edema: TREX-DME 1 year outcomes. Ophthalmology 2017;124:74-81.* Crossref
10. *Sheth JU, Gopal L, Gillies M, et al. Vitreoretinal Society of India practice pattern survey 2020: medical retina. Indian J Ophthalmol 2021;69:1430-9.* Crossref
11. *Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. Br J Ophthalmol 2021;105:216-21.* Crossref
12. *Tan GS, Cheung N, Simó R, Cheung GCM, Wong TY. Diabetic macular oedema. Lancet Diabetes Endocrinol 2017;5:143-55.* Crossref
13. *Nicolo M, Ferro Desideri L, Vagge A, Traverso CE. Faricimab: an investigational agent targeting the Tie-2/angiopoietin pathway and VEGF-A for the treatment of retinal diseases. Expert Opin Investig Drugs 2021;30:193-200.* Crossref
14. *Browning DJ, Stewart MW, Lee C. Diabetic macular edema: evidence-based management. Indian J Ophthalmol 2018;66:1736-50.* Crossref
15. *Roberts PK, Vogl WD, Gerendas BS, et al. Quantification of fluid resolution and visual acuity gain in patients with diabetic macular edema using deep learning: a post hoc analysis of a randomized clinical trial. JAMA Ophthalmol 2020;138:945-53.* Crossref
16. *Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399-405.* Crossref
17. *Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013-22.* Crossref
18. *Bressler SB, Ayala AR, Bressler NM, et al. Persistent macular thickening after ranibizumab treatment for diabetic macular edema with vision impairment. JAMA Ophthalmol 2016;134:278-85.* Crossref
19. *Tadayoni R, Sararols L, Weissgerber G, Verma R, Clemens A, Holz FG. Brolucizumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. Ophthalmologica 2021;244:93-101.* Crossref
20. *Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020;127:72-84.* Crossref
21. *Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study. Ophthalmology 2016;123:1080-9.* Crossref
22. *Tietz J, Spohn G, Schmid G, et al. Affinity and potency of RTH258 (ESBA1008), a novel inhibitor of vascular endothelial growth factor A for the treatment of retinal disorders. Invest Ophthalmol Vis Sci 2015;56:1501.*
23. *Gaudreault J, Gunde T, Floyd HS, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. Invest Ophthalmol Vis Sci 2012;53:3025.*
24. *Nimz EL, Van't Land CW, Yáñez JA, Chastain JE. Intraocular and systemic pharmacokinetics of brolucizumab (RTH258) in nonhuman primates. Invest Ophthalmol Vis Sci 2016;57:4996.*
25. *Brown DM, Emanuelli A, Bandello F, et al. KESTREL and KITE: 52-week results from two phase III pivotal trials of brolucizumab for diabetic macular edema. Am J Ophthalmol 2022;238:157-72.* Crossref
26. *Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation,*

retinal vasculitis, and retinal occlusion-related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology 2021;128:1050-9. Crossref

27. *Motevasseli T, Mohammadi S, Abdi F, Freeman WR. Side effects of brolucizumab. J Ophthalmic Vis Res 2021;16:670-5.* Crossref
28. *Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology 2020;127:1345-59.* Crossref
29. *Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolucizumab. J Vitreoretin Dis 2020;4:269-79.* Crossref
30. *Pearce I, Amoaku W, Bailey C, et al. The changing landscape for the management of patients with neovascular AMD: brolucizumab in clinical practice. Eye (Lond) 2022;36:1725-34.* Crossref
31. *Mukai R, Matsumoto H, Akiyama H. Risk factors for emerging intraocular inflammation after intravitreal brolucizumab injection for age-related macular degeneration. PLoS One 2021;16:e0259879.* Crossref
32. *Kilmartin DJ. Literature review and proposal of best practice for ophthalmologists: monitoring of patients following intravitreal brolucizumab therapy. Iran J Med Sci Epub 2022 Feb 1.* Crossref
33. *Baumal CR, Bodaghi B, Singer M, et al. Expert opinion on management of intraocular inflammation, retinal vasculitis, and vascular occlusion after brolucizumab treatment. Ophthalmol Retina 2021;5:519-27.* Crossref
34. *Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. Ophthalmology 2019;126:1155-70.* Crossref
35. *Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet 2022;399:741-55.* Crossref

Advancements in ophthalmic imaging for better understanding of pachychoroid spectrum diseases: perspective

Eva Wai Nam Wong, MRCSEd(Ophth), FHKAM(Ophthalmology); Robert Fung Lam, MPH, FHKAM(Ophthalmology); Frank Hiu Ping Lai, FRCSEd(Ophth), FHKAM(Ophthalmology)
Department of Ophthalmology, Caritas Medical Centre, Hong Kong

Correspondence and reprint requests:
Dr Frank Hiu Ping Lai, Department of Ophthalmology, Caritas Medical Centre, 111 Wing Hong Street, Sham Shui Po, Hong Kong.
Email: franklhp@gmail.com

Abstract

Pachychoroid disease spectrum encompasses entities with pathogenesis of choroidal circulatory dysfunction. Advancements in ophthalmic imaging enables better understanding of its structural and functional implications. This perspective article covers clinical features, ocular imaging findings, and management options of pachychoroid spectrum diseases including central serous chorioretinopathy, pachychoroid pigment epitheliopathy, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization, focal choroidal excavation, and peripapillary pachychoroid syndrome.

Key words: Central serous chorioretinopathy; Choroidal neovascularization; Computed tomography angiography; Fluorescein angiography; Tomography, optical coherence

Introduction

Pachychoroid disease spectrum comprises entities with pathogenesis of choroidal hyperpermeability, increased choroidal thickness, and attenuated inner choroidal layers.[1] The choroid is a vascular structure primarily supplying blood to the outer retina. It consists of the avascular Bruch's membrane, choriocapillaris, Sattler's layer, and Haller's layer.[2] The choroid is bounded by the Bruch's membrane anteriorly and the suprachoroidal layer posteriorly.[3] In normal eyes, choroidal thickness is the distance between the outer retinal pigment epithelium (RPE) and the choroidal-scleral interface.[4-6] In eyes with retinal pigment epithelial detachment (PED) or double-layer sign, the boundary of choroid starts from the Bruch's membrane instead of the outer RPE.[7] Advancements in optical coherence tomography (OCT), in particular enhanced-depth imaging OCT and swept-source OCT, enable quantitative analysis of choroidal thickness.[4,7] Subfoveal choroidal thickness of >300μm is considered a pachychoroid phenotype,[8] in which vasculature in the Haller's layer is dilated with relative thinning and compression of the overlying Sattler's layer and choriocapillaris.[9] The loss of choriocapillaris results in a local ischemic environment leading to overexpression of angiogenic factors with subsequent neovascularization.[10] Dilation of the Haller's layer may also induce mechanical damage to the overlying RPE and Bruch's membrane, resulting in invasion of pathological vessels through focal defects.[7,11]

Pachychoroid spectrum diseases can occur in eyes with normal choroidal thickness.[12] Venous overload choroidopathy is increasingly associated with various entities of venous decompensation in the choroid.[12] Increased venous pressure secondary to outflow obstruction or increased inflow may result in pathological venous wall dilatation and increased capillary hydrostatic pressure with

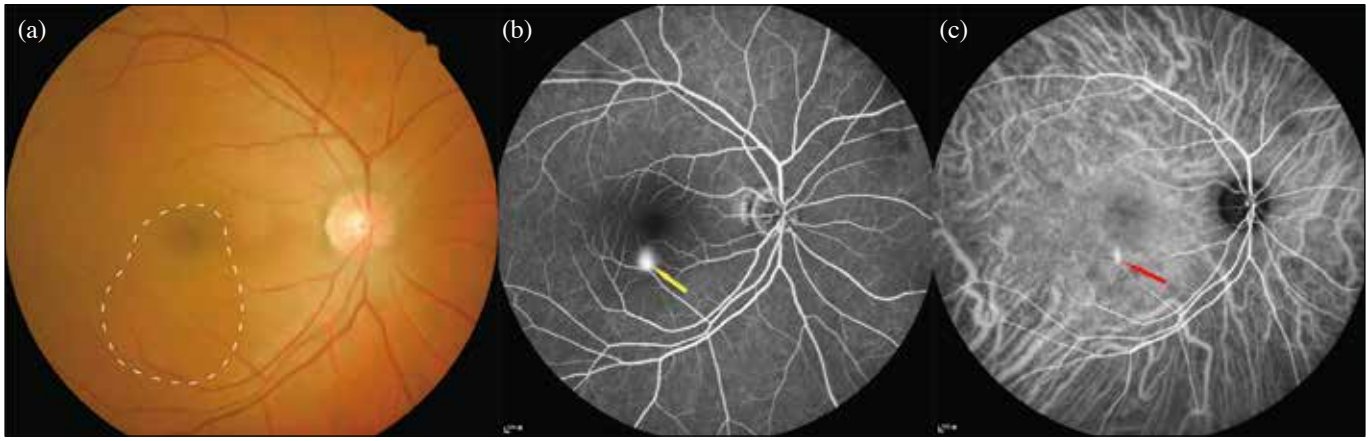


Figure 1. Central serous chorioretinopathy: (a) a fundus image showing the presence of subretinal fluid at the macular region (dashed line), (b) fluorescein angiography showing an inkblot leakage pattern (arrow), and (c) indocyanine green angiography showing hyperfluorescent areas of choroidal hyperpermeability (arrow) and dilatation of choroidal vasculature.

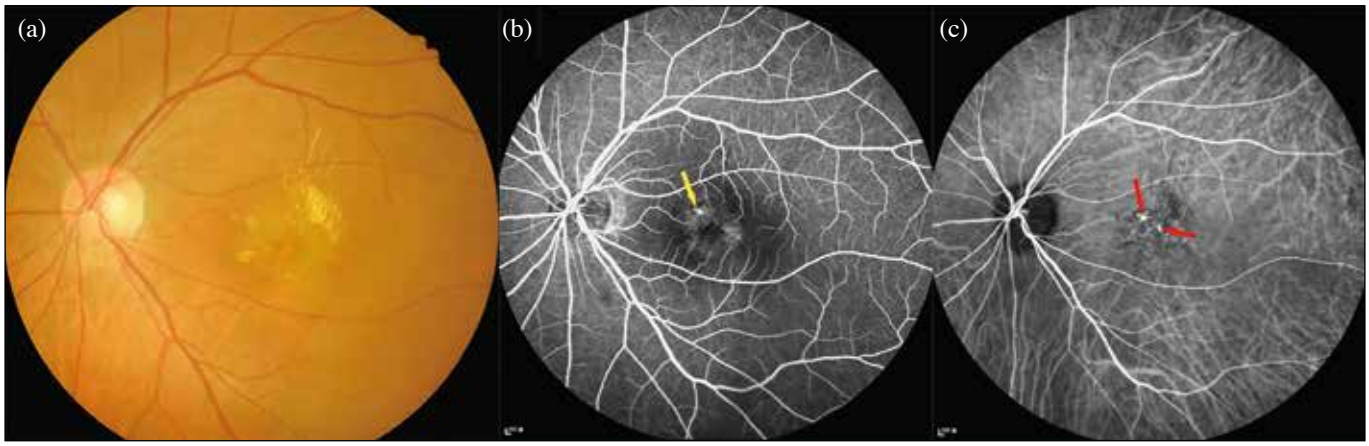


Figure 2. Polypoidal choroidal vasculopathy: (a) a fundus image showing subretinal fluid and hemorrhage with surrounding exudate, (b) fluorescein angiography showing the focal hyperfluorescent area (arrow) corresponding to (c) the region of polypoidal lesions (arrows) in indocyanine green angiography.

capillary leakage. Choroidal venous overload results in central serous chorioretinopathy (CSC) and peripapillary pachychoroid syndrome (PPS) akin to systemic chronic venous insufficiency in lower limbs, portal hypertension, and pulmonary vein varices.[12] Nonetheless, a thick choroid is not necessarily pathological, and choriocapillaris abnormalities may occur independent of choroidal thickness.[13] Ultra-widefield indocyanine green angiography (ICGA) enables identification of peripheral choroidal pathologies and their associations with macular abnormalities[7] as well as venous dilation along the entire course through the vortex vein ampulla.[14] OCT angiography enables detection of choriocapillaris signal void and vessel density for evaluation of choriocapillaris ischemia,[7] which may lead to secondary pathological neovascularization.

A classification system[4] is proposed for entities in the pachychoroid disease spectrum, which includes CSC, pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV) or aneurysmal type 1 neovascularization (AT1), focal choroidal excavation (FCE), and PPS (**Figures 1-4**). These entities are caused by choroidal dysfunction. Although there are overlapping features and progression from one entity to another, their manifestations are mutually exclusive.[1,4] Pachychoroid diseases are caused by chronic vortex vein stasis. Anastomoses can form between the vortex veins at the watershed zone to compensate for the stasis. These anastomotic vessels, known as pachyvessels, demonstrate dilation and hyperpermeability.[15] Vortex vein stasis results in choriocapillaris filling delay, which leads to occlusion of the choriocapillaris.[12] Choroidal neovascularization may arise at the site of the pachyvessels, in response to the ischemia.

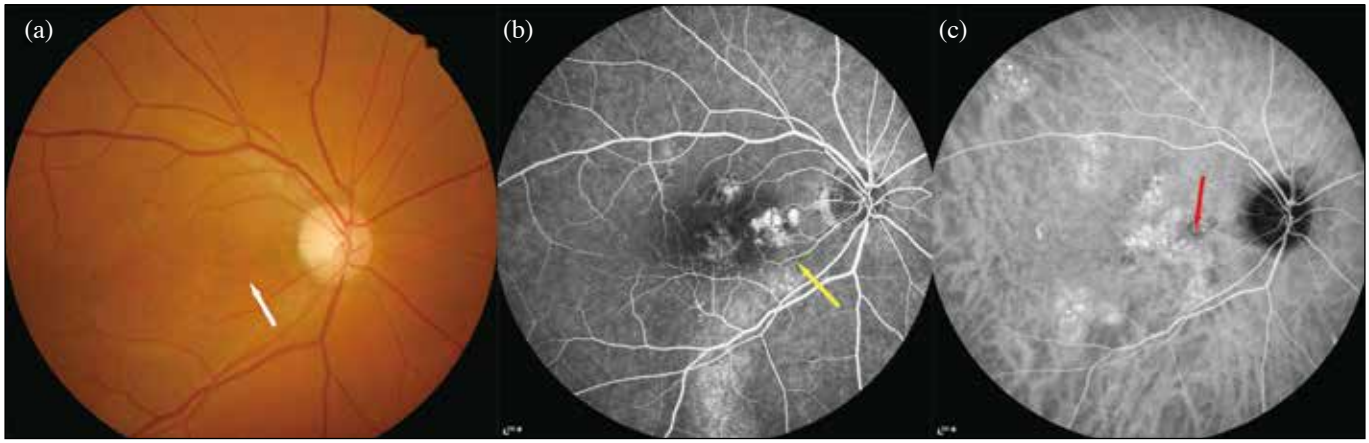


Figure 3. Peripapillary pachychoroid syndrome: (a) a fundus image showing subretinal fluid with associated mottled appearance in the retinal pigment epithelium (arrow), (b) fluorescein angiography showing multifocal hyperfluorescence and gravitational track near the optic disc (arrow), and (c) indocyanine green angiography showing pachyvessels and choroidal vascular hyperpermeability (arrow) around the optic nerve.

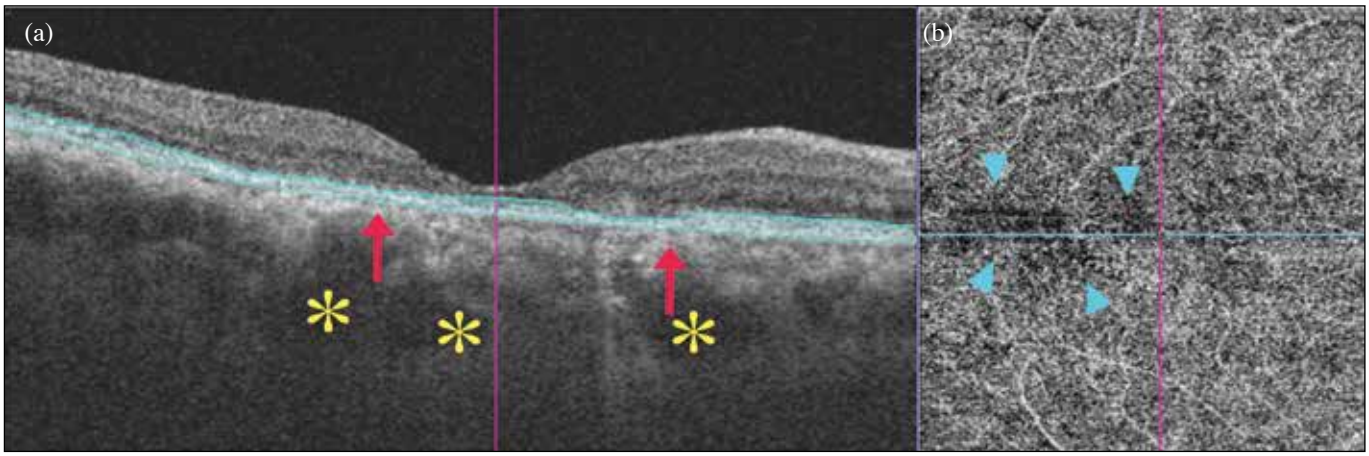


Figure 4. Chronic central serous chorioretinopathy: (a) swept-source optical coherence tomography showing pachyvessels as larger hyporeflective lumen (asterisks) and obliteration of overlying Sattler's layer and choriocapillaris (arrows). The dilated choroidal vessel from the deep layer (left arrow) appears to anteriorly impinge on the choriocapillaris layer, with the most significant flow deficit in the juxtafoveal region. The blue lines are segmentation lines that encompass the choriocapillaris just below the retinal pigment epithelium. (b) Optical coherence tomography angiography showing attenuation of flow signal within the choriocapillaris (arrowheads). Any overlying lesions on the retinal pigment epithelium such as drusen and pigment epithelial detachment may cast shadow artifact on the choriocapillaris. Blood vessels from the retina capillary plexus are superficial to the choriocapillaris secondary to projection artifact. Blood vessels situated in the choriocapillaris are normally in honeycomb configuration.

Central serous chorioretinopathy

As a prototypic disease of the pachychoroid spectrum, acute CSC is characterized by serous detachment of neurosensory retina with or without serous retinal PED.[1,16] Chronic CSC is defined as disease duration of >6 months or presence of atrophic changes in the outer retina and RPE.[4,17] A descending gravitational tract of RPE hypopigmentation may be visualized clinically or on fundus autofluorescence. Fundus fluorescein angiography typically shows an inkblot or smokestack pattern of leakage in acute CSC,[18] and multiple indistinct leaks within window defects in chronic CSC.[4] ICGA typically shows multifocal hyperfluorescent areas of choroidal hyperpermeability, dilatation of choroidal vasculature, and delayed choroidal filling.[4] The areas of hyperfluorescence are usually more extensive on ICGA than on fundus fluorescein angiography.[17] OCT (in particular enhanced-depth imaging OCT and swept-source OCT) is an invaluable tool to visualize the abnormally thickened choroid and the extent of subretinal fluid. Acute CSC typically shows well-defined areas of serous retinal detachment and PEDs, whereas chronic CSC typically shows shallow and broad subretinal fluid, intraretinal cystoid changes, subretinal hyper-reflectivities, and outer retinal atrophy.[4,16,17] The Central Serous Chorioretinopathy

International Group classifies CSC into simple and complex depending on the extent of involvement, disease course, anatomical alterations, and presence of complications.[19]

Most acute CSC resolve spontaneously; treatment is usually reserved for chronic or visually disabling CSC. The treatment goal is to maintain complete subretinal fluid resolution and avoid irreversible damage to the photoreceptors.[17,20] Photodynamic therapy (PDT) and subthreshold micropulse laser are the mainstay of treatment.[1,4,17] Half-dose or half-fluence PDTs are preferred owing to reduced risk of angiographic closure and systemic adverse effects.[17] In the PLACE trial, half-dose PDT is superior to high-density subthreshold micropulse laser treatment in patients with chronic CSC after 7 to 8 months of treatment. A significantly higher proportion of patients achieves complete resolution of subretinal fluid (67% vs 29%) and significantly more improvement in retinal sensitivity on microperimetry (3.2 vs 1.4 dB).[21] PDT is more effective in reducing choroidal vascular hyperpermeability and choroidal thickness than micropulse laser treatment.[4] Mineralocorticoid antagonists such as eplerenone and spironolactone have also been used to treat symptomatic CSC,[22] but no significant benefits of eplerenone are found compared with placebo.[23] Risk factors associated with CSC include corticosteroid usage, Cushing's syndrome, and psychological stress.[17] Creation of scleral windows and vortex vein decompression for treating the underlying choroidal venous overload should be reserved for recalcitrant CSC.[12]

Pachychoroid pigment epitheliopathy

PPE is considered to be 'forme fruste' of CSC,[4] but the natural course of eyes with PPE is highly variable and may remain stable for years. The presence of pachydrusen, which is scattered or isolated yellow white sub-RPE lesions of >125 μm in a thickened choroid, is predictive of disease progression.[24] Clinical features of PPE include focal RPE mottling and drusenoid RPE elevation over regions of choroidal thickening.[9] Subretinal fluid or exudation is typically absent. Patients with PPE may be misdiagnosed as having dry age-related macular degeneration, but patients with PPE are usually younger and absent of soft drusen. OCT features of PPE include RPE elevation and sub-RPE drusenoid deposit, with a thickened choroid directly underneath the RPE changes.[9] Small serous PEDs are occasionally present.[1] Fundus autofluorescence typically shows mixed stippled hyper- and hypo-autofluorescence. Choroidal hyperpermeability in the distribution of pigment epitheliopathy is well demonstrated with ICGA.[4] As most patients are asymptomatic, regular monitoring for any progression to symptomatic pachychoroid diseases such as CSC, PNV, and PCV is needed.[25]

Pachychoroid neovasculopathy

PNV refers to choroidal neovascularization in eyes with thick choroid.[26] It is considered a late complication of PPE or chronic CSC.[1] The presence of neovascularization is confirmed by fundus fluorescein angiography, typically in the form of late leakage, with plaque-like hyperfluorescence on ICGA.[4] Dilated choroidal vasculature and choroidal hyperpermeability in late phases of ICGA differentiates PNV from other causes of choroidal neovascularization including myopic degeneration and posterior segment inflammation.[10] OCT features of PNV include shallow irregular separation of RPE from Bruch's membrane (also known as double layer sign), hyper-reflective materials in the sub-RPE space (denoting area of neovascularization), and development of small peaked PEDs near the lesion.[4,27] Diagnosis of PNV can be made by OCT angiography, which readily identifies a tangled network of flow signal between the RPE and Bruch's membrane resembling the area of neovascularization.[28,29] Treatment options for PNV include intravitreal injection of anti-vascular endothelial growth factors (anti-VEGF), PDT, and a combination of both.[30-33] Although there are studies evaluating treatment efficacy of PNV,[34-37] randomized controlled studies to identify the optimal treatment regimen are limited.[30,37] Intravitreal injection of anti-VEGF is the usual treatment for PNV.[38] PNV requires a fewer number of injections than neovascular age-related macular degeneration, with longer treatment-free period of up to 36 months.[39,40] PDT of various dosage and fluence is effective on improving visual acuity, central macular thickness, and choroidal thickness.[26,30] PDT enables fluid absorption in patients non-responsive to anti-VEGF.[38]

Polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization

PCV is characterized by nodular dilatation of choroidal vessels and is a variant of type 1 macular neovascularization, which accounts for up to 50% of neovascular age-related macular degeneration cases in Asia.[41] PCV is increasingly known as AT1, which more accurately describes its vascular nature.[1,41] PCV/AT1 typically presents with a serosanguineous exudative maculopathy along with intraretinal/subretinal fluid and serous or fibrovascular PEDs.[42] Sudden vision loss may occur secondary to spontaneous rupture of polypoidal lesions, followed by submacular hemorrhage or breakthrough vitreous hemorrhage.[1] Its diagnosis is based on the EVEREST criteria and the Japanese Study Group Guideline,[42,43] in which ICGA is the gold standard and typically shows focal hyperfluorescent polypoidal lesions in early phases with or without branching vascular network.[42] Fundus fluorescein angiography is of limited use owing to inability to visualize sub-RPE structures,[42] but it may be used to detect and monitor leakage from pathological choroidal vessels. For non-ICGA diagnostic criteria,[41] OCT is commonly used owing to its accessibility and non-invasive nature. Swept-source OCT typically shows sub-RPE ring-like lesions, sharp-peaked PEDs, double-layer sign, and complex RPE elevations,[41,42] as well as thickening of the choroidal layer with dilated Haller's vessels (as opposed to choroidal thinning that is more typical of neovascular age-related macular degeneration).[4,41] Together with subretinal or sub-RPE hemorrhage and orange nodules on clinical examination or on color fundus photograph, PCV/AT1 can be detected independent of angiogram with high accuracy.[41] OCT angiography usually shows flow signals indicating type 1 macular neovascularization, but the detection rate of

OCT angiography for polypoidal lesions is lower than that of ICGA.[44,45]

The treatment goal for PCV/AT1 is to preserve vision and achieve polyp closure.[1] Focal laser has variable efficacy and a higher risk of adverse effects, and its use is thus limited to extrafoveal polyps or when other treatment options are not available. PDT and anti-VEGF treatment achieve significant visual gain and reduction in disease activity.[1,41,42] In the EVEREST-II trial, compared with ranibizumab alone, combination of PDT and ranibizumab achieves greater improvement in best-corrected visual acuity (8.3 vs 5.1 letters), higher polyp closure (69.3% vs 34.7%), and fewer number of injections (5.2 vs 7.3).[46] With the previous global suspension of verteporfin supply, anti-VEGF monotherapy is increasingly used. In the PLANET study involving eyes with PCV/AT1 treated with intravitreal injection of aflibercept with and without PDT, >85% of patients have improvement in visual function and >80% of patients have no signs of leakage from polypoidal lesions after aflibercept monotherapy.[47] The mean visual acuity improvement and polyp closure rate are similar between the two groups. The functional and anatomical improvements at 52 weeks are maintained up to 96 weeks.[48] However, aflibercept monotherapy usually results in a lower polyp closure rate and requires a higher number of anti-VEGF injections.[42]

Heterogeneity is high among patients with PCV/AT1 and thus variations in treatment responses are expected.[49] Differences in baseline ocular characteristics such as choroidal vascular hyperpermeability and choroidal thickness affect treatment response.[25] Future research to identify clinical and imaging biomarkers may provide guidance on the optimal management for PCV/AT1.[49]

Focal choroidal excavation

FCE is a localized choroidal concavity without posterior staphyloma or scleral ectasia occurring in patients with no secondary cause of choroidal thinning identified.[4,50] FCE is usually unilateral and more common in myopic eyes.[51] Most patients are asymptomatic, but mild blurring of vision or metamorphopsia is sometimes reported.[4] Fundus examination may appear normal or show indistinct pigmentary RPE changes in the affected area.[50] In conforming FCE, the photoreceptor tips and RPE are in direct contact, whereas in non-conforming FCE the photoreceptor tips are detached from the underlying RPE, with a hyporeflective space representing subretinal fluid.[50] OCT is the preferred diagnostic imaging modality, as it can show abrupt changes of choroidal thickness and poorly defined choroidal-scleral interface beneath the FCE.[4] Fundus fluorescein angiography shows hyperfluorescence in mid or late phase corresponding to transmission defects associated with RPE atrophy. Leakage is absent unless it is complicated by choroidal neovascularization or CSC.[4] ICGA shows filling defect in early phase and punctate hyperfluorescence in late phase.[51] Most eyes have a relatively stable clinical course, and conservative management should suffice. However, FCE can be associated with CSC, PCV, and secondary choroidal neovascularization.[4,52,53] Treatment with anti-VEGF and/or PDT may be beneficial for these conditions.[51]

Peripapillary pachychoroid syndrome

In PPS, maximal choroidal thickness occurs close to the optic nerve head rather than subfoveally.[4,54] Intervortex venous anastomoses and venous overload are found in the peripapillary region.[12] Hypermetropic eyes with short axial length and crowded discs are commonly affected.[54] Clinical features of PPS include intraretinal/subretinal fluid in the nasal macula and peripapillary region, optic nerve head edema, and chorioretinal folds.[4,51] Fundus autofluorescence shows mottled hypoautofluorescence and occasionally gravitational tracks in the peripapillary area, especially in chronic cases.[1,4] ICGA shows pachyvessels and choroidal hyperpermeability around the optic nerve, which can distinguish PPS from uveal effusion syndrome.[54] Fundus fluorescein angiography shows speckled hyperfluorescent window defects and staining typically in area between the optic disc and fovea. Disc leakage is sometimes present. Treatments for PPS include anti-VEGF injection, PDT, and use of topical and oral carbonic anhydrase inhibitors, but treatment responses vary.[1,54] In a multicenter study, PDT significantly decreases both subretinal fluid height and central macular thickness and improves visual acuity after 3 months.[55] However, in another multicenter study with a mean follow-up of 27 months, no significant visual improvement is found in patients with PPS treated with anti-VEGF injection or PDT, despite a decrease in retinal edema and choroidal thickening.[56]

Conclusion

Advancements in enhanced-depth imaging OCT, swept-source OCT, OCT angiography, and ultra-widefield ICGA enable better understanding of the pachychoroid disease spectrum by demonstrating choroidal circulatory dysfunction. Recognition of the pachychoroid state is essential for disease prognostication and management guidance. Treatment is recommended for those with symptomatic conditions and at risk of vision loss such as chronic or complex CSC, PVN, and PCV/AT1. Management options include conventional or subthreshold micropulse laser treatment, PDT, and intravitreal injection of anti-VEGF. Treatment responses vary across different clinical entities. Further studies are warranted to determine factors associated with various pachychoroid states and transition from quiescent entities to neovascular forms of PCV/AT1.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

