Small cell lung cancer recurring in the retina

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Abstract

Intraocular metastases are rare, usually isolating to the uveal tract. Retinal metastases are less common still, presenting a unique diagnostic and therapeutic challenge. This case observes a 66-year-old female ex-smoker presenting with unilateral painful vision loss 2 months from completion of definitive chemoradiotherapy for early-stage small cell lung cancer. A retinal lesion was discovered on examination and initially treated as viral retinitis without improvement. Two vitrectomy procedures were unable to confirm the diagnosis. Eventual retinal biopsy under general anaesthesia confirmed small cell lung cancer oligometastasis (7 months from completion of definitive chemoradiotherapy), without evidence of other sites of disease on imaging. She received local radiation to retina with resolution of eye pain. She eventually developed intrathoracic relapse of disease and was treated with palliative chemotherapy (14 months from completion of definitive chemoradiotherapy).

INTRODUCTION

Retinal metastases are rare and are often mistaken for other causes, presenting diagnostic and therapeutic challenges. This case demonstrates the difficulties pursuing diagnoses for metastatic retinal lesions, including the limitations of macroscopic slit-lamp examination, radiology and cerebrospinal fluid (CSF) with vitreous humour cytological analysis in confirming retinal metastases without definitive biopsy.

CASE PRESENTATION

A 66-year-old female presented to the emergency department with new onset haemoptysis with associated 2-month dry cough and 3 kg unintentional weight loss. Medical history included chronic obstructive pulmonary disease and gastro-oesophageal reflux. She presented for investigation for unexplained dyspepsia, altered bowel habit and 10 kg weight loss with normal oesophagogastroduodenoscopy and colonoscopy 3 years prior, diagnosed as irritable bowel syndrome. Surgical history included right cheek basal cell carcinoma 5 years prior, right external iliac endarterectomy 3 years prior and hysterectomy for fibroids. She was an ex-smoker (60 pack-year history) with no family history of cancer. Body mass index measured 18.5 kg/m² and performance status 2 (Eastern Cooperative Oncology Group score) at initial presentation.

A left lower lobe mass on chest X-ray lead to rapid access lung clinic referral for workup. Initial bronchoscopy was inconclusive for malignancy. Computed tomography (CT)-guided biopsy confirmed small cell lung cancer (SCLC) diagnosis. Positron emission tomography (Fig. 1) with contrast-enhanced CT of chest, abdomen and pelvis (CT-TAP) and brain demonstrated a fluorodeoxyglucose-avid 4.9 cm mass 3 mm from the pleural surface with without lymphadenopathy or distant metastases. Multidisciplinary team consensus staged disease as cT2bN0M0 (per American Joint Committee on Cancer, version 8.0). Sequential chemotherapy and definitive radiation approach were advised, accounting for the patient’s co-morbidities and objective frailty. She received Carboplatin (dosed at area under the curve 5, day 1) with Etoposide (100 mg/m², days 1–3) followed by definitive radiotherapy (40 Gy in 15 fractions). She subsequently received 25 Gy in 10 fractions prophylactic cranial irradiation (PCI).

Mild frontal headache and nausea occurred 1 month from completion of definitive therapy. Contrast magnetic resonance imaging (MRI) of brain at this time demonstrated no abnormalities. CT-TAP demonstrated primary tumour partial response (measuring 3 cm). A short steroid course improved symptoms, initially attributed to recent completion of PCI. Symptoms recurred 3 months from completion of definitive therapy with cerebellar signs, prompting admission for workup. Repeat contrast MRI brain and CT-TAP demonstrated continued response of treated primary tumour (measuring 1.3 cm) without evidence of local recurrence or distant metastases.

Neurology workup noted CSF and blood serum with unremarkable protein, glucose, serum protein electrophoresis, cytology, microbial culture, Ziehl-Neelsen
Figure 1. Initial staging positron emission tomography with CT of the thorax demonstrating a 4.9 cm fluorodeoxyglucose-avid lesion in the left lower lobe without avid lymphadenopathy or distant metastases, consistent with a primary lung malignancy of cT2bN0M0 stage per American Joint Committee on Cancer.

Figure 2. Fundal exam of right eye demonstrating dense creamy amorphous material with surface haemorrhage and extensive subretinal exudation involving the macula and temporal periphery.

Figure 3. Contrast MRI of brain and orbits with T2-weighted fluid attenuated inversion recovery demonstrating nodular retinal thickening in the posterior chamber of the right globe along its lateral aspect, marked by yellow arrow.

Figure 4. Retinal fluid biopsy demonstrating small cells with scanty cytoplasm and mixed apoptotic cells staining positive for chromogranin consistent with a diagnosis of SCLC.

stain, syphilis serology, herpes simplex polymerase chain reaction, serum interferon gamma assay, vasculitis and paraneoplastic screens (including anti-Hu, anti-Ro, anti-Ri), erythrocyte sedimentation rate and B12 with folate levels. Pain migrated behind the right eye over 1 month with associated unilateral visual acuity loss to hand motion, prompting ophthalmology assessment.

