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香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
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- President of the College

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- Originality
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- Methodology
- Presentation style

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

EDITORIAL

Non–indocyanine green angiograph diagnostic criteria for polypoidal choroidal vasculopathy

Among Asian patients with neovascular age-related macular degeneration, the proportion of polypoidal choroidal vasculopathy (PCV) based on indocyanine green angiography (ICGA) findings has been estimated to be up to 60% in clinic-based case series.[1,2] The current gold standard for diagnosing PCV requires ICGA, which is an expensive and potentially harmful procedure that may not be readily available in many ophthalmic centers.

The Asia-Pacific Ocular Imaging Society PCV Workgroup has recently published the diagnostic criteria for naïve PCV that do not require the use of ICGA.[3] The presence of three major criteria — sub-retinal pigment epithelium ring-like structure on cross-sectional optical coherence tomography (OCT), complex retinal pigment epithelium elevation on en face OCT, and sharp-peaked pigment epithelial detachment on cross-sectional OCT — achieved an area under the receiver operating characteristic curve (AUC) of 0.90, sensitivity of 0.75, specificity of 0.91, positive predictive value of 0.93, and negative predictive value of 0.68. When the criteria were applied by both residents and specialists, an accuracy of 82% was achieved. These diagnostic criteria provide a practical, quick, and non-invasive method for differentiating PCV from typical wet age-related macular degeneration, especially in clinical settings that ICGA is not accessible. It is supported that ICGA can be dispensed with under most conditions. When en face OCT was not available, the combination of the remaining two spectral-domain OCT-based criteria achieved an AUC of 0.82. The absence of these diagnostic criteria did not exclude the diagnosis of PCV.

Based on multimodal imaging and histologic studies, the terms 'polypoidal lesion' and 'branching neovascular network' were recommended, instead of 'polyp' and 'branching vascular network', respectively, which are based on ICGA appearance.

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References

1. *Kwok AK, Lai TY, Chan CW, Neoh EL, Lam DS. Polypoidal choroidal vasculopathy in Chinese patients. Br J Ophthalmol 2002;86:892-7.* Crossref
2. *Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. Ophthalmology 2018;125:708-24.* Crossref
3. *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

ORIGINAL ARTICLE

Predictors of elevated intraocular pressure after intravitreal injection of anti-vascular endothelial growth factor: a prospective observational study

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Abstract

Purpose: To investigate the patterns and predictors of intraocular pressure (IOP) changes after intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF).

Methods: This study enrolled 32 men and 16 women (mean age, 65.3±12.3 years) who underwent IVI of anti-VEGF between January and March 2020 in our department. IOPs were measured using Goldmann applanation tonometry. Potential predictors included age, sex, lens status, axial length, history of glaucoma, number of previous IVIs, diagnosis, and post-injection vitreous reflux.

Results: The respective mean IOP was 16.2 mmHg, 32.7 mmHg, 21.7 mmHg, and 18.3 mmHg at baseline and at 5, 15, and 30 minutes after IVI. IOP elevation of ≥15 mmHg was observed in 48% of eyes at 5 minutes after IVI; all spikes resolved and the IOP reduced to <21 mmHg within 60 minutes. Previous IVI number (r=0.346, p=0.016) and baseline IOP (r=0.304, p=0.04) were associated with IOP at 5 minutes after IVI. Baseline IOP was associated with IOPs at 15 and 30 minutes after IVI (r=0.488-0.573, p<0.001). In multivariate regression analysis, the previous IVI number (b=0.55, p=0.04) was an independent predictor of IOP at 5 minutes after IVI.

Conclusion: Transient but substantial IOP elevation shortly after IVI of anti-VEGF was positively correlated with the number of previous IVIs; this could be used to stratify patients for IOP spike prophylaxis, especially those with advanced glaucoma at risk of further optic nerve damage secondary to acute ocular hypertension. Ophthalmologists should assess patient susceptibility to glaucomatous damage, along with the risks and complications of prophylaxis for IOP spike prevention.

Key words: Bevacizumab; Glaucoma; Intraocular pressure; Intravitreal injections; Retina

Introduction

Intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) is widely used for the treatment of various retinal pathologies such as neovascular age-related macular degeneration,[1,2] diabetic macular edema,[3] and retinal venous occlusion.[4] Although IVI is a safe procedure, complications have been reported, including acute angle closure[5] and

substantial short-term elevated intraocular pressure (IOP) leading to retinal arterial occlusion.[6] Sudden expansions of vitreous volume are presumably responsible for these short-term increases in IOP immediately after IVI of anti-VEGF. Nonetheless, the application and protocol of IOP monitoring after IVI varies among institutions. Although the effects of elevated IOP might be transient, visual damage might occur, especially in patients with preexisting glaucoma. Research in animal models has shown that acutely elevated IOP can lead to axonal transport blockade to the optic nerve head,[7] as well as reduced juxtapapillary retinal and optic nerve head blood flow; if the IOP remains uncontrolled, these changes can result in ocular ischemia and functional damage.[8] Because the central vision is usually already impaired in patients with retinal disorders that require anti-VEGF treatment, it is important to preserve their peripheral vision and optic nerve function, both of which are important for night vision and activities of daily living. Any substantial increase in IOP (ie, an IOP spike) should be avoided and timely treatment should be offered to patients with sustained IOP elevation. To the best of our knowledge, there is no guideline for monitoring short-term IOP changes after IVI of anti-VEGF; furthermore, there have been limited studies concerning predictors of severe IOP spikes.[9] Thus, this study aimed to examine the frequency and severity of IOP elevation at 5, 15, and 30 minutes after IVI of anti-VEGF and to determine predictors of elevated IOP that can be used for risk stratification.

Materials and methods

This prospective study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (Ref: CRE-2019.162). Informed consent for enrollment in the study was obtained from each patient. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Patients were enrolled if they underwent IVI of anti-VEGF between January 2020 and March 2020 in the Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital. Exclusion criteria were known diagnosis of secondary glaucoma (including uveitic glaucoma, neovascular glaucoma, pigmentary glaucoma, pseudoexfoliation, and iridocorneal endothelial syndrome); a history of glaucoma surgery or laser procedures; and/or the use of systemic, regional, and topical steroids within 1 month of IVI.

One eye from each patient was included; the lens status, baseline IOP, and axial length were measured before IVI. IVIs were performed by two qualified retinal surgeons using standardized techniques and instruments. Each procedure was performed under topical anesthesia with 0.5% proxymetacaine, without the application of IOP-lowering eye drops. Povidone iodine (5%) was used to irrigate the conjunctival fornices, while povidone iodine (10%) was used to disinfect the lid margin and periorbital skin. A skin drape and lid speculum were applied; 0.05 mL of ranibizumab or aflibercept was then injected through displaced conjunctiva over the infero- or supero-temporal quadrant using 30-gauge needles; injections were performed at 3.5 mm and 4 mm behind the limbus in pseudophakic and phakic eyes, respectively. Firm pressure was applied to the injection site with a cotton-tip applicator for at least 5 s immediately on retrieval of the injection needle to minimize vitreous reflux. Light perception vision was checked after each injection; anterior chamber paracentesis was performed in patients who exhibited loss of visual function. Finally, the ocular surface was irrigated with 0.5% levofloxacin eye drops.

IOP at 5, 15, and 30 minutes after IVI was measured in an upright position using Goldmann applanation tonometry. For eyes with IOP of >21 mmHg at 30 minutes after IVI, additional measurements were performed at 45 and/or 60 minutes (until the IOP was <21 mmHg). Eyes with persistent IOP of >21 mmHg at 60 minutes after IVI were administered topical IOP-lowering medications and re-examined the next day. All IOPs were measured twice and the mean value was recorded when the difference was <2 mmHg. A third measurement was performed when the difference was >2 mmHg; the median of the three measurements was then recorded. The presence of vitreous reflux from the injection site and the requirement for anterior chamber paracentesis after IVI were documented.

Statistical analysis was performed using SPSS Advanced Statistical Software, version 11.0 (Chicago, IL, USA). Two-tailed Pearson correlations and Student's *t* tests were used to determine the correlations of IOPs at 5, 15, and 30 minutes after IVI with potential predictors of IOP changes (eg, age, sex, diagnosis, lens status, axial length, history of glaucoma [defined as the use of IOP-lowering medications with clinical evidence of glaucomatous optic neuropathy], presence of

Table 1. Demographics and clinical characteristics of patients who underwent intravitreal injection (IVI) of anti-vascular endothelial growth factor for the treatment of retinal pathologies*

Characteristic	
Age, y	65.3±12.3
Sex	
Female	16 (33.3)
Male	32 (66.7)
Diagnosis	
Age-related macular degeneration	22 (45.8)
Diabetic macular edema	19 (39.6)
Retinal venous occlusion	4 (8.3)
Others (punctate inner choroidopathy, juxtafoveal telangiectasia, and myopic choroidal neovascularization)	1 (6.3)
No. of previous IVIs of anti-vascular endothelial growth factor	4.6±5.6
Lens status	
Phakic	32 (66.7)
Pseudophakic	16 (33.3)
Known history of glaucoma	4 (8.3)
Axial length, mm	24.0±1.8
Vitreous reflux after IVI	6 (12.5)

* *Data are presented as mean±standard deviation or No. (%) of patients*

vitreous reflux, and type of anti-VEGF injected). A p value of <0.05 was considered statistically significant. Multivariate regression analysis of statistically significant potential predictors was performed to identify independent predictors of IOP changes.

Results

In total, 32 men and 16 women (mean age, 65.3±12.3 years) were included (**Table 1**). The most common diagnoses were age-related macular degeneration (45.8%) and diabetic macular edema (39.6%); other diagnoses comprised retinal venous occlusion (8.3%) and others (6.3%; ie, punctate inner choroidopathy, juxtafoveal telangiectasia, and myopic choroidal neovascularization). Overall, 66.7% of patients were phakic and 8.3% had a known history of glaucoma. The mean axial length was 24.0±1.8 mm.

The mean IOP was 16.2±3.2 mmHg at baseline; it increased to 32.7±10.5 mmHg at 5 minutes after IVI, then decreased to 21.7±5.3 mmHg at 15 minutes and to 18.3±3.8 mmHg at 30 minutes. The mean differences from baseline were 16.4±10.0 mmHg, 5.5±4.7 mmHg, and 2.1±3.3 mmHg, respectively.