References

1. *Borooah S, Sim PY, Phatak S, et al. Pachychoroid spectrum disease. Acta Ophthalmol 2021;99:e806-e22.* Crossref
2. *Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Histologic and morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in postmortem eyes with age-related macular degeneration and histologic examination of surgically excised choroidal neovascular membranes. Surv Ophthalmol 1999;44(Suppl 1):S10-32.* Crossref
3. *Yiu G, Pecen P, Sarin N, et al. Characterization of the choroid-scleral junction and suprachoroidal layer in healthy individuals on enhanced-depth imaging optical coherence tomography. JAMA Ophthalmol 2014;132:174-81.* Crossref
4. *Cheung CMG, Lee WK, Koizumi H, et al. Pachychoroid disease. Eye (Lond) 2019;33:14-33.* Crossref
5. *Lee CO, Zhang X, Yuan N, et al. Comparison of choroidal thickness measurements between spectral domain optical coherence tomography and swept source optical coherence tomography in children. Sci Rep 2021;11:13749.* Crossref
6. *Mrejen S, Spaide RF. Optical coherence tomography: imaging of the choroid and beyond. Surv Ophthalmol 2013;58:387-429.* Crossref
7. *Safi H, Ahmadieh H, Hassanpour K, Safi S. Multimodal imaging in pachychoroid spectrum. Surv Ophthalmol 2022;67:579-90.* Crossref
8. *Dansingani KK, Balaratnasingam C, Naysan J, Freund KB. En face imaging of pachychoroid spectrum disorders with swept-source optical coherence tomography. Retina 2016;36:499-516.* Crossref
9. *Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. Retina 2013;33:1659-72.* Crossref
10. *Pang CE, Freund KB. Pachychoroid neovasculopathy. Retina 2015;35:1-9.* Crossref
11. *Matsumoto H, Hoshino J, Mukai R, et al. Chronic choriocapillaris ischemia in dilated vortex vein region in pachychoroid neovasculopathy. Sci Rep 2021;11:16274.* Crossref
12. *Spaide RF, Gemmy Cheung CM, Matsumoto H, et al. Venous overload choroidopathy: a hypothetical framework for central serous chorioretinopathy and allied disorders. Prog Retin Eye Res 2022;86:100973.* Crossref
13. *Spaide RF, Ledesma-Gil G. Choriocapillaris vascular parameters in normal eyes and those with pachychoroid with and without disease. Retina 2021;41:679-85.* Crossref
14. *Pang CE, Shah VP, Sarraf D, Freund KB. Ultra-widefield imaging with autofluorescence and indocyanine green angiography in central serous chorioretinopathy. Am J Ophthalmol 2014;158:362-71.e2.* Crossref
15. *Pereira A, Aldrees S, Pimentel MC, Yan P. Updated review: optical coherence tomography findings of the pachychoroid disease spectrum. Can J Ophthalmol Epub 2022 Jul 19.* Crossref
16. *van Velthoven ME, Verbraak FD, Garcia PM, et al. Evaluation of central serous retinopathy with en face optical coherence tomography. Br J Ophthalmol 2005;89:1483-8.* Crossref
17. *van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: Towards an evidence-based treatment guideline. Prog Retin Eye Res 2019;73:100770.* Crossref
18. *How AC, Koh AH. Angiographic characteristics of acute central serous chorioretinopathy in an Asian population. Ann Acad Med Singap 2006;35:77-9.*
19. *Chhablani J, Cohen FB, Central Serous Chorioretinopathy International Group. Multimodal imaging-based central serous chorioretinopathy classification. Ophthalmol Retina 2020;4:1043-6.* Crossref
20. *Haga F, Maruko R, Sato C, et al. Long-term prognostic factors of chronic central serous chorioretinopathy after half-dose photodynamic therapy: a 3-year follow-up study. PLoS One 2017;12:e0181479.* Crossref
21. *van Dijk EHC, Fauser S, Breukink MB, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the PLACE Trial. Ophthalmology 2018;125:1547-55.* Crossref
22. *Bousquet E, Beydoun T, Rothschild PR, et al. Spironolactone for nonresolving central serous chorioretinopathy: a randomized controlled crossover study. Retina 2015;35:2505-15.* Crossref
23. *Lotery A, Sivaprasad S, O'Connell A, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial. Lancet 2020;395:294-303.* Crossref
24. *Zhang X, Sivaprasad S. Drusen and pachydrusen: the definition, pathogenesis, and clinical significance. Eye (Lond) 2021;35:121-33.* Crossref
25. *Mazzeo T, Leber HM, da Silva AG, et al. Pachychoroid disease spectrum: review article. Graefes Arch Clin Exp Ophthalmol 2022;260:723-35.* Crossref
26. *Tanaka K, Mori R, Wakatsuki Y, et al. Two-thirds dose photodynamic therapy for pachychoroid neovasculopathy. J Clin Med 2021;10:2168.* Crossref
27. *Sato T, Kishi S, Watanabe G, et al. Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. Retina 2007;27:589-94.* Crossref
28. *Bonini Filho MA, de Carlo TE, Ferrara D, et al. Association of choroidal neovascularization and central serous chorioretinopathy with optical coherence tomography angiography. JAMA Ophthalmol 2015;133:899-906.* Crossref
29. *Dansingani KK, Balaratnasingam C, Klufas MA, et al. Optical coherence tomography angiography of shallow irregular pigment epithelial detachments in pachychoroid spectrum disease. Am J Ophthalmol 2015;160:1243-54.e2.* Crossref

30. *Miki A, Kusuhara S, Otsuji T, et al. Photodynamic therapy combined with anti-vascular endothelial growth factor therapy for pachychoroid neovasculopathy. PLoS One 2021;16:e0248760.* Crossref
31. *Hikichi T, Kubo N, Yamauchi M. One-year comparison of anti-vascular endothelial growth factor and half-dose photodynamic for pachychoroid neovasculopathy. Eye (Lond) 2021;35:3367-75.* Crossref
32. *Karasu B, Celebi ARC. An efficacy comparison of combination of different anti-vascular endothelial growth factors and photodynamic therapy in patients with pachychoroid neovasculopathy. Int Ophthalmol 2021;41:1989-2000.* Crossref
33. *Kitajima Y, Maruyama-Inoue M, Ito A, et al. One-year outcome of combination therapy with intravitreal anti-vascular endothelial growth factor and photodynamic therapy in patients with pachychoroid neovasculopathy. Graefes Arch Clin Exp Ophthalmol 2020;258:1279-85.* Crossref
34. *Miyake M, Ooto S, Yamashiro K, et al. Pachychoroid neovasculopathy and age-related macular degeneration. Sci Rep 2015;5:16204.* Crossref
35. *Padron-Perez N, Arias L, Rubio M, et al. Changes in choroidal thickness after intravitreal injection of anti-vascular endothelial growth factor in pachychoroid neovasculopathy. Invest Ophthalmol Vis Sci 2018;59:1119-24.* Crossref
36. *Matsumoto H, Hiroe T, Morimoto M, et al. Efficacy of treat-and-extend regimen with aflibercept for pachychoroid neovasculopathy and type 1 neovascular age-related macular degeneration. Jpn J Ophthalmol 2018;62:144-50.* Crossref
37. *Jung BJ, Kim JY, Lee JH, et al. Intravitreal aflibercept and ranibizumab for pachychoroid neovasculopathy. Sci Rep 2019;9:2055.* Crossref
38. *Sartini F, Figus M, Casini G, et al. Pachychoroid neovasculopathy: a type-1 choroidal neovascularization belonging to the pachychoroid spectrum-pathogenesis, imaging and available treatment options. Int Ophthalmol 2020;40:3577-89.* Crossref
39. *Coscas G, Yamashiro K, Coscas F, et al. Comparison of exudative age-related macular degeneration subtypes in Japanese and French patients: multicenter diagnosis with multimodal imaging. Am J Ophthalmol 2014;158:309-18.e2.* Crossref
40. *Yoon J, Yoon W, Na SK, et al. Long-term outcome of intravitreal anti-vascular endothelial growth factor treatment for pachychoroid neovasculopathy. Sci Rep 2021;11:12052.* Crossref
41. *Cheung CMG, Lai TYY, Teo K, et al. Polypoidal choroidal vasculopathy: consensus nomenclature and non-indocyanine green angiograph diagnostic criteria from the Asia-Pacific Ocular Imaging Society PCV Workgroup. Ophthalmology 2021;128:443-52.* Crossref
42. *Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. Ophthalmology 2018;125:708-24.* Crossref
43. *Tan CS, Ngo WK, Lim LW, et al. EVEREST study report 3: diagnostic challenges of polypoidal choroidal vasculopathy. Lessons learnt from screening failures in the EVEREST study. Graefes Arch Clin Exp Ophthalmol 2016;254:1923-30.* Crossref
44. *Cheung CMG, Yanagi Y, Mohla A, et al. Characterization and differentiation of polypoidal choroidal vasculopathy using swept source optical coherence tomography angiography. Retina 2017;37:1464-74.* Crossref
45. *Huang CH, Yeh PT, Hsieh YT, et al. Characterizing branching vascular network morphology in polypoidal choroidal vasculopathy by optical coherence tomography angiography. Sci Rep 2019;9:595.* Crossref
46. *Lim TH, Lai TYY, Takahashi K, et al. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II randomized clinical trial. JAMA Ophthalmol 2020;138:935-42.* Crossref
47. *Lee WK, Iida T, Ogura Y, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET Study: a randomized clinical trial. JAMA Ophthalmol 2018;136:786-93.* Crossref
48. *Wong TY, Ogura Y, Lee WK, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy: two-year results of the aflibercept in polypoidal choroidal vasculopathy study. Am J Ophthalmol 2019;204:80-9.* Crossref
49. *Chaikitmongkol V, Cheung CMG, Koizumi H, et al. Latest developments in polypoidal choroidal vasculopathy: epidemiology, etiology, diagnosis, and treatment. Asia Pac J Ophthalmol (Phila) 2020;9:260-8.* Crossref
50. *Margolis R, Mukkamala SK, Jampol LM, et al. The expanded spectrum of focal choroidal excavation. Arch Ophthalmol 2011;129:1320-5.* Crossref
51. *Castro-Navarro V, Behar-Cohen F, Chang W, et al. Pachychoroid: current concepts on clinical features and pathogenesis. Graefes Arch Clin Exp Ophthalmol 2021;259:1385-400.* Crossref
52. *Lim FP, Loh BK, Cheung CM, et al. Evaluation of focal choroidal excavation in the macula using swept-source optical coherence tomography. Eye (Lond) 2014;28:1088-94.* Crossref
53. *Lim FP, Wong CW, Loh BK, et al. Prevalence and clinical correlates of focal choroidal excavation in eyes with age-related macular degeneration, polypoidal choroidal vasculopathy and central serous chorioretinopathy. Br J Ophthalmol 2016;100:918-23.* Crossref
54. *Phasukkijwatana N, Freund KB, Dolz-Marco R, et al. Peripapillary pachychoroid syndrome. Retina 2018;38:1652-67.* Crossref
55. *Iovino C, Peiretti E, Tatti F, et al. Photodynamic therapy as a treatment option for peripapillary pachychoroid syndrome: a pilot study. Eye (Lond) 2022;36:716-23.* Crossref
56. *Xu D, Garg E, Lee K, et al. Long-term visual and anatomic outcomes of patients with peripapillary pachychoroid syndrome. Br J Ophthalmol 2022;106:576-81.* Crossref

CASE REPORT

Autologous simple limbal stem cell transplantation: a case series

Mei Sze Wu, MBBS, MRCSEd, FCOphthHK, FHKAM (Ophth); Amy Wong Lee, MBBS, MSc, MRCSEd, FCOphthHK, FHKAM (Ophth); Wu Wai Kwan, MB ChB (CUHK), FRCS (Edin), FHKAM (Ophth), FCOphth(HK)
Caritas Medical Centre, Hong Kong

Correspondence and reprint requests:
Dr Mei Sze Wu, Caritas Medical Centre, Hong Kong. Email: macywu.mcgill@gmail.com

Abstract

This case series reviewed medical records of eight patients who underwent autologous simple limbal epithelial transplantation (SLET) for total limbal stem cell deficiency (LSCD) secondary to chemical injury (n=5), thermal injury (n=2), or autoimmune disorder (n=1) between 2016 and 2019 at the Caritas Medical Centre. The mean time from injury to SLET was 67 months (range, 3 weeks to 30 years). The mean time to re-epithelialization was 20 (range, 13-42) days. The follow-up duration ranged from 1 to 6 years. At the 1-year follow-up, the success rate of SLET was 37.5%, and visual gain among the three successful cases ranged from <1 line to >6 lines. Patients with Dua grade V or VI chemical injury and patients with systemic causes of LSCD had poorer prognosis, as did those with cicatricial lid changes, anterior segment necrosis, glaucoma, sterile cornea ulceration, superimposed infections, or tobacco usage. SLET should be a reconstructive procedure for chronic LSCD rather than for acute injury or inflammation.

Key words: Corneal injuries; Limbus corneae; Stem cell transplantation

Introduction

Limbal stem cell deficiency (LSCD) is caused by the loss of healthy limbal stem cells and the lack of regenerative power of the corneal epithelium and results in conjunctivalization and neovascularization of the corneal surface.[1] LSCD can be acquired or hereditary; acquired LSCD is more common in Hong Kong. Common causes of LSCD include chemical and thermal injury, severe blepharokeratoconjunctivitis, topical and systemic drug toxicity, and systemic diseases such as Steven Johnson syndrome, mucous membranous pemphigoid, graft versus host disease, and severe allergic ocular surface disease.[2-4] Treatment strategies involve replenishing limbal stem cells and include keratolimbal autografting, conjunctival-limbal autografting, ex-vivo cultivated limbal epithelial transplantation, cultivated oral mucosal epithelial transplantation, and simple limbal stem cell transplantation.[5] The latter does not require extensive laboratory support and has comparable results.[6] This case series reviewed medical records of eight patients who underwent autologous simple limbal epithelial transplantation (SLET) for LSCD to determine factors associated with successful outcome.

Case presentation

This study was approved by the Kowloon West Cluster Research Ethics Committee [KWC-REC Reference: KW/EX-22-012(169-01)]. Medical records of eight patients who underwent autologous SLET for total LSCD secondary to chemical or thermal injury or autoimmune disorder between 2016 and 2019 at the Caritas Medical Centre were retrospectively reviewed. Patients with unidentifiable causes or bilateral total LSCD were excluded. Chemical burns were classified using the Dua classification. Data recorded included the extent of LSCD, time from injury to SLET, time to re-epithelialization, and best-corrected visual acuity before and after SLET. Successful SLET was defined as complete epithelialization, stable corneal surface, and absence/recession of corneal neovascularization at 6 months.[7,8]

Patients were under general anesthesia. For the recipient eye, vascular pannus over the cornea was removed after 360° peritomy at 2 mm after the limbus (**Figure 1**).

Hemostasis was achieved with cautery. The amniotic membrane was transplanted to bare ocular surface with fibrin sealant (Tisseel; Baxter Healthcare) and tucked under surrounding healthy conjunctiva. For the donor eye, the conjunctiva was incised and subconjunctival dissection was performed using a crescent knife until 1 mm into clear cornea. The 2×2 mm block limbal tissue was excised into 15 to 20 blocks on wet nitrocellulose paper with No. 15 surgical blade. The small limbal tissues were then placed circularly on the amniotic membrane along the peripheral cornea and the epithelial side-up and were secured with fibrin sealant. Soft bandage contact lens (Air Optix Night & Day Aqua; Alcon) was inserted. Eye patch was removed on day 1. The recipient eye received prednisolone acetate 1% eye drop every 2 hours tapered over 8 weeks and chloramphenicol eye drop four times a day until epithelialization, whereas the donor eye received a 1-week course of dexamethasone 0.1% and chloramphenicol 0.5% eye drop. Preservative-free lubricants were applied as needed. The bandage contact lens was removed upon complete epithelialization.

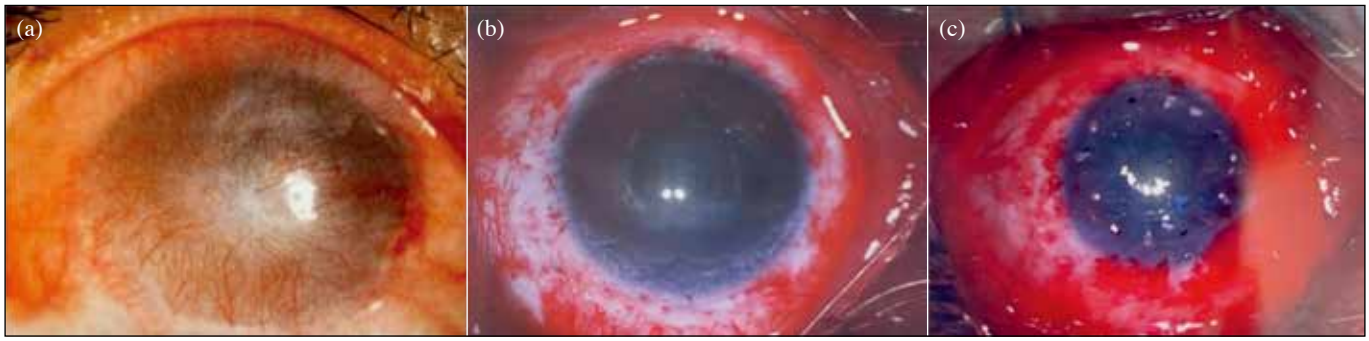


Figure 1. (a) An eye with total limbal stem cell deficiency for autologous simple limbal epithelial transplantation. (b) The overlying fibrovascular membrane is dissected at 2 mm after the limbus. (c) The amniotic membrane is tucked under conjunctival edges and secured with fibrin sealant, and the transplanted tissues are placed in a circular manner and secured with fibrin sealant.

Table. Clinical characteristics and treatment outcomes of eight patients who underwent autologous simple limbal epithelial transplantation (SLET) for total limbal stem cell deficiency

Patient	Age/ sex	Cause of injury	Dua classification	Symblepharon	Time from injury to SLET, m	Eye with SLET	Time to reepithelialization, days	Best-corrected visual acuity, logMAR			Visual gain, lines	Outcome			Latest cornea/eye status	Additional procedures after SLET	Follow-up, y
								Preop	Month 3	Latest follow-up		Month 6	Year 1	Latest follow-up			
1	49/F	Cement (alkaline)	IV	No	31	Left	27	2.4	0.7	0.4	>6	Success	Success	Success	Static conjunctivalization at 2 o'clock area	Phacoemulsification, intraocular lens	6
2	33/M	Thermal	-	No	360	Right	12	0.5	0.5	0.2	3	Success	Success	Success	No epithelial defect, superficial corneal scars	-	4
3	40/M	Thermal	-	Yes	9	Right	12	2.4	2.4	2.0	<1	Success	Success	Success	No epithelial defect, static inferior symblepharon 1.5 mm onto cornea	Multiple tarsorrphaphies, hard palate grafting, inferior labial mucosal grafting, fornix reconstruction	3.5
4	58/M	Sodium hydroxide (alkaline)	VI	No	0.75	Left	No healing	2.4	Light perception	No light perception	-	Failure	Failure	Failure	Phthisis	Penetrating keratoplasty, anterior chamber washout, pars plana vitrectomy, silicone oil injection	1
5	66/F	Lichen planus	-	Yes	54	Left	42	0.3	2.1	1.8	-	Failure	Failure	Failure	No epithelial defect, corneal stromal scars	Symblepharon lysis, fornix reconstruction, pseudopterygium excision, multiple amniotic membrane transplantations	5.5
6	41/M	Fosroc Polyurea (alkaline)	V	No	6	Right	14	1.0	0.4	0.4	6	Failure	Failure	Failure	Conjunctivalization over superior half of cornea	2nd SLET 3.5 years after 1st SLET	5
							13 (2nd SLET)	2.4	0.4	0.4	>6	Success	Failure	Failure		Subconjunctival Eylea	
7	53/M	Cement (alkaline)	V	No	1.5	Left	No healing	2.1	Light perception	Light perception	-	Failure	Failure	Failure	Vascularized corneal scar	Multiple amniotic membrane transplantations and tarsorrphaphies	3
8	55/M	Cement (alkaline)	V	Yes	72	Right	No healing	Light perception	2.1	2.4	<1	Failure	Failure	Failure	Vascularized corneal scar	Amniotic membrane transplantation	3

Of the eight patients, five had chemical injury, two had thermal injury, and one had lichen planus (**Table**). All had total LSCD. The mean time from injury to SLET was 67 months (range, 3 weeks to 30 years). The mean time to re-epithelialization was 20 (range, 13-42) days. The follow-up duration ranged from 1 to 6 years. At the 1-year follow-up, the success rate of SLET was 37.5%, and visual gain among the three successful cases ranged from <1 line to >6 lines.

Patient 1

In January 2014, a 49-year-old woman presented with a Dua grade IV chemical injury by cement to her left eye, which was amblyopic. One week later, the pH value in the eye remained raised, and the patient underwent emergency removal of the embedded cement and conjunctival resection. To facilitate epithelial healing, bandage contact lens, autologous serum, and temporary median tarsorrhaphy were applied. In July 2016, she underwent SLET. In March 2018, she underwent phacoemulsification and intraocular lens implantation, and her vision improved significantly. At the 6-year follow-up, the cornea remained clear with only limited conjunctivalization over the inferotemporal limbus area (**Figure 2**).

Patient 2

In August 2013, a 33-year-old man presented with persistent ocular discomfort of the right eye. He had a history of thermal injury by coal powder to the eye at the age of 3. The affected eye, which was likely amblyopic, showed 360° pannus with central stromal scar, with a refraction of +1.00/-3.00× 65. Nonetheless, the patient opted for SLET. The best-corrected visual acuity remained the same at logMAR 0.5 before and after SLET, whereas postoperative refraction was -1.50/-5.00× 165. Two months later, the pannus recurred at the superior cornea and remained static (**Figure 3**), which is not unusual in successful cases.[7,9,10] Nonetheless, the patient was satisfied with the much improved ocular comfort and tear film stability.

Patient 3

In November 2016, a 40-year-old man presented with a third-degree periocular burn of the right eye associated with severe periorbital swelling after a welding accident. The injured eye showed severe chemosis, total limbal ischemia, and a completely opacified cornea (**Figure 4**). Parts of the conjunctiva were also burnt away exposing bare sclera underneath. Intraocular pressure was 34 mmHg. The patient was treated with daily rodding, maximal glaucoma medications, topical and systemic antibiotics, oral vitamin C, and autologous serum. One week after injury, distichiasis and early lagophthalmos developed, and the patient underwent paramedian tarsorrhaphy for epithelial healing. However, the tarsorrhaphy broke off and showed a lower lid defect after raw lid tissues sloughed off. The patient underwent repeat paramedian tarsorrhaphy, but symblepharon occurred. In August 2017, the patient underwent symblepharon lysis and fornix reconstruction combined with SLET and amniotic membrane transplantation (AMT). However, there was progressive obliteration of the superior and inferior fornix and lagophthalmos. This necessitated further hard palate

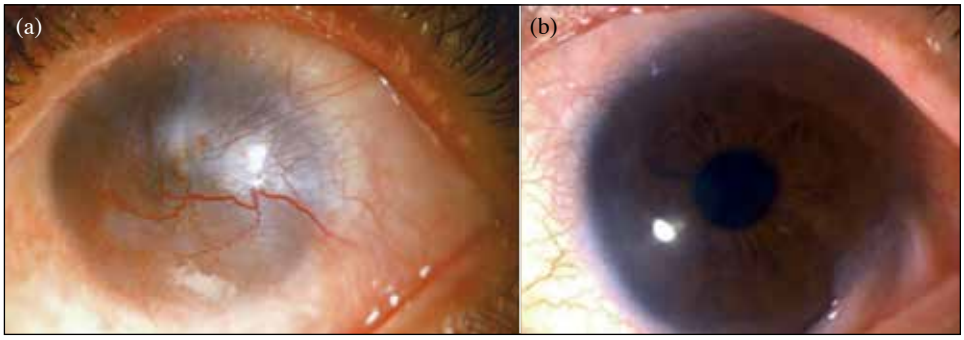


Figure 2. Patient 1: (a) Conjunctivalization of the cornea of the left eye at 4 months after chemical injury by cement. (b) Static and limited conjunctivalization after successful autologous simple limbal epithelial transplantation and intraocular lens implantation.

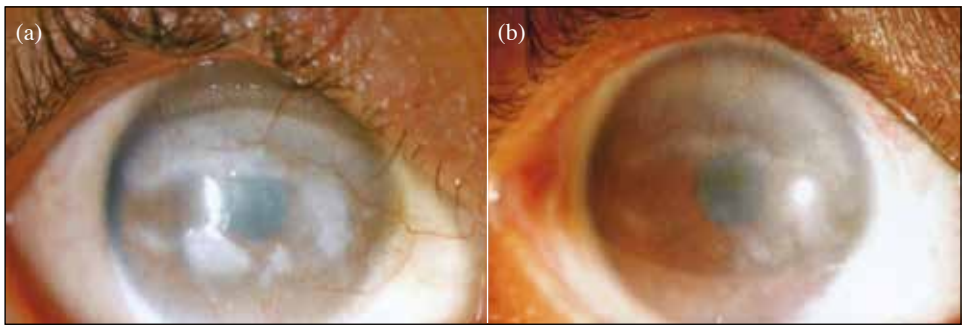


Figure 3. Patient 2: (a) Irregular corneal surface and conjunctivalization of the right eye before simple limbal epithelial transplantation. (b) Smoother ocular surface and static pannus at the superior cornea after simple limbal epithelial transplantation.

Figure 4. Patient 3: (a) Total limbal ischemia, opacified cornea, and bare sclera of the right eye after thermal injury. (b) Tarsorrhaphy breaking off prematurely owing to necrotic lid tissues and cicatricial lid changes. (c) Formation of symblepharon after repeat tarsorrhaphy. (d) Simple limbal epithelial transplantation combined with fornix reconstruction. (e) Repeat inferior fornix reconstruction with hard palate and inferior labial mucosal grafts. (f) Complete eye closure. (g) Recurrence of symblepharon.

grafting and inferior labial mucosal grafting for inferior fornix reconstruction to achieve complete eye closure. In October 2017, the cornea remained epithelialized and stable. Corneal transplantation (for stromal scarring with deep vascularization) was deferred for 4 months, owing to the recurrence of symblepharon and insufficient forniceal space. In January 2022, the cornea condition remained unchanged.

Chemical or thermal injury is usually associated with severe eyelid injury. Distichiasis, entropion, and tissue loss may affect corneal surface recovery.[11] Joint management of lid problems with oculoplastic surgeon is advised.

Patient 4

In June 2017, a 58-year-old man presented to the emergency department with a caustic injury to the face and eyes by sodium hydroxide when cleaning an air conditioner. He had minimal irrigation on the site of injury. Three hours later, he was admitted to the intensive care unit for inhalation injury and airway management. At 8 hours after injury, eye assessment revealed a pH value of 12 for both eyes. The left eye showed a Dua grade VI injury, complete opacification of the cornea, total epithelial defect, total limbal involvement, necrotic conjunctiva and tenon, absence of anterior chamber and fundal views, and severe periorbital soft tissue swelling (**Figure 5**). Applanation and tonometry failed to measure the intraocular pressure; digital palpation of the globe was high. The right eye showed Dua grade I injury, which was completely epithelialized at week 1 and had no clinical evidence of limbal ischemia. The left eye was treated with intensive lubrication, topical prednisolone 8 times per day, topical antibiotics, oral doxycycline, and high-dose Vitamin C. On day 2, digital pressure over the left globe remained high, and maximal anti-glaucomatous drugs were administered. On day 4, early symblepharon was noted, and daily glass rodding was performed in addition to daily normal saline irrigation. Nonetheless, upper lid entropion and distichiasis developed. Bandage contact lens was inserted to aid epithelialization and to protect the ocular surface, and autologous serum was prescribed for round-the-clock usage.

In view of the persistent denuded ocular surface, at 3 weeks after injury, the patient underwent AMT for the entire conjunctival surface and cornea combined with autologous SLET. The left upper lid entropion was corrected with everting sutures. However, healthy tissue was inadequate for tenoplasty or conjunctival flap, and the patient declined conjunctival autograft harvest from the completely

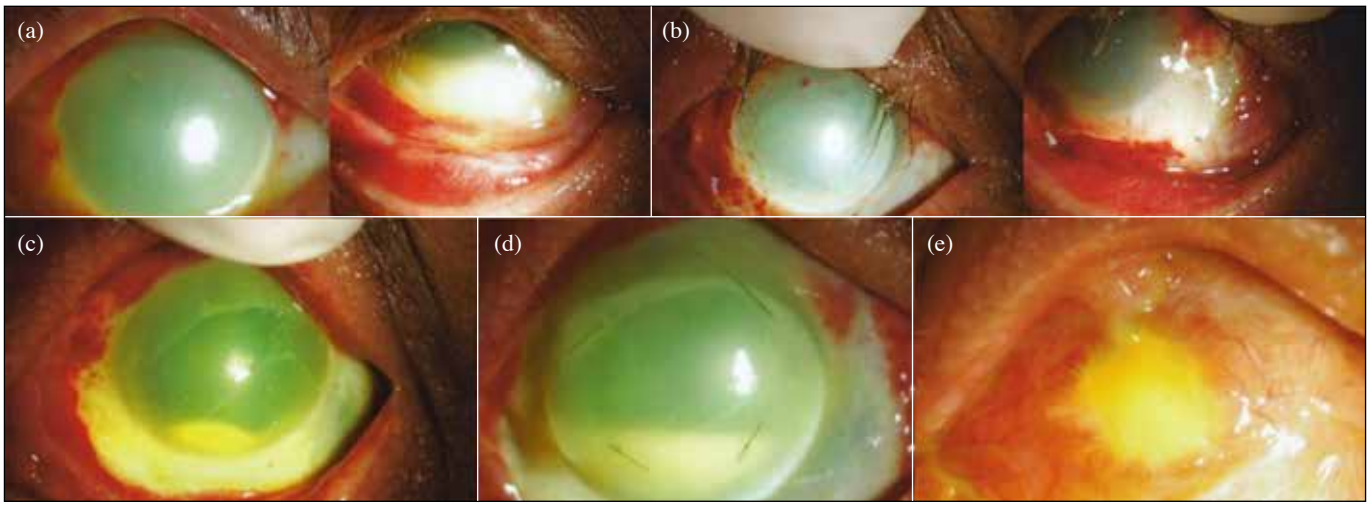


Figure 5. Patient 4: (a) Dua grade VI injury to the left eye, with total limbal and conjunctival involvement, complete corneal opacification, and scarring of forniceal conjunctiva. (b) No conjunctival reperfusion after the amniotic membrane dissolved. (c) Persistent epithelial defect, reactive hypopyon, conjunctival loss, and non-reperfusion after the amniotic membrane dislodged prematurely. (d) Double-layered amniotic membrane transplantation, with the inner layer secured with 10-0 nylon sutures. The outer layer is dissolved on day 5 and the inner layer is dislodged after 2 weeks. (e) Development of phthisis bulbi.

recovered right eye. On day 5, the transplanted limbal tissues and bandage contact lens dislodged. On day 6, the amniotic membrane showed early melting but no evidence of conjunctival reperfusion. On day 10 after the first AMT, the patient underwent the second AMT; the amniotic membrane was secured with fibrin sealant to the corneal and conjunctival surface, but it dislodged again 2 days later. The third AMT was performed, with the inner layer secured to the corneal surface with 10-0 nylon stitches, and the outer layer secured to the bare sclera, and the entire cornea overlaid the first layer with 8-0 vicryl. However, the outer layer dissolved 5 days later, and the inner layer was out of position 2 weeks later. Anterior segment optical coherence tomography showed left eye hyperechoicity throughout the entire cornea and 4-mm hypopyon secondary to persistent inflammation (**Figure 6**). After scheduled for a temporary tarsorrhaphy, the patient consulted another ophthalmologist and underwent large-sized penetrating keratoplasty, anterior chamber washout, pars plana vitrectomy, and silicone oil injection. However, the epithelial defect persisted, and the eye became phthisical and progressed to no light perception.

