A Rare Clinical Case of Unexplained Unilateral Vision Loss on a Background of Metastatic Breast Cancer

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ABSTRACT

A rare clinical case of unexplained unilateral vision loss occurring in a 59-year-old Caucasian female is described. The vision loss occurred in association with an ipsilateral afferent pupil defect and on a background of primary breast carcinoma with extensive bony metastases. However, there was no clinically detectable orbital infiltration, orbital pseudo-tumour, compressive visual pathway lesion, optic neuritis or retinal pathology that could account for the ocular symptomatology. The patient was receiving palliative oral capecitabine chemotherapy at the time of presentation. Findings on clinical examination, perimetry testing, fundus photography, optical coherence tomography and magnetic resonance imaging are presented. Other differential diagnoses underlying this case of severe, sub-acute vision loss are discussed.

Keywords: breast cancer, metastatic, capecitabine, chemotherapy, cytotoxicity

INTRODUCTION

The development of vision impairment in the setting of an underlying malignancy is not uncommon and can range from mild to severe with unilateral or bilateral involvement. Vision loss is often but not always owing to the cancer itself or cancer-related treatment.[1-7] Specific causes of vision loss in patients with a history of cancer include metastatic involvement of the visual pathway;[1-2] paraneoplastic syndromes, such as cancer-associated retinopathy and melanoma-associated retinopathy;[8-10] ocular toxicity to chemotherapeutic agents;[3,11] and side effects from irradiation, particularly that applied to the head and/or orbits.[5-7]

Of note, the ocular side effects of both old and new-aged cancer therapies are emerging as more longitudinal data arises and the frequency of reporting increases.[11] In some cases, vision loss can precede the development of cancer in a patient.[2,10,12] When this occurs, one aetiology of consideration is non-paraneoplastic autoimmune retinopathy/optic neuropathy.[2,10,12] This atypical immune-mediated process occurs in the absence of any known systemic malignancy and can precede the development of cancer by months or even years.[2,10,12]

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Some cases of vision loss occurring in the setting of cancer represent a diagnostic dilemma and the aetiology remains unclear. In such cases, a presumptive diagnosis is sometimes made by combining clinical features, examination findings and ancillary test results into a cohesive rationale. In the absence of any concrete findings, the diagnosis is reached

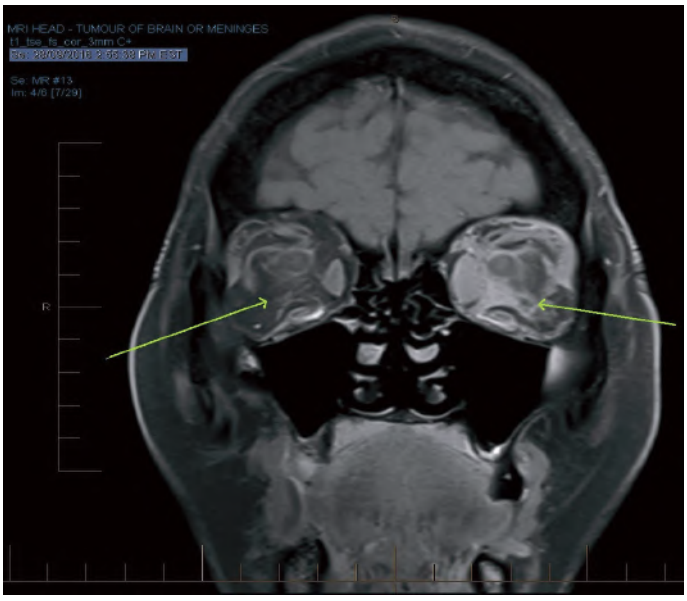

Figure 1. MRI of the brain and orbits showing bilateral orbital inflammatory process (L>R). Fusiform severe swelling of the left medial rectus, mild swelling of the left lateral and inferior recti, and slight swelling of the right medial and lateral recti.

by a process of exclusion rather than being definitive. Whilst no definitive diagnosis is available, these atypical cases are deserving of attention and it is equally important that they be reported such that other cases with similar phenotypical presentation may, when taken collaboratively, cast insight on the medically unknown.

We describe one patient with a background of advanced metastatic breast cancer who experienced a severe, unilateral loss of vision and had an accompanying ipsilateral afferent pupil defect that could not be explained by obvious aetiological factors. The patient was receiving palliative oral capecitabine chemotherapy at the time of presentation. Neuro-imaging studies and ophthalmic examination did not reveal any clinical evidence for the ocular symptomatology. The clinical findings are described, and several differential diagnoses are discussed. In discussing this case, we seek to highlight the complexity of aetiologies underlying vision impairment in cancer patients.

