CASE REPORT

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

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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

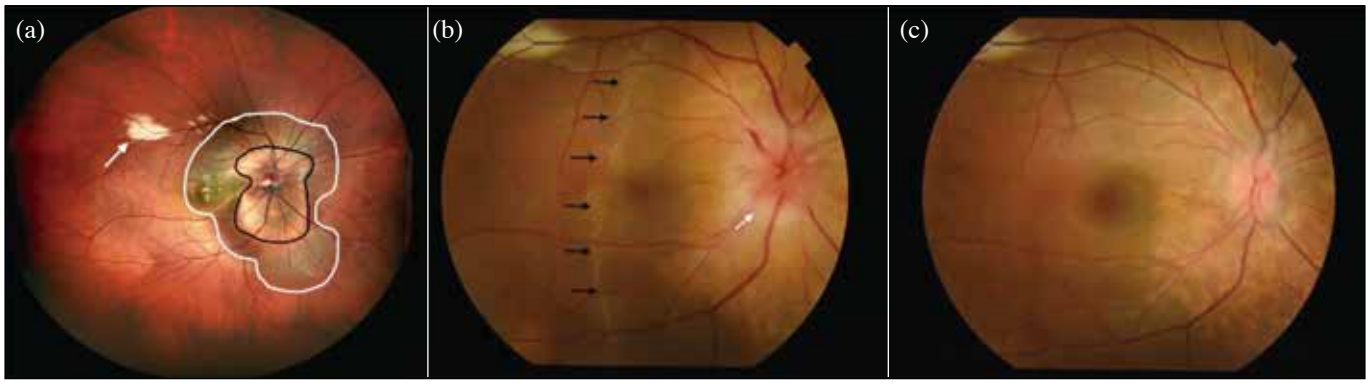

Figure 1. (a) Ultra-wide field pseudo color fundus photograph on presentation showing a peripapillary yellowish creamy choroidal mass (black outline) and surrounding exudative retinal detachment (white outline) and an incidental finding of myelinated nerve fiber layer (arrow). (b) Color fundus photograph 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.