After chemical injury, the time to first irrigation and early normalization of pH are very important.[12] Sodium hydroxide is strongly alkali and may cause high-grade chemical injury with poor visual prognosis. Early referral to anterior segment ophthalmologists for evaluation is important. Despite early SLET, surgical outcome of patient 4 was suboptimal owing to persistent inflammation and 'marbalization' of the ocular surface.[13] Integration of the transplanted amniotic membrane to the avascular host surface was difficult despite the use of fibrin sealant and sutures. Eyes with high-grade chemical injury are at risk of phthisis, uncontrollable glaucoma, and superimposed infection. The use of free autologous conjunctival flap from the contralateral eye can be a viable option for reperfusion of the cornea, and further rehabilitative surgery can be considered in the long run.

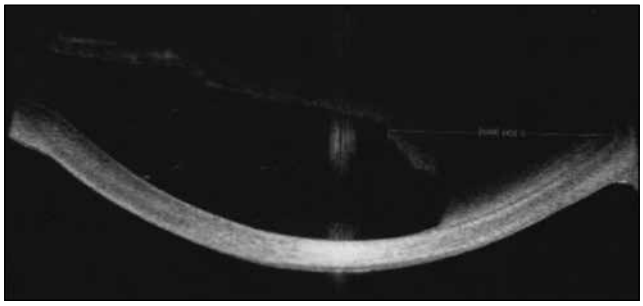


Figure 6. Patient 4: Anterior segment optical coherence tomography showing left eye hyperechoicity throughout the entire cornea and 4-mm hypopyon secondary to persistent inflammation.

Patient 5

In May 2005, a 55-year-old woman presented with occasional redness and grittiness of both eyes, which were relieved with topical lubricants. In 2007 to 2009, she developed bilateral upper and lower eyelid trichiasis that required regular epilation. In March 2012, she presented with similar symptoms and was diagnosed to have inferior fornix shortening of the right eye. She also complained of frequent oral and genital ulcers. Buccal mucosa biopsy revealed lichenoid inflammation. Microscopic examination of the buccal mucosa revealed subepidermal bullous formation and a layer of parakeratosis. Dermis showed

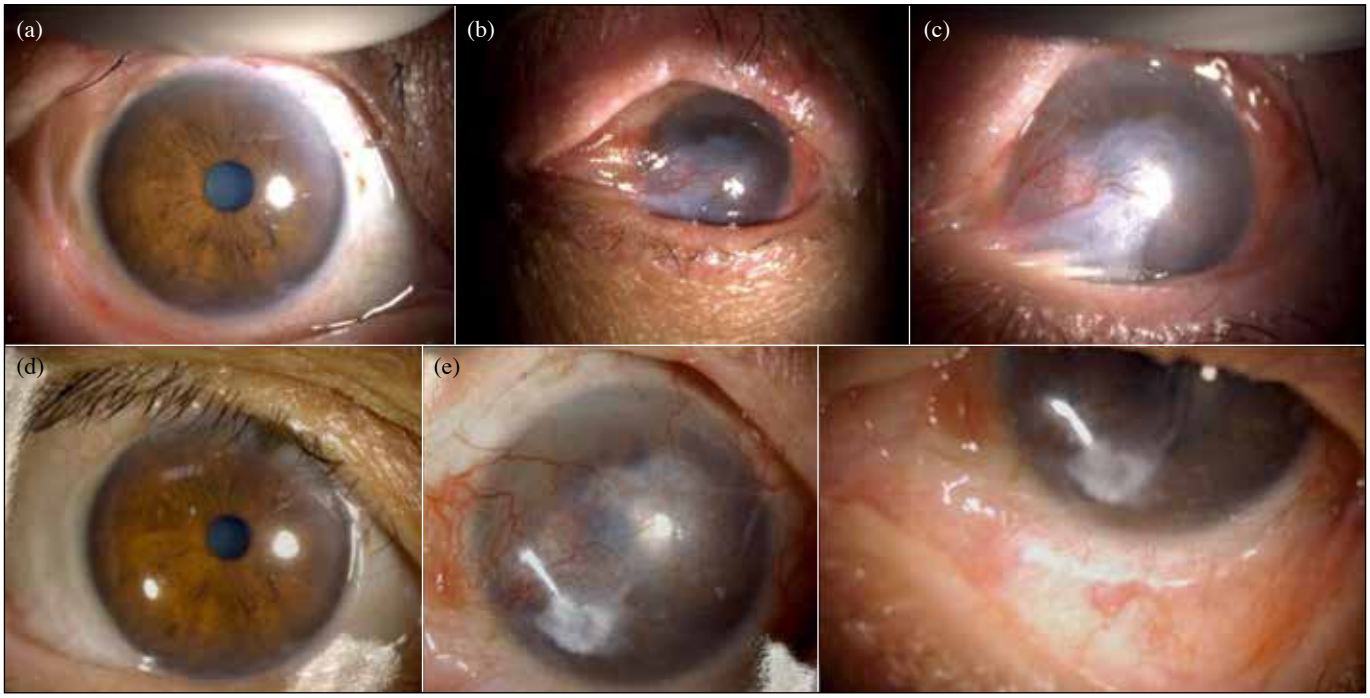


Figure 7. Patient 5: (a) The donor right eye. (b) Lower eyelid symblepharon and limbal stem cell deficiency of the left eye before simple limbal epithelial transplantation. (c) Recurrence of symblepharon causing complete gaze restriction. At the 6-month follow-up, (d) the donor right eye remains healthy, and (e) the left eye showing successful symblepharon lysis

a dense band-like lymphoplasmacytic infiltrate with occasional eosinophils. Immunofluorescent study showed no staining of immunoglobulin (Ig) G, C3, IgA, and IgM at the dermoepidermal junction.

In May 2013, the patient underwent symblepharon lysis of the right eye lower lid and AMT with fornix forming sutures, with perioperative steroid cover. Pathology of the lysed conjunctiva showed discontinuous bland non-keratinized stratified squamous epithelium. Subepithelial stroma was collagenous, mildly edematous, and chronically inflamed. In June 2014, she underwent grey line splitting follicles removal for bilateral upper eyelid trichiasis, which recurred continually and necessitated regular epilation. In October 2014, symblepharon of the left eye lower lid progressed and caused upgaze restriction. There was progressive lid margin keratinization, corneal neovascularization, and LSCD. In September 2015, she had an episode of infective corneal ulcer of the left eye that resulted in more stromal vascularization and scarring; her visual acuity decreased to logMAR 0.3. In November 2016, she underwent symblepharon lysis and fornix reconstruction with AMT and SLET of the left eye (**Figure 7**).

Pathology report showed stratified squamous epithelium lining fibrous stromal tissue with mild mixed acute and chronic inflammatory cells infiltration. There was focal parakeratosis in the surface epithelium but no subepidermal bulla. Immunofluorescence studies were negative of IgA, IgG, IgM, C3, C1q, and fibrin. Thus, the rheumatologist did not prescribe systemic immunosuppression medications despite years of ocular inflammation. In April 2017, SLET failed and symblepharon recurred, and the pseudopterygium covered three-quarter of the cornea. In March 2018, based on the first buccal mucosa biopsy, the patient was treated for lichen planus with high-dose oral steroid for systemic control of the condition. However, the patient was unable to tolerate oral steroid despite rapid tapering and had palpitations, rapid weight gain, and raised lipid levels. She was then treated with methotrexate.

In November 2018, she underwent another symblepharon lysis, pseudopterygium removal, AMT, and fornix forming sutures for the left eye. Recovery was complicated with persistent epithelial defects necessitating another AMT. The defect healed with time but a tuft of symblepharon recurred and encroached onto cornea surface. In April 2019, her visual acuity was logMAR 2.00. In October 2021, she had complete gaze restriction and underwent extensive pseudopterygium excision, symblepharon lysis, AMT, temporary spacer, and fornix forming sutures. In March 2022, she had unrestricted gaze movement and no recurrence of symblepharon, with visual acuity improved to logMAR 1.80.

Early and repeat conjunctival biopsy is useful after inconclusive biopsy results for buccal mucosa. Without a tissue diagnosis or other rheumatological symptoms, initiating immunosuppression is debatable. In Hong

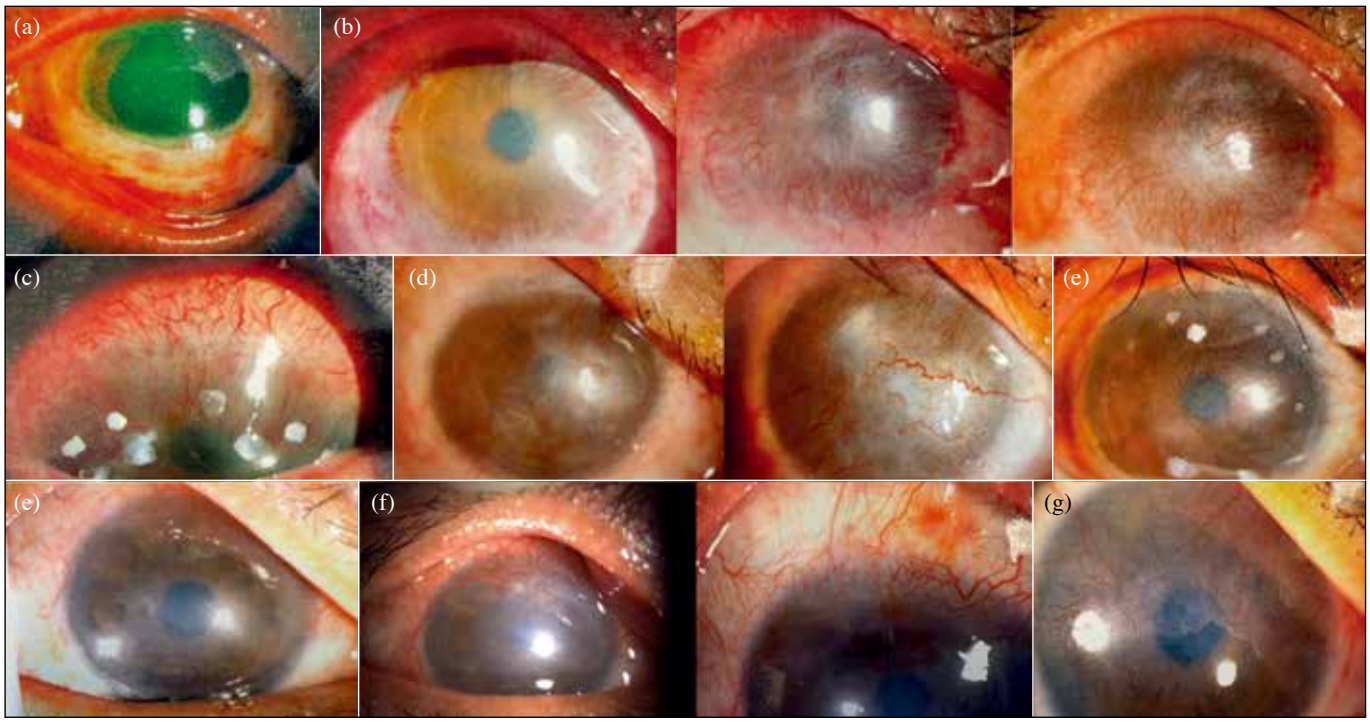


Figure 8. Patient 6: (a) Near total limbal stem cell deficiency and 80% conjunctival involvement of the right eye after Dua grade V injury. (b) Early formation and then progression of conjunctivalization. (c) Early vascularization at the superior cornea after the first simple limbal epithelial transplantation. (d) Recurrence of fibrovascular membrane. (e) The epithelium is stable after the second simple limbal stem cell transplantation. (f) Superior vascularization recurs 8 months later and is halted by subconjunctival aflibercept. (g) Conjunctivalization recurs 2 months later and obscures the superior half of the cornea.

Kong, the decision to initiate immunosuppression when patients have no rheumatological diagnosis is usually made by ophthalmologists. Early immunosuppression may decrease the degree and complexity of cicatricial changes. Reconstructive procedures can achieve better outcome when underlying inflammation is adequately controlled. Cornea and oculoplastic specialists should work together to manage recurring lid and eyelash problems because lid margin health affects cornea surface health and visual outcome.

Patient 6

In November 2016, a 41-year-old man presented with chemical injury by Fosroc Polyurea WPE liquid to the right eye (Dua grade V) and left eye (Dua grade II). The pH value of both eyes was 11. The patient was treated with daily irrigation, intensive topical steroid, antibiotics, lubrication, oral vitamin C, and doxycycline. One week later, autologous serum and bandage contact lens were added for treating persistent total epithelial defect of the right eye, whereas the left eye cornea healed without LSCD. In January 2017, the right eye developed total LSCD. In April 2017, the right eye was treated with SLET (**Figure 8**). One month later, the right eye showed early failure with progressive 360° revascularization and conjunctivalization. In September 2018, the patient underwent second SLET. Eight months later, the cornea surface showed superior vascularization, and subconjunctival aflibercept 2 mg was injected to halt the vascularization. Bandage contact lens was used to prevent breakdown of epithelium. However, in July 2019, conjunctivalization recurred. In June 2022, conjunctivalization and visual acuity remained static.

Patient 7

In December 2018, a 52-year-old man presented with a Dua grade V chemical injury by cement to the left eye. The patient underwent removal of the cement embedded in fornices and was treated with daily irrigation with Morgan lens for 1 week. 11 days after injury, AMT was performed, but residual epithelial defect and progressive corneal neovascularization persisted (**Figure 9**). In January 2019, the patient underwent SLET. Two days later, the donor limbal tissues and the amniotic membrane were shifted downwards after the patient rubbing the eye. Two weeks later, the epithelial defect and corneal vascularization persisted, despite transplantation of the AmnioTek-C. The patient underwent total tarsorrhaphy after multiple limited tarsorrhaphies for an unhealing neurotrophic ulcer. In April 2021, the tarsorrhaphy was released and the ocular surface was found to have epithelialized with dense scarring. The patient opted for conservative treatment. Eye rubbing causes early dislodgement of the amniotic membrane and transplanted tissues.

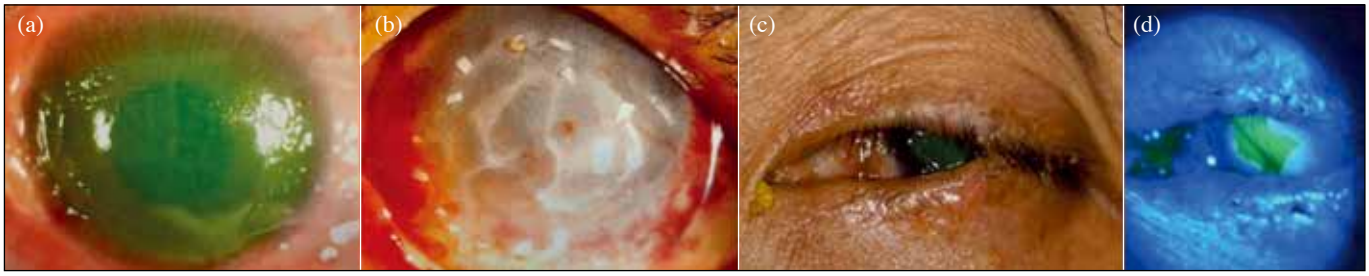


Figure 9. Patient 7: (a) Large epithelial defect despite amniotic membrane transplantation with 360° corneal vascularization. (b) The amniotic membrane and limbal tissues shift downwards secondary to eye rubbing. (c) Persistent epithelial defect necessitates lateral tarsorrhaphy to aid epithelial healing. (d) Complete tarsorrhaphy is performed as repeat limited tarsorrhaphies fail to aid epithelialization.

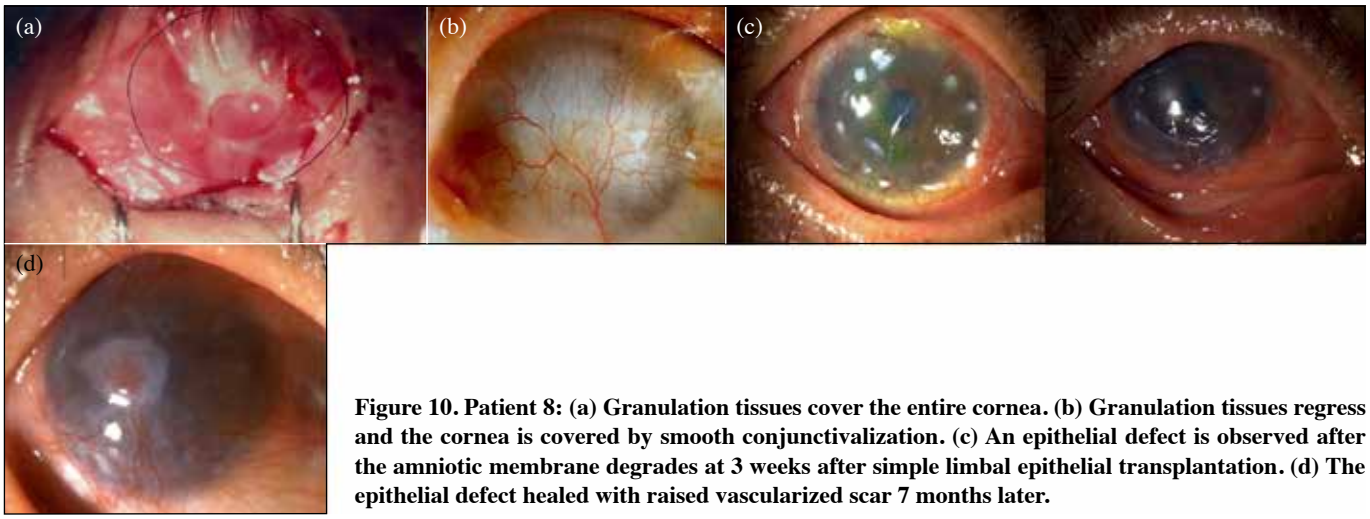


Figure 10. Patient 8: (a) Granulation tissues cover the entire cornea. (b) Granulation tissues regress and the cornea is covered by smooth conjunctivalization. (c) An epithelial defect is observed after the amniotic membrane degrades at 3 weeks after simple limbal epithelial transplantation. (d) The epithelial defect healed with raised vascularized scar 7 months later.

Patient 8

In August 2013, a 55-year-old man presented with infectious keratitis and persistent epithelial defect of the right eye secondary to a Dua grade V chemical injury by cement. One month after injury, the patient underwent paramedian tarsorrhaphy. However, 1 month later, the cornea healed with conjunctivalization and granulation tissues (**Figure 10**). Granulation tissues regressed with time, and the cornea was covered by smooth conjunctivalization. In April 2019, the patient underwent SLET. Three weeks later, an elliptical epithelial defect was observed after the amniotic membrane degraded. Amniotic membrane overlay was performed, but the cornea showed revascularization and conjunctivalization, which is suspected to be caused by heavy tobacco consumption (two packs a day) during the perioperative period.

Discussion

According to the consensus on classification and diagnosis of LSCD,[14] symptoms of LSCD include ocular discomfort, foreign body sensation, redness, tearing or dryness, photophobia, decreased vision, and pain. Patients with partial LSCD may remain asymptomatic. Early clinical signs can be detected by slit lamp examination with the aid of fluorescein stain and include sectoral and curve-like punctate epitheliopathy at the peripheral cornea, which later evolved into a whorl-like pattern and spreading into the central cornea. Clinical signs at later stages include tongue-like hazy opaque or grayish epithelium, superficial vascularization, and pannus formation. Advanced stage of LSCD may show subepithelial fibrosis, conjunctivalization, stromal scarring, neovascularization, and recurrent epithelial defects. Diagnostic tools include impression cytology and/or immunohistochemistry, in vivo confocal microscopy, and anterior segment optical coherence tomography.[15] However, these are not considered as quantitative tools. Quantification of severity of LSCD enables better preoperative counselling for patients.

The success rate of SLET may be higher in cases of thermal injury than of chemical injury, likely owing to the

extent of initial injury being more localized. Chemicals may stay in the fornices or conjunctivae for a prolonged period and hence a longer duration of insult. Higher grades of chemical injury have poorer prognosis. Cicatricial lid changes and symblepharon formation worsen treatment outcomes. The success rate of SLET is lower in patients with systemic causes, as in patient 5, owing to questionable quality of transplanted autologous limbal tissues and ongoing systemic inflammation, particularly when immunosuppression is not achieved before and during recovery.

The amniotic membrane has anti-inflammatory and wound-healing properties. However, these properties may not work in cases that require longer time to achieve normal pH or in cases with alarmingly raised intraocular pressure. The transplanted tissue may hinder accurate intraocular pressure measurement and decrease absorption of topical intraocular pressure–lowering and anti-inflammatory agents. As in patients 3 and 4, we opted for topical autologous serum and/or temporary tarsorrhaphy rather than an early AMT.

The time from injury to SLET is associated with treatment outcome. SLET is a reconstructive procedure for chronic LSCD rather than acute injury or inflammation.[16] For acute cases, treatment options of free conjunctival autografting from the contralateral eye, tenonplasty,[17] and conjunctival flap should be considered for reperfusion of avascular corneal surface and prevention of corneoscleral melting. Tarsorrhaphy should be considered for persistent epithelial defect. Selective cases may benefit from allogenic stem cell transplantation from cadaveric eyes for temporary epithelial healing during early post-injury period.[18] Limbal stem cells of the contralateral eye should not be harvested for treating acutely inflamed eye because of the high failure rate, as in patient 4. In contrast, in patients 1, 2, and 3 with stable chronic LSCD, SLET was successful.

Patient 7 rubbed his eye after SLET and displaced the amniotic membrane and transplanted tissue on postoperative day 3. He developed persistent epithelial defect and required further AMT and tarsorrhaphies.

Patient 8 was thought to be a good candidate for SLET because of the long time since injury, stable ocular surface, and healthy contralateral limbus. However, he had persistent epithelial defect and recurrence of conjunctivalization despite the amniotic membrane overlay. The patient smoked heavily perioperatively. Delayed epithelial healing has been reported in smokers.[19]

The success rate of SLET has been reported to be 70% at 1.1-year follow-up,[7] 76% at 2.96-year follow-up,[10] 66% at 6.2-month follow-up,[20] and 83% at 1-year follow-up.[9] When smaller studies are included, the success rate can vary from 25%[21] to 100%.[22] In our cohort, the success rate was lower (37.5%) because all our patients had total LSCD (other studies include patients with partial LSCD); in addition, three had severe symblepharon, one had displacement of implants secondary to eye rubbing, and one had lichen planus. The criteria to define success, partial success, and failure vary among studies; thus, comparison of outcomes among different studies is difficult.

In patients with bilateral injuries or asymmetrical involvement of the eyes from systemic disease, all donor eyes showed no clinical evidence of limbal stem cell damage preoperatively and did not develop iatrogenic LSCD postoperatively. We opted for autologous SLET because prior to 2019 the evidence of success of allogenic SLET and the consensus of immunosuppressant usage were limited. With local eye bank updating donor suitability for allogenic SLET and better understanding of risk factors, allogenic stem cell transplantation is the future direction, particularly for patients with bilateral LSCD. Collaboration between ophthalmologists and immunologists is needed for the safe and prolonged usage of multiple systemic immunosuppressants.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

This study was approved by The Kowloon West Cluster Research Ethics Committee [KWC-REC Reference: KW/EX-22-012(169-01)]. The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

References

1. *Jhagta HS, Jain P. Limbal stem cell deficiency: a review. J Clin Ophthalmol Res 2015;3:71-5.* Crossref
2. *Singh P, Tyagi M, Kumar Y, Gupta KK, Sharma PD. Ocular chemical injuries and their management. Oman J Ophthalmol 2013;6:83-6.* Crossref
3. *Sekhon A, Wang JYF, Tan JCH, Holland SP, Yeung SN. Limbal stem cell deficiency secondary to systemic paclitaxel (Taxol) for breast cancer: a case report. BMC Ophthalmol 2020;20:400.* Crossref
4. *Mehta U, Farid M. Dupilumab induced limbal stem cell deficiency. Int Med Case Rep J 2021;14:275-8.* Crossref
5. *Deng SX, Kruse F, Gomes JAP, et al. Global consensus on the management of limbal stem cell deficiency. Cornea 2020;39:1291-302.* Crossref
6. *Shanbhag SS, Nikpoor N, Rao Donthineni P, Singh V, Chodosh J, Basu S. Autologous limbal stem cell transplantation: a systematic review of clinical outcomes with different surgical techniques. Br J Ophthalmol 2020;104:247-53.* Crossref
7. *Gupta N, Joshi J, Farooqui JH, Mathur U. Results of simple limbal epithelial transplantation in unilateral ocular surface burn. Indian J Ophthalmol 2018;66:45-52.* Crossref
8. *Le Q, Chauhan T, Yung M, Tseng CH, Deng SX. Outcomes of limbal stem cell transplant: a meta-analysis. JAMA Ophthalmol 2020;138:660-70.* Crossref
9. *Vazirani J, Ali MH, Sharma N, et al. Autologous simple limbal epithelial transplantation for unilateral limbal stem cell deficiency: multicentre results. Br J Ophthalmol 2016;100:1416-20.* Crossref
10. *Basu S, Sureka SP, Shanbhag SS, Kethiri AR, Singh V, Sangwan VS. Simple limbal epithelial transplantation: long-term clinical outcomes in 125 cases of unilateral chronic ocular surface burns. Ophthalmology 2016;123:1000-10.* Crossref
11. *Shanbhag SS, Patel CN, Goyal R, Donthineni PR, Singh V, Basu S. Simple limbal epithelial transplantation (SLET): review of indications, surgical technique, mechanism, outcomes, limitations, and impact. Indian J Ophthalmol 2019;67:1265-77.* Crossref
12. *Soleimani M, Naderan M. Management strategies of ocular chemical burns: current perspectives. Clin Ophthalmol 2020;14:2687-99.* Crossref
13. *Dua HS, Miri A, Faraj LA, Said DG. Free autologous conjunctival grafts. Ophthalmology 2012;119:2189-2189.e2.* Crossref
14. *Deng SX, Borderie V, Chan CC, et al. Global consensus on definition, classification, diagnosis, and staging of limbal stem cell deficiency. Cornea 2019;38:364-75.* Crossref
15. *Le Q, Chauhan T, Deng SX. Diagnostic criteria for limbal stem cell deficiency before surgical intervention: a systematic literature review and analysis. Surv Ophthalmol 2020;65:32-40.* Crossref
16. *Dua HS, Miri A, Said DG. Contemporary limbal stem cell transplantation: a review. Clin Exp Ophthalmol 2010;38:104-17.* Crossref
17. *Kuckelkorn R, Schrage N, Reim M. Treatment of severe eye burns by tenonplasty. Lancet 1995;345:657-8.* Crossref
18. *Iyer G, Srinivasan B, Agarwal S, Tarigopula A. Outcome of allo simple limbal epithelial transplantation (alloSLET) in the early stage of ocular chemical injury. Br J Ophthalmol 2017;101:828-33.* Crossref
19. *Dhillon HK, Bahadur H, Raj A. A comparative study of tarsorrhaphy and amniotic membrane transplantation in the healing of persistent corneal epithelial defects. Indian J Ophthalmol 2020;68:29-33.* Crossref
20. *Jain R, Kanaujia V, Sahu S, Das S. Management of unilateral limbal stem cell deficiency by simple limbal epithelial transplantation: our experience. MOJ Surg 2014;1:4-7.* Crossref
21. *Mittal V, Jain R, Mittal R, Vashist U, Narang P. Successful management of severe unilateral chemical burns in children using simple limbal epithelial transplantation (SLET). Br J Ophthalmol 2016;100:1102-8.* Crossref
22. *Amescua G, Atallah M, Nikpoor N, Galor A, Perez VL. Modified simple limbal epithelial transplantation using cryopreserved amniotic membrane for unilateral limbal stem cell deficiency. Am J Ophthalmol 2014;158:469-75.e2.* Crossref

CASE REPORT

Orbital mycobacterial infection: a case report

Christina KY Ip, MBChB; Cheong-Yi Fong, MBChB, MRCSEd (Ophth), FCOphth (HK), FHKAM (Ophth); Pui-Fan Lam, MBChB, MPH, FCOphth (HK), FHKAM (Ophth); Shu-Kwan Ip, MBBS, FRCS (Glasg) (Ophth), FCOphth (HK), FHKAM (Ophth)
Department of Ophthalmology, Tuen Mun Eye Centre, Hong Kong

Correspondence and reprint requests:
Dr Christina KY Ip, Department of Ophthalmology, Tuen Mun Eye Centre, Hong Kong. Email: christinaip55@gmail.com

Abstract

A 69-year-old Chinese man presented with proptosis was found to suffer from orbital mycobacterial infection. As acid-fast bacilli were identified from orbital excisional biopsy, the patient was treated with an anti-tuberculous regimen. He responded well and was asymptomatic at 13-month follow-up. This case is documented for its rarity.

Key words: Orbit; Tuberculosis, ocular

Case presentation

A 69-year-old Chinese man presented to Tuen Mun Eye Centre with a 1-month history of right eye proptosis and pain in June 2020. He was a non-smoker with a past medical history of Type 2 diabetes mellitus, hyperlipidemia, and complete heart block with permanent pacemaker implanted. There was no history of ocular trauma or surgery.

The best-corrected visual acuity was Snellen 0.13 OD. Pupils were equal and reactive to light, there were no relative afferent pupillary defect. Exophthalmometer showed right non-axial proptosis by 2 mm. Intraocular pressure (IOP) of both eyes were normal. Anterior segment examination showed right eye mild chemosis. Extraocular movement was full with no diplopia. Fundal examination revealed mild non-proliferative diabetic retinopathy of both eyes and a macula hole over his right eye. There were no signs of optic neuropathy. Blood tests were unremarkable except glycated hemoglobin level of 9.9%. Orbital computed tomography (CT) was arranged.

A follow-up IOP measurement at 4 weeks after initial presentation revealed an elevated IOP of 30 mmHg. There were also lagophthalmos, hypoglobus, and restricted motility over his right eye with markedly reduced elevation and abduction. Anterior segment examination showed exposure keratopathy. Fundus examination findings were similar to those on initial presentation. Imaging with orbital CT revealed a 2.4 cm right orbital post septal rim enhancing mass (**Figure 1**).

The working diagnosis was orbital abscess, right eye lateral canthotomy and drainage yielded yellowish necrotic materials with minimal fluid pus. Histological examination revealed lymphoid rich inflammatory lesions with necrotic features, no obvious malignant cells were identified (**Figure 2**). Gram stain and culture were negative. Postoperatively, intravenous broad-spectrum antibiotics were given but right eye proptosis and exposure keratopathy persisted.

A follow-up CT scan at postoperative 1-week revealed no interval reduction in the size of the lesion. The lesion was excised subsequently with lateral orbitotomy. Proptosis resolved and exposure keratopathy improved. IOP and extraocular movement returned to normal. The excised lesion was 1.8 cm in diameter and well circumscribed (**Figure 3**). The lacrimal gland was left intact. The features of necrotizing inflammation in histopathological analysis and the scanty acid-fast bacilli (AFB) on Ziehl-Neelsen stain (**Figure 4**) were suggestive of mycobacterial infection. Polymerase chain reaction for *Mycobacterium tuberculosis* complex was negative, as were periodic acid-Schiff, Grocott methenamine silver, and mucicarmine stains for other organisms.