CASE REPORT

A 59-year-old Caucasian female was referred by her medical oncologist to an ophthalmology clinic complaining of a four-week history of right-sided orbital pain, especially on horizontal gaze, and a gradual worsening of vision in this eye. There was no history of floaters or photopsia, and no changes were reported in the left eye. There was no significant past ocular history and no family history of eye disease.

The patient had a past medical history of controlled hypertension and depression for which she was taking oral irbesartan and venlafaxine. In addition, she had a de novo presentation of Stage IV, oestrogen-receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast carcinoma with widespread bony metastases but no visceral disease. Following her initial diagnosis in March 2015, the patient commenced palliative treatment with letrozole and denosumab, as well as radiotherapy to the cervical spine.

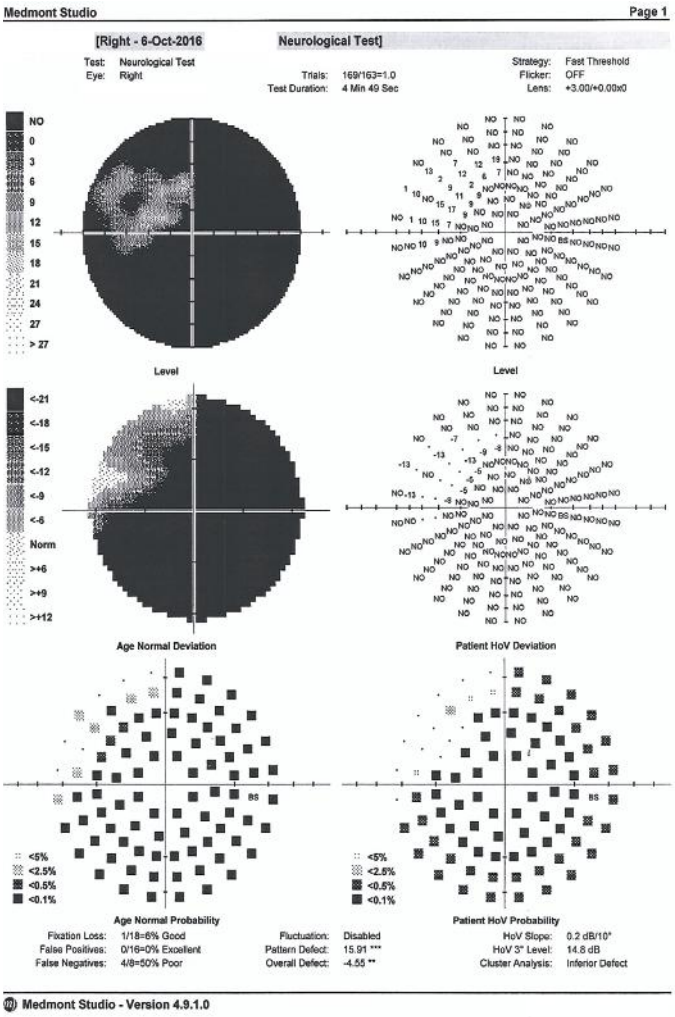

Figure 2. Medmont neurological visual field of the right eye at initial presentation showing severe widespread field loss with intact area superonasally.