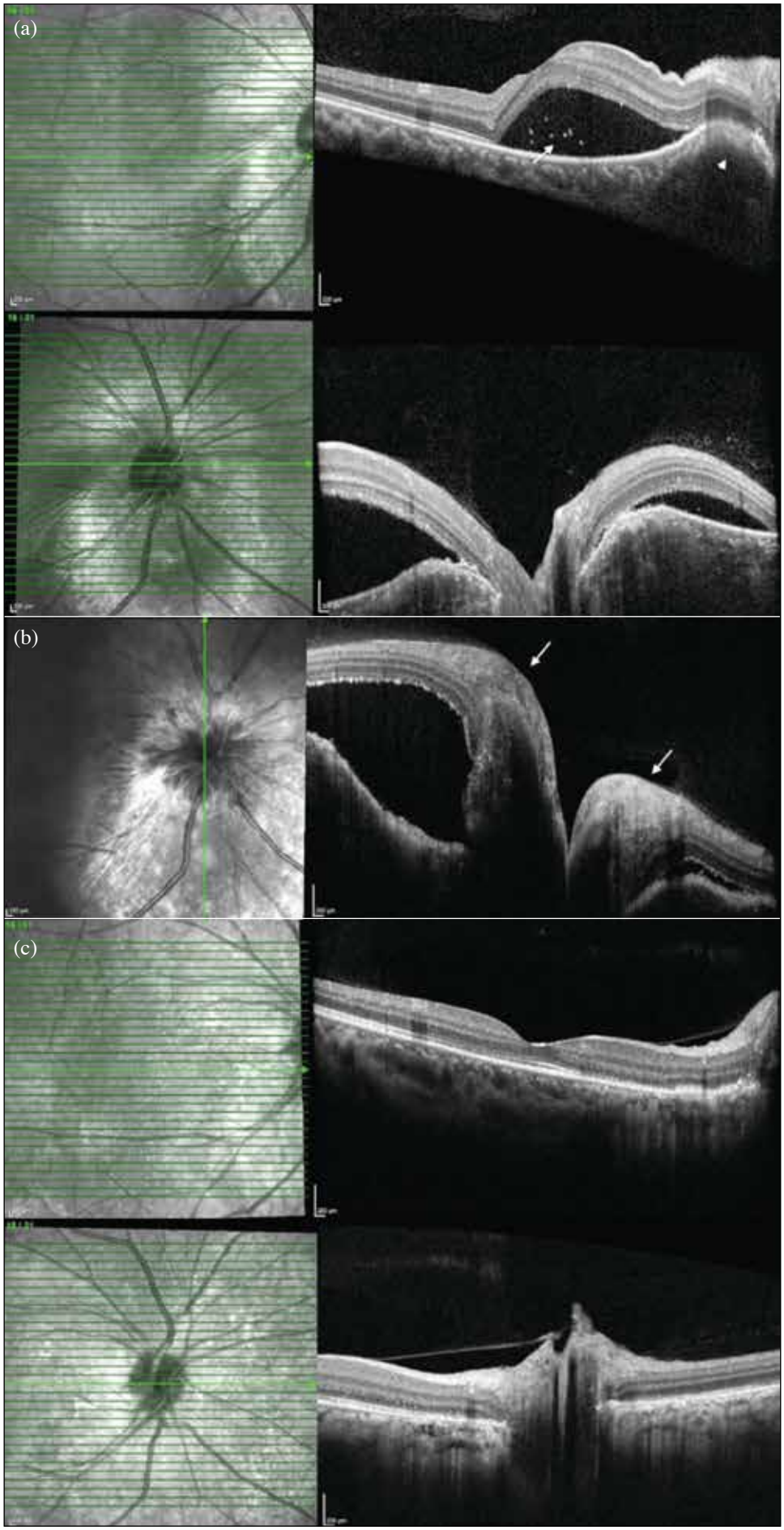

Figure 2. Spectral domain optical coherence tomography showing (a) subretinal hyper-reflective dots within the subretinal space (arrow), choroidal elevation with optical shadowing (arrowhead), and no optic nerve head swelling despite peripapillary serous retinal detachment on presentation, (b) swelling 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.

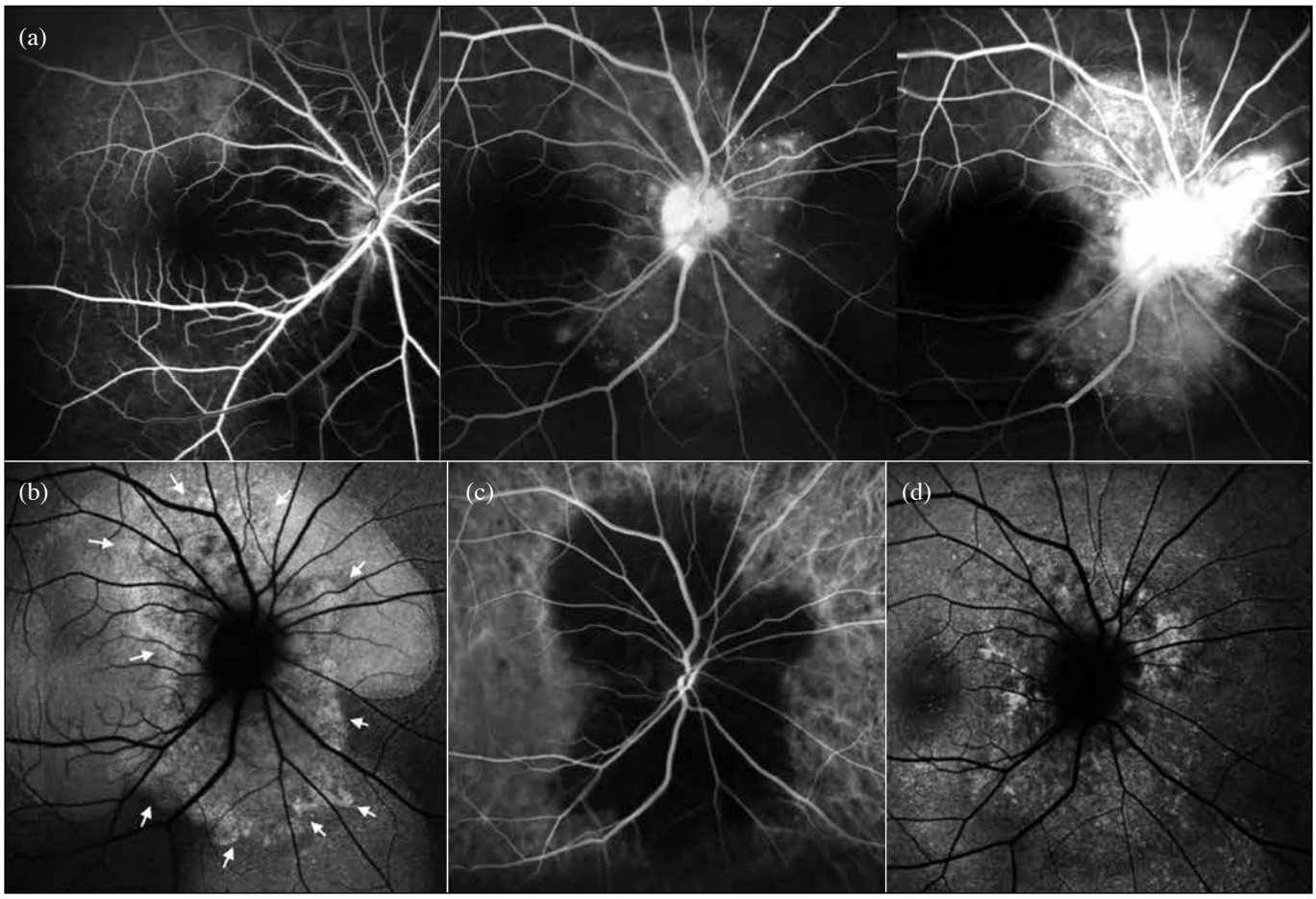

Figure 3. (a) Fluorescein angiography on presentation showing hypofluorescence in early phase followed by progressive diffuse and pinpoint leakage in late phase. (b) Fundus autofluorescence on presentation showing hyper-autofluoresence delineating the margin of a choroidal mass (white arrows) and speckles 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.