On retrospective review, the patient had no history or contact of pulmonary tuberculosis (TB). He was born in Mainland

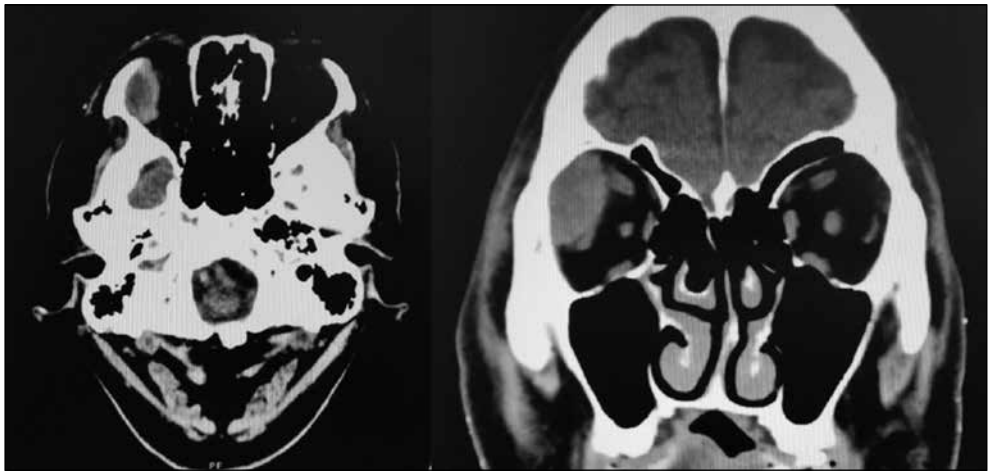


Figure 1. Computed tomography of the orbit showing a 2.4 cm rim-enhancing mass located at the extraconal region of the right orbit in the post-septa region displacing the lateral rectus muscle inferiorly. The mass is abutting on the superior and lateral orbital wall, lacrimal gland, and right globe, causing proptosis. The right lacrimal gland cannot be delineated from this lesion. There is no bony erosion, thickening, or lysis.

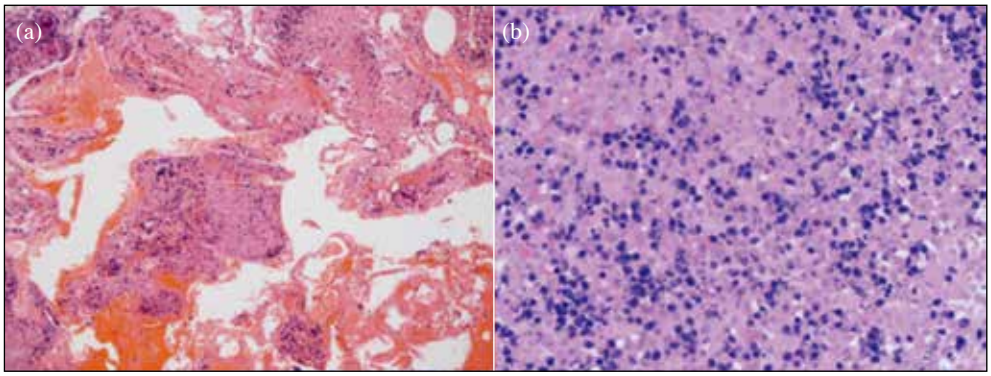


Figure 2. Histopathology showing (a) fibrinous tissue with atypical necrosis (100×). (b) small lymphocytic inflammatory cell infiltrate (400×).

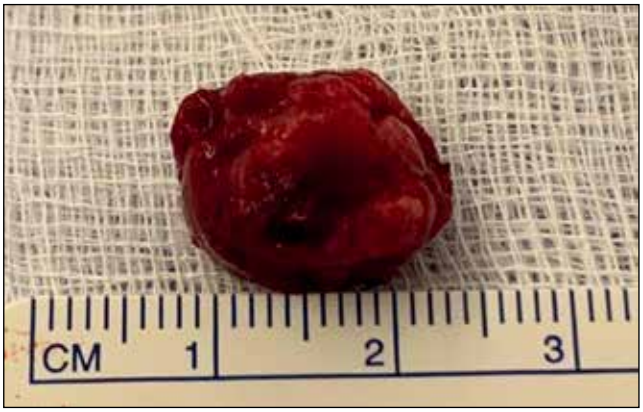


Figure 3. Clinical photograph showing the well circumscribed excised lesion.

China and did not receive Bacillus Calmette-Guérin vaccination. He did not have any signs and symptoms of systemic TB infection; chest X-ray was clear with no features of pulmonary TB. Sputum and blood AFB culture were negative, as was HIV antigen.

The patient was referred to a local chest clinic as microbiologist suggested. He was then treated as extrapulmonary TB with an anti-TB regimen consisting of isoniazid 300 mg daily, rifampicin 600 mg daily, pyrazinamide 1500 mg daily, and levofloxacin 500 mg daily.

Further CT scan at postoperative 1-month revealed no recurrence of proptosis. IOP and extraocular movement remained normal. Follow-up at 13-month showed no clinical evidence of recurrence (**Figure 5**). The patient completed 16-month anti-TB regimen. The lesion resolved completely with no further complications in May 2022. Regular follow-up has been scheduled.

Discussion

Orbital mycobacterial infection is rare. Most of the existing literatures regarding orbital tuberculosis (OTB) and non-tuberculous mycobacterial (NTM) orbital infection are limited to case reports or case series. There were 79 identified cases of OTB in an extensive literature search.[1] In a systematic review, only 11 (2.6%) of 420 cases of NTM ocular infections were orbital infections.[2]

Orbital involvement of TB may be a result of direct spread from paranasal sinuses, or hematogenous spread from a primary source, with or without pulmonary TB.[1,3] Therefore,

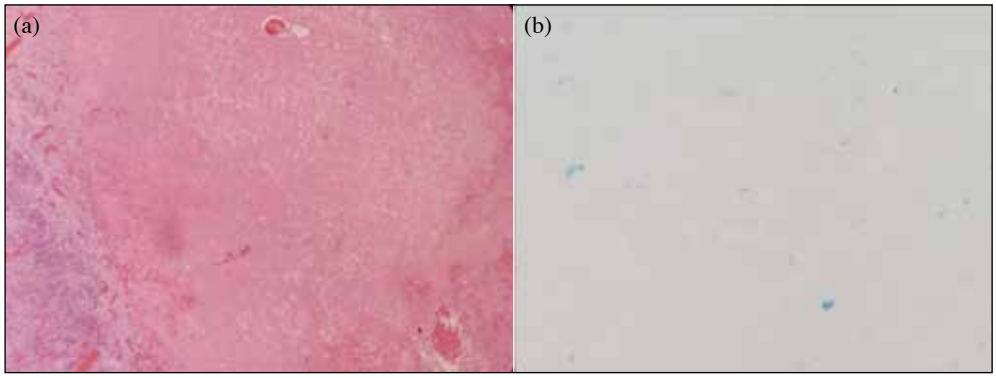


Figure 4. Histopathology showing (a) fibrous stromal tissue with necrotic center rimmed by histiocytes, fibroblastic proliferation and crushed reactive lymphoid infiltrate (100×). (b) Scanty acid-fast bacilli on Ziehl-Neelsen stain (400×).

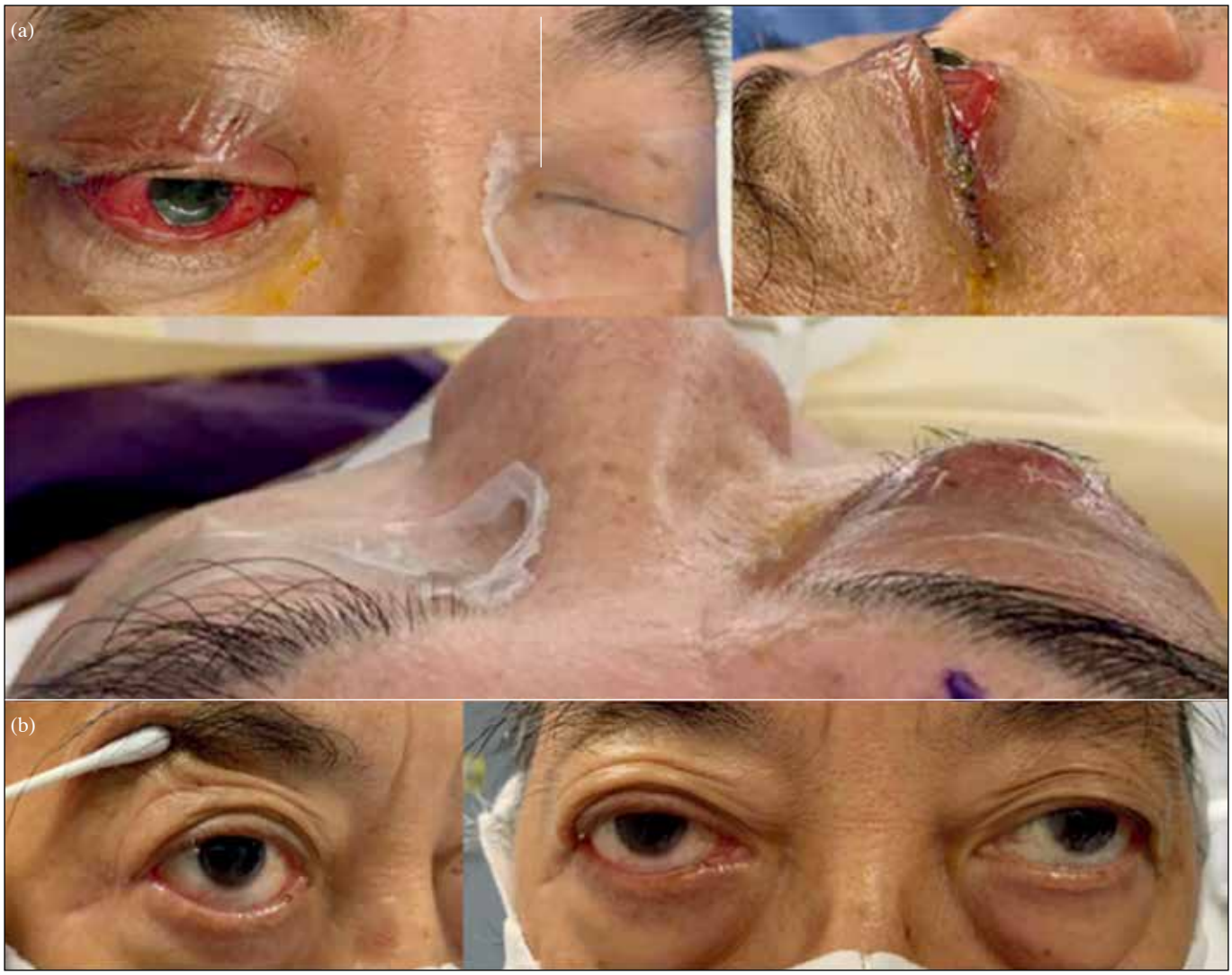


Figure 5. Clinical photographs showing (a) right eye chemosis and proptosis before lateral orbitotomy. (b) no recurrence of right eye chemosis and proptosis after lateral orbitotomy at 13-month follow-up.

it cannot be excluded in the absence of pulmonary infection. In fact, a case of OTB without primary source identified was reported.[4] Extrapulmonary TB has become more common in immunocompromised patients.[1] As OTB is a rare form of extrapulmonary TB, the association between immunocompromised condition and OTB is uncertain. Increased risk of OTB in immunocompromised patients secondary to poor control of diabetes mellitus is

inconclusive. Our patient did not receive Bacillus Calmette-Guérin vaccination and may be at an increased risk of TB infection, but he had no known TB history or contact.

It was found that orbital fat allowed NTM to escape from the host immune system by protecting them from enzymatic action or phagocytosis,[5] thus predisposing NTM orbital infection. Also, NTM orbital infection is associated with risk factors such as prior corticosteroid therapy, history of interventions or recent accidental ocular trauma.[6] Our patient did not have any recent interventions or ocular trauma or any signs of injury and inflammation, the origin of infection could not be ascertained.

Manifestations of orbital mycobacterial infection is non-specific. Patient may present with an intraconal mass that leads to proptosis and restricted motility, or orbital inflammation such as draining sinus tracts, periorbital cellulitis, and orbital abscess. Extradural abscess formation, soft tissue tuberculoma, caseating granuloma, and orbital apex syndrome can also occur.[2,7] Destructive complications to the bone and soft tissue may be resulted.[8] The wide variety of possible presentations of orbital mycobacterial infection pose a challenge to a straightforward diagnosis.

It is difficult to establish and confirm the diagnosis of orbital mycobacterial infection. Diagnosis is challenging due to its rarity, non-specific manifestations, difficulty in obtaining orbital specimen for histological and microbiological analysis, and low yield from orbital specimen.[8] Extrapulmonary TB infection is often paucibacillary, and false negative may occur. As reported, only 19 of 79 identified cases of OTB yielded positive cultures.[1] In our patient, the delay in diagnosis was accounted for by the absence of systemic symptoms and predisposing risk factors. In addition, the histology of the necrotic materials obtained from lateral canthotomy and drainage was unrevealing. It was the identification of scanty AFB from the orbital excisional biopsy shed light on the diagnosis and the choice of treatment.

There are no specific guidelines for the treatment of orbital mycobacterial infection. Possible treatment options include surgical means such as drainage or excision of lesion, and medical treatment with antibiotics. Surgical excision of lesions can be diagnostic and therapeutic. Medications for OTB are individualized,[8] but mainly comprising multiple anti-TB drugs with duration ranged from 6 to 18 months.[1] For NTM infections, the choice of antibiotics depends on drug sensitivity of the causative agent. In general, slow-growers are sensitive to those for anti-TB, whereas rapid-growers are sensitive to macrolides, fluoroquinolones, and aminoglycosides.[9] Complete surgical excision with anti-TB therapy can be the treatment of choice to achieve resolution of orbital mycobacterial infection as illustrated in this case.

Conclusion

We report a rare case of orbital mycobacterial infection with no primary source identified. Our case demonstrates the possibility of orbital mycobacterial infection in the absence of apparent risk factors and the importance of obtaining appropriate specimen for diagnostic investigations. Ophthalmologists should be aware of the different manifestations of orbital mycobacterial infection and be alert to the possibility of mycobacterial infection.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures and for publication.

References

1. *Madge SN, Prabhakaran VC, Shome D, Kim U, Honavar S, Selva D. Orbital tuberculosis: a review of the literature. Orbit 2008;27:267-77.* Crossref
2. *Kheir WJ, Sheheitli H, Abdul Fattah M, Hamam RN. Nontuberculous mycobacterial ocular infections: a systematic review of the literature. Biomed Res Int 2015;2015:164989.* Crossref
3. *Pillai S, Malone TJ, Abad JC. Orbital tuberculosis.*

Ophthalmic Plast Reconstr Surg 1995;11:27-31. Crossref
4. *Aggarwal D, Suri A, Mahapatra AK. Orbital tuberculosis with abscess. J Neuroophthalmol 2002;22:208-10*. Crossref
5. *Gonzalez-Fernandez F, Kaltreider SA. Orbital lipogranulomatous inflammation harboring* Mycobacterium abscessus. *Ophthalmic Plast Reconstr Surg 2001;17:374-80*. Crossref
6. *Klapper SR, Patrinely JR, Kaplan SL, Font RL. Atypical mycobacterial infection of the orbit. Ophthalmology 1995;102:1536-41*. Crossref
7. *Dalvin LA, Smith WM. Orbital and external ocular manifestations of* Mycobacterium tuberculosis*: a review of the literature. J Clin Tuberc Other Mycobact Dis 2015;4:50-7*. Crossref
8. *Yao A, Aboltins C, McNab AA, Rosa CS, Denholm J, Khong JJ. Orbital tuberculosis: perspectives from Victoria, Australia. Graefes Arch Clin Exp Ophthalmol 2018;256:2443-8*. Crossref
9. *Moorthy RS, Valluri S, Rao NA. Nontuberculous mycobacterial ocular and adnexal infections. Surv Ophthalmol 2012;57:202-35*. Crossref

CASE REPORT

Reversal of inverse Bell's reflex after sling removal and scar lysis in an 11-year-old patient: a case report

Cheuk Ling Yim, MBChB, AFCOphthHK; Yuen Ting Kwok, MB ChB, FCOphthHK; Hunter Kwok Lai Yuen, MBChB, FRCOphth, FRCS(Ed), FCOphthHK, FHKAM (Ophthalmology), DipClinDerm (London)
Department of Ophthalmology, Hong Kong Eye Hospital & Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong

Correspondence and reprint requests:
Dr Hunter Kwok Lai Yuen, Department of Ophthalmology, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong. Email: hunterklyuen@gmail.com

Abstract

We report a case of inverse Bell's reflex of the right eye in an 11-year-old boy who underwent frontalis suspension ptosis correction at the age of 1 year and developed scarring secondary to exposure and infection of the sling implant 5 months later. At the age of 11 years, the patient had an episode of right eye infective keratitis secondary to corneal exposure and was first noted to have developed the inverse Bell's reflex. The patient underwent removal of sling, scar lysis, and limited full thickness blepharotomy. At postoperative 11 months, the Bell's reflex was completely normal. This suggests that eyelid scar tissue may contribute to the development of inverse Bell's reflex and that scar lysis, despite delayed, may resolve the problem.

Key words: Blinking; Eyelid diseases; Keratitis; Reflex

Introduction

Bell's reflex, in which the globe turned upward during eyelid closure, is an important mechanism to protect the cornea, particularly in patients with congenital ptosis who require ptosis correction surgery, because lid lag and lagophthalmos are common postoperative complications that may lead to exposure keratopathy and visual debilitation. Inverse Bell's reflex, in which the globe turn downward, is a variation in a small proportion of patients.

Case presentation

In November 2006, a 32-day-old male infant presented to Hong Kong Eye Hospital with right eye congenital ptosis. On presentation, the visual axis was partially obscured. The patient was noted to have a chin-up head posture. He developed right eye amblyopia at 8 months old. Despite good compliance to left eye patching, the visual acuity was 6/12 for the right eye and 6/9.5 for the left eye based on the Cardiff acuity test. At the age of 1 year, the patient underwent frontalis sling operation for the right eye using the double trapezoid technique with a silicone rod. The visual acuity of the right eye improved to 6/9.5. Five months later, the patient had exposure and infection of the sling implant, which was immediately treated with wound revision, drainage, and intralesional antibiotic injection. Nonetheless, scarring developed on the upper lid and resulted in lid notching, upper lid retraction, and lagophthalmos. The palpebral fissure height was 10 mm for the right eye and 8 mm for the left eye. The margin to reflex distance was 4 mm for the right eye and 2 to 3 mm for the left eye. A revision surgery for eyelid retraction and exposure keratopathy was proposed but was declined by the parents. The patient was thus managed conservatively with topical lubricants.

At the age of 6 years, the patient underwent bilateral lateral rectus recession with upward transposition for intermittent

Figure. Clinical photographs showing (a) right eye upper lid retraction and (b) lagophthalmos and eyeball rolling down during eye closing, consistent with the inverse Bell's reflex; (c) correction of right eye upper lid retraction and (d) reversal of inverse Bell's reflex at 41 months after sling removal and scar lysis.

exotropia; recovery was uneventful. At the age of 11 years, the patient had an episode of right eye infective keratitis secondary to corneal exposure. On examination, he was first noted to have developed inverse Bell's reflex (**Figure**). The inverse Bell's reflex aggravated the exposure keratopathy and contributed to the episode of keratitis, which was resolved after intensive topical antibiotic eyedrops and copious lubricants application.

One months later, the patient underwent removal of sling, scar lysis, and limited full thickness blepharotomy. Reverse frost suture was placed. Intra-operatively, right upper lid extensive middle lamellar scarring and shortening of right upper lid skin were noted. Scar above tarsus was lysed, the posterior and middle lamellar were completely freed. Subcutaneous adhesions were released as much as possible. Postoperatively, the upper lid retraction was corrected, and the palpebral fissure height was 5 mm for the right eye and 6 mm for the left eye. Residual lagophthalmos was mild. The inverse Bell's reflex normalized. At 4 months, there were occasional occurrences of inverse Bell's reflex. At 11 months, the Bell's reflex was completely normal. The cornea condition significantly improved with no further episodes of exposure keratopathy. At 41 months, the visual acuity was 0.8 for both eyes, and the cosmetic outcome was satisfactory, with no limitation in the extraocular movement (**Figure**).

Discussion

Assessing the Bell's reflex is essential before any ptosis correction surgery. In the normal Bell's reflex, the eyes turn upward during eyelid closure to protect the cornea from exposure. The inverse Bell's reflex, in which the eye turn downward, can be observed in 2% of the population and also in patients with Bell's palsy.[1]

Development of inverse Bell's reflex has been reported after repeat levator resection surgery for congenital ptosis and after a frontalis sling surgery, with the inverse Bell's reflex spontaneously resolved few weeks later.[2-7] Development of inverse Bell's reflex after levator surgery for ptosis correction is rare. The exact mechanism is unknown; possible causes include intra-operative tissue trauma and postoperative soft tissue edema or injury to the nervous system causing aberrant connections.[7,8] Our patient underwent the initial operation at the age of 1 year, which is much younger than that of other patients reported.[3-7] The inverse Bell's reflex was first noted 10 years after the initial surgery, probably owing to its difficulty to detect at young age with poor patient cooperation for clinical examination. Spontaneous recovery did not occur in our patient, which is different from other cases reported.[2-7] The inverse Bell's reflex resolved after scar lysis. This suggests that the presence of scarring may be a cause of the inverse Bell's reflex and that removal of scar tissue may reverse the inverse Bell's reflex. Although development of inverse Bell's reflex is rare, it is important to assess the Bell's reflex pre- and post-operatively for patients with congenital ptosis, particularly in those with coexisting lagophthalmos who are at higher risk of cornea complications. Copious lubricants and close monitoring are useful to prevent exposure keratopathy until normalization of the Bell's reflex. Prolonged placing of a frost suture to prevent exposure keratopathy is recommended.[4]

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors

had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient/parents provided written informed consent for all treatments and procedures and for publication.

References

1. *Gupta JS, Chatterjee A, Kumar K. Inverse Bell's phenomenon as a protective mechanism. Am J Ophthalmol 1965;59:931-3.* Crossref
2. *Pandey TR, Limbu B, Rajkarnikar Sthapit P, Gurung HB, Saiju R. Transient inverse Bell's phenomenon following frontalis sling-suspension ptosis surgery: a rare ophthalmic phenomenon. Int Med Case Rep J 2019;12:325-7.* Crossref
3. *Shitole S, Jakkal T, Khaire B. Inverse Bell's phenomenon: rare ophthalmic finding following ptosis surgery. J Clin Diagn Res 2015;9:ND01-2.* Crossref
4. *Betharia SM, Sharma V. Inverse Bell's phenomenon observed following levator resection for blepharoptosis. Graefes Arch Clin Exp Ophthalmol 2006;244:868-70.* Crossref
5. *Kumar DA, Agarwal A. Transient inverse bells phenomenon following frontalis sling surgery. Int J Ocul Oncol Oculoplasty 2016;2:258-9.*
6. *Morawala A, Sharma A, Naik MN. Inverse Bell's phenomenon: a rare complication of levator resection surgery in a case of congenital ptosis. BMJ Case Rep 2019;12:e232451.* Crossref
7. *Na KS, Yang SW. Two cases of inverse Bell's phenomenon following levator resection: a contemplation of the mechanism. Eur J Ophthalmol 2009;19:285-7.* Crossref
8. *Evinger C, Manning KA. Pattern of extraocular muscle activation during reflex blinking. Exp Brain Res 1993;92:502-6.* Crossref

CASE REPORT

Surgical management for macular folds after macular epiretinal membrane surgery: a report of two cases

Lai Ting Yip[1], *FCOphth (HK)*; *Alvin Kwan Ho Kwok*[2], *MD (HK), MD (CUHK), PhD (HK), FRCS (UK), FRCOphth (UK), FHKAM (Ophth), PostGrad DipEpidem & Biostat (CUHK), MBBS (HK)*; *Chai Fong Woo*[3], *FCOphth (HK)*

[1]*Tung Wah Eastern Hospital, Hong Kong*
[2]*Hong Kong Sanatorium & Hospital, Hong Kong*
[3]*The Hong Kong Ophthalmic Service, Hong Kong*

Correspondence and reprint requests:
Dr Lai Ting Yip, 9/F Ophthalmic Center, Tung Wah Eastern Hospital, 19 Eastern Hospital Road, Causeway Bay, Hong Kong.
Email: drfannyip@gmail.com

Abstract

We report two rare cases of macular fold development after membrane peeling operation for epiretinal membrane. Patient 1 developed both inner and outer retinal folds, and patient 2 developed inner retinal fold; both were partial thickness macular folds. There was no evidence of retinal detachment or any preoperative macular fold. These configurations of retinal folds after macular epiretinal membrane surgery have not been reported before. In patient 1, four retinotomy sites were required to induce a complete macula detachment, as the retina was abnormally adherent than usual. In patient 2, no macular detachment was induced, and no intravitreal tamponade was used. Soft-tip cannula was used to relieve the inner retinal attachments. To the best of our knowledge, this is the first reported case using this method to successfully manage a retinal fold. This technique avoids the potential risks associated with retinotomies, macular re-detachment, and intravitreal tamponade. Both patients achieved resolution of macular folds and improvement in visual acuity.

Key words: *Macula lutea; Retina; Visual acuity*

Introduction

First reported in 1984, macular folds after vitrectomy usually occur in patients with retinal detachment.[1,2] Risk factors known to cause macular folds include bullous rhegmatogenous retinal detachment and its associated giant retinal tears, incomplete drainage of subretinal fluid, and poor compliance to postoperative posturing. Based on optical coherence tomography (OCT), macular folds can be categorized into inner retinal folds, outer retinal folds, and full-thickness retinal folds.[1] Inner retinal folds exhibit corrugations of the inner retina, whereas outer retinal folds display hyper-reflective lesions located just above the retinal pigment epithelium that may extend into the outer nuclear layer. In full-thickness retinal folds, all layers of the neurosensory retina may separate altogether from the retinal pigment epithelium, with retinal reduplication and base-to-base photoreceptor orientation.[1] We report two cases of macular folds after macular membrane peeling operation for epiretinal membrane without retinal detachment.

Case presentation

Patient 1

In November 2018, a 41-year-old man presented to Hong Kong Sanatorium & Hospital with increased right eye distortion, which necessitated right eye occlusion for near work. Two months earlier, the patient had undergone right

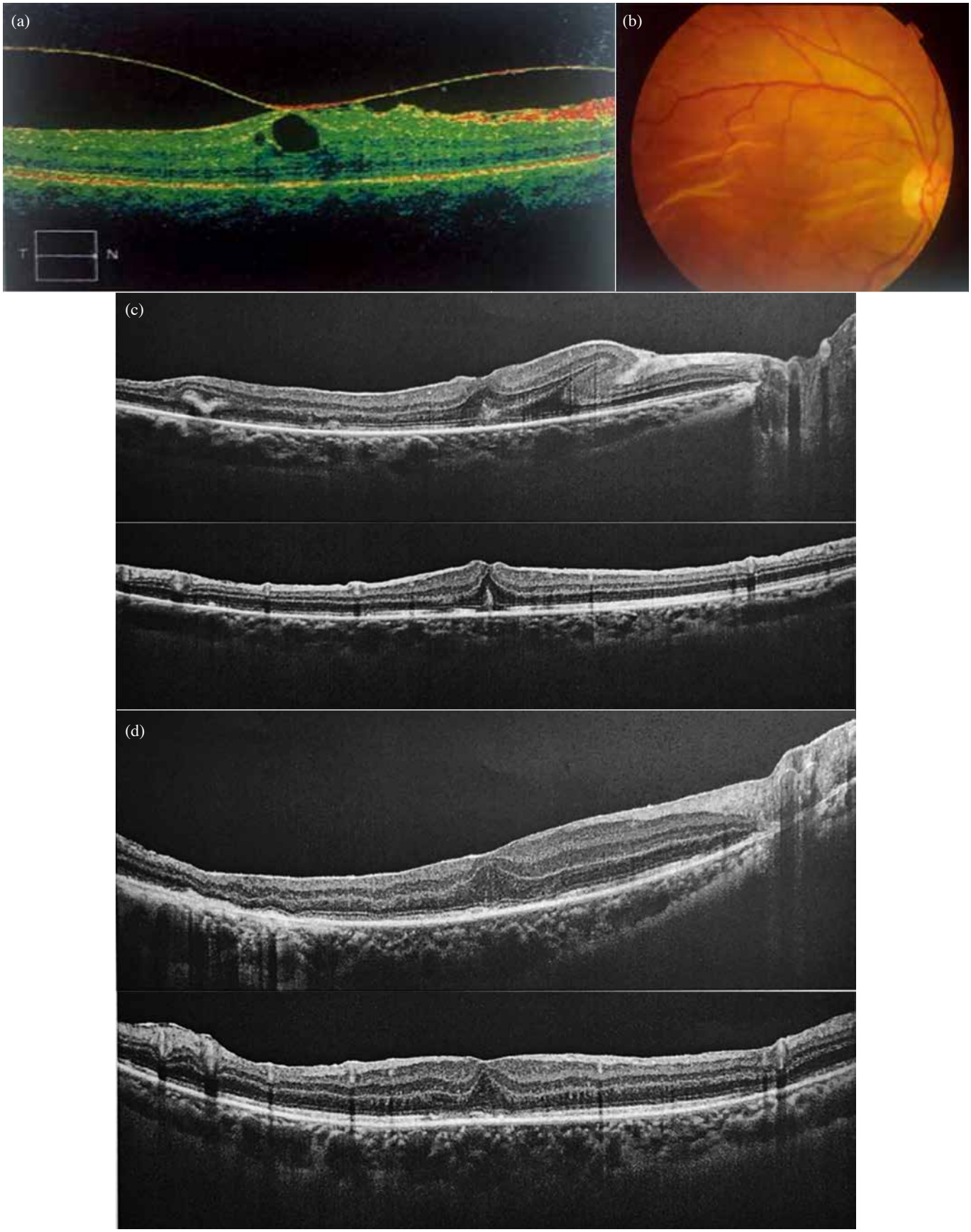


Figure 1. Patient 1: (a) optical coherence tomography before the previous operation showing epiretinal membrane with cystoid macular edema and vitreomacular traction, (b) fundus photograph at presentation showing multiple horizontal and oblique retinal folds involving fovea, (c) optical coherence tomography at presentation showing horizontal and vertical cuts of inner retinal folds involving outer plexiform layer and outer retinal folds across fovea, and (d) optical coherence tomography at postoperative 1 month showing resolution of macular folds.

eye vitrectomy and macular membrane peeling operation elsewhere for macular epiretinal membrane with cystoid macular edema and vitreomacular traction (**Figure 1a**). The patient reported that no tamponade was used in the operation and no special posturing was required after the operation. At the current presentation, the visual acuity was 20/100 for the right eye and 20/20 for the left eye. Fundus photograph showed multiple horizontal and oblique retinal folds involving the fovea in the right eye (**Figure 1b**). The right eye had four retinal holes surrounded by retinal photocoagulation inferiorly and almost 360° laser marks and lens opacities. The patient denied receiving any retinal laser procedure prior to the surgery. OCT scans showed both inner retinal folds and outer retinal folds in the right eye (**Figure 1c**). The left eye was unremarkable except for an old inferior barrier laser performed 2 months earlier.