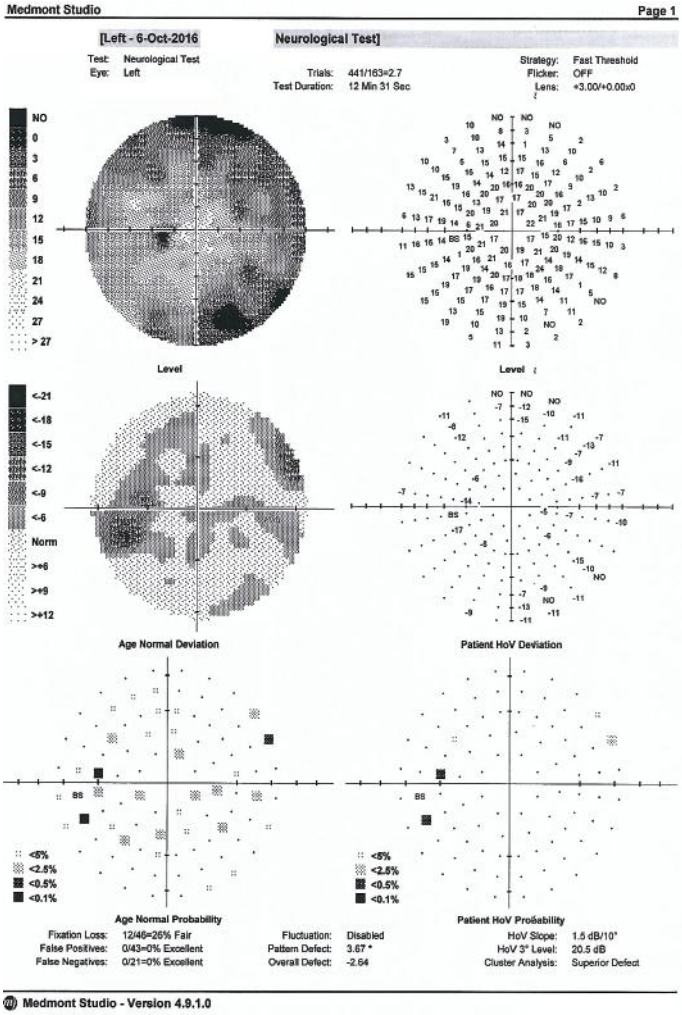

Figure 3. Medmont neurological visual field of the unaffected left eye at initial presentation.

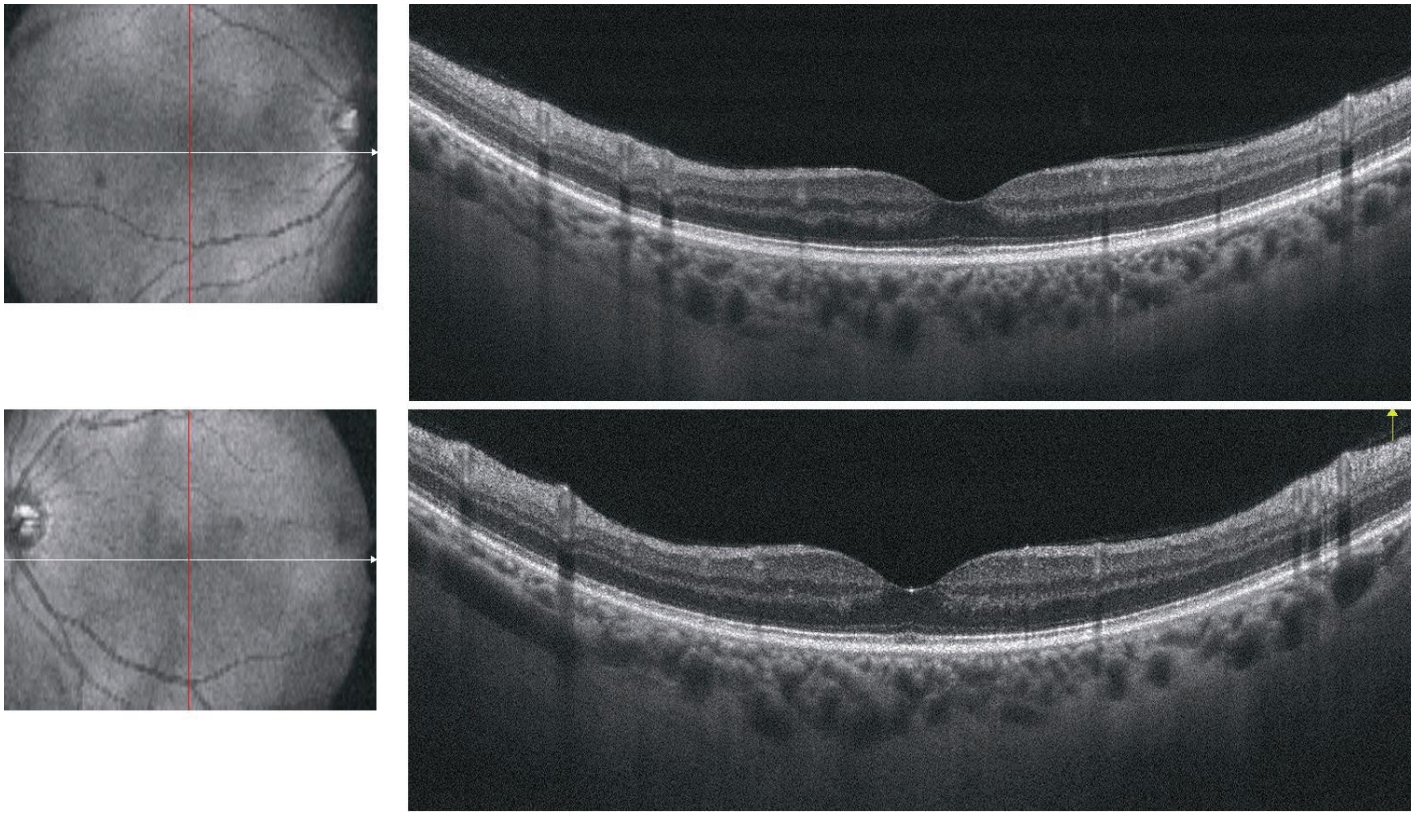

Figure 4. Spectral-domain OCT of the right and left maculae, demonstrating a normal appearance.