At 5 minutes after IVI, IOP had increased to ≥25 mmHg in 70.8% of patients (**Table 2**); moreover, IOP had increased by ≥10 mmHg in 68.8% of patients. Notably, IOP had increased to >50 mmHg in three patients (2.1%), with the maximum value of 57.9 mmHg (an increase of 40.6 mmHg). At 15 minutes after IVI, IOP remained ≥25 mmHg in 22.9% of patients. At 30 minutes after IVI, IOP remained ≥25 mmHg in only 4.2% of patients; 20.8% of patients exhibited an increase of ≥5 mmHg from baseline. At 45 minutes after IVI, IOP in eight (16.7%) patients remained ≥21 (range, 21.1-22.2) mmHg but reduced to <21 mmHg within 60 minutes. No IOP-lowering medications were required, nor was anterior chamber paracentesis necessary to prevent loss of visual function. Vitreous reflux after IVI was noted in 12.5% of patients.

The number of previous IVIs (r=0.346, p=0.016) and baseline IOP (r=0.304, p=0.04) were associated with IOP at 5 minutes after IVI. Baseline IOP was also associated with IOPs at 15 and 30 minutes after IVI (r=0.488-0.573, p<0.001) (**Table 3**). Patient diagnosis was not associated with IOPs at 5, 15, or 30 minutes after IVI (**Table 4**). Multivariate regression analysis showed that the number of previous IVIs (b=0.55, standard error=0.26, p=0.04) was an independent predictor of IOP at 5 minutes after IVI, after controlling for baseline IOP (**Table 5**).

Discussion

Consistent with the findings in previous studies,[10-14] the present study showed substantial IOP spikes at 5 minutes after IVI. However, these spikes were transient and the IOP reduced to <21 mmHg at 30 minutes in 83.3% of patients. In the remaining patients, the IOP continued to gradually decrease to <21 mmHg at 60 minutes. At 30 minutes after IVI, an IOP increase of 2.1±3.3 mmHg from baseline is not clinically significant. This indicates that short-term IOP elevation after IVI has a good safety profile. However, at 5 minutes after IVI, 77% of patients had an IOP of ≥40 mmHg; notably, three patients had an IOP of ≥50 mmHg. Such IOP spikes secondary to sudden volume expansion in the vitreous cavity can potentially deform the contour of the lamina cribrosa at the optic nerve head,[15] induce a reduction in ocular perfusion pressure that exceeds the auto-regulatory range of the optic nerve head blood flow,[16] and disturb axonal transport.[7] In an animal study, low perfusion pressure was associated with variable outer retinal layer damage and

Table 2. Intraocular pressure (IOP) at baseline and at 5, 15, and 30 minutes after intravitreal injection (IVI) of anti-vascular endothelial growth factor*

IOP, mmHg	Baseline	5 minutes after IVI	Difference from baseline	15 minutes after IVI	Difference from baseline	30 minutes after IVI	Difference from baseline
Mean	16.2±3.2	32.7±10.5	16.4±10.0	21.7±5.3	5.5±4.7	18.3±3.8	2.1±3.3
<0	0	0	0	0	5	0	15
0-<5	0	0	7	0	20	0	23
5-<10	2	0	8	0	16	0	9
10-<15	16	1	10	3	6	6	1
15-<20	24	5	5	14	0	31	0
20-<25	6	8	8	20	1	9	0
25-<30	0	6	6	8	0	2	0
30-<35	0	7	2	2	0	0	0
35-<40	0	10	1	1	0	0	0
40-<45	0	4	1	0	0	0	0
45-<50	0	4	0	0	0	0	0
50-<55	0	2	0	0	0	0	0
≥55	0	1	0	0	0	0	0

* *Data are presented as mean ± standard deviation IOP or No. of eyes*

severe atrophy of the ganglion cells, nerve fiber layer, and optic nerve.[17] Substantially elevated IOP during laser-assisted in situ keratomileusis has been shown to reduce retinal nerve fiber layer thickness; this reduction can be induced by sustained IOP of >65 mmHg for >20 s.[18] Furthermore, losses of fixation[19] and visual fields[20] secondary to IOP spikes after cataract extraction in patients with advanced glaucoma also imply that transiently elevated IOP can cause optic nerve damage. Although a short-term IOP spike after IVI is likely to be trivial in healthy eyes, it can have detrimental effects on the remaining nerve fiber layers in patients with pre-existing advanced glaucoma.[21] Thus, the cumulative long-term structural and physiological sequelae should be considered, especially when repeated IVIs are required. Each patient's IOP should be measured within 5 to 15 minutes of IVI because IOP tends to be greatest immediately after injection.

Table 3. Correlations of intraocular pressures at 5, 15, and 30 minutes after intravitreal injection (IVI) with potential predictors.

Potential predictor	Correlation coefficient / mean difference (standard error)	p Value
Age		
5 minutes after IVI	0.013	0.93
15 minutes after IVI	-0.010	0.95
30 minutes after IVI	-0.114	0.44
No. of previous IVIs		
5 minutes after IVI	0.346	0.02
15 minutes after IVI	0.242	0.10
30 minutes after IVI	0.187	0.20
Baseline intraocular pressure		
5 minutes after IVI	0.304	0.04
15 minutes after IVI	0.488	<0.001
30 minutes after IVI	0.573	<0.001
Axial length		
5 minutes after IVI	-0.061	0.68
15 minutes after IVI	0.076	0.61
30 minutes after IVI	0.137	0.35
Sex		
5 minutes after IVI	3.36 (3.22)	0.30
15 minutes after IVI	1.88 (1.63)	0.25
30 minutes after IVI	1.13 (1.15)	0.33
Lens status		
5 minutes after IVI	4.05 (3.20)	0.21
15 minutes after IVI	0.61 (1.65)	0.71
30 minutes after IVI	0.36 (1.16)	0.76
History of glaucoma		
5 minutes after IVI	4.06 (5.52)	0.47
15 minutes after IVI	2.06 (2.81)	0.47
30 minutes after IVI	1.63 (1.97)	0.41
Vitreous reflux		
5 minutes after IVI	1.31 (4.64)	0.78
15 minutes after IVI	1.25 (2.35)	0.60
30 minutes after IVI	0.13 (1.66)	0.94

In the present study, the number of previous IVIs was an independent predictor of IOP at 5 minutes after IVI. Each previous IVI was associated with an IOP increase of 0.55 mmHg at 5 minutes after the current injection. The number of previous IVIs has been identified as a risk factor for ocular hypertension.[22-26] Delayed elevated IOP was reported after repeated IVIs of bevacizumab/ranibizumab over a mean of 15 months, typically after 10 injections.[27] The odds ratio of sustained IOP elevation is 16.1-fold greater in eyes with ≥29 injections than in those with ≤12 injections.[28] In some instances, surgical intervention (eg, filtration surgery) is required for severe ocular hypertension.[29] Possible mechanisms for the development of severe ocular hypertension after IVIs include toxic or inflammatory effects of repeated IVIs on the trabecular meshwork, as well as mechanical alternation and blockage of outflow facilities by protein aggregates or contaminant particles (eg, silicone microdroplets in the packaging and injection vehicles).[30] Cumulative injury to the trabecular meshwork also contributes to acute exaggeration of elevated IOP shortly after IVI, in addition to the impact of a sudden increase in vitreous volume. Recurring substantial IOP spikes from previous injections alone can also perpetuate trabecular meshwork damage and result in further outflow obstruction and IOP elevation.[24]

The long-term effect of glaucoma development/progression secondary to repeated transient IOP spikes after IVI has not yet been elucidated. Withholding IVIs of anti-VEGF is not a desirable option given the potential comorbidities and visual loss that can arise from uncontrolled pre-existing retinal conditions. Therefore, prophylactic IOP-lowering

Table 4. Correlations of diagnosis with intraocular pressure (IOP) at 5, 15, and 30 minutes after intravitreal injection (IVI)

Diagnosis	Mean±SD IOP, mmHg		
	5 minutes after IVI	15 minutes after IVI	30 minutes after IVI
Age-related macular degeneration	32.6±10.5	21.6±5.3	18.2±4.3
Diabetic macular edema	33.3±12.0	21.6±6.3	18.3±3.8
Retinal venous occlusion	29.1±1.3	21.7±1.6	18.5±0.8
Others (punctate inner choroidopathy, juxtafoveal telangiectasia and myopic choroidal neovascularization)	32.5±10.6	21.6±5.4	18.3±3.8
p Value	0.92	1.00	0.99

Table 5. Multivariate regression analysis of potential predictors for intraocular pressure at 5 minutes after intravitreal injection

Potential predictor	b (standard error)	p Value
No. of previous intravitreal injections	0.55 (0.26)	0.04
Baseline intraocular pressure	0.79 (0.46)	0.09

measures are suggested to avoid IOP spikes and minimize trabecular damage, which may result in ocular hypertension or glaucomatous changes in the optic nerve. In a review that summarized the evidence concerning pharmacological and non-pharmacological methods for blunting acute IOP elevation, the topical application of IOP-lowering medications (eg, apraclonidine, timolol, dorzolamide-timolol, brimonidine-timolol, and brinzolamide-timolol) was considered mildly effective for reducing short-term IOP spikes.[31] However, IOP cut-offs and observation intervals vary among studies, making comparisons difficult, and the clinical benefits of these topical IOP-lowering eye drops remain uncertain. Although prophylactic oral acetazolamide can reduce IOP at 15-30 minutes after IVI, it is ineffective for minimizing IOP spikes immediately after injection (ie, when IOP elevation is greatest).[32,33] Non-pharmacological methods such as anterior chamber paracentesis and ocular decompression have beneficial effects in terms of preventing IOP spikes but carry important risks.[34] Complications such as endophthalmitis,[35] infective keratitis,[36] and anterior lens capsule laceration with localized cataract formation[37] have been reported after anterior chamber paracentesis. The benefits of these prophylactic measures in dampening the transient IOP spike after IVI remain unclear. Nonetheless, in patients susceptible to glaucomatous progression from substantial IOP spikes—especially those with advanced glaucoma and known transient visual loss related to severe acute IOP spikes and a history of repeated IVIs—these measures may be appropriate for minimizing the potential damage,[38] but they should only be implemented after a full explanation of the risks and benefits to each patient. In addition to the assessment of post-IVI visual acuity, some have suggested routine fundus examinations for signs of central retinal arterial occlusion immediately after IVI.[39] This may help to detect substantial IOP spikes in susceptible patients and allow timely administration of IOP-lowering treatment.