One week later, the patient underwent second vitrectomy (by AKHK) for the right eye under general anesthesia. Three-port 25-gauge pars plana vitrectomy was performed using the Constellation Vision System (Alcon, Forth Worth, USA). Intra-operatively, thorough vitrectomy was noted. Complete macular internal limiting membrane removal in the previous operation was confirmed with MembraneBlue-Dual (DORC International, Zuidland, Netherlands). Superotemporal sclerotomy was changed to 20-gauge for submacular BSS PLUS (Alcon Laboratories, Fort Worth [TX], USA) solution injection with 42-gauge needle tip cannula through retinotomies at four sites: mid-superotemporal arcade, mid-inferotemporal arcade, peripheral temporal macula, and peripheral inferotemporal macula. Multiple retinotomies were needed as the macula was strongly adherent to the underlying retinal pigment epithelium. Regions with outer retinal folds were explored, and no subretinal fibrotic membrane was identified. Air-fluid exchange was performed to ensure detachment over the whole areas of macular folds. After air removal, the macular folds were lessened but remained rigid in nature. Endolaser was performed to the retinotomies with the aid of heavy liquid. In second air-fluid exchange, 12% C3F8 was injected. The macula remained detached at the end of the operation. Conjunctival wound and the sclerotomies were sutured with 8 'o' vicryl, and the patient was instructed to adopt a face-down position for 2 weeks.

Postoperative recovery was uneventful, with improvement of the macular folds. At 1 month, OCT scans revealed resolution of outer retinal folds, with minimal residual inner retinal undulation (**Figure 1d**). At 2 months, visual acuity improved to 20/50. At 5 months, the patient underwent uneventful cataract operation, and visual acuity improved to 20/20 after 1 week and to 20/15 after 1 year.

Patient 2

In March 2017, a 46-year-old woman underwent right eye phacoemulsification, intraocular lens implantation, macular membrane peeling, and air injection (by CFW) for macular epiretinal membrane. Preoperative OCT scan showed the epiretinal membrane (**Figure 2a**). The baseline visual acuity was 20/40 for the right eye. One day after the operation, she was noted to have hypotony with small choroidal detachment, which resolved spontaneously after a week of conservative treatment. Seven weeks after the operation, OCT scan showed an inner retinal fold involving the fovea with self-bending and apposition to the surrounding retina (**Figure 2b**), and the visual acuity for the right eye was 20/100.

One day later, the patient underwent re-operation (by CFW) using 2-port 23-gauge vitrectomy with illuminated infusion chandelier (Synergetic; O'Fallon [MO], USA). The macular fold was loosened with soft tip cannula by direct manipulation. No intravitreal gas was used. On postoperative day 1, the visual acuity was 20/120 for the right eye, but OCT scan showed much reduced inner macula fold without any inner retinal tissue apposition (**Figure 2c**). Subsequent OCT of the right eye showed the fold gradually improved and then mostly resolved at 20 months (**Figure 2d**), with visual acuity improved to 20/40.

Discussion

Postoperative retinal folds mostly occur after retinal detachment repair.[1] It is a rare complication after pars plana vitrectomy without pre-existing retinal detachment. Patient 1 developed both inner and outer retinal folds, and patient 2 developed inner retinal fold. These configurations of retinal folds after macular epiretinal membrane surgery have not been reported before. Iafe et al[3] reported the first case of outer retinal folds as a complication of epiretinal membrane peeling. The folds resolved spontaneously after 4 months, with improvement in visual acuity. It was hypothesized that the retinal folds could be induced by transient macular detachment during peeling of adherent epiretinal membrane, or secondary to hypotony, which might be mild or transient and was not evident clinically.

In patient 2, hypotony was evidenced by the choroidal detachment. In patient 1, details of previous intra- and post-operative findings were not available. We hypothesized that transient hypotony could be the cause of retinal folds in cases with flat retina, as hypotony can cause retinal folds. Gass[4] first used the term 'hypotony maculopathy' in 1972 to describe undulating macular chorioretinal folds in the presence of low intraocular pressure. Although rare, hypotony (rather than the characteristic undulating chorioretinal folds) can give rise to more severe retinal folds including appositional full thickness retinal folds.[5]

There is no consensus in the management of postoperative macular folds. For full-thickness folds involving fovea, most studies suggest surgical management because of the risk of photoreceptor loss and outer nuclear layer thinning, which may cause permanent vision loss.[6] There can be no improvement in vision even the folds resolve spontaneously.[7,8] Therefore, early/urgent operation should be considered for full-thickness macula folds involving fovea. For partial thickness folds involving fovea, management is

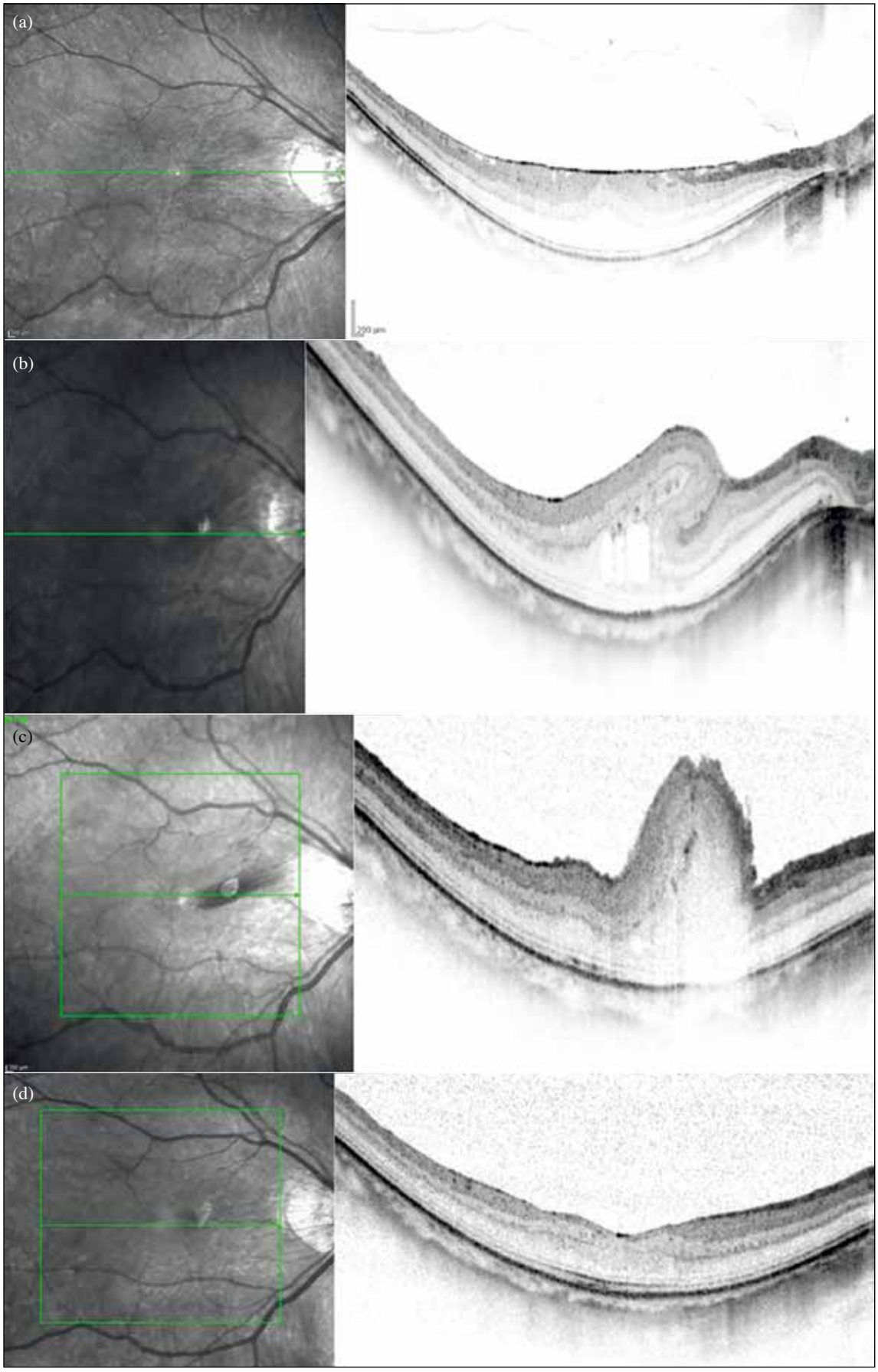


Figure 2. Patient 2: optical coherence tomographic scans showing (a) the epiretinal membrane before the first operation, (b) the inner retinal fold involving fovea at 7 weeks after the first operation, (c) the much reduced inner macula fold without inner retinal tissue apposition at 1 day after re-operation, and (d) the largely resolved macular fold at 20 months after re-operation.

more controversial. In some cases, the folds may resolve spontaneously without any surgical intervention. Three cases of symptomatic partial thickness macula folds after retinal detachment repair were reported to resolve spontaneously, with visual improvement within 2 months.[9] A case of large outer retinal fold was reported to resolve spontaneously, with visual acuity restored to 20/20.[10] Both our patients had partial thickness macular folds involving fovea. The decision of early surgical intervention was made because both patients were highly symptomatic and had severe partial thickness folds with inner retina–to–inner retina apposition.

Different surgical techniques for the management of retinal folds have been reported. All involve induction of macular detachment with injection of intravitreal tamponade agent. Fluid-air exchange is performed to merge submacular blebs after multiple injection of subretinal balanced salt solution in some cases.[10] In patient 1, four retinotomy sites were required to induce a complete macula detachment, as the retina was abnormally adherent than usual. This is likely because there was no prior retinal detachment that might have weakened the adhesion between the retinal pigment epithelium and the retina. In patient 2, no macular detachment was induced, and no intravitreal tamponade was used. Soft-tip cannula was used to relieve the inner retinal attachments. To the best of our knowledge, this is the first reported case using this method to successfully manage a retinal fold. This technique avoids the potential risks associated with retinotomies, macular re-detachment, and intravitreal tamponade.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

References

1. *Gupta RR, Iaboni DSM, Seamone ME, Sarraf D. Inner, outer, and full-thickness retinal folds after rhegmatogenous retinal detachment repair: a review. Surv Ophthalmol 2019;64:135-61.* Crossref
2. *Pavan PR. Retinal fold in macula following intraocular gas. An avoidable complication of retinal detachment surgery. Arch Ophthalmol 1984;102:83-4.* Crossref
3. *Iafe NA, Law S, Sarraf D, Tsui I. Outer retinal folds following pars plana vitrectomy with membrane peel. Retin Cases Brief Rep 2017;11 Suppl 1:S31-S33.* Crossref
4. *Gass JDM. Hypotony maculopathy. In: Bellows JG, editor. Contemporary Ophthalmology: Honouring Sir Stewart Duke-Elder. Baltimore: Williams and Wilkins; 1972: 343-66.*
5. *Williams BK Jr, Chang JS, Flynn HW Jr. Optical coherence tomography imaging of chorioretinal folds associated with hypotony maculopathy following pars plana vitrectomy. Int Med Case Rep J 2015;8:199-203.* Crossref
6. *Hayashi A, Usui S, Kawaguchi K, et al. Retinal changes after retinal translocation surgery with scleral imbrication in dog eyes. Invest Ophthalmol Vis Sci 2000;41:4288-92.*
7. *Ahn SJ, Woo SJ, Ahn J, Park KH. Spontaneous resolution of macular fold following retinal reattachment: morphologic features on SD-OCT. Ophthalmic Surg Lasers Imaging 2011;42:e81-3.* Crossref
8. *Saatci AO, Barut Selver O, Parlak M. Long-term follow-up of the postoperative macular fold following the vitreoretinal surgery with air tamponade. Case Rep Ophthalmol Med 2013;2013:408351.* Crossref
9. *Sheng J, Levinson JD, Reilly G, Patronas M, Lai MM. Imaging characteristics and natural history of macular pseudo-folds mimicking full-thickness postoperative macular folds following retinal detachment repair. Ophthalmic Surg Lasers Imaging Retina 2017;48:488-92.* Crossref
10. *Alhabshan R, Sabbagh O, Patronas M. Resolution of large outer retinal fold following retinal detachment surgery with visual acuity restoration to 20/20: a case report and literature review. J Vitreoretin Dis 2018;2:305-11.* Crossref

CASE REPORT

Immunoglobulin G4-related ophthalmic disease presenting as a steroid-resistant choroidal mass: a case report

Cherie YK Wong[1,2], MRCSEd(Ophth); Moon-ho Leung[3], PhD(HKU), FRCP, FHKCP, FHKAM(Med); Vanissa WS Chow[1,2], FRCSEd(Ophthalmology), FCOphthHK, FHKAM(Ophth); Shaheeda Mohamed[1,2], MPH, MMed, FRCSEd(Ophth), FRCOphth, FCOphthHK, FHKAM(Ophth); NM Lam[1,2], FCOphthHK, FHKAM(Ophth); Hunter KL Yuen[1,2], FRCOphth, FRCSEd, FCOphthHK, FHKAM(Ophth); Carmen KM Chan[1,2], FRCP(Lond), FRCOphth, FRCSEd(Ophth), FCOphthHK, FHKAM(Ophth)

[1]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong*
[2]*Hong Kong Eye Hospital, Hong Kong*
[3]*Department of Medicine, Queen Elizabeth Hospital, Hong Kong*

Correspondence and reprint requests:
Dr Carmen KM Chan, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong. Email: kmcc2001@hotmail.com

Abstract

Immunoglobulin G4-related ophthalmic disease (IgG4-ROD) is a cause for orbital and ocular inflammation. Involvement of the sclera and intraocular tissues is less common, and presentation is mostly unilateral. We hereby describe a probable case of steroid-resistant intraocular IgG4-ROD presenting as a choroidal mass in the left eye, with sequential anterior uveitis and scleritis of the fellow right eye. The diagnostic path was not straightforward and included subconjunctival biopsy, blood tests, magnetic resonance imaging, positron emission tomography–computed tomography, and biopsies in two extra-ocular sites. Disease progression was rapid in the left eye despite high-dose oral steroids, while the inflammation of the fellow eye was controlled with the use of rituximab and second-line immunosuppressants. At the 3-year follow-up, the ocular inflammation was well controlled. The left eye was phthisical, but the right eye maintained a visual acuity of 20/20.

Key words: Choroid diseases; Immunoglobulin G4-related disease; Scleritis; Uveitis

Case presentation

In June 2019, a 27-year-old woman presented to Hong Kong Eye Hospital with a 4-week history of left eye redness and pain. On physical examination, she appeared to have left eye superonasal sectoral scleritis associated with 1+ anterior chamber cells (**Figure 1a**). Dilated fundal examination of the left eye showed a superonasal choroidal mass and posterior vitreous cells. (**Figure 1b**). The right eye was unremarkable. Ultrasound B-scanning showed a choroidal mass with choroidal effusion and mild vitritis in the left eye (**Figure 1c**). Magnetic resonance imaging of the orbits showed an intraocular mass in the left eye and mildly enlarged lacrimal glands bilaterally (**Figure 1d**). Blood tests for complete blood count, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies (classic and perinuclear), rheumatoid factor, syphilis, human immunodeficiency virus were all normal/negative. The erythrocyte sedimentation rate was 49 mm/hr. Chest X-ray showed multiple radiopaque masses up to 2.8 cm in both lungs non-typical of tuberculous infection, and interferon-gamma-releasing assay was negative. A non-infective inflammatory cause was suspected, and the patient was put on a therapeutic trial of oral prednisolone 50 mg daily (1 mg/kg) for 2 weeks. However, the eye symptoms and signs were progressive.

As the response to high-dose oral steroid was poor,

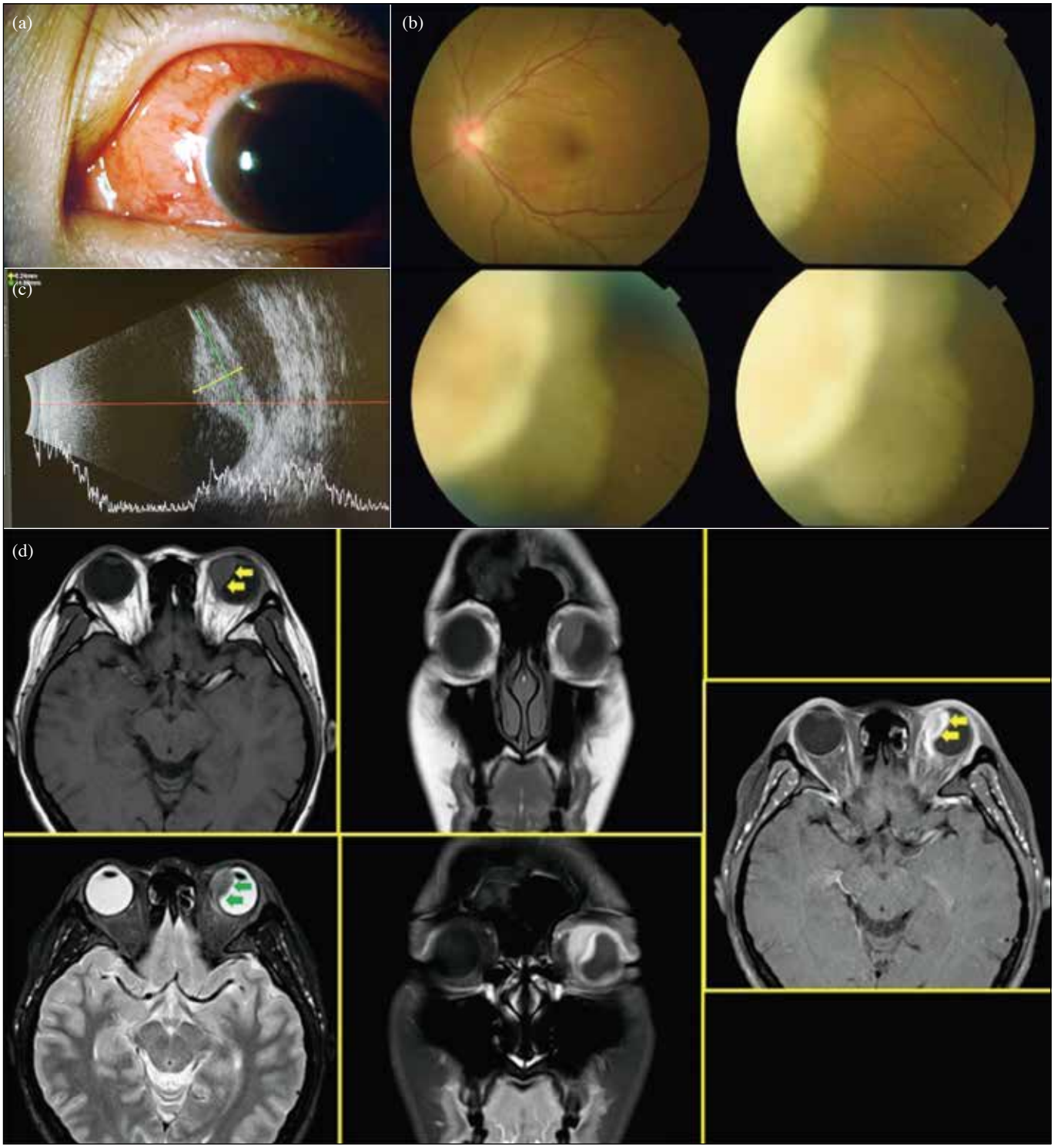


Figure 1. (a) Slit lamp photograph showing left eye sectoral scleritis, (b) dilated fundal examination showing a superonasal choroidal mass, (c) an ultrasound B-scan of the left eye showing a hyperechogenic choroidal mass with choroidal effusion, and (d) a magnetic resonance image of the orbits showing a left intraocular mass and mildly enlarged lacrimal glands bilaterally.

lymphoproliferative/neoplastic causes were suspected. Scleral biopsy (which is less invasive than intraocular biopsy) of the choroidal mass was planned after stopping oral prednisolone for 2 weeks. During the procedure, a subconjunctival (rather than scleral) mass was found and biopsied (**Figure 2a**). The specimen showed vascularized stromal tissue infiltrated by a large number of plasma cells and lymphocytes (**Figure 2b**). Immunostaining showed mixed populations of B (CD20+) and T (CD3+) cells. There were 133 immunoglobulin G4+ (IgG4+) plasma cells per high power field, but the ratio of IgG4+ cells to IgG+ cells was only 20% (**Figure 2c**). Serum IgG4 level (taken

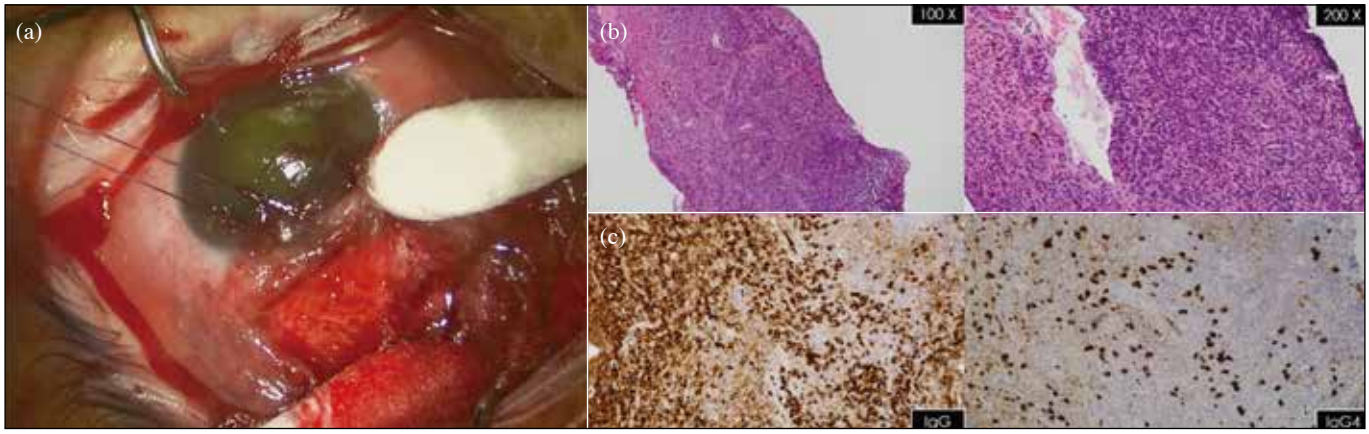


Figure 2. (a) Biopsy of the subconjunctival mass overlying the site of choroidal lesion. (b) Histology showing vascularized stromal tissue infiltrated by a large number of plasma cells and lymphocytes. There is no evidence of granulomas, vasculitis, or malignancy. (c) Immunostaining showing mixed populations of B (CD20+) and T (CD3+) cells. There are 133 IgG4+ plasma cells per high power field that constitute approximately 20% of the IgG+ cells.

after commencement of high-dose steroid) was 1.28 g/L (normal range, <0.86 g/L). These findings were suggestive of IgG4-related ophthalmic disease (IgG4-ROD) but did not completely fulfill the diagnostic criteria. Polymerase chain reaction and acid-fast bacilli culture of the specimen was negative for *Mycobacterium tuberculosis* complex.

Owing to the unusual disease presentation, abnormal chest X-ray findings, and the lack of response to high-dose oral prednisolone, positron emission tomography–computed tomography was performed and showed a hypermetabolic intraocular mass in the left eye (maximum standardized uptake value [SUVmax], 16.5), multiple pulmonary masses (SUVmax of the largest mass, 9.7), and prominent bilateral tonsillar uptake (SUVmax, 9.8 on left side and 10.5 on right side) [**Figure 3**]. Lymphoma was suspected. To delineate the nature and systemic involvement of the disease, bilateral tonsillectomy and tongue base lymphoid biopsy were performed. The specimen showed reactive lymphoid hyperplasia with a small number of IgG4+ plasma cells. Transbronchial biopsy showed no significant pathology. Polymerase chain reaction and acid-fast bacilli culture of the bronchial aspirate was negative for *M tuberculosis* complex.

Open lung biopsy was performed. The specimen showed heavy lymphoplasmacytic infiltrate, fibrosis, and obliterative vasculitis, which were suggestive of IgG4-related disease (IgG4-RD). The left eye intraocular mass continued to progress, filling and expanding the globe and causing proptosis (**Figure 4**).

A provisional diagnosis of IgG4-ROD with systemic involvement was made. The patient was started on intravenous methylprednisolone 1 g/day for 3 days followed by a course of high-dose oral prednisolone 50 mg daily. However, the patient developed anterior uveitis in the fellow right eye. Two doses of rituximab (1 g 2 weeks apart) were given as a steroid-sparing agent to reduce the adverse effects of high-dose steroids and for better disease control. However, the condition of both eyes progressed. The right eye developed scleritis with intraocular extension, whereas the left eye became phthisical with light perception only. In view of the aggressive nature of the eye and systemic conditions, mycophenolate mofetil was added at 8 weeks (up to 1000 mg twice daily) after rituximab therapy, and tacrolimus was also commenced at 12 weeks (up to 1 mg twice daily). The right eye responded well, with resolution of anterior uveitis and scleritis (**Figure 5**). IgG4 level was normalized at 0.59 g/L.

At the 3-year follow-up, the ocular inflammation was well controlled by a maintenance dose of mycophenolate mofetil 250 mg twice daily and tacrolimus 0.5 mg daily with no topical or systemic corticosteroid. The left eye was phthisical, but the right eye maintained a visual acuity of 20/20. The patient had no symptoms or signs of lymphoma or tuberculous infection, and her inflammatory markers were within normal limits.

Discussion

IgG4-RD is a multi-system fibro-inflammatory disease secondary to infiltration of IgG4+ plasma cells in various organs. It can affect the pancreas, hepatobiliary ducts, salivary glands, lungs, etc. Whereas IgG4-ROD refers to IgG4-RD targeting ocular structures including extraocular muscles, orbital soft tissue, cavernous sinus, sclera, choroid, and nasolacrimal system. IgG4-ROD was first reported to be associated with chronic sclerosing dacryoadenitis in 2007. Lacrimal gland is the most common site of ophthalmic involvement. The overall frequency of IgG4-ROD in IgG4-RD is 4% to 34%.[1]

Reports of intraocular IgG4-ROD are less common. Presenting manifestations of intraocular IgG4-ROD include unilateral scleritis, bilateral multifocal choroiditis,

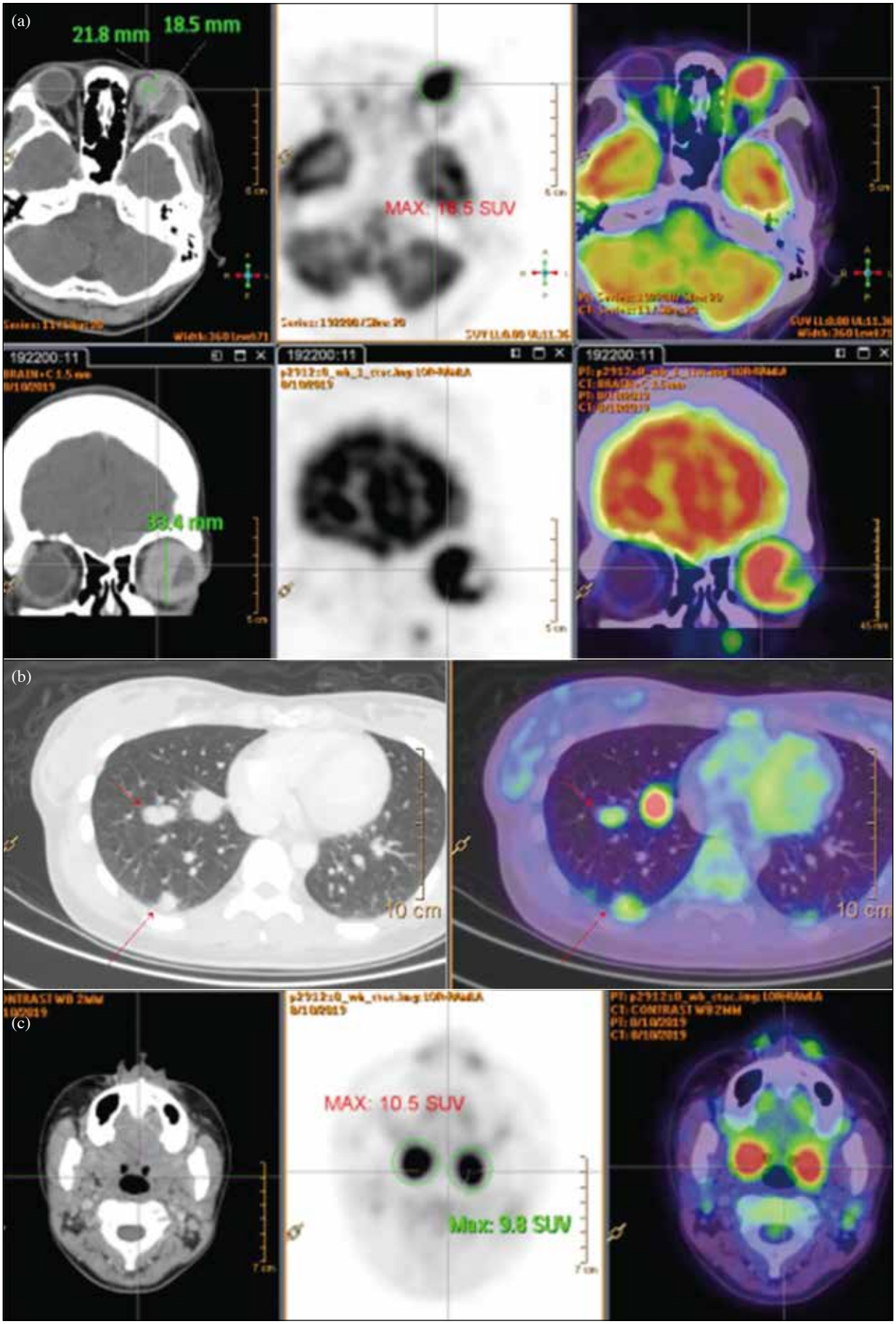


Figure 3. Positron emission tomography–computed tomography showing (a) a hypermetabolic intraocular mass in the left eye, (b) multiple pulmonary masses, and (c) prominent bilateral tonsillar uptake.

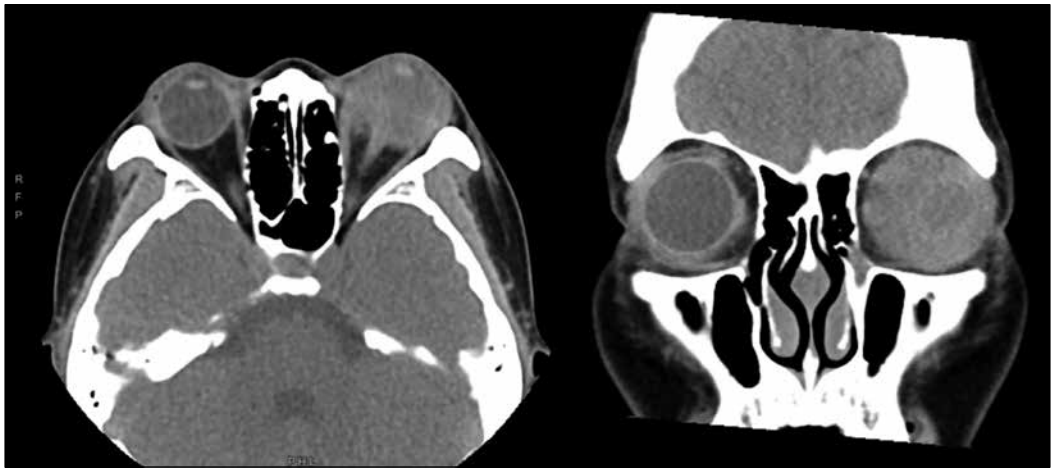


Figure 4. Computed tomography of the orbits showing progressive enlargement of the left eye intraocular mass filling and expanding the globe and causing left eye proptosis.