Nine months after diagnosis, increasing metastases were detected, including bony progression and a new hepatic metastasis. The patient subsequently undertook three cycles of intravenous (IV) nab-paclitaxel chemotherapy, which was poorly tolerated. Whilst re-staging demonstrated improvement in the liver metastasis, there was progression of her bony disease. She was then switched to oral capecitabine chemotherapy and was continued on denosumab. A steady improvement in all areas of metastatic disease was demonstrated on subsequent imaging.

Oral capecitabine chemotherapy was continued for six months when new onset ocular and visual symptoms developed, as described above. Magnetic resonance imaging (MRI) of the brain and orbits revealed bilateral orbital inflammatory changes, left greater than right, not convincing for orbital metastases, but rather suggestive of orbital pseudo-tumour or an orbital inflammatory process (Figure 1). There was marked thickening of the left medial rectus and to a lesser extent, left lateral and inferior recti. However, this was not consistent with the symptomatic right-sided vision loss. There was no evidence of superior ophthalmic vein or cavernous sinus thrombosis. At this point, capecitabine was interrupted and ophthalmological opinion sought.

Upon first presentation to the ophthalmology clinic, best-corrected visual acuity (BCVA) was right 6/48 and left 6/6, using a rear-illuminated Bailey-Lovie LogMAR chart. Medmont neurological visual field testing confirmed severe, widespread field loss in the right eye with only a small intact arc of vision superonasally (Figure 2). The left visual field was full (Figure 3). Dilated fundus examination was unremarkable in each eye. Spectral-domain optical coherence tomography (OCT) revealed both maculae (Figure 4) and retinal nerve fibre layer (RNFL) (Figure 5) to be normal. Anterior segment examination was unremarkable. On Ishihara colour vision testing, the patient was unable to detect any plates with the right eye but demonstrated normal colour vision in the left. Light-brightness sensitivity was reduced in the right eye and a right afferent pupil defect was present. Ocular movements were full and no diplopia was reported, with no apparent exophthalmos or nystagmus. A presumptive diagnosis of right retrobulbar optic neuritis was made and the patient went on to commence same-day pulsed IV methylprednisolone delivered over four days, followed by high dose oral prednisolone (60mg daily) which was subsequently weaned at home.

Upon follow-up examination four days post hospital discharge, right visual acuity had improved negligibly to 6/36(pt) with steroid treatment, however the patient still had no useful vision in this eye owing to the extensive field loss and need for significant head movement to achieve this acuity. The left visual acuity remained 6/6. Repeat visual field testing was performed and the results remained unchanged. Light-brightness sensitivity had improved