The limitations of this study included its small sample size and the involvement of few patients who had pre-existing glaucoma, which led to underpowered subgroup analyses and correlation studies. Furthermore, the diversity of patient diagnoses did not allow clear identification of correlations between individual diagnoses and IOP spike patterns. Nevertheless, this heterogeneous group of patients is representative of real-world patient populations and thus the results are applicable to clinical practice. Notably, a history of steroid response could be a predictor of substantial IOP spikes because of the potentially reduced trabecular outflow reserve. However, patients with steroid use within 1 month of IVI were excluded from the analysis; therefore, the potential effects of steroids on IOP spikes could not be assessed.

Conclusion

Transient but substantial IOP elevation shortly after IVI of anti-VEGF was positively correlated with the number of previous IVIs. This finding can aid in patient stratification concerning pharmacological and non-pharmacological prophylaxis for IOP spikes, especially among patients with pre-existing advanced glaucoma who are at risk of further optic nerve damage secondary to acute ocular hypertension. Ophthalmologists are advised to assess patient susceptibility to glaucomatous damage, as well as the risks and complications of various prophylactic measures for the prevention of IOP spikes.

Authors contributions

Concept or design: JT, AY
Acquisition of data: JT, IL
Analysis or interpretation of data: JT, SL
Drafting of the article: JT, NC
Critical revision for important intellectual content: all authors

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.

Conflict of interest

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Ethics approval

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References

1. *Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina 2016;36:1418-31.* Crossref
2. *Ho M, Lo EC, Young AL, Liu DT. Outcome of polypoidal choroidal vasculopathy at 1 year by combined therapy of photodynamic therapy with ranibizumab and predictive factors governing the outcome. Eye (Lond) 2014;28:1469-76.* Crossref

3. Bahrami B, Hong T, Gilles MC, Chang A. Anti-VEGF therapy for diabetic eye diseases. Asia Pac J Ophthalmol (Phila) 2017;6:535-45. Crossref
4. Jiang Y, Mieler WF. Update on the use of anti-VEGF intravitreal therapies for retinal vein occlusions. Asia Pac J Ophthalmol (Phila) 2017;6:546-53. Crossref
5. Jeong S, Sagong M, Chang W. Acute angle closure attack after an intravitreal bevacizumab injection for branch retinal vein occlusion: a case report. BMC Ophthalmol 2017;17:25. Crossref
6. Mansour AM, Bynoe LA, Welch JC, et al. Retinal vascular events after intravitreal bevacizumab. Acta Ophthalmol 2010;88:730-5. Crossref
7. Quigley HA, Anderson DR. Distribution of axonal transport blockade by acute intraocular pressure elevation in the primate optic nerve head. Invest Ophthalmol Vis Sci 1977;16:640-4.
8. Quigley H, Anderson DR. The dynamics and location of axonal transport blockade by acute intraocular pressure elevation in primate optic nerve. Invest Ophthalmol 1976;15:606-16.
9. Yannuzzi NA, Patel SN, Bhavsar KV, Sugiguchi F, Freund KB. Predictors of sustained intraocular pressure elevation in eyes receiving intravitreal anti-vascular endothelial growth factor therapy. Am J Ophthalmol 2014;158:319-27.e2. Crossref
10. Lee JW, Park H, Choi JH, et al. Short-term changes of intraocular pressure and ocular perfusion pressure after intravitreal injection of bevacizumab or ranibizumab. BMC Ophthalmol 2016;16:69. Crossref
11. Farhood QK, Twfeeq SM. Short-term intraocular pressure changes after intravitreal injection of bevacizumab in diabetic retinopathy patients. Clin Ophthalmol 2014;8:599-604. Crossref
12. Hollands H, Wong J, Bruen R, Campbell RJ, Sharma S, Gale J. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. Can J Ophthalmol 2007;42:807-11. Crossref
13. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol 2008;146:930-4.e1. Crossref
14. Park J, Lee M. Short-term effects and safety of an acute increase of intraocular pressure after intravitreal bevacizumab injection on corneal endothelial cells. BMC Ophthalmol 2018;18:17. Crossref
15. Yan DB, Coloma FM, Metheetrairut A, Trope GE, Heathcote JG, Ethier CR. Deformation of the lamina cribrosa by elevated intraocular pressure. Br J Ophthalmol 1994;78:643-8. Crossref
16. Michelson G, Groh MJ, Langhans M. Perfusion of the juxtapapillary retina and optic nerve head in acute ocular hypertension. Ger J Ophthalmol 1996;5:315-21.
17. Anderson DR, Davis EB. Sensitivities of ocular tissues to acute pressure-induced ischemia. Arch Ophthalmol 1975;93:267-74. Crossref
18. Tsai YY, Lin JM. Effect of laser-assisted in situ keratomileusis on the retinal nerve fiber layer. Retina 2000;20:342-5. Crossref
19. Kolker AE. Visual prognosis in advanced glaucoma: a comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans Am Ophthalmol Soc 1977;75:539-55.
20. Savage JA, Thomas JV, Belcher CD 3rd, Simmons RJ. Extracapsular cataract extraction and posterior chamber intraocular lens implantation in glaucomatous eyes. Ophthalmology 1985;92:1506-16. Crossref
21. Tranos P, Bhar G, Little B. Postoperative intraocular pressure spikes: the need to treat. Eye (Lond) 2004;18:673-9. Crossref
22. Menke MN, Salam A, Framme C, Wolf S. Long-term intraocular pressure changes in patients with neovascular age-related macular degeneration treated with ranibizumab. Ophthalmologica 2013;229:168-72. Crossref
23. Baek SU, Park IW, Suh W. Long-term intraocular pressure changes after intravitreal injection of bevacizumab. Cutan Ocul Toxicol 2016;35:310-4. Crossref
24. Hoang QV, Mendonca LS, Della Torre KE, Jung JJ, Tsuang AJ, Freund KB. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. Ophthalmology 2012;119:321-6. Crossref
25. Agard E, Elchehab H, Ract-Madoux G, Russo A, Lagenaite C, Dot C. Repeated intravitreal anti-vascular endothelial growth factor injections can induce iatrogenic ocular hypertension, especially in patients with open-angle glaucoma. Can J Ophthalmol 2015;50:127-31. Crossref
26. Beato J, Pedrosa AC, Pinheiro-Costa J, et al. Long-term effect of anti-VEGF agents on intraocular pressure in age-related macular degeneration. Ophthalmic Res 2016;56:30-4. Crossref
27. Pershing S, Bakri SJ, Moshfeghi DM. Ocular hypertension and intraocular pressure asymmetry after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina 2013;44:460-4. Crossref
28. Hoang QV, Tsuang AJ, Gelman R, et al. Clinical predictors of sustained intraocular pressure elevation due to intravitreal anti-vascular endothelial growth factor therapy. Retina 2013;33:179-87. Crossref
29. Eadie BD, Etminan M, Carleton BC, Maberley DA, Mikelberg FS. Association of repeated intravitreous bevacizumab injections with risk for glaucoma surgery. JAMA Ophthalmol 2017;135:363-8. Crossref
30. Liu L, Ammar DA, Ross LA, Mandava N, Kahook MY, Carpenter JF. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. Invest Ophthalmol Vis Sci 2011;52:1023-34. Crossref
31. Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: a review. Surv Ophthalmol 2018;63:281-95. Crossref
32. Murray CD, Wood D, Allgar V, Walters G, Gale RP. Short-term intraocular pressure trends following intravitreal ranibizumab injections for neovascular age-related macular degeneration-the role of oral acetazolamide in protecting glaucoma patients. Eye (Lond) 2014;28:1218-22. Crossref
33. El Chehab H, Le Corre A, Agard E, Ract-Madoux G, Coste O, Dot C. Effect of topical pressure-lowering medication on prevention of intraocular pressure spikes after intravitreal injection. Eur J Ophthalmol 2013;23:277-83. Crossref
34. Knip MM, Valimaki J. Effects of pegaptanib injections on intraocular pressure with and without anterior chamber paracentesis: a prospective study. Acta Ophthalmol 2012;90:254-8. Crossref
35. Helbig H, Noske W, Kleineidam M, Kellner U, Foerster MH. Bacterial endophthalmitis after anterior chamber paracentesis. Br J Ophthalmol 1995;79:866. Crossref
36. Azuara-Blanco A, Katz LJ. Infectious keratitis in a paracentesis tract. Ophthalmic Surg Lasers 1997;28:332-3. Crossref
37. Trivedi D, Denniston AK, Murray PI. Safety profile of anterior chamber paracentesis performed at the slit lamp. Clin Exp Ophthalmol 2011;39:725-8. Crossref
38. Aref AA. Management of immediate and sustained intraocular pressure rise associated with intravitreal antivascular endothelial growth factor injection therapy. Curr Opin Ophthalmol 2012;23:105-10. Crossref
39. Peters S, Heiduschka P, Julien S, et al. Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. Am J Ophthalmol 2007;143:995-1002. Crossref

CASE REPORT

Quantitative polymerase chain reaction test for molecular diagnosis of intraocular relapse of acute lymphoblastic leukemia: a case report

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Abstract

Leukemia relapse rarely presents with ophthalmic manifestations. We report on a 62-year-old woman with relapse of Philadelphia chromosome–positive acute lymphoblastic leukemia who presented with ocular infiltration as the sole presentation. The diagnostic difficulties are also discussed.

Key words: Leukemia, lymphoid; Molecular diagnostic techniques; Polymerase chain reaction

Introduction

Patients with leukemia often have ocular manifestations secondary to direct leukemic infiltration or indirect effects of hematological abnormalities, central nervous system involvement, infections, or therapy.[1] However, leukemia relapse presenting with ocular involvement is uncommon. We report a case of adult Philadelphia chromosome–positive acute lymphoblastic leukemia relapse with orbital infiltration as the sole presentation. The diagnostic difficulties are also discussed.

Case presentation

In April 2019, a 62-year-old woman was referred to our ophthalmology department with a 2-day history of sudden vision loss, swelling, and redness of the right eye. She had been diagnosed with Philadelphia chromosome–positive acute lymphoblastic leukemia 1 year earlier. After the first course of chemotherapy, she relapsed but responded to further chemotherapy and haplo-allogeneic bone marrow transplant. She was receiving blinatumomab immunotherapy, along with low-dose steroids, prophylactic antivirals, antibiotics, and antifungals. During the first year of treatment, she had fungal lung infection and made a full recovery.