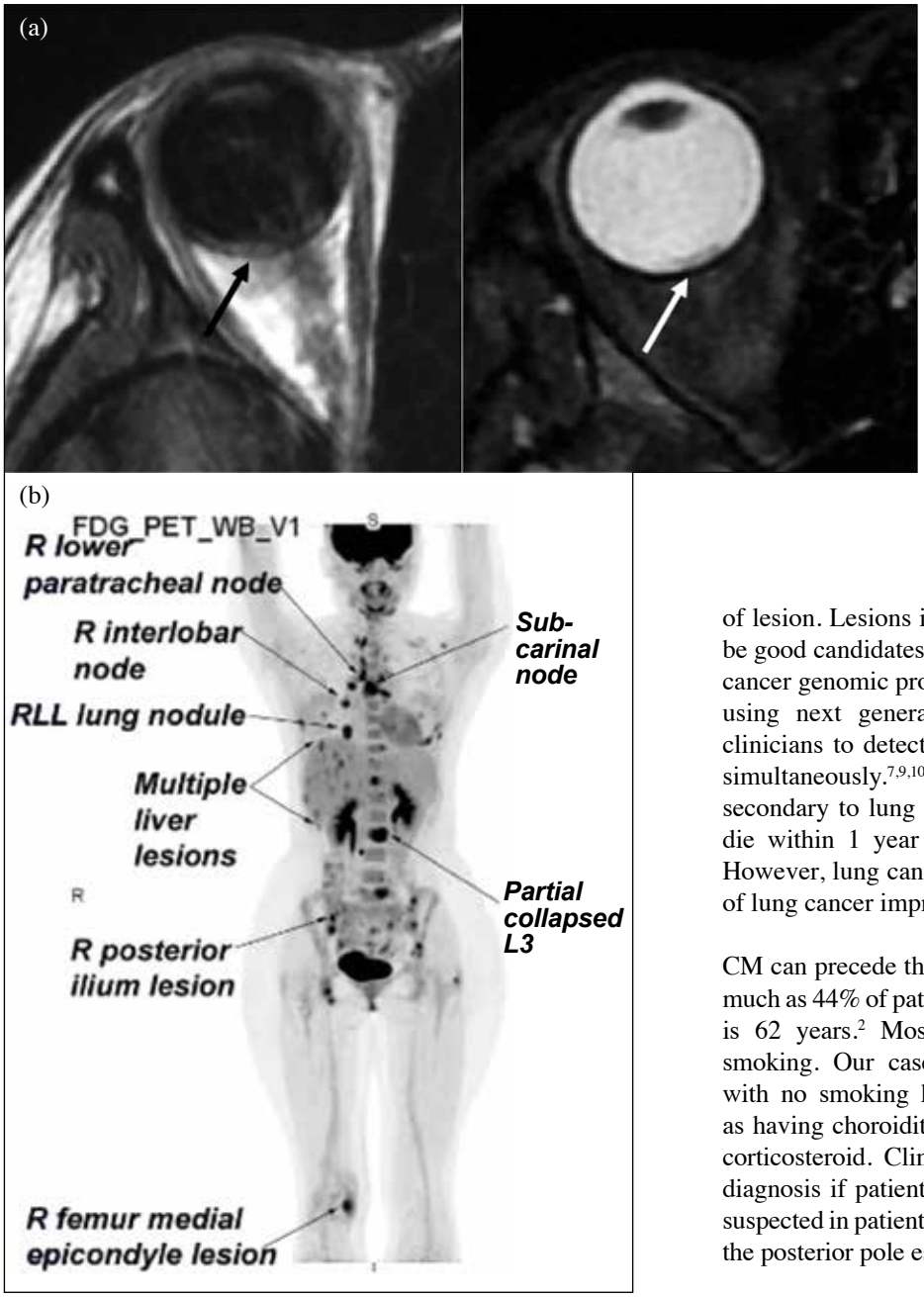

Figure 4. (a) Magnetic resonance imaging of the orbit on presentation showing a peripapillary choroidal mass hyperintense on T1-weighted image (black arrow) and hypointense on T2-weighted image (white arrow). (b) Positron emission tomography on presentation showing multiple hypermetabolic pulmonary nodules, 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.

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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.

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