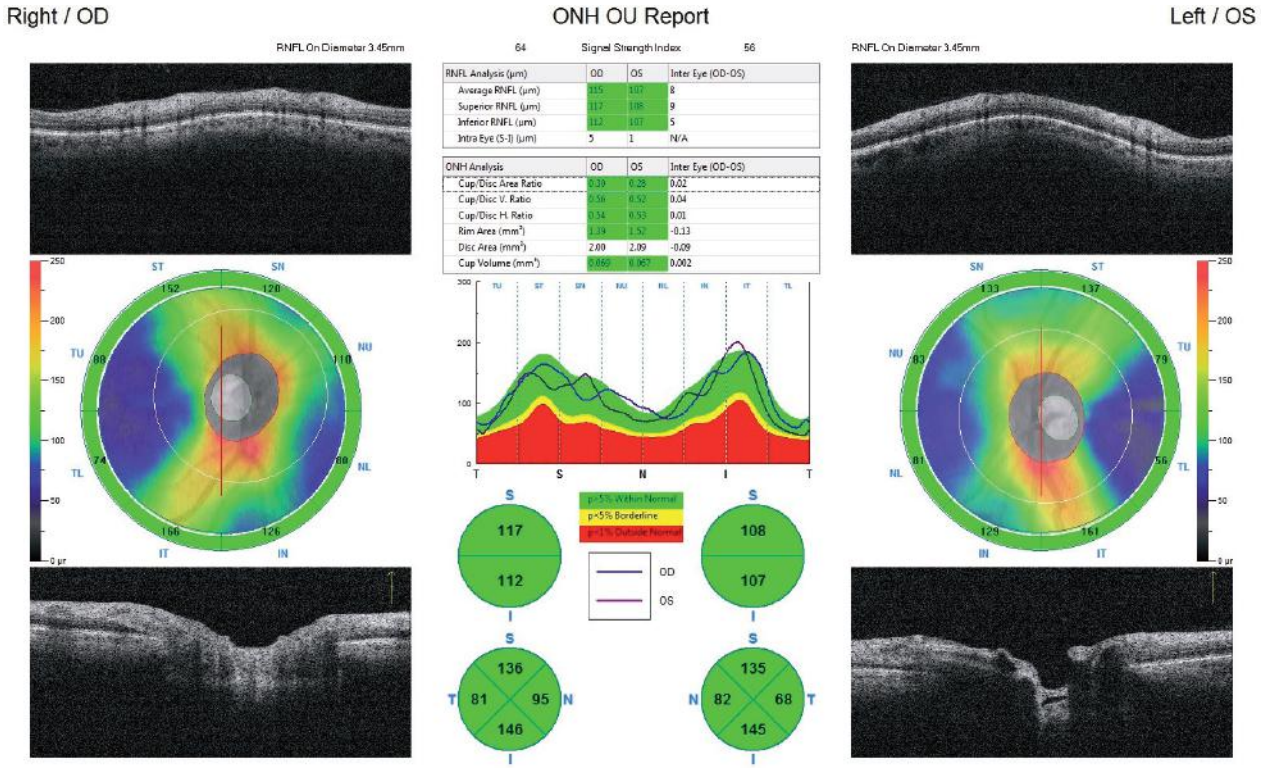

Figure 5. Bilateral OCT RNFL scan depicting RNFL thickness within normal limits, healthy optic nerve heads and normal inter-eye cup-to-disc symmetry.

but right colour vision remained affected. The right optic disc appearance was unremarkable and anterior segment examination was normal. The patient remained off oral capecitabine.

Repeat MRI conducted three weeks later revealed persistent, severe fusiform swelling of the left medial rectus with enhancement, and mild to moderate oedema within the intraconal fat bilaterally, left greater than right (Figure 6). There were skull base and frontal bone metastases with mild pachymeningeal thickening and enhancement, right greater than left, as well as subtle nodularities in the right frontoparietal and temporal lobe regions consistent with leptomeningeal carcinomatosis. The appearance was now more suggestive of underlying orbital metastases rather than an inflammatory process, although there remained no obvious focal lesion in either orbit. A two-week course of bilateral orbital and skull base radiotherapy was undertaken.

A diagnosis of diffuse skull base metastatic disease with extension particularly into the left orbit seemed fitting, albeit the right-sided visual impairment was not consistent with the MRI findings of disease greater on the left than the right and there was no obvious, identifiable right-sided orbital infiltration. A subjective improvement in vision was reported following radiotherapy, but no objective improvement was observed.

Repeat brain MRI was undertaken three months later to determine the patient's response to radiotherapy. Imaging revealed that the pre-existing orbital soft tissue oedema was basically unchanged from earlier studies. There was persistent bilateral orbital inflammatory process, most severe on the left side with marked swelling and enhancement of the medial and inferior recti, as well as marked oedema in the intraconal fat and around the globe (Figure 7). There remained no focal lesion apparent in either orbit to suggest metastasis causing this appearance. No further orbital radiotherapy was indicated. MRI also identified more advanced leptomeningeal changes in the posterior cranial fossa as well as extensive nodular pachymeningeal thickening around the entire brain (Figure 8). The patient subsequently underwent a two-week course of radiotherapy to the whole brain, excluding the orbits and optic chiasm (30Gy in 10 fractions), managing this further radiotherapy without problems.

At one-day post radiation therapy, BCVA was 6/60 (single optotype) in the right eye and 6/6 in the left. However, at this visit there was right optic disc pallor not evident previously (Figure 9) and the left disc was now oedematous and haemorrhagic (Figure 10). Intraocular pressures were 17 and 16 mmHg in the right and left eyes, respectively.

Several weeks later, the patient was re-commenced on her capecitabine chemotherapy. By that stage her blood film morphology was consistent with extensive skeletal marrow infiltration, including falling haemoglobin and decreased platelet count. Sadly, she became increasingly transfusion dependent and not long after, succumbed to her battle with cancer.

DISCUSSION

This represented a rare case of severe, unilateral vision loss with accompanying pupil defect that could not be fully explained upon clinical examination or neuro-imaging studies. Whilst no definitive diagnosis was available, there remain several plausible aetiologies that cannot be excluded with certainty.