She had no ocular history of laser, surgery, or trauma except for right eye retinal barrier laser over 30 years earlier. On examination, visual acuity was light perception in the right eye and 20/20 in the left eye. The right eye had relative afferent pupillary defect. Intraocular pressure was 20 mmHg. Extraocular movements were restricted in all directions, with marked proptosis. Biomicroscopy examination showed severe chemosis and conjunctival injection. The anterior chamber was quiet with no cells, with an immature cataract. Fundoscopy revealed optic disc swelling with whitish infiltrate at the macula, along with

retinal hemorrhages in all four quadrants. The vitreous was clear with no cells. Ocular coherence tomography of the macula and disc showed marked thickening of the macula and disc with significant subretinal fluid (**Figure 1**). Anterior segment examination and dilated fundoscopy of the left eye was unremarkable. Orbital infiltration secondary to leukemia relapse was suspected, with proptosis and compression of the optic nerve resulting in a central retinal vein occlusion pattern and orbital inflammation. One differential diagnosis was orbital infection secondary to the immunocompromised state. However, the patient had no history of fever, and her vitals were stable, and her peripheral blood count did not show any leukocytosis suggestive of sepsis. In addition, she had no history of diabetes mellitus, hypertension, or hypercoagulable states that might have contributed to the central retinal vein occlusion. Another differential diagnosis was idiopathic orbital inflammatory syndrome. It was important to rule out leukemia relapse.

Peripheral blood smear did not show any blasts and was negative for bcr-abl p190 quantitative polymerase chain reaction (qPCR). Owing to existing thrombocytopenia, the patient did not undergo lumbar puncture or bone marrow aspirate. Magnetic resonance imaging of the brain and orbit showed proptosis of the right eye with increased heterogenous enhancement at the intraconal space (**Figure 2**). Sclerochoroidal complex, extraocular muscles, and optic nerve were also thickened with contrast enhancement along the nerve. The eyelid and preseptal fat also enhanced abnormally. These findings suggested orbital inflammation with possible infiltration of the optic nerve and orbit.

Owing to the high index of suspicion for leukemia relapse, the patient was treated with a tapering course of intravenous dexamethasone. She also received topical levofloxacin, timolol 0.5% and intensive lubricants.

To obtain a molecular diagnosis and rule out infection, orbital tissue biopsy was proposed, but it has a high risk of hemorrhage owing to the patient's thrombocytopenia. The patient refused invasive procedure but agreed to undergo an aqueous tap for cytological examination and microbiological cultures, although aqueous was likely to have a lower yield of positive results because of the lack of cells in the anterior chamber. Flow cytometry result was negative for leukemic cells, but qPCR result was positive for bcr-abl p190, which provided a molecular diagnosis of localized leukemia relapse (**Figure 3**).

Within 2 days of starting intravenous steroids, orbital inflammation improved markedly, with eventual resolution of chemosis and disc swelling, resulting in a pale and atrophic disc. The patient underwent orbital radiotherapy (15 Gy) over the next 3 weeks. Unfortunately, her vision did not recover, with no light perception. The patient continued with immunotherapy, but the disease continued to progress. She eventually received palliative care overseas and died 4 months later.

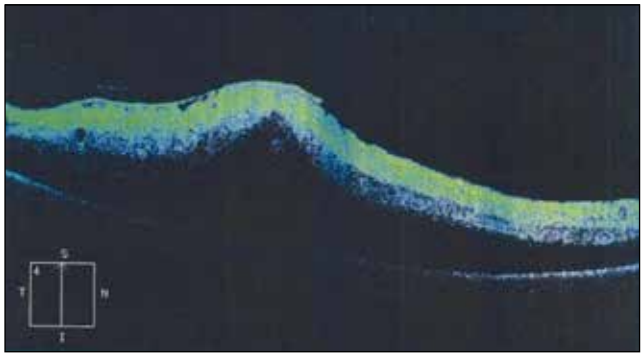

Figure 1. Ocular coherence tomography of the right eye showing marked thickening of the macula and disc with significant subretinal fluid.

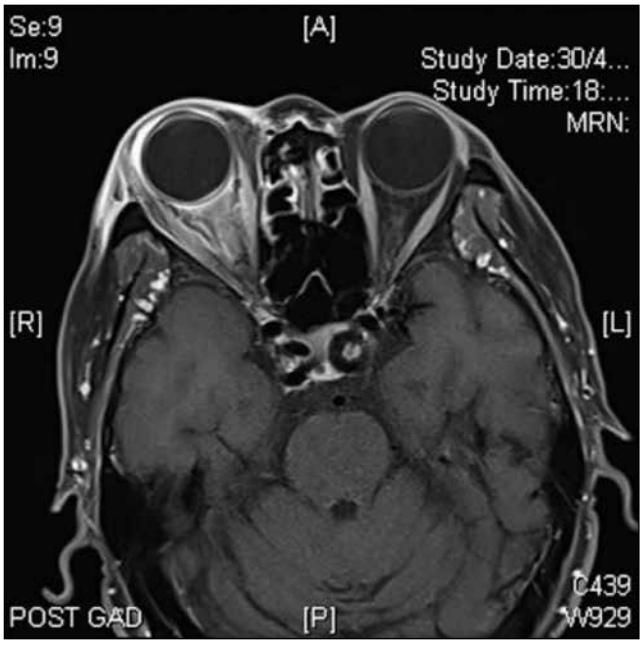

Figure 2. T1-weighted magnetic resonance imaging of the brain and orbit showing proptosis of the right eye with heterogenous enhancement in the intraconal space and thickened optic nerve. Sclerochoroidal complex and extraocular muscles are also thickened. The eyelid and preseptal fat enhance abnormally.

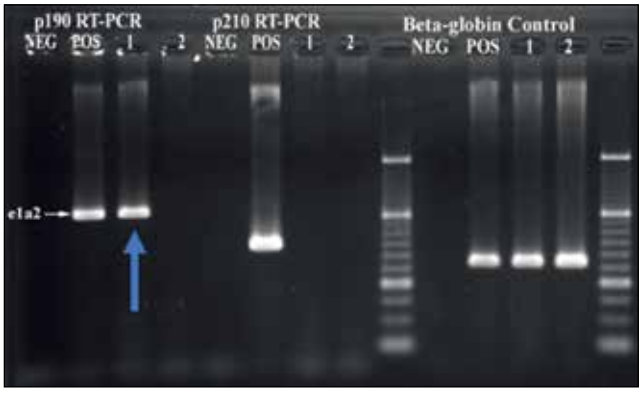

Figure 3. Quantitative polymerase chain reaction result from an aqueous sample is positive for bcr-abl p190 genetic abnormality (arrow).

Discussion

To the best of our knowledge, this is the first case in which aqueous aspirate flow cytometry was negative for leukemic cells but positive for molecular PCR diagnostics. This case highlights the diagnostic difficulties and the importance of molecular diagnostics in addition to flow cytometry, especially when tissue biopsy is not feasible.

Leukemia may affect the eye in various ways (**Table**). Leukemia manifested as direct infiltration of the eye is uncommon. Indirect manifestations secondary to hematological abnormalities (such as hyperviscosity syndromes and thrombocytopenia), chemotherapy, radiation, bone marrow transplantation, and infection are more common.[1] Epidemiological studies have reported that around 40% of patients with newly diagnosed leukemia exhibit ocular signs, although they may not necessarily cause visual symptoms.[2,3] Leukemia relapse with sole involvement of the orbit is rare and is likely to occur in acute lymphoblastic leukemia. The central nervous system (CNS) may act as a sanctuary for leukemic cells, because the blood-brain barrier prevents systemic chemotherapy from entering the CNS.[4] Malignant cells may infiltrate the optic nerve and orbit and cause relapse. Orbital involvement may present as an orbital abscess secondary to infection of necrotic infiltrated orbital tissues.[5] In a review of 2780 children with acute lymphoblastic leukemia followed up over 10 years, only 20 had intraocular relapse, accounting for 2% of all acute lymphoblastic leukemia relapses.[6] For adults, isolated cases of eye involvement during relapse have been reported. In a review of 458 adults with remission from acute myeloid leukemia, the 5-year cumulative incidence of meningeal relapse was only 0.3% in those treated with modern chemotherapy protocols,[7] compared with 5% in adult patients with acute lymphoblastic leukemia in remission.[8] Optic nerve infiltration may be categorized as disease relapse involving the CNS; therefore, the proportion of patients with intraocular involvement in relapse is even smaller. CNS relapse of leukemia is associated with a poor prognosis. In a UK study in 1992, the 5-year survival rate was 21.4% in pediatric patients with ocular involvement of acute leukemia, compared with 45.7% in those without ocular involvement.[9]

Treatment for leukemic infiltration of the eye should target the underlying systemic malignancy. Newly diagnosed patients should undergo a treatment protocol of induction, consolidation, and maintenance, usually involving intensive systemic chemotherapy. Intrathecal chemotherapy and radiotherapy may be required for CNS involvement. Allogeneic bone marrow transplants may be required for leukemias with aggressive clinical course and unfavorable cytogenetics. Relapse protocols depend on the affected site. Relapse at the orbit or optic nerve is usually managed as CNS relapse. Patients usually require orbital or cranial irradiation as well as systemic and intrathecal chemotherapy.[5] However, no formal guidelines exist for the treatment of orbital relapse.

Diagnosing leukemia relapse in immunosuppressed patients is difficult, as they are susceptible to opportunistic infections that may mask or mimic relapse. Ocular leukemic infiltration may masquerade as uveitis and infection, and therefore a high index of suspicion and a cytological or molecular diagnosis is important to initiate prompt and appropriate treatment. In our patient, the severe proptosis, chemosis, vision loss, and optic nerve swelling indicated possible orbital infection or inflammation in addition to leukemic infiltration.

Ideally, vitreous, retinal, or optic nerve biopsy should be performed for immunohistochemistry and direct visualization of leukemic cells. However, biopsy of such tissue samples may not be safe, as in our case, optic nerve biopsy may have resulted in irreversible visual loss, and the bleeding risk was high owing to thrombocytopenia. Lumbar puncture should

Table. Leukemic involvement in the eye (adapted from Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. Eye 2004;18:663-72.)

Eye part	Manifestation
Lids	Ectropion, edema, mechanical ptosis
Conjunctiva	Chemosis, conjunctival mass, corkscrew vessels, conjunctivitis
Cornea	Keratitis-limbal infiltration or secondary to immunosuppression or graft-versus-host disease, sterile ring ulcers, pannus, melt syndrome, dry eyes, epithelial changes secondary to chemotherapy
Orbit	Exophthalmos, orbital/preseptal cellulitis, endophthalmitis, dacryocystitis
Iris, angle, anterior chamber, and lens	Glaucoma, uveitis, hyphema, pseudohypopyon (yellow/grey), heterochromia, cataract secondary to treatment
Retina	Hemorrhage at all levels, perivascular infiltrates, retinitis, vitreous hemorrhage, microaneurysms, cotton wool spots, peripheral neovascularization, retinal detachments, drusen, vascular occlusion, retinitis secondary to opportunistic infections
Choroid	Thickened with associated serous retinal detachment
Optic nerve and central nervous system	Nausea, vomiting, lethargy, seizures, diplopia, asymptomatic papilloedema, blurred vision as a result of compromised optic nerve function
Miscellaneous	Anterior segment ischemia, lacrimal gland infiltration, opportunistic infections
Extramedullary relapse in eye	Uveitis, proptosis due to retro-orbital mass, retinal detachment, disc swelling

be considered to confirm CNS relapse involving the optic nerve, but it was contraindicated in our patient owing to thrombocytopenia.