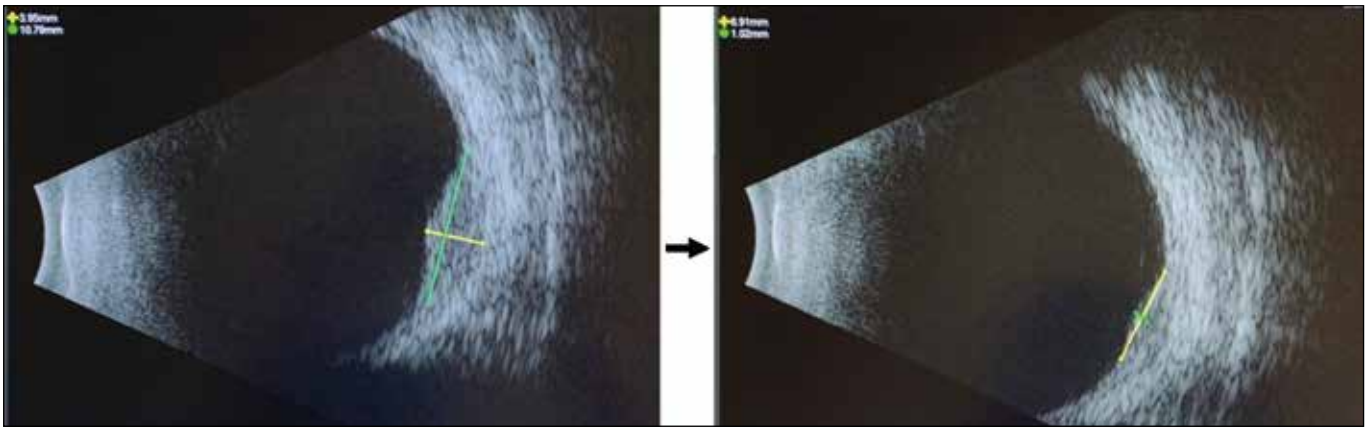


Figure 5. Resolution of the intraocular mass in the fellow right eye after treatment with mycophenolate mofetil and tacrolimus.

choroidal mass, and ciliary body mass.[1] Most reported cases of intraocular involvement were unilateral. There are six reported cases of IgG4-related choroidal mass[2-7] and one reported case of choroidal effusion.[8] Our case is the first case that demonstrates sequential but heterogeneous involvement of the fellow eye, which developed anterior uveitis while on high-dose steroids. With the prompt commencement of rituximab and second-line immunosuppressants, the condition of the fellow eye was brought under control with visual acuity preserved.

As IgG4-ROD can mimic infective, inflammatory, or malignant conditions, thorough workup and systemic examination should be performed. Malignancy such as lymphoma and choroidal melanoma must be ruled out, especially in cases with atypical presentations. Biopsy is the gold standard for diagnosing IgG4-ROD. Histopathological findings include lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, obliterative and non-obliterative phlebitis, and frequent germinal centers.[1] Serum IgG4 level is often elevated but can be normal in 30% to 40% of patients.[5]

Diagnostic criteria for IgG4-ROD comprise radiological, histological, and serological criteria:[9] (1) Imaging studies show enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscle as well as masses, enlargement, or hypertrophic lesions in various ophthalmic tissues. (2) Histopathologic examination shows marked lymphocyte and plasmacyte infiltration and sometimes fibrosis. A geminal center is frequently observed. IgG4+ plasmacytes fulfill the following: (a) the ratio of IgG4+ cells to IgG+ cells being ≥40% or (b) >50 IgG4+ cells per high power field (x400). (3) Blood test shows elevated serum IgG4 of ≥1.35 g/L. Diagnosis is classified as definitive when (1), (2), and (3) are fulfilled, probable when (1) and (2) are fulfilled, and possible when (1) and (3) are fulfilled.

In our patient, histological findings of the subconjunctival mass showed >50 IgG4+ cells per high power field, but the ratio of IgG4+ to IgG+ cells did not reach 40%. Open lung biopsy showed heavy lymphoplasmacytic infiltrate, fibrosis, and obliterative vasculitis, which were suggestive of IgG4-RD. The serum IgG4 level was elevated to 1.28 g/L but did not reach the diagnostic criteria of ≥1.35 g/L.

Both the histology and serum IgG4 level could have been affected by prior high-dose steroid treatment. Therefore, the condition was treated as a probable IgG4-ROD. The main differential diagnoses include multicentric Castleman's disease, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and sarcoidosis, but all these were not supported by the histological and serological findings.

Corticosteroids are the mainstay of treatment for IgG4-ROD. Initial treatment response to oral prednisolone is good, but a limited window of steroid efficiency is suggested, and relapses are common. Suggested dosage is approximately 0.6 to 1 mg/kg/day, with long tapering and maintenance dose between 2.5 and 10 mg/day of prednisolone to prevent relapse and involvement of other organs.[10] Second-line treatment options include immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, and biologics such as infliximab and rituximab.[11,12] Rituximab, in particular, is effective as second or third-line treatment, with high rates of remission in both IgG4-RD and IgG4-ROD.[1] The optimal frequency or duration of rituximab is not known; initial treatment with two doses of rituximab separated by 15 days is suggested.[13] In our patient, mycophenolate and tacrolimus were chosen over azathioprine and methotrexate for their faster onset of action.

In our case, the diagnostic path was not straightforward and required supportive evidence from biopsies in two extra-ocular sites (lung and tonsil). Disease progression in the left eye was rapid despite high-dose oral steroid. Although malignant lymphoma was a differential diagnosis and IgG4-RD is associated with an increased risk of lymphoma,[14] the patient did not have any B symptoms (fever, night sweats, and loss of >10% of body weight over 6 months) and the diagnosis of lymphoma was not supported by histological findings. The involvement of the fellow right eye was treated promptly with rituximab and second-line immunosuppressants, which led to resolution of scleritis and choroidal mass. At the 3-year follow-up, the ocular inflammation was well controlled by a maintenance dose of low-dose mycophenolate mofetil and tacrolimus. The patient achieved disease remission in the right eye with preserved visual acuity and had no signs or symptoms of ocular or systemic lymphoma or tuberculous infection, but the left eye was phthisical.

Conclusion

IgG4-ROD is a cause for intraocular, scleral or orbital inflammation. Biopsy is the gold standard for diagnosis. Malignancy and systemic involvement should be ruled out, particularly in patients with atypical presentation and disease course. Prompt diagnosis and treatment with systemic steroids lead to better outcomes.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all invasive procedures according to prevailing clinical guidelines, and for publication.

Acknowledgement

The authors would like to thank Dr David Liu and Dr Alex Wong for providing supplementary clinical images, and Dr Wah Cheuk for his help with histology.

References

1. *Derzko-Dzulynsky L. IgG4-related disease in the eye and ocular adnexa. Curr Opin Ophthalmol 2017;28:617-22.* Crossref
2. *Ohno K, Sato Y, Ohshima K, et al. IgG4-related disease involving the sclera. Mod Rheumatol 2014;24:195-8.* Crossref
3. *Goto H, Ueda S. Immunoglobulin G4-related ophthalmic disease involving the sclera misdiagnosed as intraocular tumor: report of one case. Ocul Oncol Pathol 2016;2:285-8.* Crossref
4. *Reynolds GL, Norris JH, Aslam S, Sharma S. IgG4-related disease presenting as posterior scleritis and vitritis, progressing to multifocal orbital involvement. BMJ Case Rep 2017;2017:bcr2017219568.* Crossref
5. *Gange WS, Holland SM, De Alba F. IgG4-related ophthalmic disease presenting as choroidal and orbital lesions. Retin Cases Brief Rep 2019;13:283-6.* Crossref

6. *Aragona E, Miserocchi E, Arrigo A, et al. Immunoglobulin G4-related ophthalmic disease mimicking intraocular lymphoma: a case report. Retin Cases Brief Rep 2022;16:32-5.* Crossref
7. *Attiku Y, Rishi P, Biswas J, Krishnakumar S. Intraocular IgG4 disease masquerading as nodular scleritis. Indian J Ophthalmol 2020;68:1935-6.* Crossref
8. *Koenigstein D, Neudorfer M, Goldenberg D, Habot-Wilner Z. Choroidal effusion as an ocular manifestation of immunoglobulin G4-related disease. Retin Cases Brief Rep 2016;10:197-200.* Crossref
9. *Goto H, Takahira M, Azumi A; Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol 2015;59:1-7.* Crossref
10. *Philippakis E, Cassoux N, Charlotte F, et al. IgG4-related disease masquerading as recurrent scleritis and chronic conjunctivitis. Ocul Immunol Inflamm 2015;23:168-72.* Crossref
11. *Löhr JM, Beuers U, Vujasinovic M, et al. European Guideline on IgG4-related digestive disease: UEG and SGF evidence-based recommendations. United European Gastroenterol J 2020;8:637-66.* Crossref
12. *Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol 2015;67:1688-99.* Crossref
13. *Wallace ZS, Mattoo H, Mahajan VS, et al. Predictors of disease relapse in IgG4-related disease following rituximab. Rheumatology (Oxford) 2016;55:1000-8.* Crossref
14. *Yu T, Wu Y, Liu J, Zhuang Y, Jin X, Wang L. The risk of malignancy in patients with IgG4-related disease: a systematic review and meta-analysis. Arthritis Res Ther 2022;24:14.* Crossref

CASE REPORT

Dacryocystosclerotherapy with doxycycline injection for chronic dacryocystitis: a case report

Kenneth KH Lai[1], *AFCOphth; Yuen Ting Kwok*[2], *FHKAM (Ophthalmology); Hunter KL Yuen*[2,3] *FRCSEd, FRCOph*
[1]*Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong*
[2]*Hong Kong Eye Hospital, Hong Kong*
[3]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong*

Correspondence and reprint requests:
Dr Hunter KL Yuen, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong. Email: yuenkl1@ha.org.hk

Abstract

We report a case of chronic dacryocystitis treated with dacryocystosclerotherapy with doxycycline injection in an 89-year-old woman. At the 12-month follow-up, the dacryocystitis was resolved, and there was a residual sac cavity with a trace amount of mucoid discharge without requiring further treatment.

Key words: Dacryocystitis; Doxycycline

Introduction

Dacryocystitis is inflammation of the lacrimal sac that typically occurs in patients with nasolacrimal duct obstruction (NLDO).[1] Prompt treatment is required as dacryocystitis can lead to life-threatening conditions such as orbital cellulitis, meningitis, and cavernous sinus thrombosis.[2] Dacryocystorhinostomy (DCR) is indicated in patients with dacryocystitis secondary to NLDO.[3]

Sclerotherapy is a non-surgical procedure that injects sclerosants into the lesions. Good outcomes have been reported for orbital lesions such as vascular or lymphatic malformation. Dacryocystosclerotherapy (DCST) is a less invasive alternative to DCR for primary acquired NLDO.[4] Sclerosants that have been reported in DCST include ethanolamine oleate, sodium tetradecyl sulphate, and bleomycin.[4,5] We report a case of chronic dacryocystitis secondary to NLDO treated with DCST with doxycycline injection.

Case presentation

In October 2020, an 89-year-old Chinese woman presented to Hong Kong Eye Hospital with a 1-month history of increasing right eye discharge and lower eyelid swelling. She has been regularly followed up at our clinic for right eye NLDO and advanced primary open-angle glaucoma. The patient had undergone transcatheter aortic valve replacement for severe aortic stenosis 6 years earlier. She was recently diagnosed with breast cancer and has been receiving hormonal therapy. Given multiple comorbidities and a high risk for anesthesia, the patient did not undergo surgical intervention for NLDO.

Physical examination revealed mucoid discharge regurgitated from both the upper and lower punctum of the right eye, with early signs of dacryocystitis including tenderness, swelling, and skin induration. There was no proptosis, and the ocular motility was normal in both eyes. The microbiological culture of the discharge yielded heavy growth of *Escherichia coli*, which was sensitive to amikacin, ceftazidime, trimethoprim-sulfamethoxazole, and meropenem. She underwent canalicular irrigation with benzylpenicillin (100 000 U/mL) and expression of lacrimal sac secretion. One week later, she was prescribed 1% amikacin eyedrop four times per day for 8 weeks.

Three months later, the right dacryocystitis persisted despite biweekly canalicular antibiotics irrigation. Given the patient's high risk for anesthesia, DCST was performed as

Figure. Doxycycline is injected slowly around the right swollen lacrimal sac.

an alternative to dacryocystectomy and DCR. Under local anesthesia, the patient underwent lacrimal sac tapping and doxycycline injection using a three-way stop-clock system with two 3 mL syringes and one 16-gauge butterfly needle. 10 mg of doxycycline was diluted in 10 mL of normal saline. Minimal content was yielded upon lacrimal sac tapping, and 2 mL of doxycycline was injected slowly around the right swollen lacrimal sac (**Figure**). The patient complained of tolerable pain during the perilesional injection. The patient was then prescribed 1 week of oral Augmentin. At the 6-week follow-up, the dacryocystitis improved gradually with mild mucoid discharge. Second DCST was performed without lacrimal sac tapping, and local anesthesia was not required. At the 12-month follow-up, the dacryocystitis was resolved, and there was a residual sac cavity with a trace amount of mucoid discharge without requiring further treatment.

Discussion

Dacryocystitis is inflammation of the lacrimal sac; its symptoms include reddening, swelling, and severe tenderness overlying the nasolacrimal sac. Without prompt treatment, patients can develop orbital cellulitis, cavernous sinus thrombosis, and endophthalmitis (in those with intraocular surgery). Systemic antibiotic is the first-line treatment for acute dacryocystitis. Refractory cases require lacrimal sac massage, lacrimal irrigation, and surgery.[6] DCR is indicated in patients with dacryocystitis secondary to NLDO by connecting the lacrimal sac to the nasal cavity. Both external and endoscopic approaches to DCR have a high success rate.[3] Nonetheless, patients with multiple comorbidities may not be able to tolerate surgical intervention owing to the high risk for anesthesia. Our patient with a high risk for anesthesia opted to avoid surgical intervention. We, therefore, performed DCST with doxycycline injection as the less invasive alternative to DCR or dacryocystectomy.

Sclerotherapy is the first-line treatment in most vascular and lymphatic malformation lesions, particularly for non-distensible lesions with low blood flow and thus with increased reaction time for sclerosants.[7] The common pathway of sclerosants is to irritate and destroy the endothelial surfaces, which leads to vascular thrombosis and intimal fibrosis.[8] A good balance between efficacy and toxicity of the sclerosants is critical; sclerosants may cause tissue injuries if extravasation occurs, particularly in slow-flow lesions.[9] Ethanolamine oleate is the most potent sclerosant, but histological analysis of its structure effect was not available.[4] Both sodium tetradecyl sulphate and bleomycin are safe and effective in DCST and are able to preserve the histopathological data for subsequent analysis.[5]

DCST was first reported in 2001 in nine patients with primary NLDO or previous incomplete dacryocystectomy using ethanolamine oleate.[4] Three of the nine patients had a recurrence of dacryocystitis, and two of them underwent a second DCST with good outcomes. In 10 patients with primary NLDO treated with sodium tetradecyl sulphate or bleomycin, two patients treated with bleomycin required additional DCST, whereas one patient treated with sodium tetradecyl sulphate had persistent moderate inflammation and required low-dose oral steroid.[5] All 10 patients underwent dacryocystectomy 4 weeks after DCST; histopathological analysis suggested that sodium tetradecyl sulphate was a better sclerosing agent than bleomycin, with a more prominent effect on the sac wall vessels and intra-sac wall hemorrhages.

Our patient underwent repeat DCST at the 6-week follow-up and achieved good outcomes at the 12-month follow-up. Minimal content was yielded from the lacrimal sac tapping, and the sclerosant was injected perilesionally. The exact mechanism of sclerosing action of doxycycline is unclear, and both the inhibition of matrix metalloproteinase and suppression of vascular endothelial growth factors may cause collagen and fibrin deposition and result in dense adhesion and fibrosis.[7,10] We postulate that the perilesional injection may diffuse doxycycline into the lacrimal sac cavity and result in inflammation with secondary fibrosis and adhesions, which leads to shrinkage of the lacrimal sac. Interstitial sclerotherapy has been reported to be effective in treating vascular malformation lesions.[11,12] Further investigation of the histological changes and the sclerosing mechanism is warranted.

Doxycycline is effective in treating lymphatic malformation, but its role in treating dacryocystitis as a sclerosant is unknown. To the best of our knowledge, our patient is the first reported case of DCST with doxycycline injection. Doxycycline has an additional antimicrobial effect for lesions caused by infections. Doxycycline is an antibiotic in the tetracycline group that inhibits bacterial protein synthesis by binding to the 30S ribosome subunit.[13] Sodium tetradecyl sulphate and ethanolamine oleate can cause skin hyperpigmentation and necrosis.[7,13] Doxycycline has minimal local and systemic complications.[14] Although bleomycin is routinely prepared by trained pharmacists, its availability may be limited in hospitals without an oncology department. Whereas doxycycline is easily prepared and

widely available in many ophthalmic centers of Hong Kong.[14] DCST with doxycycline injection is a less invasive alternative to surgical intervention in patients at high risk for anesthesia.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures and for publication.

References

1. *Mills DM, Bodman MG, Meyer DR, Morton AD 3rd; ASOPRS Dacryocystitis Study Group. The microbiologic spectrum of dacryocystitis: a national study of acute versus chronic infection. Ophthalmic Plast Reconstr Surg 2007;23:302-6.* Crossref
2. *Mauriello JA Jr, Wasserman BA. Acute dacryocystitis: an unusual cause of life-threatening orbital intraconal abscess with frozen globe. Ophthal Plast Reconstr Surg 1996;12:294-5.* Crossref
3. *Sobel RK, Aakalu VK, Wladis EJ, Bilyk JR, Yen MT, Mawn LA. A comparison of endonasal dacryocystorhinostomy and external dacryocystorhinostomy: a report by the American Academy of Ophthalmology. Ophthalmology 2019;126:1580-5.* Crossref
4. *Vasilakis M, Brouzas D, Charakidas A, Koukoulomatis P, Chatzoulis D. Dacryocystosclerotherapy. Ophthalmic Plast Reconstr Surg 2001;17:111-4.* Crossref
5. *Ali MJ, Dave TV, Mishra DK, Naik MN. Dacryocystosclerotherapy as an alternative to dacryocystectomy. Orbit 2019;38:300-4.* Crossref
6. *Pinar-Sueiro S, Sota M, Lerchundi TX, et al. Dacryocystitis: systematic approach to diagnosis and therapy. Curr Infect Dis Rep 2012.* Crossref
7. *Horbach SE, Lokhorst MM, Saeed P, de Goüyon Matignon de Pontouraude CM, Rothová A, van der Horst CM. Sclerotherapy for low-flow vascular malformations of the head and neck: a systematic review of sclerosing agents. J Plast Reconstr Aesthet Surg 2016;69:295-304.* Crossref
8. *Jacobson BF, Franz RC, Hurly EM, et al. Mechanism of thrombosis caused by sclerotherapy of esophageal varices using sodium tetradecyl sulphate. Surg Endosc 1992;6:4-9.* Crossref
9. *Duffy DM. Sclerosants: a comparative review. Dermatol Surg 2010;36 Suppl 2:1010-25.* Crossref
10. *Mann MW. Sclerotherapy: it is back and better. Clin Plast Surg 2011;38:475-87.* Crossref
11. *Jin Y, Zou Y, Hua C, et al. Treatment of early-stage extracranial arteriovenous malformations with intralesional interstitial bleomycin injection: a pilot study. Radiology 2018;287:194-204.* Crossref
12. *Mack JM, Peterson EC, Crary SE, et al. Pharmacokinetics of bleomycin sclerotherapy in patients with vascular malformations. Pediatr Blood Cancer 2022;69:e29733.* Crossref
13. *Lam SC, Yuen HKL. Medical and sclerosing agents in the treatment of orbital lymphatic malformations: what's new? Curr Opin Ophthalmol 2019;30:380-5.* Crossref
14. *Cheng J. Doxycycline sclerotherapy in children with head and neck lymphatic malformations. J Pediatr Surg 2015;50:2143-6.* Crossref

CASE REPORT

Multimodal imaging features of choroidal metastasis of non-small-cell lung cancer: a case report

Simon KH Szeto[1,2], FCOph(HK); Shaheeda Mohamed[1,2], FCOph(HK); Chi Wai Tsang[1,2], FCOph(HK); Timothy YY Lai[1], FRCOph; Vivian WK Hui[1,2], MBChB; Carmen KM Chan[1,2], FCROph(HK)

[1]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR*

[2]*Hong Kong Eye Hospital, Hong Kong SAR*

Correspondence and reprint requests:

Dr Simon KH Szeto, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong SAR. Email: citokaho@gmail.com

Abstract

We describe multimodal imaging features of right eye choroidal metastasis of non-small-cell lung cancer in a 25-year-old woman. This case report highlights the importance of multimodal imaging and liquid biopsy in making the diagnosis of choroidal metastasis. Spectral domain optical coherence tomography showed a dome-shaped choroidal elevation with subretinal fluid and subretinal hyper-reflective foci. Fundus autofluorescence showed hyper-autofluorescence with alternating spots of hypo-autofluorescence. Fluorescein angiography showed hypofluorescence followed by diffuse and pin-point leakage. Indocyanine green angiography showed a hypofluorescence lesion. The patient was initially misdiagnosed as having choroiditis and treated with oral corticosteroid. However, the exudative retinal detachment progressed and optic disc edema developed. The working diagnosis was thus shifted towards choroidal neoplasm. Positron emission tomography and lung biopsy confirmed the diagnosis of metastatic non-small-cell lung cancer. Blood-based comprehensive genomic profiling detected a rare epidermal growth factor receptor mutation. Target therapy with osimertinib achieved good oncological response. Vision improved to 6/7.5, and the choroidal lesion and subretinal fluid regressed. At 1-year follow-up, the patient had no systemic or ocular relapse.

Key words: Carcinoma, non-small-cell lung; Choroid neoplasms; Fluorescein angiography; Liquid biopsy; Tomography, optical coherence

Introduction

Choroidal metastasis (CM) is the most common intraocular neoplasm, with breast cancer, followed by lung cancer, being the most common primary tumor.[1-3] The diagnosis of CM may precede the diagnosis of primary cancer in as much as 56% to 64% of patients.[1-3] Symptomatic CM is estimated to occur in 1.4% of all metastatic lung cancers.[3] Symptoms of CM include blurring of vision, flashes, and floaters. Most CM are associated with exudative retinal detachment and present as a unilateral solitary creamy yellow-white subretinal mass with a plateau or dome-shaped configuration in the post-equatorial region.[1,3] Nonetheless, diagnosing CM remains a challenge for ophthalmologists, particularly in young patients without known primary tumor, as the primary tumor can only be detected in roughly 50% of cases and the mean patient age at diagnosis is 62 years.[1] Differential diagnosis of a solitary yellow-white choroidal mass in a young patient includes primary benign or malignant choroidal neoplasms (choroidal osteoma, hemangioma, and amelanotic melanoma), inflammatory choroidal lesions (choroiditis and choroidal granuloma), and infective choroidal lesions (tuberculous choroidal granuloma). In the past, the diagnosis of CM can only be confirmed at the time of autopsy or enucleation.[4]

Multimodal retinal imaging may assist clinicians in making a prompt diagnosis.[4,5] In autofluorescence, lipofuscin deposits in CM show hyper-autofluorescence, which can be used to delineate tumor surface characteristics and progression of tumor margin. In fluorescein angiography, CM exhibits hypofluorescence in early phase and hyperfluorescence in late venous phase; these features may help differentiate CM from choroidal melanoma. In optical coherence tomography (OCT), CM may reveal choroidal elevation, serous retinal

detachment, optical shadowing, thickened retinal pigment epithelium (RPE)–choriocapillaris complex, and subretinal highly reflective dots.[4,6] In magnetic resonance imaging (MRI), CM may show a well-demarcated mass isointense on T1-weighted images and hypointense on T2-weighted images.[5]

We present a case of right eye CM of non-small-cell lung cancer in a 25-year-old woman and describe serial clinical and multimodal imaging features of CM in making the diagnosis and during anti-epidermal growth factor receptor (EGFR) therapy.

Case presentation

In April 2021, a 25-year-old woman presented to Hong Kong Eye Hospital with a 4-day history of subacute loss of central vision in her right eye. On examination, the visual acuity was 20/40 for the right eye and 20/25 for the left eye. Dilated fundal examination of the right eye revealed a solitary, six-disc-diameter, confluent, peripapillary, creamy, yellow-white, plateau-shaped, choroidal lesion, with serous macular detachment involving the fovea. The optic disc was pink with no swelling. There was also an incidental finding of myelinated nerve fiber layer along the superotemporal vascular arcade (**Figure 1a**). Nonetheless, the vitreous was clear with no signs of vitritis or vitreous hemorrhage, and there was no retinal hemorrhage. The retina of the left eye was normal. Bilaterally, the anterior segment was unremarkable with no signs of intraocular inflammation, and the intraocular pressure was normal.

Ultrasound B-scanning of the right eye showed a shallow, plateau-shaped, hyperechoic, choroidal mass, with no acoustic shadowing. Spectral domain OCT of the right eye showed a peripapillary dome-shaped choroidal elevation with low internal reflectivity. The mass was associated with serous retinal detachment affecting the macula. Subretinal hyper-reflective dots overlying the choroidal mass were observed, as were thickened RPE layers that were more hyper-reflective than adjacent RPE with optical shadowing and the compressed choriocapillaris (**Figure 2a**). On fundus autofluorescence, the choroidal mass appeared as hyper-autofluorescence with speckles of alternating hypo-autofluorescence (**Figure 3a**). On fluorescein angiography, early hypo-fluorescence was observed, followed by diffuse and pinpoint dye leakage (**Figure 3b**). On indocyanine green angiography, the outline of the choroidal mass was delineated by blocked fluorescence (**Figure 3c**).

In view of a symptomatic creamy-yellowish choroidal lesion in a young woman with good past health, differential diagnoses of choroiditis, choroidal granuloma, and CM were considered. Hematological investigations excluded infective cause, and autoimmune serological panel was negative. Oral corticosteroid was given as a therapeutic trial before systemic investigation results were available. After a week of oral prednisolone of 1 mg/kg daily, worsening serous macular detachment was observed. There was a new onset of right optic disc swelling (**Figure 1b**) and optic nerve head swelling (**Figure 2b**). Therefore, the working diagnosis was shifted towards choroidal neoplasm. On further history taking, patient reported that she had a recent onset of lower back pain and right knee pain. The right eye vision remained stable at 20/50.

Blood test showed elevated alkaline phosphatase level to 263 IU/L (reference range, 34-97 IU/L). A normal gamma glutamyl transferase and alkaline phosphatase heat stability test confirmed that the elevated alkaline phosphatase level was of bone origin. Complete blood count, syphilis serology, and autoimmune markers were normal. MRI of the orbit and brain revealed an enhancing soft-tissue thickening in the posterior aspect of the right globe mildly hyperintense on T1-weighted image and hypointense on T2-weighted image (**Figure 4a**). Multiple enhancing lesions were found

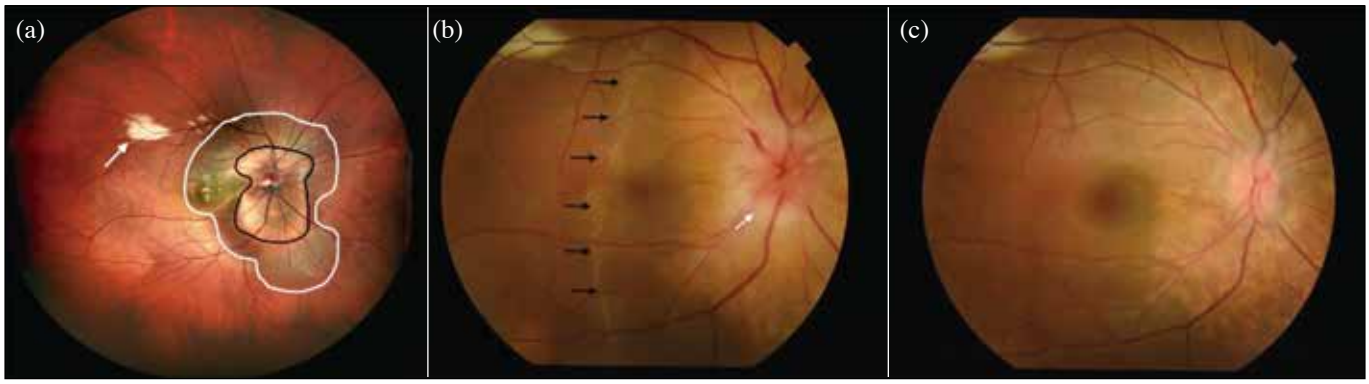


Figure 1. (a) Ultra-wide field pseudo color fundus photograph on presentation showing a peripapillary yellowish creamy choroidal mass (black outline) and surrounding exudative retinal detachment (white outline) and an incidental finding of myelinated nerve fiber layer (arrow). (b) Color fundus photograph after a week of oral prednisolone showing a new onset optic disc swelling (white arrow) and the border of serous macular detachment (black arrows). (c) Color fundus photograph after 3 months of target therapy with osimertinib showing resolution of the choroidal mass into an atrophic chorioretinal scar and leopard spot–like appearance of the retinal pigment epithelium.