Drug toxicity to chemotherapy agents such as capecitabine is possible, given the temporal relationship between the commencement of oral chemotherapy and symptom onset. However, the use of combination therapy and previous exposure to other chemotherapy agents make it difficult to draw conclusions. Ocular toxicity induced by chemotherapy is not uncommon but is frequently under-reported in the literature. With respect to capecitabine use specifically, there exist only a few reported cases of adverse ocular effects.[13,14] Although rare, conjunctivitis is the most common ocular side effect, affecting 5% of patients receiving capecitabine.[13] There have also been two reported cases of corneal toxicity, severe ocular irritation and decreased vision associated with capecitabine use.[14] Both patients presented with superficial punctate keratitis and multiple white granular sub-epithelial corneal deposits.[14] Treatment was discontinued in both instances with resolution of the corneal deposits and ocular symptoms, including restoration of normal vision. Common to both cases was a past ocular history of keratoconjunctivitis sicca.

Several differences exist between these reported cases and that of our own. In the case of our patient, vision loss was asymmetric and the left visual acuity remained unaffected. Biomicroscopy was normal in our patient and thus, not suggestive of ocular surface toxicity. Furthermore, symptoms did not improve with cessation of capecitabine treatment.

Our patient had had previous exposure to other chemotherapy agents that have known ocular side effects. Prior to commencing capecitabine, she had undergone three cycles of IV nab-paclitaxel chemotherapy. Taxane-based chemotherapeutic agents, including paclitaxel and docetaxel, have been associated with adverse ocular side effects.[15-19] Of note, cystoid macular oedema (CMO) has been reported, although uncommon.[15-19] In most presenting cases, dilated fundus examination revealed bilateral CMO which was then confirmed on OCT imaging.[15-19] This association was further supported by the reversibility of the CMO after discontinuation of chemotherapy in all cases.[15-19] It is important to highlight that there was no evidence of CMO in our patient. Macular OCT repeated over consecutive visits was unremarkable in both eyes. Ocular involvement was also unilateral in our patient. Nab-paclitaxel chemotherapy was poorly tolerated and there was bony progression on re-staging. As such, it was discontinued after just three cycles and the patient was switched to oral capecitabine. Ocular symptoms developed later and occurred six months after commencing capecitabine. Our patient discontinued capecitabine chemotherapy upon oncology recommendation and was off capecitabine for approximately eight months in total, without resolution or reversal of ocular symptoms.

Initial observations draw the attention towards possible

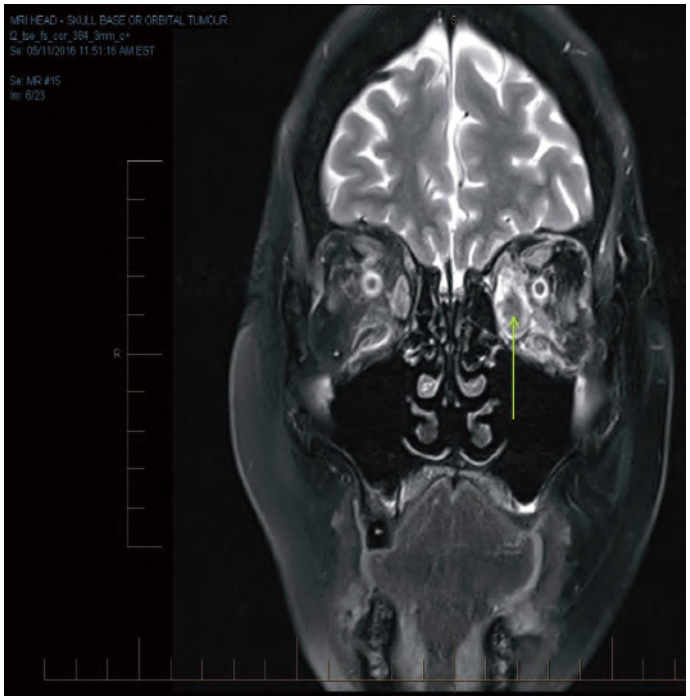

Figure 6. Coronal T2 fat suppressed MRI of the brain and orbits post steroid treatment showing persistent, severe swelling of the left medial rectus with enhancement.