An aqueous tap is relatively safe and easy to obtain, with low infection risk. Vitreous taps may have lower yield because vitreous may plug the needle during aspiration, preventing large amounts of vitreous fluid from being aspirated. Aqueous aspirate can be sent for microbiological examination and cultures, cytological examination, flow cytometry, and/or molecular diagnostics such as gPCR. The feasibility and logistics of performing qPCR and flow cytometry on aqueous samples or vitreous biopsies should be discussed with laboratories on a case-by-case basis, as not all laboratories have the capability of performing and validating these tests on such samples.

Flow cytometry uses a laser probe to detect, count, and profile cells within the fluid sample. Cell surface markers are fluorescently labelled to enable detection by the laser. Flow cytometry is useful to aid in the diagnosis of intraocular lymphoma.[10] Several case reports described using flow cytometry and qPCR to diagnose intraocular infiltration of leukemia.[11,12]

The success of cytological examination and flow cytometry depends on obtaining sufficient leukemic cells for detection. Some recommend >10 mL of cerebrospinal fluid, which is not feasible for aqueous aspirate assuming that affected aqueous humor has similar cell counts to cerebrospinal fluid.[13] Turbid aqueous, such as those taken from hypopyons, may act like highly proteinaceous effusions with large amounts of cell debris and reactive cells that may obscure leukemic cells.[10] All these samples should be processed in a timely fashion, as cells may deteriorate rapidly for adequate identification.

In our patient, flow cytometry of the aqueous aspirate was negative for leukemic cells. This could be due to a low lymphocyte cell count within the sample, as CD45+ lymphocytes accounted for 10.5% of nucleated cells, and B cells accounted for only 7% of these lymphocytes.

qPCR is a molecular diagnostic test widely used in the diagnosis of leukemia.[4] It amplifies and detects specific target DNA sequences or gene rearrangements in a sample. Our patient had bcr-abl p190 abnormal RNA sequence based on genetic phenotyping of her Philadelphia chromosome–positive acute lymphoblastic leukemia when she was initially diagnosed. We could extract RNA from the aqueous sample and detect an abnormal bcr-abl p190 sequence through qPCR to confirm the diagnosis.

The positive result from qPCR may be due to a small number of infiltrative tumor cells causing subclinical uveitis in the anterior chamber or the presence of tumor cells within the chemotic conjunctiva that contaminated the aqueous sample (but the latter cannot be proven without orbital tissue biopsy). qPCR is a useful and sensitive test to confirm leukemia relapse, owing to its ability to amplify DNA and RNA sequences. This test should be promptly processed to prevent RNA-ase degrading the sample. To confirm suspected intraocular involvement of leukemia, qPCR and flow cytometry of intraocular specimens should be performed promptly. Close cooperation with the hematologist and histopathologist may speed up the process. To improve the diagnostic yield, larger samples taken from vitreous, retinal, or optic nerve biopsy are preferred, in addition to lumbar puncture. However, patients with systemic condition may not be suitable for invasive procedures, especially retinal biopsy, which requires post-operative posturing for intraocular gas or oil tamponade. Instead, aqueous or vitreous taps should be considered, although they have a lower yield and may not be supported by all laboratories. qPCR is preferable to flow cytometry, as it requires a smaller sample cell count to detect disease, but qPCR is not widely available. If qPCR is not available, then cytology may be the first step to identify disease relapse. Lumbar puncture should be performed, if possible, to support a histopathological diagnosis of intraocular leukemic involvement.

Conclusion

A high index of suspicion is needed to diagnose leukemia relapse in patients presenting with ocular symptoms only. Infection may mimic leukemic infiltration. Aqueous aspirate is a useful and safe procedure to obtain samples for cytological and molecular diagnosis. qPCR may confirm the diagnosis even if flow cytometry result is negative. Urgent orbital or cranial radiotherapy should be performed to reduce the risk of irreversible visual loss. Full peripheral blood and marrow examination should be performed to identify other systemic relapse.

Ethics approval

This study was approved by the Medical Group Research Committee of the Hong Kong Sanatorium Hospital (reference: RC-2020-07), and the patient was treated in accordance with the Declaration of Helsinki. Written informed consent for publication was not obtained from the patient before she died. Her next of kin was unable to be contacted for consent.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Author contributions

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.

References

1. *Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. Curr Opin Ophthalmol 2016;27:545-51.* Crossref
2. *Koshy J, John MJ, Thomas S, Kaur G, Batra N, Xavier WJ. Ophthalmic manifestations of acute and chronic leukemias presenting to a tertiary care center in India. Indian J Ophthalmol 2015;63:659-64.* Crossref
3. *Reddy SC, Jackson N, Menon BS. Ocular involvement in leukemia: a study of 288 cases. Ophthalmologica 2003;217:441-5.* Crossref
4. *Larson RA. Managing CNS disease in adults with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59:3-13.* Crossref
5. *Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. Eye (Lond) 2004;18:663-72.* Crossref
6. *Somervaille TC, Hann IM, Harrison G, et al. Intraocular relapse of childhood acute lymphoblastic leukaemia. Br J Haematol 2003;121:280-8.* Crossref
7. *Martínez-Cuadrón D, Montesinos P, Pérez-Sirvent M, et al. Central nervous system involvement at first relapse in patients with acute myeloid leukemia. Haematologica 2011;96:1375-9.* Crossref
8. *Larson RA. Managing CNS disease in adults with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59:3-13.* Crossref
9. *Ohkoshi K, Tsiaras WG. Prognostic importance of ophthalmic manifestations in childhood leukaemia. Br J Ophthalmol 1992;76:651-5.* Crossref
10. *Davis JL, Miller DM, Ruiz P. Diagnostic testing of vitrectomy specimens. Am J Ophthalmol 2005;140:822-9.* Crossref
11. *Cerdà-Ibáñez M, Bayo-Calduch P, Manfreda-Domínguez L, Duch-Samper A. Acute vision loss as the only sign of leukemia relapse. Retin Cases Brief Rep 2018;12:10-1.* Crossref
12. *Hiraoka M, Ohguro H, Ikeda H, Furuya D, Takahashi S. Intraocular infiltration of Philadelphia chromosome-positive acute lymphoblastic leukemia diagnosed by polymerase chain reaction from the aqueous humor: a case report. Medicine (Baltimore) 2020;99:e18872.* Crossref
13. *Leach M, Drummond M, Doig A. Limitations. In: Practical Flow Cytometry in Haematology Diagnosis. John Wiley & Sons: 2013:20-30.*

CASE REPORT

Dry eyes — vitamin A deficiency is a differential diagnosis not to be missed: a case report

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Abstract

We describe a 53-year-old woman who presented with dry eye disease with poor vision in both eyes secondary to vitamin A deficiency.

Key words: Cornea; Dry eye syndromes; Night blindness; Vitamin A deficiency; Xerophthalmia

Introduction

Dry eye is classified as aqueous deficient or evaporative or a combination of the two. In a multi-center study of >1800 Chinese adults aged 18 to 45 years, 41.4% were diagnosed with dry eye disease. Most of them had evaporative dry eyes caused by a reduced tear film break-up time; only about 25% had aqueous deficiency based on the Schirmer test. We present a case of dry eye disease with low vision in both eyes secondary to vitamin A deficiency.

Case presentation

In December 2018, a 53-year-old Chinese woman was referred to our clinic with a 2-year history of bilateral dry eyes, corneal erosions, and blurring of vision. Her vision was worse at night. The patient had no family history of night blindness. The ocular dryness could not be resolved despite hourly instillation of preservative-free artificial tears. In 2014, she had hematuria secondary to urinary tract infection and bilateral renal stones. In 2015, the patient had undergone bilateral mastectomies for breast cancer (T1aN0M0), after which she declined hormonal therapy and opted for traditional Chinese medicine treatment. She was in remission since then.

On examination, corrected visual acuity in both eyes were 6/200 despite pinhole correction. Slit-lamp examination revealed the presence of whitish plaque-like lesions with crisscrossing lines over the nasal and temporal bulbar conjunctiva (**Figure 1**). The ocular surface appeared dull with marked conjunctival xerosis. Fluorescein staining revealed severe erosions of both corneas. The patient was very sensitive to light during examination. Fundal examination revealed diffuse pigmentary changes in the peripheral retinas of both eyes. Schirmer's test showed normal levels of aqueous tear production.

Differential diagnoses of dry eyes and depositions of keratin on the ocular surface include keratoconjunctivitis sicca, with or without underlying autoimmune diseases such as Sjögren syndrome, systemic lupus erythematosus, and thyroid disorders. Results of serological tests were negative for anti-nuclear antibodies, anti-neutrophil cytoplasmic antibody, and anti-double stranded DNA antibodies. Serum thyroid stimulating hormone was within normal levels. Cicatricial conjunctivitis such as Stevens-Johnson syndrome and atopic keratoconjunctivitis may also give rise to a keratinized surface, but patient had no history of generalized skin eruption or rash or ocular itch (a hallmark feature in ocular atopy). Neoplastic causes such as ocular surface squamous neoplasia may be a masquerade, but simultaneous bilateral involvement is rare unless in immunocompromised individuals.

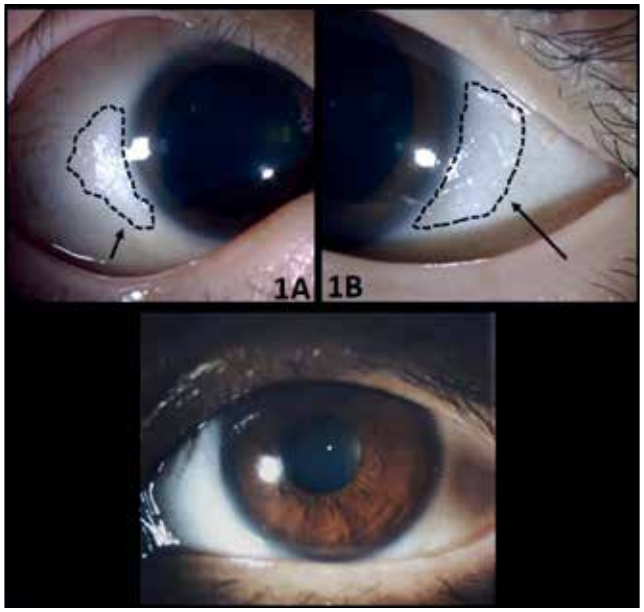

Figure 1. (a) The presence of Bitot's spots on the interpalpebral conjunctiva. (b) Disappearance of Bitot's spots and restoration of the normal luster of the ocular surface after vitamin A supplementation.