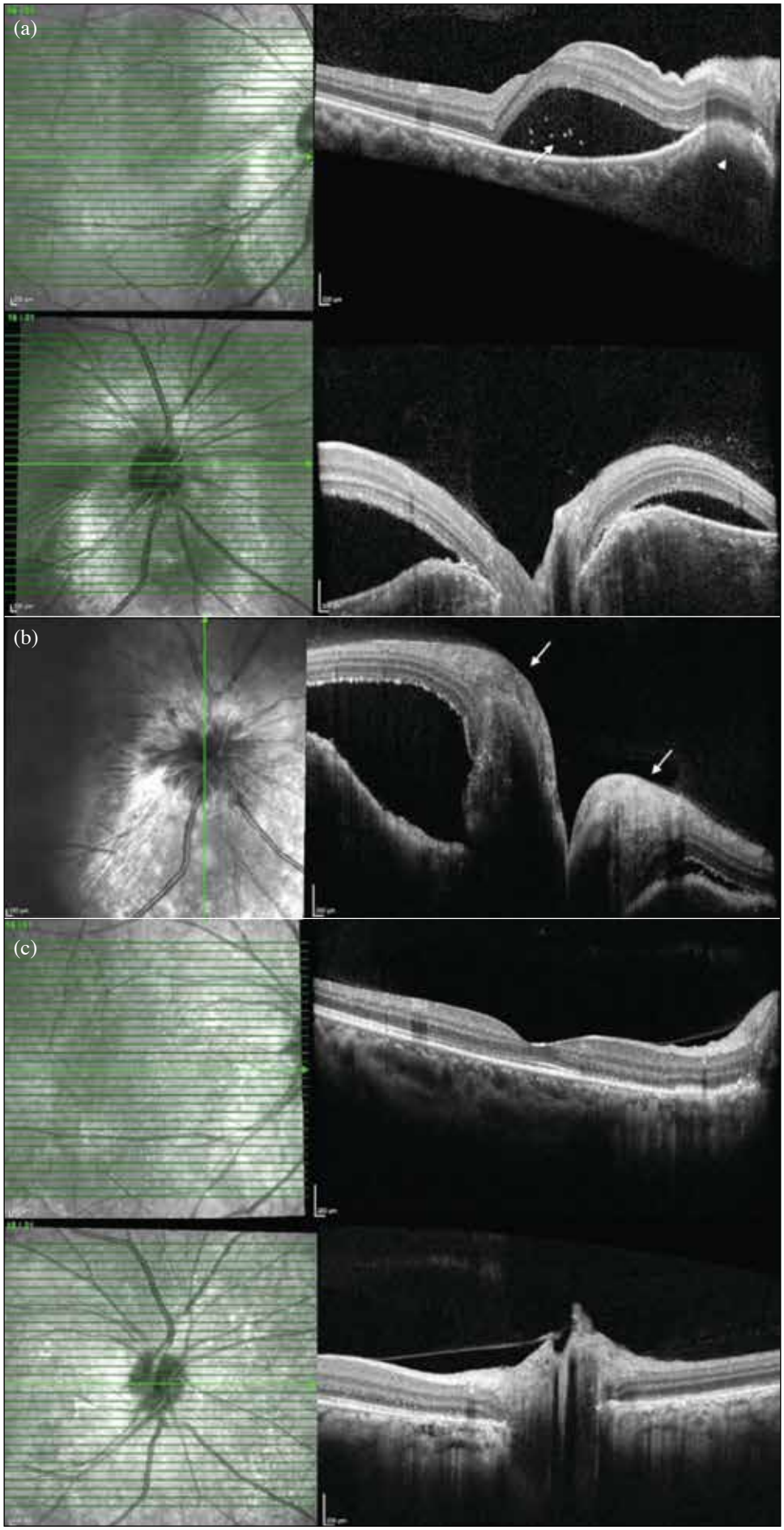


Figure 2. Spectral domain optical coherence tomography showing (a) subretinal hyper-reflective dots within the subretinal space (arrow), choroidal elevation with optical shadowing (arrowhead), and no optic nerve head swelling despite peripapillary serous retinal detachment on presentation, (b) swelling and protrusion of the optic nerve head and juxta-papillary retinal tissue (arrows) after a week of oral prednisolone, and (c) complete resolution of choroidal elevation, subretinal fluid, subretinal hyper-reflective foci, and optic nerve head swelling after 3 months of target therapy with osimertinib.

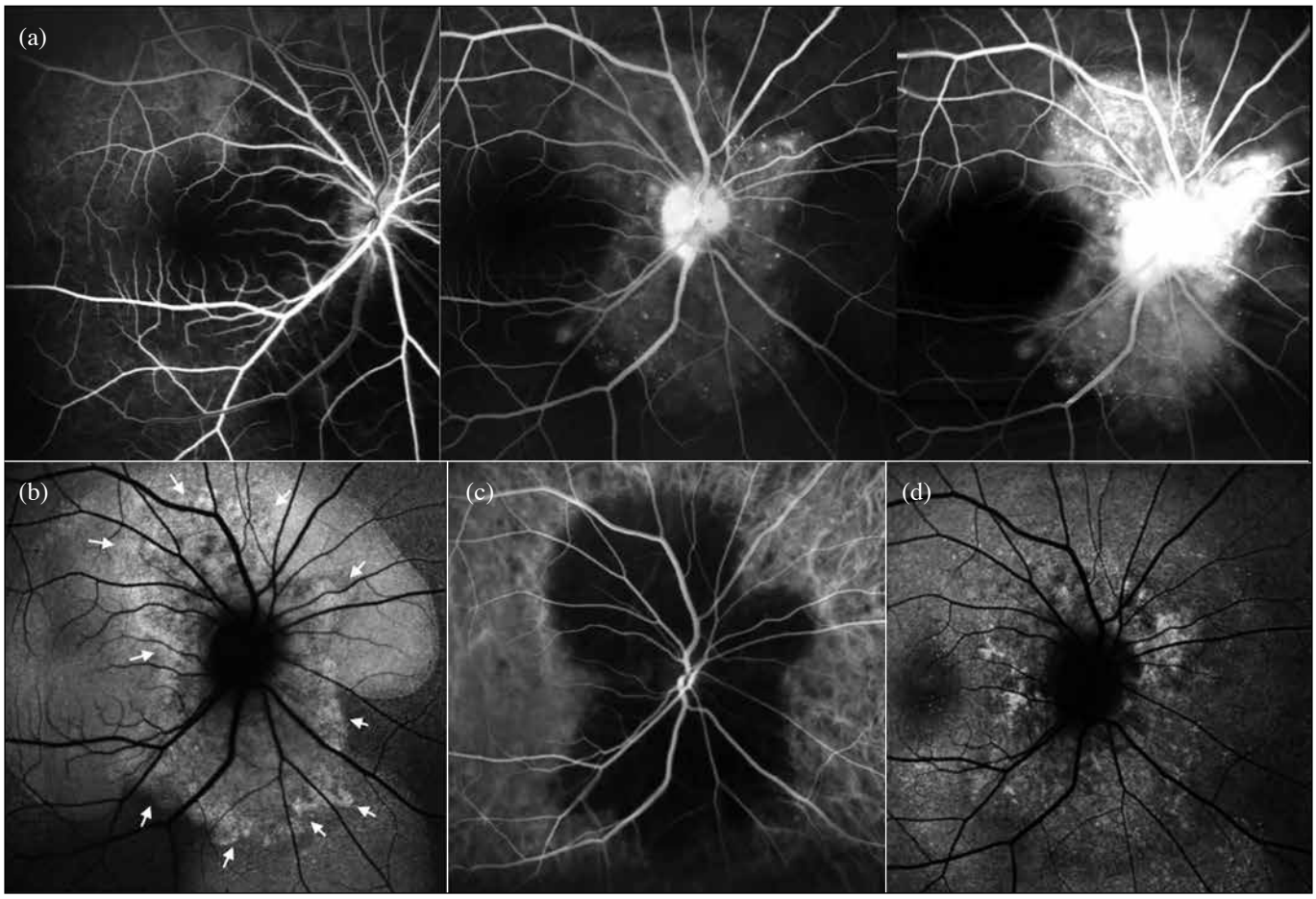


Figure 3. (a) Fluorescein angiography on presentation showing hypofluorescence in early phase followed by progressive diffuse and pinpoint leakage in late phase. (b) Fundus autofluorescence on presentation showing hyper-autofluoresence delineating the margin of a choroidal mass (white arrows) and speckles of hypo-autofluorescence within the choroidal mass. (c) Indocyanine green angiography on presentation showing the outline of the choroidal mass delineated by blocked fluorescence. (d) Fundus autofluorescence after 3 months of target therapy with osimertinib showing resolution of the hyper-autofluorescence that delineated the choroidal mass.

in the left frontal lobe and cerebellar hemisphere. MRI of the lumbar spine showed pathological collapse of the L3 vertebra body. The most likely diagnosis was malignancy with multiple metastases to the right eye choroid, bone, and brain. Positron emission tomography showed multiple hypermetabolic pulmonary and mediastinal lymph nodes, and metastatic lesions in the liver, lumbar spine, and the right femur medial epicondyle (**Figure 4b**). The right eye choroidal lesion showed minimal thickening with only minimal activity. Positron emission tomography findings were suggestive of primary lung malignancy at the right lower lobe, with multiple intrapulmonary and mediastinal lymph nodes and liver and bone metastases.

The patient was referred to an oncologist for management. Computed tomography–guided biopsy of the right lower lobe lung nodule confirmed the diagnosis of metastatic pulmonary adenocarcinoma. Initial histopathology failed to identify specific driver mutation amenable for target therapy. Blood-based comprehensive genomic profiling detected rare EGFR mutation. Target therapy with osimertinib, a tyrosine kinase inhibitor, was initiated. Palliative radiotherapy was applied to the right knee for pain control.

Three months after initiation of target therapy, a good response was achieved ophthalmologically and systemically. Her right eye vision improved from 20/40 to 20/25. The right eye CM regressed to an atrophic chorioretinal scar, with resolution of disc swelling and serous macular detachment as well as resolution of subretinal fluid (SRF) and subretinal hyper-reflective dots (**Figure 1c**). The thickened RPE-choriocapillaris complex and choroidal elevation resolved, with improved visualization of the underlying choroid (**Figure 2c**). Fundus autofluorescence showed resolution of the hyper-autofluorescence that delineated the choroidal mass (**Figure 3d**). Repeat positron emission tomography–computed tomography showed resolution of intrapulmonary metastatic lung nodules, mediastinal lymph nodes, and liver and bone metastases. The primary right lung lower lobe lesion showed a significant decrease in size and metabolism, consistent with good response to treatment. At the 1-year follow-up, there was no relapse of the malignancy locally and systemically.

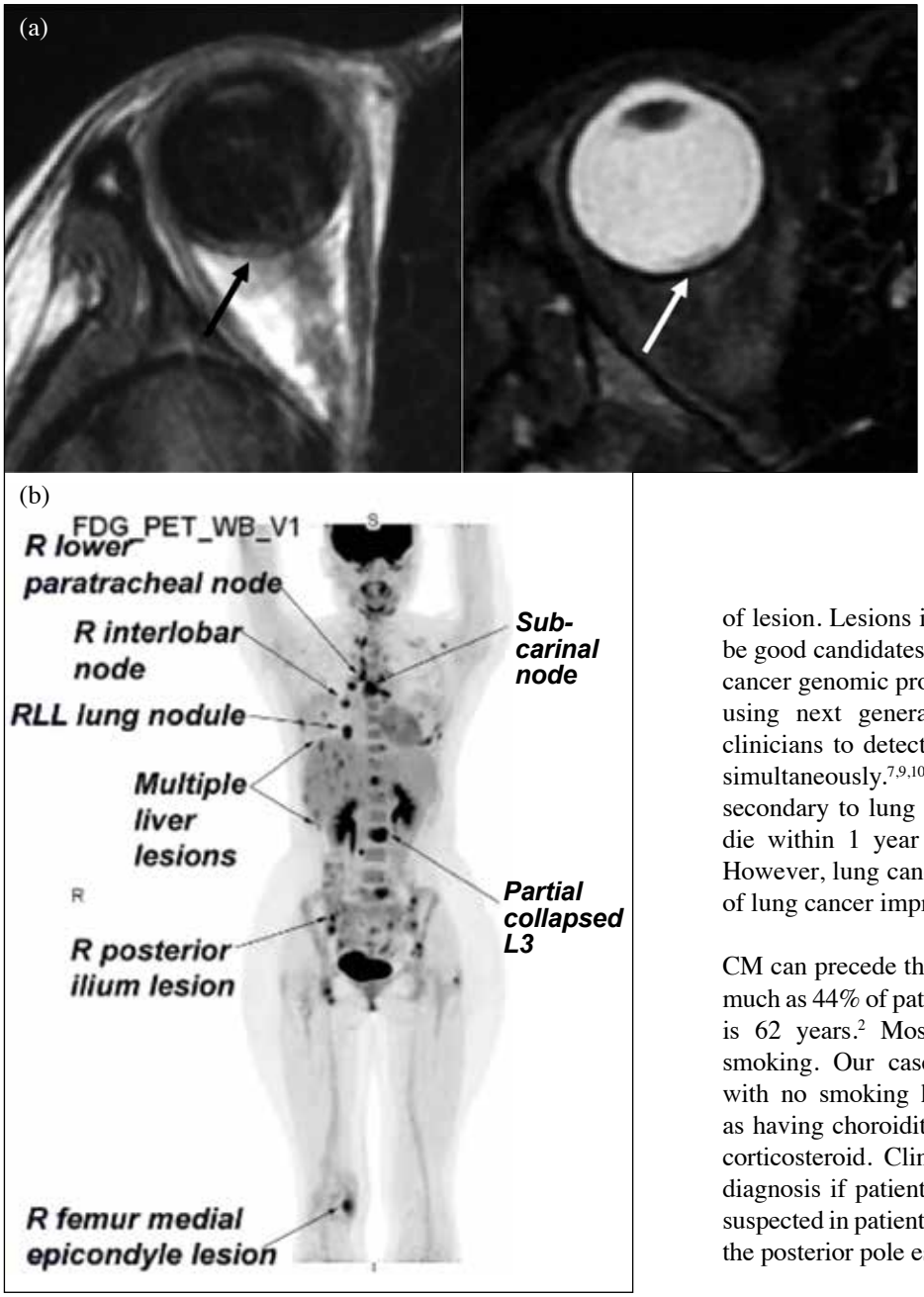


Figure 4. (a) Magnetic resonance imaging of the orbit on presentation showing a peripapillary choroidal mass hyperintense on T1-weighted image (black arrow) and hypointense on T2-weighted image (white arrow). (b) Positron emission tomography on presentation showing multiple hypermetabolic pulmonary nodules, mediastinal lymph nodes, and metastatic lesions in the liver, lumbar spine, and the right femur medial epicondyle.

Discussion

The diagnosis of CM, particularly in young patients without known primary malignancy, can be challenging. In the past, a diagnosis of CM was made solely based on clinical examination and ultrasonography, and the diagnosis could only be confirmed at the time of enucleation or autopsy.[4] Improvement in multimodal retinal imaging enable prompt diagnosis of CM.[4-7] When primary tumor cannot be determined after thorough systemic workup, biopsy of the choroidal mass should be considered.[7,8] However, intraocular biopsy may be complicated with tumor cells seeding and other severe ocular complications. The feasibility of intraocular biopsy also depends on the location of lesion. Lesions in peripapillary or macular area may not be good candidates for biopsy. Blood-based comprehensive cancer genomic profiling can detect circulating tumor DNA using next generation sequencing technology, enabling clinicians to detect a panel of actionable driver mutations simultaneously.[7,9,10] The prognosis of uveal metastasis secondary to lung cancer is poor, as 54% of patients may die within 1 year of the diagnosis of uveal metastasis.[2] However, lung cancer screening and advances in treatment of lung cancer improve the overall survival of lung cancer.

CM can precede the diagnosis of primary lung cancer in as much as 44% of patients.[2,8] The mean patient age at diagnosis is 62 years.[2] Most patients have a history of cigarette smoking. Our case is atypical, as our patient is young with no smoking history. She was initially misdiagnosed as having choroiditis and was treated with a course of oral corticosteroid. Clinicians should be vigilant to revise the diagnosis if patient's condition deteriorates. CM should be suspected in patients with a creamy-yellow choroidal mass in the posterior pole especially when associated with SRF.[1,2,7,8]

Optic disc swelling is an uncommon manifestation of CM.[11] In our patient, the optic disc swelling was not associated with a significant decrease in vision or CM enlargement. The optic nerve involvement may be due to several mechanisms. First, optic nerve head swelling may arise from compression secondary to the mass effect of CM. Second, the optic nerve head may be directly invaded by neoplastic cells. Third, the choroidal mass may cause focal constriction of the optic nerve at the level of lamina cribrosa, disturbing axoplasmic flow and impairing microcirculation causing relative hypoxia of the optic nerve head.[12] Unlike choroidal melanoma, in which optic nerve invasion has a poor prognosis,[13] the significance of optic disc swelling in CM is rarely discussed in the literature[1,2,7,8] and thus warrants further studies.

Multimodal retinal imaging can help differentiate CM from other differential diagnoses.[4,6,7] Ultrasound can determine

the dimensions and location of choroidal lesions. The slight dome-shaped elevation with low-to-medium reflectivity and the lack of acoustic shadowing may differentiate CM from choroidal melanoma. Nonetheless, ultrasonography is operator dependent and may fail to detect small and shallow lesions. On OCT, common features of CM are dome-shaped or plateau-shaped choroidal elevation, presence of SRF, subretinal hyper-reflective dots, RPE alteration, optical shadowing, choriocapillaris compression, and internal hypo-reflectivity.[6,7] The subretinal hyper-reflective dots may represent shed photoreceptor outer segments in chronic retinal detachment.[14] Dome-shaped choroidal elevation may differentiate CM from choroidal granuloma, choroiditis, and choroidal invasion of lymphoma. Choroidal granuloma appears as a round hypo-reflective lesion, with an increased transmission effect and enhanced visualization of underlying structure,[15] as opposed to the reduced transmission effect seen in our patient. Choroiditis is usually associated with choriocapillaris hypoperfusion and appears as hypo-reflectivity beneath RPE and disruption of the outer retina layers, sometimes accompanied with hyper-reflective dots.[15] Lymphoma invasion of the choroid may appear as irregular undulated sub-RPE lesions, with RPE detachment or separation of Bruch's membrane. Fundus auto-fluorescence detects lipofuscin in the RPE, and CM usually appears as a hyper-autofluorescent lesion with areas of alternating hypo-autofluorescence, whereas fluorescein angiography does not distinguish CM from other choroidal tumors, as almost all choroidal tumors share similar pattern of early hypo-fluorescence followed by heterogenous dye leakage in the late phase.[6,7] Indocyanine green angiography is useful to distinguish CM from other choroidal tumors, as CM appear as hypo-fluorescent lesion at all phases. Indocyanine green angiography can delineate a broader border of CM that is otherwise not visible on clinical examination, whereas fluorescein angiography can distinguish CM from choroidal melanoma based on the absence of dual circulation.[6,7] Our patient demonstrated classical findings of CM on MRI; the CM appears as a well-defined mass iso- to hyper-intense on T1-weighted images and hypointense on T2-weighted images. High-resolution MRI may differentiate CM from primary ocular tumor.[7]

In our patient, tissue-based genomic profiling failed to detect any actionable mutations, whereas blood-based comprehensive cancer genomic profiling, also known as liquid biopsy, detected a rare EGFR mutation. The addition of blood-based genotyping of circulating DNA to tissue-based genotyping has increased the detection of actionable mutation by as much as 50% in non-small-cell lung cancer,[10] as tissue biopsy commonly yields inadequate sample for comprehensive next generation sequencing.[10] Liquid biopsy is widely used to identify actionable mutations at diagnosis of non-small-cell lung cancer. In patients with ocular metastasis who are systemically unfit for tissue biopsy, liquid biopsy is an alternative to confirm the primary tumor and guide molecular therapy.[7] Liquid biopsy can also be used to monitor treatment response and resistance.[7]

The choroidal vasculature is highly permeable to systemic drugs owing to the presence of fenestrated endothelium in the vascularized choriocapillaris. Therefore, our patient responded well to target therapy alone, with no relapse in 1 year. Successful treatment of CM secondary to lung and breast cancer with systemic chemotherapy or target therapy alone has been reported.[7,8] However, systemic therapy alone may have a lower initial response rate and a higher ocular relapse rate, compared with local treatment.[2,7] Secondary resistance to target therapy may develop owing to clonal resistance.[7] The decision to local or systemic therapy should take into consideration the survival prognosis, histology of the primary tumor, and the extent of CM involvement. External beam radiotherapy, proton beam therapy, and plaque brachytherapy have been used as local treatment for CM.[2,8] Novel treatment such as photodynamic therapy and intravitreal anti-vascular endothelial growth factor agents have been reported to have favorable results.[7,8] Enucleation may be considered in patients with painful blind eyes (secondary to total retinal detachment or neovascular glaucoma) or when extraocular extension occurs.[2,8]

This case report has several limitations. Swept-source OCT should have been used, as it enables deeper penetration and better visualization of choroidal lesions and hence improves delineation of the size and inner structure of CM.[16] OCT angiography should have been used to differentiate CM from melanoma, hemangioma, and osteoma, as there is no pathological flow in the choroidal and outer retinal layer in CM.[17] The follow-up period was only 1 year, so the patient remains at risk of relapse of CM and the primary malignancy. Prospective studies with a larger cohort are warranted to determine the pathogenesis, imaging features, and optimal treatment for CM.

Conclusion

CM of non-small-cell lung cancer is difficult to be diagnosed in a young patient without a history of smoking or other risk factors or known malignancy. Thorough medical history taking, multimodal retinal imaging, systemic investigation, and clinical examination can help ophthalmologists to make a timely diagnosis. OCT can help differentiate CM from choroiditis and choroidal granuloma. Optic disc swelling is a manifestation of CM, and its significance warrants further investigation. Plasma-based genomic profiling enables detection of actionable mutations that are undetectable by tissue-based genomic profiling. Prompt diagnosis and treatment may preserve vision in patients with CM.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors

had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures and for publication.

References

1. *Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. Ophthalmology 1997;104:1265-76.* Crossref
2. *Shah SU, Mashayekhi A, Shields CL, et al. Uveal metastasis from lung cancer: clinical features, treatment, and outcome in 194 patients. Ophthalmology 2014;121:352-7.* Crossref
3. *Kreusel KM, Bechrakis NE, Wiegel T, Krause L, Foerster MH. Incidence and clinical characteristics of symptomatic choroidal metastasis from lung cancer. Acta Ophthalmol 2008;86:515-9.* Crossref
4. *Arevalo JF, Fernandez CF, Garcia RA. Optical coherence tomography characteristics of choroidal metastasis. Ophthalmology 2005;112:1612-9.* Crossref
5. *Arepalli S, Kaliki S, Shields CL. Choroidal metastases: origin, features, and therapy. Indian J Ophthalmol 2015;63:122-7.* Crossref
6. *Cennamo G, Montorio D, Carosielli M, Romano MR, Cennamo G. Multimodal imaging in choroidal metastasis. Ophthalmic Res 2021;64:411-6.* Crossref
7. *Mathis T, Jardel P, Loria O, et al. New concepts in the diagnosis and management of choroidal metastases. Prog Retin Eye Res 2019;68:144-76.* Crossref
8. *Konstantinidis L, Rospond-Kubiak I, Zeolite I, et al. Management of patients with uveal metastases at the Liverpool Ocular Oncology Centre. Br J Ophthalmol 2014;98:92-8.* Crossref
9. *Heitzer E, Ulz P, Geigl JB. Circulating tumor DNA as a liquid biopsy for cancer. Clin Chem 2015;61:112-23.* Crossref
10. *Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res 2019;25:4691-700.* Crossref
11. *Shields JA, Shields CL, Singh AD. Metastatic neoplasms in the optic disc: the 1999 Bjerrum Lecture: part 2. Arch Ophthalmol 2000;118:217-24.* Crossref
12. *Brown GC, Shields JA. Mechanisms of optic disc swelling with diffuse choroidal melanomas: clinicopathologic correlations. Br J Ophthalmol 1982;66:77-82.* Crossref
13. *Szalai E, Wells JR, Grossniklaus HE. Mechanisms of optic nerve invasion in primary choroidal melanoma. Ocul Oncol Pathol 2017;3:267-75.* Crossref
14. *Demirci H, Cullen A, Sundstrom JM. Enhanced depth imaging optical coherence tomography of choroidal metastasis. Retina 2014;34:1354-9.* Crossref
15. *Pichi F, Invernizzi A, Tucker WR, Munk MR. Optical coherence tomography diagnostic signs in posterior uveitis. Prog Retin Eye Res 2020;75:100797.* Crossref
16. *Ishida T, Morohoshi K, Takeuchi Y, Soma R, Uchida M, Ohno-Matsui K. Swept-source optical coherence tomographic findings in eyes with metastatic choroidal tumor. Am J Ophthalmol Case Rep 2017;8:44-7.* Crossref
17. *Cennamo G, Romano MR, Breve MA, et al. Evaluation of choroidal tumors with optical coherence tomography: enhanced depth imaging and OCT-angiography features. Eye (Lond) 2017;31:906-15.* Crossref

PHOTO ESSAY

Keratitis with double hypopyon to illustrate differences between corneal ulcer and corneal abscess: a photo essay

Noel Hong-Kei Wat, MbCHb, MRCS(Ed); Gillian Denise Ji-Yee Siu, MBChB, MRCS(Ed), FCOphth(HK), FHKAM(Ophthalmology); Amy Lee Wong, MBBS, MRCS(Ed), MMed(Ophth Singapore), MSc OVS(CUHK), FCOphth(HK), FHKAM(Ophthalmology)
Department of Ophthalmology, Caritas Medical Centre, Hong Kong

Correspondence and reprint requests:
Dr Gillian DJY Siu, Department of Ophthalmology, Caritas Medical Centre, Hong Kong. Email: sjy638@ha.org.hk

Abstract

We report a case of keratitis with double hypopyon in a 70-year-old man to illustrate differences between corneal ulcer and corneal abscess.

Key words: Abscess; Corneal ulcer; Keratitis; Pseudomonas aeruginosa

Case presentation

In September 2020, a 70-year-old man presented with right eye keratitis 3 days after a metallic foreign body injury. He had a history of bilateral cataract surgery. At presentation, his best-corrected visual acuity was light perception. Slit lamp examination showed a central ulcer with 20% thinning involving the central 70% of the cornea, with a 1-mm intrastromal hypopyon and a 1.5-mm anterior chamber hypopyon (**Figure 1**). Ultrasonography showed mild anterior vitreous condensation. Computed tomography of the orbit did not show any intraorbital foreign body. Anterior segment ocular coherence tomography demonstrated a cystic space with a thin posterior wall containing the intrastromal abscess collection (**Figure 2**). Corneal scraping yielded *Pseudomonas aeruginosa*, which was sensitive to ceftazidime, ciprofloxacin, gentamicin, levofloxacin, Sulperazon, and Tazocin. The patient was initially treated with topical 1.4% gentamicin and 5% vancomycin as well as oral 500 mg ciprofloxacin daily for 1 week. The regimen was tapered to topical 0.5% levofloxacin after culture and sensitivity results were available. At the 3-month follow-up, the corneal ulcer healed with a thinned scar, and his best-corrected visual acuity improved to 1/60.

Discussion

Double hypopyon in keratitis is a good illustration to differentiate corneal ulcer from corneal abscess. Corneal ulcer is a lesion with superficial loss of tissue secondary to infectious or non-infectious causes, whereas corneal abscess is a collection of pus within a tissue space.[1] With the help of slit beam examination and anterior segment ocular coherence tomography, corneal abscess should only be called if there is an intrastromal collection of pus or hypopyon. In our patient, pus in the intrastromal cavity gave rise to the second hypopyon in the anterior chamber.

Corneal ulcer and corneal abscess are often used interchangeably in the literature.[2-6] Chhabra et al[7] described a case of postoperative keratitis as a corneal abscess although anterior segment ocular coherence tomography did not show a discrete lesion within the cornea. Infective corneal lesions were termed corneal abscesses even when there was no evidence of collection of infective material within the cornea.[8-10] Rubino et al[5] described a case of toxic keratopathy as corneal abscess when corneal ulcer may have been a more accurate term.[5] There is a misconception that

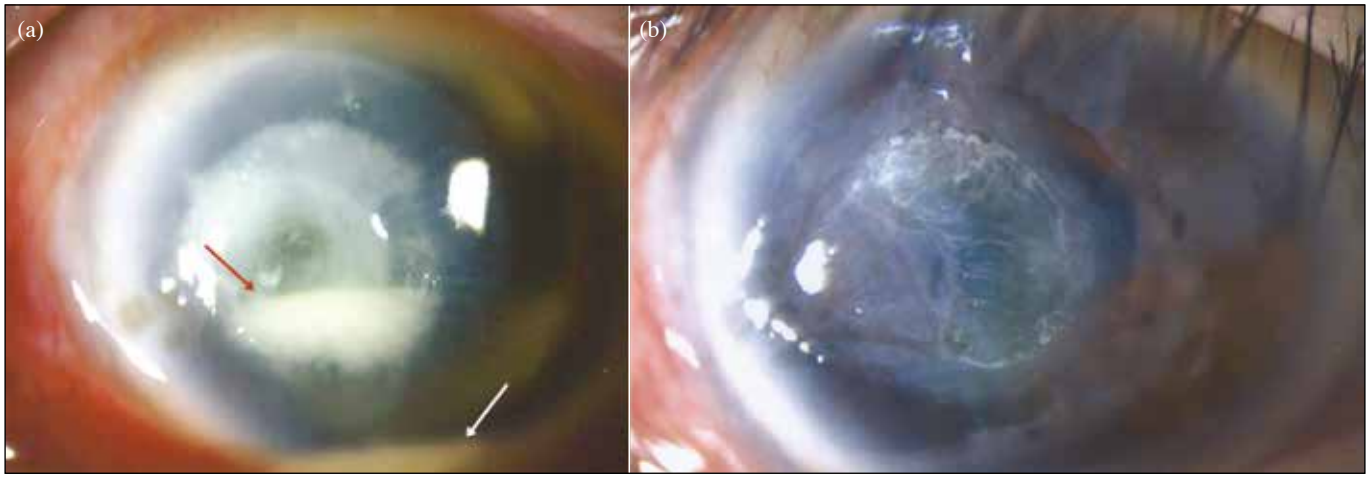


Figure 1. Slit lamp examination showing (a) a 1-mm intrastromal hypopyon in the central cornea (red arrow) and a 1.5-mm hypopyon in the anterior chamber (white arrow) and (b) a thinned corneal scar at 1 month after healing.