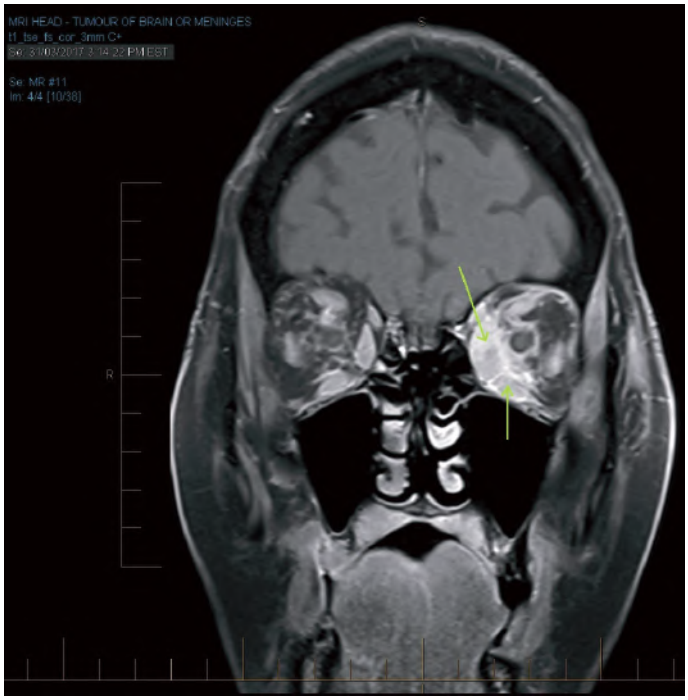

Figure 7. Coronal T1 fat suppressed MRI of the brain and orbits post radiotherapy showing persistent bilateral orbital inflammatory process (L>R). Marked swelling of the left medial and inferior recti is seen.

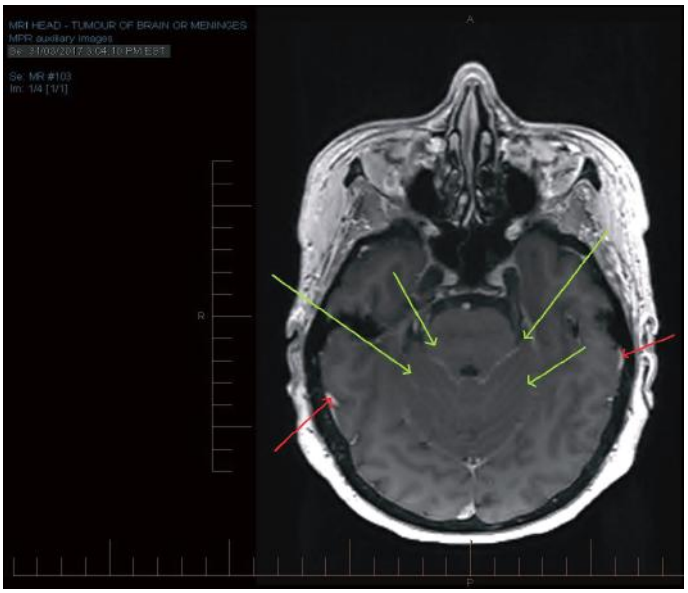

Figure 8. MRI brain (axial view) showing leptomeningeal tumour infiltration in the posterior fossa. Green arrows denote multiple linear hyperintensities representative of enhancing metastatic involvement of the cerebellar folia and brainstem. There is also nodular thickening of the pachymeninges consistent with metastatic infiltration (red arrows).

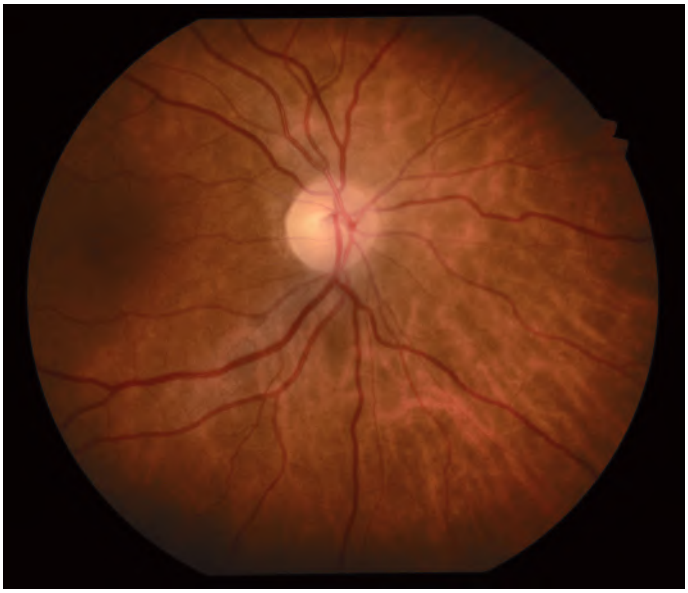

Figure 9. Fundus photograph of the right optic disc depicting disc pallor.