Results of automated perimetry were unreliable, as the patient could not identify or fixate on the target. Full-field electroretinogram revealed both delayed and reduction in the amplitudes of a and b waves following a light stimulus in both light and dark adaptation, with a diminished 30-Hz flicker response (**Figure 2**). All these suggested a generalized rod and cone dysfunction in both eyes. Vitamin A deficiency with xerosis and night blindness was suspected. Blood test revealed a borderline reduction in serum zinc level at 10.0 (normal range, 10.7-18.0) μmol/L and reduced vitamin A level at 26 (normal range, 38-98) μg/dL. A nutrition history revealed that the patient had avoided vegetables, eggs, melons, and milk in diet owing to 'irritable bowels'. She was counselled on change in diet and use of oral vitamin supplementation, but she refused the latter.

Two months after a change in diet, her vision improved to 18/200 bilaterally. Pinhole correction further improved the vision to 20/40. In March 2020, she eventually opted for vitamin supplement. In May 2020, she reported improvement in night vision, with resolution of photopsia, tearing, and eye discharge. In July 2020, her vision with spectacles improved to 20/40 and 20/30 in the right and left eyes, respectively.

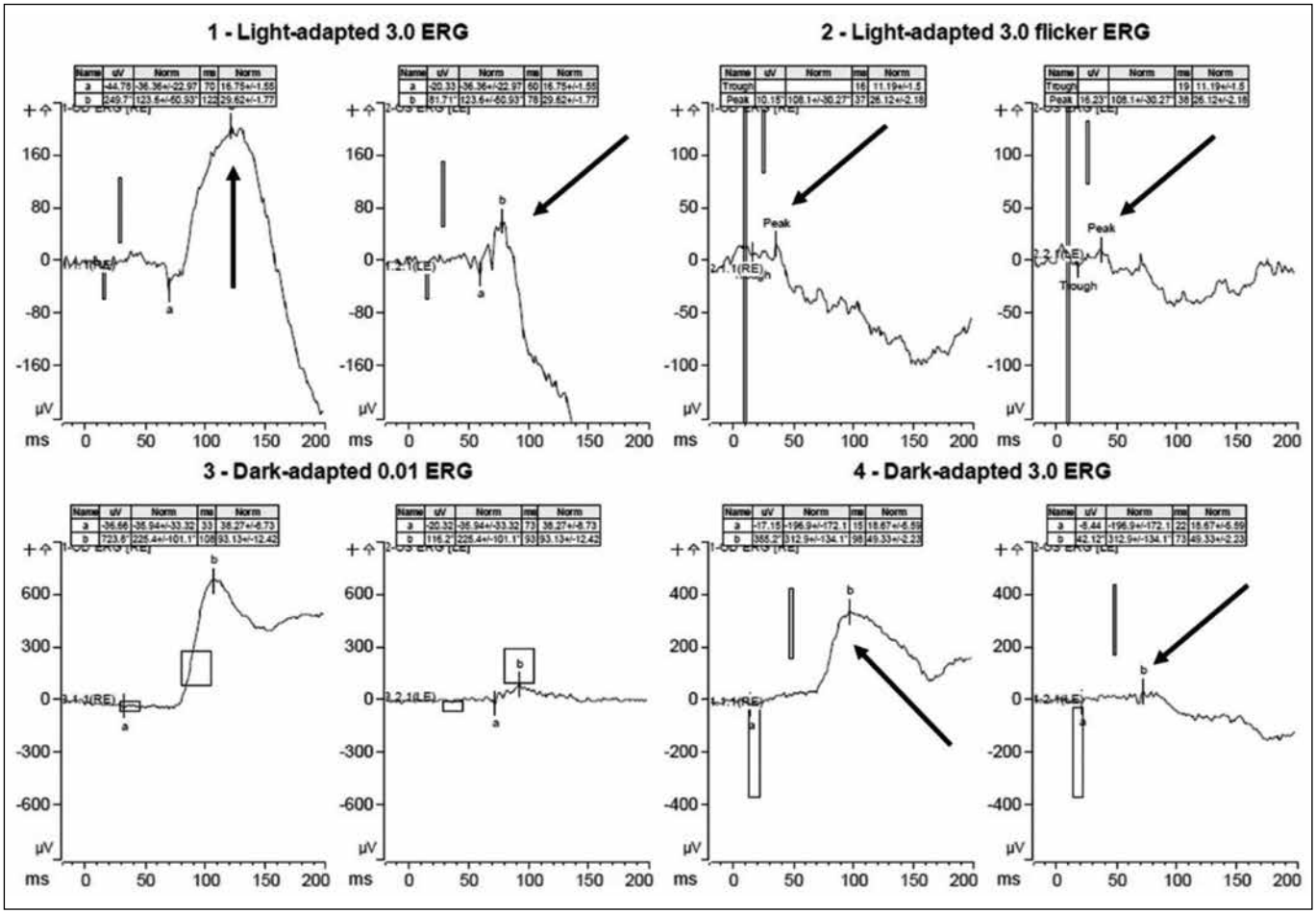

Figure 2. Light- and dark-adapted full-field electroretinogram showing the delayed and reduced amplitudes of a and b waves after a light stimulus suggestive of a generalized dysfunction of rod and cone photoreceptors in right and left eyes.

Examination revealed disappearance of punctate epithelial erosions on both corneas and restoration of a stable tear film with a break-up time of >5 s. Pigmentary retinopathy resolved in both fundi.

Discussion

Vitamin A deficiency is a rare cause of dry eyes and a common cause of night blindness. Globally, vitamin A deficiency is the leading cause of preventable blindness in children in low-income countries.[1] In developed countries, vitamin A deficiency usually occurs in patients with bariatric surgery, pancreato-hepato-biliary surgery, bowel diseases, and psychiatric disorders with dietary restrictions. Xerophthalmia is an ocular complication of vitamin A deficiency.[2] Our patient had night blindness, conjunctival xerosis, Bitot's spots, and corneal xerosis, all of which are reversible upon treatment.

Vitamin A is fat-soluble micronutrients essential in the visual cycle.[3] These compounds include retinol, retinal, retinoic acid, and carotenoids; they can be found in animal liver, egg yolk, and vegetables. Vitamin A is responsible for the recycling of rhodopsin, a visual pigment found in rod photoreceptors accountable for night vision. Absorption, metabolism, hepatic release, transport, and tissue utilization of vitamin A rely on adequate zinc in the system.[4] Zinc regulates the metabolic conversion of retinol to retinal in the retina by mediating a zinc-dependent enzyme known as alcohol dehydrogenase. Conversely, severe vitamin A deficiency limits the absorption and lymphatic transportation of zinc by altering the synthesis of a zinc-dependent binding protein. Vitamin A and zinc have a synergetic effect in maintaining the structures of corneal and conjunctival epithelium.[5] Hypovitaminosis leads to a loss of goblet cells, which is an important source of glycoproteins that wet the ocular surface. This is followed by squamous cell metaplasia in the conjunctiva leading to xerosis and deposition of keratin in the perilimbal areas of the interpalpebral conjunctiva.

Diagnosing vitamin A deficiency relies on detailed clinical history taking and a blood test for serum level of vitamin A. In Hospital Authority, only serum zinc level test is available. Patients with suspected vitamin A deficiency are referred to private laboratories for a diagnosis. Causes of vitamin A deficiency include dietary insufficiency, defects in absorption (eg, chronic diarrhea, malabsorption syndrome, and bile salt deficiency), transportation (Kwashiorkor disease) or storage (liver disease) of vitamin A. Medication for xerophthalmia in adolescents and adults consists of three oral doses of vitamin A at 200 000 international units. The first dose should be given immediately on diagnosis, the second on the next day, and the third at least 2 weeks later. Women of reproductive age or during pregnancy should be given smaller doses unless the xerophthalmia is severe. In severe cases or patients unable to take oral medications, intramuscular injections of 100 000 international units of vitamin A is an alternative. Topical vitamin A ophthalmic ointment is not available in Hong Kong, but the ointment itself is inadequate to treat underlying systemic hypovitaminosis. Zinc supplementation is rarely required especially in developed countries. Children with zinc deficiency in resource-limited countries may benefit from zinc supplementation at 1-2 mg/kg/day for 4 to 6 weeks.

Conclusion

Vitamin A deficiency is rare in developed countries. It can cause treatable ocular dryness and blindness. Workup for dry eyes should include a nutritional history for any food restrictions and a medical history for any relevant gastrointestinal tract disorders to reveal any underlying vitamin A deficiency.

Author contributions

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 no conflicts of interest to disclose.

Funding/support

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed consent for the treatment/procedures and publication.

References

1. *Sherwin JC, Reacher MH, Dean WH, Ngondi J. Epidemiology of vitamin A deficiency and xerophthalmia in at-risk populations. Trans R Soc Trop Med Hyg 2012;106:205-14.* Crossref
2. *Control of vitamin A deficiency and xerophthalmia. World Health Organ Tech Rep Ser 1982;672:1-70.*
3. *Wald G. Molecular basis of visual excitation. Science 1968;162:230-9.* Crossref
4. *Christian P, West KP Jr. Interactions between zinc and vitamin A: an update. Am J Clin Nutr 1998;68(2 Suppl):435S-441S.* Crossref
5. *Kanazawa S, Kitaoka T, Ueda Y, Gong H, Amemiya T. Interaction of zinc and vitamin A on the ocular surface. Graefes Arch Clin Exp Ophthalmol 2002;240:1011-21.* Crossref

CASE REPORT

Metastatic versus metachronous adenoid cystic carcinoma in the lacrimal gland fossa: a case report

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Abstract

A 53-year-old woman presented with a left painless enlarging lacrimal fossa lesion with hypoglobus and choroidal folds. 18 months earlier, she had undergone surgery and chemoradiotherapy for right maxillary sinus adenoid cystic carcinoma. After initial 1.5T magnetic resonance imaging, a double primary of left lacrimal gland adenoid cystic carcinoma with tricompartmental (frontal bone, lacrimal and temporalis fossa) involvement was suspected. However, subsequent high-field multi-parametric 3T magnetic resonance imaging suggested a solitary metastasis with a subperiosteal location and an uninvolved lacrimal gland. The solitary metastasis was confirmed intraoperatively and pathologically.