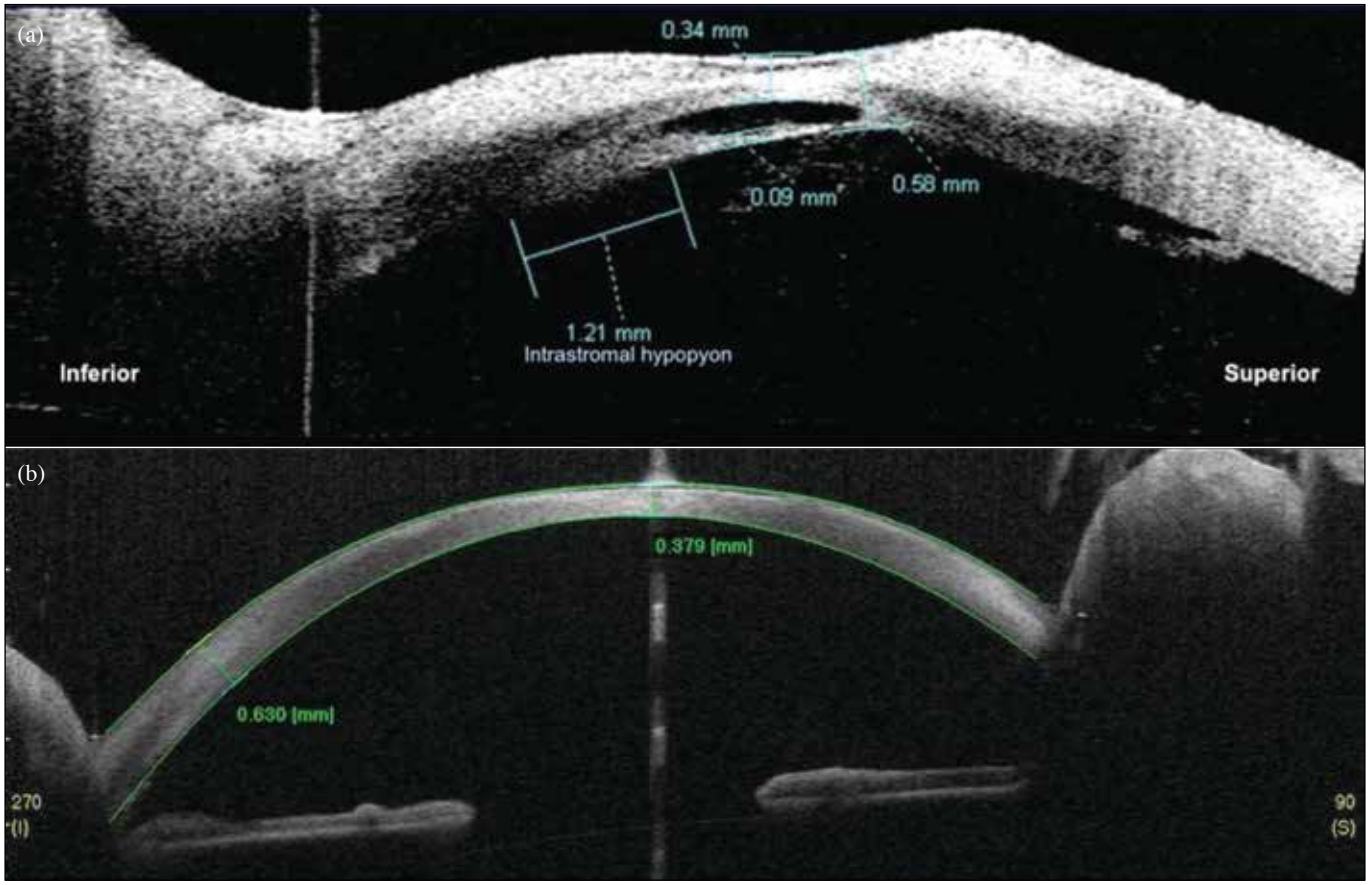


Figure 2. Anterior segment ocular coherence tomography of the cornea in a vertical cut showing (a) the corneal abscess with a 1.21-mm intrastromal hypopyon. An empty pocket in the center of the cornea indicates a bulla in the deep stromal area. Inferior to the bullae is an area of higher density signal correlating to the hypopyon filling up the inferior part of the bulla. (b) A thinned cornea with scarring at 22 months.

a corneal abscess is equivalent to a more severe corneal ulcer.[11] The term 'corneal abscess' has not been properly defined. Thus, there is no evidence that corneal abscess takes longer to recover than corneal ulcer. Corneal abscess is a rare form of corneal ulcer but not equivalent to corneal ulcer and therefore should not be used interchangeably.

Although management of corneal abscess and ulcer is similar and requires intensive fortified antibiotic treatment, a corneal abscess does not necessarily imply

longer treatment duration. However, there may be further implications for a corneal ulcer in the form of an abscess. The corneal abscess involves thinned corneal walls around infective material and therefore has a risk of rupture. If the abscess wall ruptures into the anterior chamber, a sudden flare in anterior chamber activity and hypopyon may occur. This increases the risk of keratitis-induced endophthalmitis, as infective material is released into the anterior chamber from the cornea. Ironically, the cornea may even recover faster after the infective material is removed. However, the thin-walled abscess may rupture anteriorly causing corneal perforation.[12] Therefore, correct differentiation between corneal abscess and corneal ulcer is important.

Contributors

GDJYS and NHKW designed the study, acquired the data, and analyzed the data. All authors drafted the manuscript and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures and for publication.

References

1. *Mannis M, Mannis M, Holland E. Cornea. 4th ed. Elsevier; 2017: 241-5.*
2. *Barsam A, Patel N, Laganowski HC, Perry HD. Recurrent corneal ulceration in presence of synthetic microfibrils. Clin Ophthalmol 2011;5:837-9.* Crossref
3. *Cuadros J, Gros-Otero J, Gallego-Angui P, et al.* Aspergillus tamarii *keratitis in a contact lens wearer. Med Mycol Case Rep 2017;19:21-4.* Crossref
4. *Li YC, Zeldovich A, Chua BJ, Rowe NJ, Martin FJ, McClellan KA. Hazardous contact: a case of visual loss following Pseudomonas keratitis from novelty contact lens wear. Med J Aust 2006;185:173-4.* Crossref
5. *Rubino P, Orsoni JG, Rampini A, Mora P. Over-treated corneal abscess may be toxic keratopathy. Case Rep Ophthalmol 2010;1:20-3.* Crossref
6. *Zloto O, Barequet IS, Weissman A, Ezra Nimni O, Berger Y, Avni-Zauberman N. Does PACK-CXL change the prognosis of resistant infectious keratitis? J Refract Surg 2018;34:559-63.* Crossref
7. *Chhabra M, Goel R, Khanam S, Singh S. Role of intrastromal vancomycin in recalcitrant corneal abscess after phacoemulsification. BMJ Case Rep 2021;14:e241709.* Crossref
8. *Gupta B, Jain AK, Saini M, Sardana M, Soni R, Angrup A.* Globicatella sanguinis *corneal abscess with endophthalmitis. J AAPOS 2022;26:46-8.* Crossref
9. *Dorin J, Debourgogne A, Zaïdi M, Bazard MC, Machouart M. First unusual case of keratitis in Europe due to the rare fungus* Metarhizium anisopliae. *Int J Med Microbiol 2015;305:408-12.* Crossref
10. *Morley AM, Tuft SJ.* Rothia dentocariosa *isolated from a corneal ulcer. Cornea 2006;25:1128-9.* Crossref
11. *Borderie VM, Bourcier TM, Poirot JL, Baudrimont M, Prudhomme de Saint-Maur P, Laroche L. Endophthalmitis after* Lasiodiplodia theobromae *corneal abscess. Graefes Arch Clin Exp Ophthalmol 1997;235:259-61.* Crossref
12. *Hassan A, Rampat R, Vasquez-Perez A. Severe keratitis and corneal perforation by* Paenibacillus glucanolyticus. *Cornea 2021;40:1062-4.* Crossref

Acknowledgements

The Editor-in-Chief is grateful to the following individuals who acted as reviewers for the Journal during the past year.

Carmen KM Chan
Karen Chan
Yvonne Chan
Andy Cheng
Arthur Cheng
Thomas Chiu
Kelvin Chong
Loraine Chow
Sharon Chow
Bonnie Choy
Wai Kit Chu
Derek Chung
Dorothy Fan
Angie Fong
Nicholas Fung
Mary Ho
Wing Lau Ho
Lawrence Iu
Simon Ko
Andrew Kuk
Jeremy John Kwok
Connie Lai
Frank Lai
Robert Lam
Winnie Lau
Brian Li
Fiona Luk
Andrew Mak
Shiu Ting Mak
Alex Ng
Danny Ng
Kendrick Shih
Helena Sin
Emily Tang
Heather Tang
Chi Wai Tsang
Kelvin Wan
Hunter Yuen

Announcement for the best original article award 2021:

Category: Fellows + Members:
Award recipient: Dr Loraine Chow

Refixation of dislocated intraocular lens using the double needle flanged technique by Loraine Chow, Stephanie Yuk, and Nicholas Fung published in Hong Kong J Ophthalmol 2021;25:34-8.

Category: Trainees:
Award recipient: Dr Jolly Tsui

Predictors of elevated intraocular pressure after intravitreal injection of anti-vascular endothelial growth factors: a prospective observational study by Jolly Tsui, Ivan Hong-wan Lau, Sophia Ling Li, Noel Ching-yan Chan, and Alvin L Young published in Hong Kong J Ophthalmol 2021;25:6-11.

THE ULTIMATE EXPERIENCE OF CONTROL AND CLARITY

Clareon® AutonoMe™. Automated delivery of unsurpassed clarity.§[1-4]

Introducing the **Clareon® IOL** with the **AutonoMe™** automated, disposable, preloaded delivery system. With its intuitive, ergonomic design, the **AutonoMe™** delivery system enables easy, single-handed control of IOL advancement and protects incisions as small as 2.2 mm.[1,5-8] Preloaded with the **Clareon® IOL**, it delivers a new monofocal lens with an advanced design and unsurpassed optic clarity.[1-4,9-12]

1. Clareon® AutonoMe™ Directions for Use. 2-12. Alcon Data on File.
§Based on aggregate results from *in vitro* evaluations of haze, SSNGs and glistenings compared to TECNIS® OptiBlue® ZCB00V (Abbott), TECNIS® ZCB00 (Abbott), Eternity Natural Uni® W-60 (Sanyen), Vivinex® XY-1 (HOYA) and enVista® MX60 (B&L; Bausch & Lomb)
§§Trademarks are the property of their respective owners.

Alcon

Clareon. AutonoMe. | Advancing CATARACT SURGERY

Enquiry Hotline: (852) 3972 7350

HK-CLA-2200001 App. 202211

enVista®

one-piece hydrophobic acrylic intraocular lens

enVista® toric

One-piece Hydrophobic Acrylic Toric Intraocular Lens

The Design is Distinctive.

The Outcomes Are Clear.

More than 3 million eyes already enjoying the enVista® experience worldwide[1]

1. Data on file, Bausch & Lomb. enVista® and Enhanced enVista® data in 2013 - Q1 2020

HK-SU-2022-12-011

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road, Tsim Sha Tsui, Kowloon, Hong Kong. Tel: +852 2213 3333

CATARACT LASER RETINA

BAUSCH + LOMB
See better. Live better.

LUXSMART™

PRELOADED

PURE

Refractive Optics

HYDROPHOBIC IOL

The extended depth of focus intraocular lens for your daily range of vision

HYDROPHOBIC PRO TECHNOLOGY* PRELOADED EDOF

Scan this QR code to have additional information about LuxSmart™

* PRO TECHNOLOGY: Pure refractive Optics Technology

HK-SU-2022-10-004

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road, Tsim Sha Tsui, Kowloon, Hong Kong Tel: +852 2213 3333

CATARACT LASER RETINA

BAUSCH+LOMB
See better. Live better.

EYLEA®
(aflibercept solution for injection)

BAYER

GAINS BEYOND VISION

GAIN LETTERS | Robust visual gains[1–3]

GAIN TIME | Gains that last[1–3]

GAIN FREEDOM | Extend with confidence[4]

GAIN INNOVATION | Designed to last[4]

GAIN CONFIDENCE | Real-world outcomes you can trust[1–3]

You and your patients can achieve gains beyond vision with EYLEA®

References: 1. Kaiser P, *et al. Ophthalmol Retina* 2017;1:304–313. **2.** Lukic M, *et al. Eur J Ophthalmol* 2021;31:1940–1944. **3.** Wykoff CC, *et al. Br J Ophthalmol* 2018;102:631–636. **4.** EYLEA® (aflibercept solution for injection) Full Prescribing Information. Hong Kong May 2021.

Eylea Abbreviated PI

Eylea® 40mg/mL solution for injection in pre-filled syringe. Prescribing Information (Please refer to the full prescribing information before prescribing) **Indication for Use:** Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to the following conditions: macular oedema secondary to retinal vein occlusion (branch or central RVO), diabetic macular oedema (DME), myopic choroidal neovascularisation (myopic CNV). **Composition:** 1mL solution for intravitreal injection contains 40 mg aflibercept. One pre-filled syringe contains 90 microlitres, equivalent to 3.6 mg aflibercept. **Posology and Method of Administration:** The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres. Eylea is for intravitreal injection only, please do refer to section 6.6 in the full prescribing information for step-by-step instructions for use. **Contraindications:** Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1 of the full PI; Active or suspected ocular or periocular infection; Active severe intraocular inflammation. **Warnings and Precautions:** ***Traceability:*** To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded; ***Intravitreal injection-related reactions:*** Proper aseptic injection techniques must always be used when administering Eylea. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). ***Immunogenicity:*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea; ***Systemic effects:*** Non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition; ***Populations with limited data:*** There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy; ***Excipients:*** This medicine contains less than 1 mmol sodium (23 mg) per dosage unit; ***Incompatibilities:*** this medicinal product must not be mixed with other medicinal products; ***Storage:*** Store in a refrigerator (2°C to 8°C), do not freeze. Store in the original package in order to protect from light. The unopened vial may be stored outside the refrigerator below 25 °C for up to 24 hours. After opening the blister, proceed under aseptic conditions. **Adverse Effects:** ***Very common:*** Visual acuity reduced, retinal haemorrhage, conjunctival haemorrhage, eye pain. ***Common:*** Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia. For ***uncommon and rare adverse reactions,*** please refer to section 4.8 in the full prescribing information. **(PP-EYL-HK-0151 | 09 Oct 2022)** Reference cited as: Eylea 40 mg/mL solution for injection in pre-filled syringe, Hong Kong Prescribing Information (May 2021)

Eylea 40mg/mL solution for intravitreal injection in a vial. Abbreviated Prescribing Information (Please refer to the full prescribing information before prescribing) **Indication for Use:** Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to the following conditions: macular oedema secondary to retinal vein occlusion (branch or central RVO), diabetic macular oedema (DME), myopic choroidal neovascularisation (myopic CNV). **Composition:** 1mL solution for intravitreal injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. **Posology and Method of Administration:** The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres. Eylea is for intravitreal injection only, please do refer to section 6.6 in the full prescribing information for step-by-step instructions for use. **Contraindications:** Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1 of the full PI; Active or suspected ocular or periocular infection; Active severe intraocular inflammation. **Warnings and Precautions:** ***Intravitreal injection-related reactions:*** Proper aseptic injection techniques must always be used when administering Eylea. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). ***Immunogenicity:*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea; ***Systemic effects:*** Non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition; ***Populations with limited data:*** There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy; ***Incompatibilities:*** this medicinal product must not be mixed with other medicinal products; ***Storage:*** Store in a refrigerator (2°C to 8°C), do not freeze. Store in the original package in order to protect from light. The unopened vial may be kept at room temperature below 25 °C for up to 24 hours. After opening the vial, proceed under aseptic conditions. **Adverse Effects:** ***Very common:*** Visual acuity reduced, conjunctival haemorrhage, eye pain. ***Common:*** Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia. For ***uncommon and rare adverse reactions***, please refer to section 4.8 in the full prescribing information. **(PP-EYL-HK-0149-1 | 24 Oct 2022)** Reference cited as: Eylea 40 mg/mL solution for intravitreal injection in a vial, Hong Kong Prescribing Information (June 2019)

For further prescribing information, please contact:
Bayer HealthCare Limited
14/F, Oxford House, Taikoo Place, 979 King's Road, Quarry Bay, Hong Kong
Tel: (852) 8100 2755 Fax: (852) 3526 4750 Website: www.bayer.com

PP-EYL-HK-0169-1

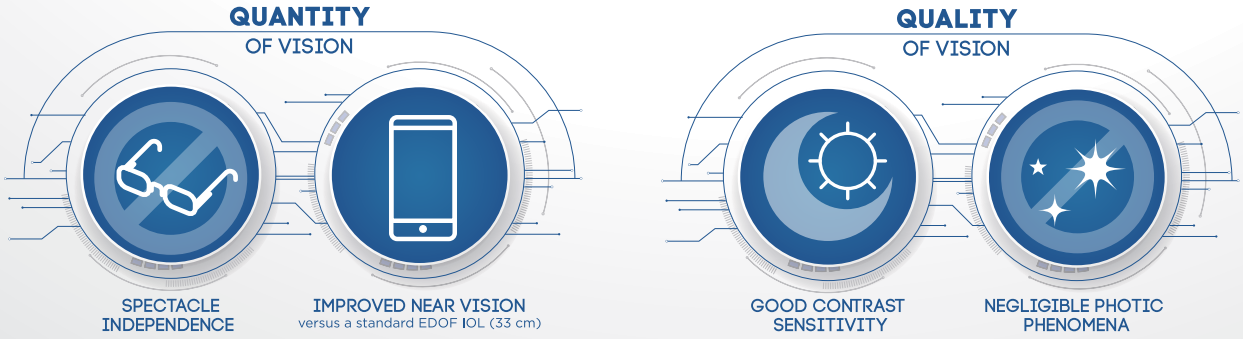
THE UNIQUE **WELL FUSION®** OPTICAL SYSTEM, WHICH COMBINES **MINI WELL®** AND **MINI WELL PROXA®**, OFFERS UNINTERRUPTED HIGH-QUALITY VISION, WITHOUT GLASSES.

well FUSION VISION UNINTERRUPTED

A UNIQUE OPTICAL SYSTEM BASED ON A COMPLEMENTARY OPTICS DESIGN USING THE SAME WAVEFRONT ENGINEERING TECHNOLOGY.[1,2]

WELL FUSION®

HAS BEEN DESIGNED TO PROVIDE PATIENTS WITH:



References:
1. Bellucci R, Curatolo MC. A new extended depth of focus intraocular lens based on spherical aberration. J Refract Surg. 2017;33(6):389-94.
2. SIFI internal data.

Abbreviations:
EDOF: extended depth of focus, **IOL:** intraocular lens, **WELL:** Wavefront Engineering Leading Lens.

CE 0123

www.affamed.com

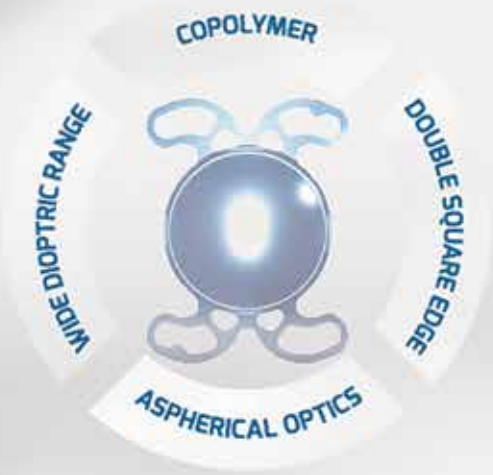
AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8595
Email: info@primal.com.hk

mini READY 4
INTRAOCULAR LENS

Aspherical IOL for mini-incision to reduce postoperative astigmatism and corneal aberrations

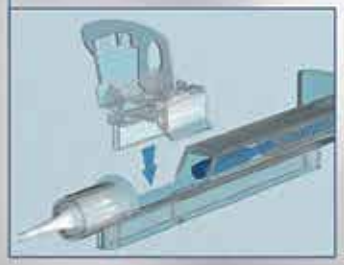


TECHNICAL SPECIFICATIONS

Material	Copolymer
Positioning	Bag
Total diameter	10.75 mm
Diameter of optical surface	6 mm
Vaulting	5°
Optics shape	Aspheric biconvex / Concave convex
Square edge	Double
Estimated A constant	118.6 (0D to +40D) 119.9 (-3D to -1D)
Estimated A.C.D.	5.32 mm (0D to +40D) 6.08 mm (-3D to -1D)
Dioptric range	-10D to +30D (-10D to +10D incr. 1D; +10D to +30D incr. 0.5D)
Size of incision	1.8 mm (wound assisted); ~2.2 mm (into the bag)
Refractive index	1.46 at 35°C UV absorber

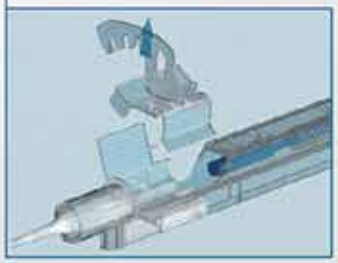
INSTRUCTION FOR USE OF THE PRELOADED VERSION

1. Insert the cartridge, containing the IOL, into the injector.



2. Apply viscoelastic solution first through the front hole (until is filled) and then a little through the rear hole.

3. Remove the clip of safety block by lifting it using your index and thumb fingers.



4. Close the cartridge sides together until the "click-lock" mechanism engages. Push forward the plunger softly and ensure that the silicone cushion correctly enters into the cartridge loading chamber.

CE 0123

www.affamed.com

AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8595
Email: info@primal.com.hk

EXTENDING THEIR HORIZONS

GIVE YOUR PATIENTS UNINTERRUPTED HIGH-QUALITY VISION

TRUE EXTENDED DEPTH OF FOCUS* FOR HIGH-QUALITY VISION[1,2]

- A unique, patented refractive lens design for sharp vision from far to near, including excellent intermediate distance vision[1,2]
- Consistent, uninterrupted performance in different lighting conditions over the full 24-hour day with negligible halos and glare[2-4]
- Excellent contrast sensitivity, even under mixed lighting conditions[1,3]

IN YOUR APPROPRIATELY SELECTED PATIENTS, YOU CAN NOW HAVE CONFIDENCE IN OFFERING UNINTERRUPTED, HIGH-QUALITY VISION AT ALL DISTANCES AND AT ALL TIMES

- EXCELLENT INTERMEDIATE AND FAR VISION, WITH GOOD NEAR VISUAL ACUITY
- NEGLIGIBLE HALOS AND GLARE
- CLOSELY MATCHES THE VISUAL RESULTS OF THE HUMAN EYE
- EXCELLENT CONTRAST SENSITIVITY, EVEN UNDER MIXED LIGHTING CONDITIONS

*EDOF

1. Savini G, et al. Visual performance of a new extended depth-of-focus intraocular lens compared to a distance-dominant diffractive multifocal intraocular lens. J Cataract Refract Surg. 2018;34(4):228-235.
2. Savini G, et al. Functional assessment of a new extended depth-of-focus intraocular lens. Eye (Lond). 2019;33(3):404-410.
3. Bellucci R, et al. Clinical and aberrometric evaluation of a new extended depth-of-focus intraocular lens based on spherical aberration. J Cataract Refract Surg. 2019;45(7):919-926.
4. Focus Study, Study code PSM15, data on file. SIFI.

CE 0123

www.affamed.com

AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

AffaMed Technologies

Primal Chemical Co., Ltd.
Tel: (852) 2343 3212
Fax: (852) 2797 8555
Email: info@primal.com.hk

REDUCTION OF ELEVATED INTRAOCULAR PRESSURE
IN PATIENTS WITH OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION

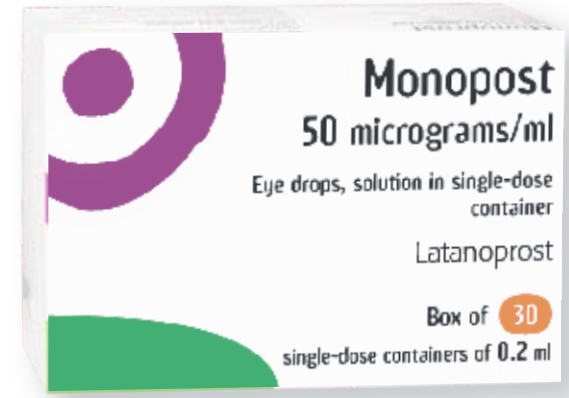
Monopost®

Eye drops solution in single dose container

Latanoprost 0.005%

The first preservative-free latanoprost formulation[1]

with PROVEN[2] EFFICACY



- **N°1** Prostaglandin in Europe[1]
- Supported by **22 publications**[3]
- More than **1 million patients** treated with Monopost® every month in more than **40 countries**[4]
- Good tolerability profile
- Innovative & preservative-free formulation
- Stored at room temperature

HMS-MNPTHEA-AD/202210

HMS WORLD'S LOCAL PARTNER

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
E-mail: sales@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

REFERENCES

1. Market Data August 2022 (SU and Values). **2.** Rouland JF. et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. Br J Ophtalmol 2013;97(2):196-200.5. DOI: 10.1136/bjophthalmol-2012-302121. **3.** Data available upon request. **4.** Laboratoires Théa, internal data, August 2022.

Théa let's open our eyes

NOW AVAILABLE!

THE EYLEA® PRE-FILLED SYRINGE

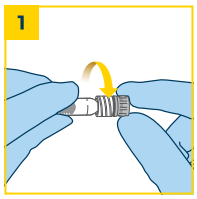
EYLEA® (aflibercept solution for injection)

WHAT'S INSIDE MAKES THE DIFFERENCE

Pre-filled syringe instructions for use and handling

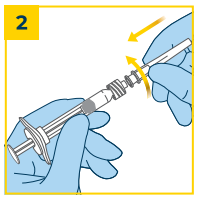
For full Prescribing Information, please refer to the EYLEA SmPC

TWIST OFF SYRINGE CAP



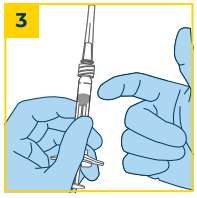
Using aseptic technique, remove the syringe from the sterilized blister pack. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. Please note: Twist off (do not snap off) the syringe cap. To avoid compromising the sterility of the product, do not pull back on the plunger.

ATTACH SYRINGE TIP



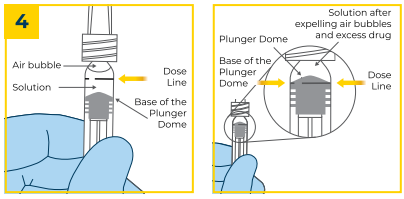
Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

CHECK FOR BUBBLES



Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

ELIMINATE ANY BUBBLES



To eliminate all bubbles and to expel excess drug, slowly depress the plunger rod to align the cylindrical base of the plunger dome with the black dose line on the syringe (equivalent to 50 microliters).

The pre-filled syringe is for single use only. After injection, any unused product must be discarded.

References: EYLEA® (aflibercept solution for injection) Summary of Product Characteristics. Hong Kong: Bayer HealthCare Limited.

Eylea Abbreviated PI

Eylea® 40mg/mL solution for injection in pre-filled syringe. **Prescribing Information** (Please refer to the full prescribing information before prescribing) **Indication for Use:** Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to the following conditions: macular oedema secondary to retinal vein occlusion (branch or central RVO), diabetic macular oedema (DME), myopic choroidal neovascularisation (myopic CNV). **Composition:** 1mL solution for intravitreal injection contains 40 mg aflibercept. One pre-filled syringe contains 90 microlitres, equivalent to 3.6 mg aflibercept. **Posology and Method of Administration:** The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres. Eylea is for intravitreal injection only, please do refer to section 6.6 in the full prescribing information for step-by-step instructions for use. **Contraindications:** Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1 of the full PI; Active or suspected ocular or periocular infection; Active severe intraocular inflammation. **Warnings and Precautions:** ***Traceability:*** To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded; ***Intravitreal injection-related reactions:*** Proper aseptic injection techniques must always be used when administering Eylea. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). ***Immunogenicity:*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea; ***Systemic effects:*** Non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition; ***Populations with limited data:*** There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy; ***Excipients:*** This medicine contains less than 1 mmol sodium (23 mg) per dosage unit; ***Incompatibilities:*** this medicinal product must not be mixed with other medicinal products; ***Storage:*** Store in a refrigerator (2°C to 8°C), do not freeze. Store in the original package in order to protect from light. The unopened vial may be stored outside the refrigerator below 25 °C for up to 24 hours. After opening the blister, proceed under aseptic conditions. **Adverse Effects:** ***Very common:*** Visual acuity reduced, retinal haemorrhage, conjunctival haemorrhage, eye pain. ***Common:*** Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia. For ***uncommon and rare adverse reactions,*** please refer to section 4.8 in the full prescribing information. **(PP-EYL-HK-0151 | 09 Oct 2022)** Reference cited as: Eylea 40 mg/mL solution for injection in pre-filled syringe. Hong Kong Prescribing Information (May 2021)

Eylea 40mg/mL solution for intravitreal injection in a vial. Abbreviated Prescribing Information (Please refer to the full prescribing information before prescribing) **Indication for Use:** Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to the following conditions: macular oedema secondary to retinal vein occlusion (branch or central RVO), diabetic macular oedema (DME), myopic choroidal neovascularisation (myopic CNV). **Composition:** 1mL solution for intravitreal injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. **Posology and Method of Administration:** The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres. Eylea is for intravitreal injection only, please do refer to section 6.6 in the full prescribing information for step-by-step instructions for use. **Contraindications:** Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1 of the full PI; Active or suspected ocular or periocular infection; Active severe intraocular inflammation. **Warnings and Precautions:** ***Intravitreal injection-related reactions:*** Proper aseptic injection techniques must always be used when administering Eylea. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg). ***Immunogenicity:*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea; ***Systemic effects:*** Non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition; ***Populations with limited data:*** There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy; ***Incompatibilities:*** this medicinal product must not be mixed with other medicinal products; ***Storage:*** Store in a refrigerator (2°C to 8°C), do not freeze. Store in the original package in order to protect from light. The unopened vial may be kept at room temperature below 25 °C for up to 24 hours. After opening the vial, proceed under aseptic conditions. **Adverse Effects:** ***Very common:*** Visual acuity reduced, conjunctival haemorrhage, eye pain. ***Common:*** Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia. For ***uncommon and rare adverse reactions***, please refer to section 4.8 in the full prescribing information. **(PP-EYL-HK-0149-1 | 24 Oct 2022)** Reference cited as: Eylea 40 mg/mL solution for intravitreal injection in a vial, Hong Kong Prescribing Information (June 2019)

For further prescribing information, please contact:

Bayer HealthCare Limited

14/F, Oxford House, Taikoo Place, 979 King's Road, Quarry Bay, Hong Kong

Tel: (852) 8100 2755 Fax: (852) 3526 4750 Website: www.bayer.com

PP-EYL-HK-0169-1

FASTER.[1-4]
EASIER.[*,5,6]
BETTER.[1,2,7,8]

INTRODUCING

The ***NEW*** **ARGOS® Biometer with Image Guidance by Alcon®** is the smarter planning solution that keeps efficiency and accuracy flowing through your clinic.

*Compared to VERION™ Reference Unit.
†Trademarks are the property of their respective owners.

1. Tamaoki A, Kojima T, Hasegawa A, et al. Clinical evaluation of a new swept-source optical coherence biometer that uses individual refractive indices to measure axial length in cataract patients. *Ophthalmic Res.* 2019;19:1-13. **2.** Shammas HJ, Ortiz S, Shammas MC, Kim SH, Chong C. Biometry measurements using a new large-coherence-length swept-source optical coherence tomographer. *J Cataract Refract Surg.* 2016;42:50-61. **3.** Hussaindeen JR, Mariam EG, Arunachalam S, et al. Comparison of axial length using a new swept-source optical coherence tomography-based biometer. *PLOS ONE.* December 2018. **4.** ZEISS† IOLMaster† 700 510k Submission 2015. **5.** VERION™ Reference Unit User Manual 2019. **6.** ARGOS® Biometer User Manual 2019. **7.** Whang W, Yoo Y, Kang M, Joo C. Predictive accuracy of partial coherence interferometry and swept-source optical coherence tomography for intraocular lens power calculation. *Sci Rep.* 2018;8(1):13732. **8.** Shammas HJ. Accuracy of IOL power formulas with true axial length versus simulated axial length measurement in 318 eyes using an OCT biometer. 2019 ASCRS ASOA Annual Meeting. May 2019.

Alcon

Vision Planner | Advancing CATARACT SURGERY

HK-ARB-2100001 App. 202111