sub-clinical ophthalmic side effects associated with oral capecitabine therapy. However, this cannot be verified and to our knowledge, there are no reported cases in the literature of capecitabine cytotoxicity aside from those few cases discussed above with respect to ocular surface toxicity.[13,14]

In addition to drug toxicity, another diagnosis of consideration is infiltration of the right optic nerve sheath and/or partial compression of the right optic nerve. This is prudent to discuss given the presence of oedema within the intraconal fat and particularly in the setting of advanced metastatic disease. However, infiltrative disease or partial optic nerve compression were not readily apparent on imaging. The normal appearance of the right optic nerve head and lack of any associated findings such as exophthalmos, also failed to lend support to this diagnosis. There was late infiltration of the cavernous sinus and this could have contributed to compression of the optic chiasm or optic tract given its close anatomical proximity. However, given the partial decussation of nerve fibres at the chiasm, a chiasmal or post-chiasmal lesion would result in a visual field defect in the fellow eye which was not the case herein. The left visual field remained unaffected even late in the disease course. Moreover, there was no evidence of a posteriorly displaced chiasm which may have resulted in compression of the optic nerve before the chiasm secondary to a cavernous sinus lesion. The patient's initial symptom of pain on eye movement was thought to be due to the intraorbital oedema in the absence of any other significant findings.

One final causal possibility here is an autoimmune neuro-ophthalmic entity, paraneoplastic autoimmune optic neuritis, which is defined by collapsin response mediated protein 5 (CRMP-5-IgG). There are several documented cases of this in the literature.[20] A case series of 16 patients who were sero-positive for the auto-antibody CRMP-5-IgG, and who had optic neuritis, reported that almost all cases presented with sub-acute, painless loss of vision over weeks to months, swollen and haemorrhagic optic discs, and anomalous visual fields.[20] However, unlike in our case, most of these patients had a history of small-cell lung carcinoma and vision loss was typically bilateral. To confirm this diagnosis, serology testing specific for CRMP-5-IgG is necessary, however this was not performed in our patient. As such, it remains unknown whether she was positive for this marker auto-antibody.

Our case of unexplained vision loss highlights the complexity of the aetiologies underlying vision loss in patients with cancer and that sometimes the cause remains unknown. Cancer patients should be advised to remain alert to any visual or ocular changes whilst undergoing treatment and to promptly report any such changes. Ophthalmic evaluation/referral is warranted in patients with new onset of symptoms. As a minimum, appropriate workup includes a detailed history, clinical examination and imaging studies. Biochemistry and electrophysiology testing may also help to improve diagnostic yield and inform treatment in instances where the aetiology is not overtly apparent.

CONCLUSION

This represents a rare case of unexplained, unilateral vision loss. There remain several aetiologies that can be neither excluded nor concluded with certainty, including but not limited to: drug toxicity to chemotherapy agents; right-sided orbital infiltration or an undetected compressive lesion; and

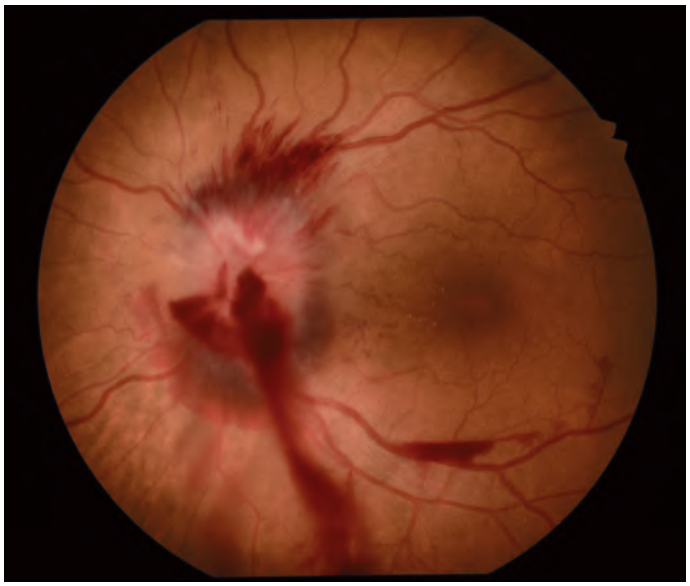

Figure 10. Fundus photograph of the left optic disc depicting a grossly oedematous disc with haemorrhages.

paraneoplastic autoimmune optic neuritis. Whilst this case does not lend itself to a definitive diagnosis, it is important to document cases of unexplained vision loss or suspected ocular drug toxicity such that others who encounter patients with similar clinical presentation and medical history might collectively be able to help solve these diagnostic riddles.

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