Key words: Carcinoma, adenoid cystic; Lacrimal apparatus; Multiparametric magnetic resonance imaging

Introduction

Adenoid cystic carcinoma (ACC) is the most common lacrimal gland epithelial cancer, accounting for up to 60% of all cases in one series.[1] Primary tumor excision, exenteration and/or craniofacial resection together with intra-arterial chemotherapy and external beam irradiation are treatment options depending on tumor staging and clinician experience.[2,3] We herein describe a patient who presented with an expanding solitary subperiosteal metastasis of maxillary sinus ACC mimicking a double primary of contralateral lacrimal gland ACC.

Case presentation

In December 2019, a 53-year-old woman presented to our hospital with worsening of the left lower visual field loss. In January 2018, she had undergone subtotal maxillectomy, free fibular flap reconstruction, and adjuvant chemoradiotherapy elsewhere for a pT3N0 ACC of the right maxilla. On examination, her left eye had 7-mm proptosis, 3-mm hypoglobus, limited elevation and superotemporal choroidal folds, and a vaguely palpable non-tender swelling over the lacrimal gland fossa. 1.5T magnetic resonance imaging (MRI) of the orbit showed a well-circumscribed, homogenously contrast-enhancing, T1-hyperintense lesion measuring 2.0×1.7×0.8 cm over the left lacrimal gland fossa, with frontal bone involvement and suspicious contiguous lymphadenopathy (**Figure**).

In March 2020, 3T MRI showed a 2.4×2.4×1.7 cm subperiosteally located lesion in the lacrimal gland fossa indenting onto the left globe with interval increase in size. It was slightly T1-hyperintense to the extraocular muscle and lacrimal gland, heterogeneous T2-hyperintense with small cystic component and a higher degree of contrast enhancement. A normal looking lacrimal gland was inferiorly displaced. Bony dehiscence and extension of the lesion into the temporalis fossa was demonstrated (Figure). Positron emission tomography showed additional multiple nodules in bilateral lungs.

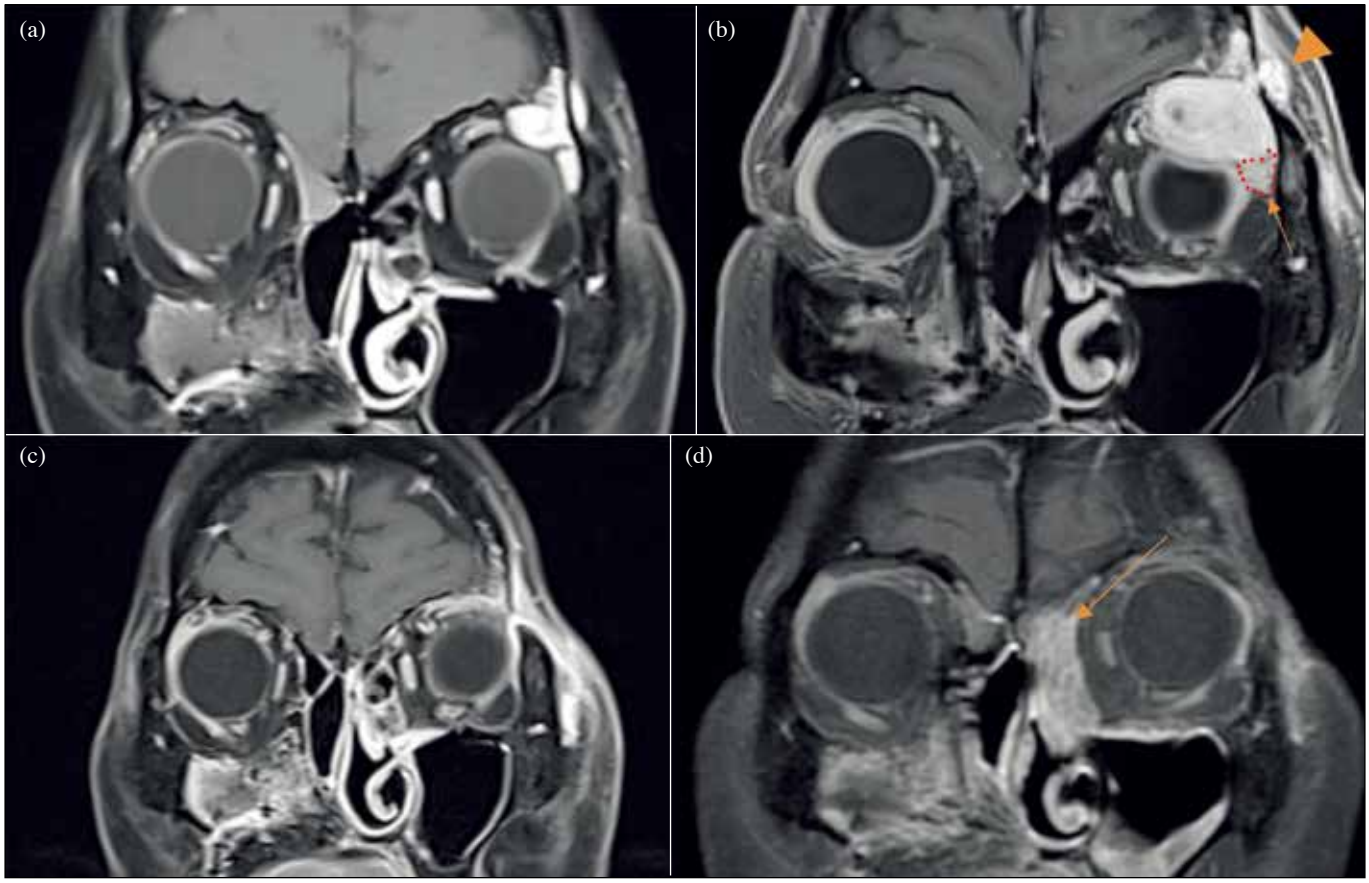

Figure. Post-contrast T1-weighted fat-suppressed coronal magnetic resonance imaging (MRI) of the orbit: (a) In December 2019, 1.5T MRI showing a homogenously contrast-enhancing lesion suspicious of lacrimal fossa tumor over the left lacrimal gland fossa with frontal bone involvement. (b) In March 2020, 3T MRI showing the enlarging lesion and ultra-fine anatomical details, including its subperiosteal location, a small cystic (necrotic) component, normal-looking lacrimal gland displaced inferiorly (arrow), and bony invasion at the frontozygomatic suture extending into the temporalis fossa (arrowhead). (c) In July 2020, 1.5T MRI showing the reduced subperiosteal lesion at 3 months after surgical excision. (d) In December 2020, 1.5T MRI showing no recurrence over the lacrimal fossa at postoperative 7 months, but new enhancing soft tissue (arrow) over the left medial orbit suspicious of metastatic deposit.

In March 2020, the patient underwent left subbrow orbitotomy and excisional biopsy. The subperiosteal location of the tumor, the frontozygomatic bone defect, and normal lacrimal gland were confirmed intraoperatively. She received postoperative adjuvant radiotherapy. In July 2020 and November 2020, postoperative MRI showed no recurrent metastatic disease but suspicious growth over the medial orbit or lacrimal sac region (**Figure**).

Discussion

This case illustrates the importance of superior anatomical delineation of complex orbital lesions using high-field 3T MRI, which provides valuable roadmap for pre-operative planning. Multiparametric MRI involves diffusion and perfusion-weighted sequences and provides valuable functional information in addition to anatomical details.[4] The additional use of diffusion-weighted imaging significantly improves the differentiation of benign from malignant orbital masses.[5] Substantial enlargement of a noninflammatory lacrimal fossa lesion within a short period together with invasion to the surrounding frontal bone and temporalis fossa was highly suggestive of malignancy. However, on high-field 3T MRI, the subperiosteal location and the normal lacrimal gland concluded that the diagnosis of an advanced primary lacrimal gland ACC was unlikely.

Only one case of metachronous primary ACC has been reported; the patient had a history of an index maxillary sinus ACC with esophageal carcinoma 14 years later.[6] Whereas there have been 12 cases of lacrimal gland or maxillary sinus ACC with metastasis to other organs including liver, kidneys, and lungs.[7-16] Therefore, primary versus metachronous ACC are differential diagnoses. High-field multiparametric MRI is an important tool to assess orbital masses.

Author contributions:

Concept or design: KKLC
Acquisition of data: KKLC, WCWC

Analysis or interpretation of data: PPYW, KKLC
Drafting of the article: PPYW
Critical revision for important intellectual content: KKWC & KKLC, WCWC
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

The authors have no conflicts of interest to disclose.

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Patient consent

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed consent for the treatment/procedures. The patient provided consent for publication.