Anterior segment demonstrated shallow anterior chamber with raised intraocular pressure (IOP) of 50 mmHg. Gonioscopy demonstrated 270° angle neovascularization of the iris. Fundoscopy demonstrated creamy amorphous material, surface haemorrhage and subretinal exudation involving macula and temporal periphery (Fig. 2) with normal vitreous and no seeding appreciated. B-scan demonstrated uniformly echogenic posterior globe mass without choroidal excavation, fluorescein angiography optic disc hyperfluorescence and contrast MRI orbital thickening of the posterolateral chamber (without post-contrast enhancement) (Fig. 3). Consensus opinion sought from a uveitis sub-specialist agreed with the initial diagnosis of viral retinitis. Differential diagnoses included inflammatory retinitis, vascular telangiectasia or SCLC metastasis.

IOP proved refractory to oral (acetazolamide, steroids) and topical (brinzolamide, apraclonidine) therapy. Cyclo- diode therapy (2 cycles) and a course of oral valganciclovir provided limited-to-no benefit. Two pars plana vitrectomy sampling procedures performed were inconclusive for aetiology (namely malignant or infectious process). The lesion progressed over 6 months, invading the optic nerve causing retinal detachment on slit-lamp examination with progressive right ocular pain and thickening of the right globe lesion on serial MRI, concerning for a malignant process. Subretinal fluid biopsy with silicone oil tamponade was performed under general anaesthetic, 7 months from completion of definitive therapy. Histopathology demonstrated small cells, scant cytoplasm and staining for cytokeratin AE1/3 and chromogranin (Fig. 4), consistent with SCLC oligometastasis. CSF sampling performed at the time of subretinal biopsy demonstrated no atypical cells with normal protein and glucose.

Contrast MRI brain and CT-TAP at the time of confirming oligometastasis did not demonstrate any active malignancy outside the retina. The patient was treated with radiotherapy of 30 Gy in 10 fractions to the right retina, with improvement in pain symptoms. Further systemic chemotherapy was offered after confirming oligometastasis, being advised that risk of further SCLC...
recurrence was high. The patient instead opted for clinical observation. She remained well until development of intrathoracic disease recurrence on CT-TAP surveillance 14 months from completion of definitive therapy and commenced palliative chemotherapy. MRI of brain and orbits at this time demonstrated post-radiation changes without intraocular or intracranial metastases.

**DISCUSSION**
Metastases should be suspected in definitively treated cancers when unexplained examination or radiological findings are observed. SCLC rarely metastasizes to the retina and may present as neovascular glaucoma [1]. This case highlights the diagnostic limitations of CSF cytology and vitrectomy compared to formal retinal biopsy confirming metastases. Retinal biopsies have uncertain associated morbidity, often being considered ‘last resort’ in evaluating atypical lesions [2].

Most ocular metastases are described through autopsy studies [3], with incidence falling over time attributable to improved cancer diagnostics and therapies [4]. Incidence of asymptomatic choroidal metastasis of up to 5% has been observed [5]. Another study of 520 cases with uveal metastases found breast cancer accounted for half of cases, followed by lung cancer [6]. Prospective screening for intraocular metastases has yielded dissatisfactory results, with incidence rates as low as 2% observed in lung cancer [7].

The uveal tract is the most commonly involved intraocular site. Ciliary body and iris metastases constitute ~10% of intraocular metastases [8], often presenting as uveitis, episcleritis and raised IOP. Only a handful of retinal metastases cases are described, often mimicking unilateral retinitis [9]. Symptomatic metastases have been treated with radiation, though often yield limited improvement in symptoms [10]. The role of systemic chemotherapy in isolated retinal oligometastases is not established.

**CONSENT**
The patient provided written and informed consent to have her case published in a medical journal with associated images, namely retinal images (from fundoscopy), computed tomography of chest, MRI of orbits and images of pathological specimen, as specified in the signed patient consent form. Written consent was provided by the patient in February 2019 using a standard template form with all radiological and pathological imaging available prior to date of patient consent. The patient was unable to provide her approval for manuscript versions submitted to the journal, having been confirmed deceased at time of original manuscript submission and revision process. However, based on written and informed consent originally provided by the patient, we judge that this approval extends to provided images provided in the manuscript.

**AUTHORS’ CONTRIBUTIONS**
S.M. wrote paper, obtained patient consent and obtained radiology/pathology/retinal images. B.W. wrote paper. M.H. and P.C. edited paper and paper oversight.

**CONFLICT OF INTEREST STATEMENT**
There are no conflicts of interest to declare for any of the authors involved.

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