References

1. *Shields JA, Shields CL, Epstein JA, Scartozzi R, Eagle RC Jr. Review: primary epithelial malignancies of the lacrimal gland: the 2003 Ramon L. Font lecture. Ophthalmic Plast Reconstr Surg 2004;20:10-21.* Crossref
2. *Tse DT, Kossler AL, Feuer WJ, Benedetto PW. Long-term outcomes of neoadjuvant intra-arterial cytoreductive chemotherapy for lacrimal gland adenoid cystic carcinoma. Ophthalmology 2013;120:1313-23.* Crossref
3. *Woo KI, Kim YD, Sa HS, Esmaeli B. Current treatment of lacrimal gland carcinoma. Curr Opin Ophthalmol 2016;27:449-56.* Crossref
4. *Purohit BS, Vargas MI, Ailianou A, et al. Orbital tumours and tumour-like lesions: exploring the armamentarium of multiparametric imaging. Insights Imaging 2016;7:43-68.* Crossref
5. *Russo C, Strianese D, Perrotta M, et al. Multi-parametric magnetic resonance imaging characterization of orbital lesions: a triple blind study. Semin Ophthalmol 2020;35:95-102.* Crossref
6. *Chang HY, Jiang H, Zhou F. A rare case of metachronous triple cancers involving the tympanic membrane. Pak J Med Sci 2013;29:218-9.* Crossref
7. *Blanco M, Garcia-Fontan E, Rios J, Rivo JE, Fernandez-Martin R, Canizares MA. Pulmonar collision tumor: metastatic adenoid cystic carcinoma and lung adenocarcinoma. Rev Port Pneumol 2012;18:42-5.* Crossref
8. *Lin WY, Hsu WH. Tumor-to-tumor metastasis: maxillary sinus adenoid cystic carcinoma metastasizing to double primary lung adenocarcinoma. Ann Thorac Surg 2010;90:e59-61.* Crossref
9. *Satake N, Yoshida S, Jinnouchi O, Sekita T. Adenoid cystic carcinoma of maxillary sinus with metastatic hepatocellular carcinoma. Case report. APMIS 2005;113:450-5.* Crossref
10. *Park DY, Lee JH, Suh YL, Woo KI, Kim YD. Metastatic adenoid cystic carcinoma of the eyelid. Ophthalmic Plast Reconstr Surg 2012;28:e111-2.* Crossref
11. *Jedrych J, Galan A. Multiple cutaneous metastases: a rare and late sequelae of lacrimal gland adenoid cystic carcinoma. J Cutan Pathol 2013;40:341-5.* Crossref
12. *Petrelli RL, Labay GR, Schwarz GS. Adenoid cystic carcinoma with orbital and cranial metastases: case report. Ann Ophthalmol 1978;10:611-5.*
13. *Kaur A, Harrigan MR, MeKeever PE, Ross DA. Adenoid cystic carcinoma metastatic to the dura: report of two cases. J Neurooncol 1999;44:267-73.* Crossref
14. *Bacalja J, Magazin M, Ulamec M, Rako D, Trnski D, Kruslin B. Adenoid cystic carcinoma of the lacrimal gland metastatic to the kidney: case report and review of the literature. Scott Med J 2014;59:e14-7.* Crossref
15. *Maamari RN, Custer PL, Harocopos GJ. Incidentally discovered adenoid cystic carcinoma of the lacrimal gland with isolated liver metastases. Ocul Oncol Pathol 2017;3:262-6.* Crossref
16. *Zeidan BA, Abu Hilal M, Al-Gholmy M, El-Mahallawi H, Pearce NW, Primrose JN. Adenoid cystic carcinoma of the lacrimal gland metastasising to the liver: report of a case. World J Surg Oncol 2006;4:66.* Crossref

PHOTO ESSAY

Retinal arterial macroaneurysm: multimodal imaging

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Abstract

We present multimodal images of a retinal arterial macroaneurysm in terms of fundus photo, swept source optical coherence tomography, spectral domain optical coherence tomography, fluorescein angiography, and swept source optical coherence tomography angiography.

Key words: *Fluorescein angiography; Retinal arterial microaneurysm; Tomography, optical coherence*

In March 2020, a 66-year-old woman with a history of stroke, hypertension, and coronary artery disease experienced visual decline in her right eye for 3 weeks. Fundus photo showed a retinal arterial macroaneurysm along the inferotemporal vascular arcade with a cuff of intraretinal and subretinal hemorrhage (**Figure a**). Swept source optical coherence tomography showed the retinal arterial macroaneurysm extending vertically from the internal limiting membrane to the external limiting membrane, with intraretinal fluid and multiple hyperreflective dots (pearl necklace sign[1]) surrounding the inner wall of large cystoid space in the outer plexiform layer (**Figure b**). Spectral domain optical

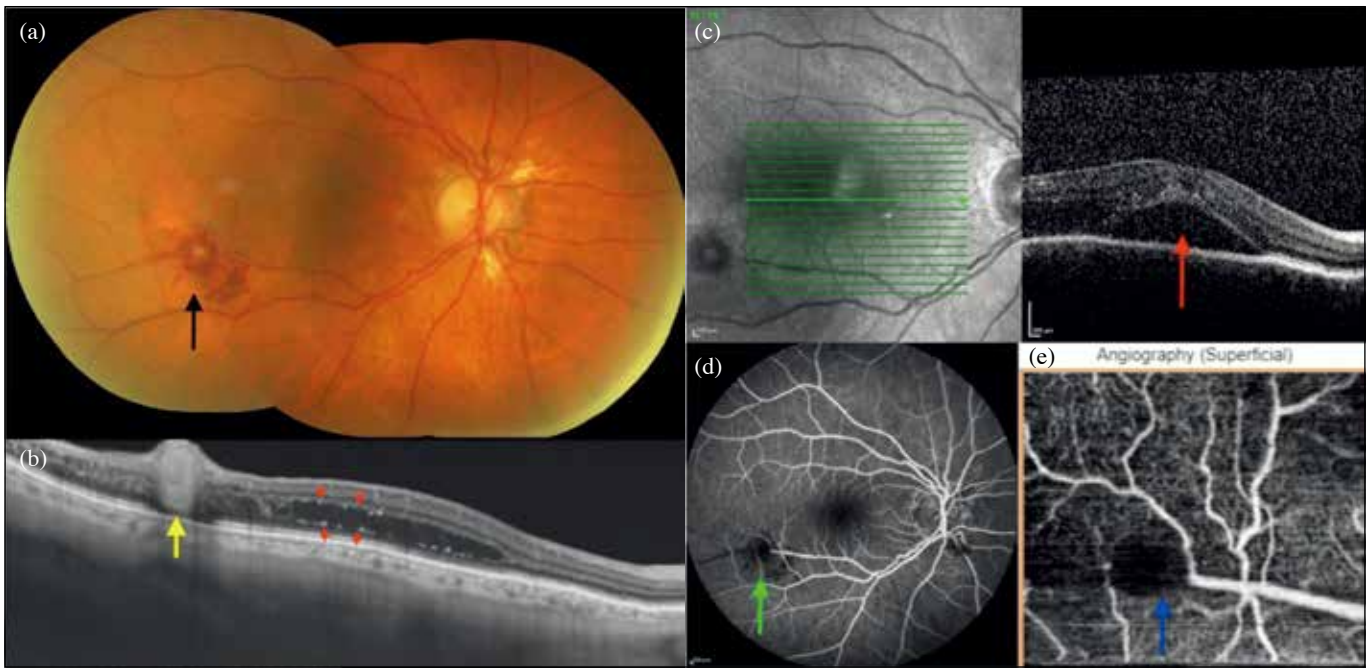

Figure. (a) Fundus photo showing a retinal arterial macroaneurysm (arrow) along the inferotemporal vascular arcade with a cuff of intraretinal and subretinal hemorrhage. (b) Swept source optical coherence tomography showing the retinal arterial macroaneurysm (arrow) extending vertically from the internal limiting membrane to the external limiting membrane, with intraretinal fluid and multiple hyperreflective dots (pearl necklace sign) [arrowheads] surrounding the inner wall of large cystoid space in the outer plexiform layer. (c) Spectral domain optical coherence tomography section through the fovea showing the presence of subretinal fluid (arrow). (d) Fluorescein angiography showing no sign of flow inside the retinal arterial macroaneurysm on the venous phase (arrow). (e) Swept source optical coherence tomography angiography showing sluggish or no flow on the superficial capillary slab (arrow).

coherence tomography section through the fovea showed the presence of subretinal fluid (**Figure c**). Fluorescein angiography showed no sign of flow inside the retinal arterial macroaneurysm on the venous phase (**Figure d**). Swept source optical coherence tomography angiography showed sluggish or no flow on the superficial capillary slab (**Figure e**). A diagnosis of retinal arteriolar obstruction distal to the retinal arterial macroaneurysm was made. We planned to inject dexamethasone implant for treatment as the patient had a history of stroke, but the patient was lost to follow-up owing to the Covid-19 pandemic and the subsequent curfew.

Author contributions

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.

Conflict of interest

The authors have no conflicts of interest to disclose.

Funding/support

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

Patient consent

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Reference

1. *Gelman SK, Freund KB, Shah VP, Sarraf D. The pearl necklace sign: a novel spectral domain optical coherence tomography finding in exudative macular disease. Retina 2014;34:2088-95.* Crossref

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REFERENCES

1. Market data, September 2020 (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, January 2021.

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Reference: 1) Press Release for the Media: Questions and Answers about AREDS2, National Eye Institute, 2013 2) The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: the Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial. JAMA. 2013, 15;309(19): 2005-15 3) Chew EY. Nutrition, Genes, and Age-Related Macular Degeneration: What Have We Learned from the Trials? Ophthalmologica. May 6, 2017 4) Product Insert of Ocuvite® AREDS 2 5) Hobbs RP. Bernstein PS; Nutrient Supplementation for Age-related Macular Degeneration, Cataract, and Dry Eye. J Opthalmic Vis Res. 2014, 9(4): 487-93 6) Aronow ME, Chew EY; Age-related Eye Disease Study 2: perspectives, recommendations, and unanswered questions. Curr Opin Ophthalmol. 2014, 25(3): 186-9

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AEs=adverse effects; IOP=intraocular pressure.

References: 1. Cavet ME, DeCory HH. The Role of Nitric Oxide in the Intraocular Pressure Lowering Efficacy of Latanoprostene Bunod: Review of Nonclinical Studies. J Ocul Pharmacol Ther 2018; 34(1-2): 52-60. **2.** Braunger BM, Fuchshofer R, Tamm ER. The aqueous humor outflow pathways in glaucoma: A unifying concept of disease mechanisms and causative treatment. Eur J Pharm Biopharm 2015; 95(Pt B): 173-81. **3.** Cavet ME, Vollmer TR, Harrington KL, et al, Regulation of Endothelin-1-Induced Trabecular Meshwork Cell Contractility by Latanoprostene Bunod. Invest Ophthalmol Vis Sci 2015; 56(6): 4108-16. **4.** Wiederholt M, Sturm A, Lepple-Wienhues A. Relaxation of trabecular meshwork and ciliary muscle by release of nitric oxide. Invest Ophthalmol Vis Sci 1994; 35(5): 2515-20. **5.** VYZULTA® Hong Kong prescribing information (version: 06/2018). **6.** Weinreb RN, Liebmann JM, Martin KR, et al. Latanoprostene Bunod 0.024% in Subjects With Open-angle Glaucoma or Ocular Hypertension: Pooled Phase 3 Study Findings. J Glaucoma 2018; 27(1): 7-15. **7.** Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015; 99(6): 738-45.

INDICATION VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. **Dosage and Administration** The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect. If VYZULTA® is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart. **IMPORTANT SAFETY INFORMATION** • Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. • Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation. • Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA® should generally not be used in patients with active intraocular inflammation. • Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. • There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients. • Contact lenses should be removed prior to the administration of VYZULTA® and may be reinserted 15 minutes after administration. • The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation. Please refer to full package insert for the detail.

For healthcare professional only. Please refer to full Prescribing Information and additional Important Safety Information for VYZULTA®.

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