



## Case report

## Rapid visual field progression in a patient with glaucoma as the presenting manifestation of sarcoidosis



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## ABSTRACT

**Purpose:** To report a case of accelerated visual field progression secondary to a new orbital apex lesion in a patient with a longstanding history of fatigue and cough.

**Observations:** A 73-year-old myopic female with known open angle glaucoma presented with accelerated unilateral visual field progression. Maximally tolerated medical therapy was instituted over a period of 1–2 years with imminent discussions of surgical intervention. Around this time the patient reported worsening cough and fatigue, which were initially attributed to glaucoma medication side effects. Consideration of the patient's remote history of melanoma and the current asymmetry of the visual field progression triggered a computerized tomography (CT) scan of the orbits as part of the management. An orbital apex lesion was discovered, raising suspicion for metastatic melanoma, and restaging CT imaging uncovered renal, hepatic, and mediastinal masses. Unexpectedly, biopsies revealed non-necrotizing granulomatous inflammatory processes consistent with a diagnosis of sarcoidosis. It is perhaps noteworthy that the patient had received interferon therapy for management of her melanoma; previous reports have associated interferon exposure with subsequent sarcoid disease, regardless of duration of therapy or elapsed time since exposure.

**Conclusions and importance:** Although rare, sarcoidosis can occur virtually anywhere in the body, including the orbital apex. Its common early symptoms, fatigue and cough, are insidious and seen frequently in this patient's age group and medication side effect profile. It is important to maintain an appropriate index of suspicion when monitoring atypical visual field progression in a patient with glaucoma. In this case, imaging, subsequent biopsy, and a multi-specialty team were integral to this patient's diagnosis and management.

## 1. Introduction

Sarcoidosis is an inflammatory disorder of unknown etiology, characterized by the presence of inflammatory granulomata with associated fibrosis in virtually any organ. The incidence varies widely by demographic group but overall is estimated to be 7.6–8.4 cases per 100,000.<sup>1</sup> The average age of onset is 40–55 years with a younger peak age at diagnosis in men (30–50 years) than women (50–60 years).<sup>2</sup> In the largest reported cohort of systemic sarcoidosis patients (n = 345), ocular involvement occurred in 7%–15% of cases and presented most

commonly (61%) as granulomatous uveitis.<sup>3</sup> In the absence of uveitic symptoms, orbital involvement occurs in approximately 7% of ocular cases and 1%–1.5% involve the optic nerve sheath.<sup>4,5</sup>

## 2. Case report/case presentation

A 73-year-old woman of Northern European descent was routinely followed over a decade for glaucoma. Past medical history included bilateral cataract surgery, acephalgic migraines, sleep apnea, hypercholesterolemia, cardiovascular disease, and transient ischemic attack.

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Medications at time of presentation were lorazepam, loperamide, sennoside, and an acetylsalicylic acid/caffeine/codeine combination medication, as needed; with atorvastatin, acetylsalicylic acid, and ramipril taken daily. The patient also had a prior cutaneous left arm melanoma (T4B N0 M0 with lymphovascular space invasion) managed with wide excision, sentinel lymph node biopsy and adjuvant interferon alfa-2b therapy five years previously.

The patient’s ophthalmic history was complicated by a high degree of anisometropic myopia and right refractive amblyopia but no history of ocular inflammatory disease. At first presentation, visual acuity was 20/150 in the right eye (OD) and 20/25 in the left eye (OS). A right afferent pupillary defect was noted. There was no clinically evident ptosis or proptosis noted at any point. Her intraocular pressures (IOP) were elevated to 26 mmHg in both eyes (OU) at baseline. Refractive status was  $-7.24-0.75 \times 052$  OD and  $-9.00-2.00 \times 155$  OS.

The patient initially declined medical management and opted to undergo selective laser trabeculoplasty (SLT) for intraocular pressure (IOP) control. One month after bilateral inferior 180° treatments, IOP had decreased to 14 mmHg OD and 13 mmHg OS. Over the following three years IOP slowly climbed to a maximum of 21 mmHg OU, measured a few months before scheduled cataract surgery OU. Together with the patient, it was decided to defer further IOP management until IOP had stabilized post-operatively. During the first post-operative month, IOP’s fluctuated between 16 mmHg and 20 mmHg then began to decrease, and for three years following cataract surgery IOPs remained stable at 12 mmHg OU. Over this period, her visual field progression was modest. However, over the most recent two years, her visual fields demonstrated hastened and asymmetrical progression — most significantly on the right. These findings warranted a lower IOP target.

The patient was resistant to proceeding to incisional glaucoma surgery and thus underwent rapid escalation of medical therapy. Despite maximally tolerated medical therapy, the right superior arcuate scotoma further progressed over a 1-year period to a complete superotemporal defect and near complete superonasal defect (Fig. 1). Soon after, the patient became intolerant to maximal medical therapy, experiencing significant cough with combination topical alpha2-agonist/beta-blocker therapy as well as bradycardia, cough, and fatigue with combination topical carbonic anhydrase inhibitor/beta-blocker therapy.

Discontinuation of maximal medical therapy alleviated the patient’s side effects, however discussions regarding imminent glaucoma filtration surgery then became more pressing as this was felt to be the only remaining option to achieve the patient’s target IOP.

The patient remained resistant to the idea of incisional glaucoma surgery and expressed concern that a metastasis of her previous melanoma would limit her life expectancy such that losing her vision to glaucoma would be less of a concern. Although it is rare for cutaneous melanoma to metastasize to the orbit,<sup>6</sup> the possibility of a metastatic lesion impinging on the orbital apex/optic nerve and eliciting the rapid right-sided visual field progression observed in this patient prompted neuroimaging.

A computed tomography (CT) scan of the head and orbits was performed and demonstrated a new 0.7 × 1.1 cm enhancing lesion centered at the superior medial aspect of the right orbital apex (Fig. 2A). It appeared to be intraconal and was indistinguishable from the superior oblique, superior rectus, and medial rectus muscles. It caused a local mass effect with crowding of the apical structures. The left orbit and both globes appeared normal. Orbital imaging was normal bilaterally six years prior. A tentative plan for palliative radiotherapy to the orbital lesion for a presumed diagnosis of metastatic melanoma was initiated and restaging imaging was undertaken on suspicion that the patient may have systemic disease elsewhere and would require palliative systemic therapy in addition to the radiotherapy.

Surprisingly, CT imaging of the abdomen and pelvis demonstrated a large 4 cm lesion within the renal midpole (Fig. 2B) concerning for a solid mass as well as an ill-defined 0.4 cm lesion in the liver (Fig. 2C) raising the possibility of other diagnoses such as a new primary renal cell carcinoma. Abdominal imaging was normal 5 years earlier. Pathological examination of ultrasound-guided core biopsies of the renal mass was remarkable for diffuse involvement of renal tissue by a non-necrotizing granulomatous process (Fig. 3A) with no evidence of mycobacterial or fungal organisms, vasculitis, or malignancy.

To better characterize the orbital apex mass a diagnostic and potentially therapeutic MRI-guided, stereotactic, neuronavigation-assisted, transnasal, right-orbital-apex biopsy and optic nerve decompression was carried out. An irregular white subdural tissue was found in the location of the mass on imaging, and this was biopsied. The patient was followed up four weeks after surgery. Nasal debridement was

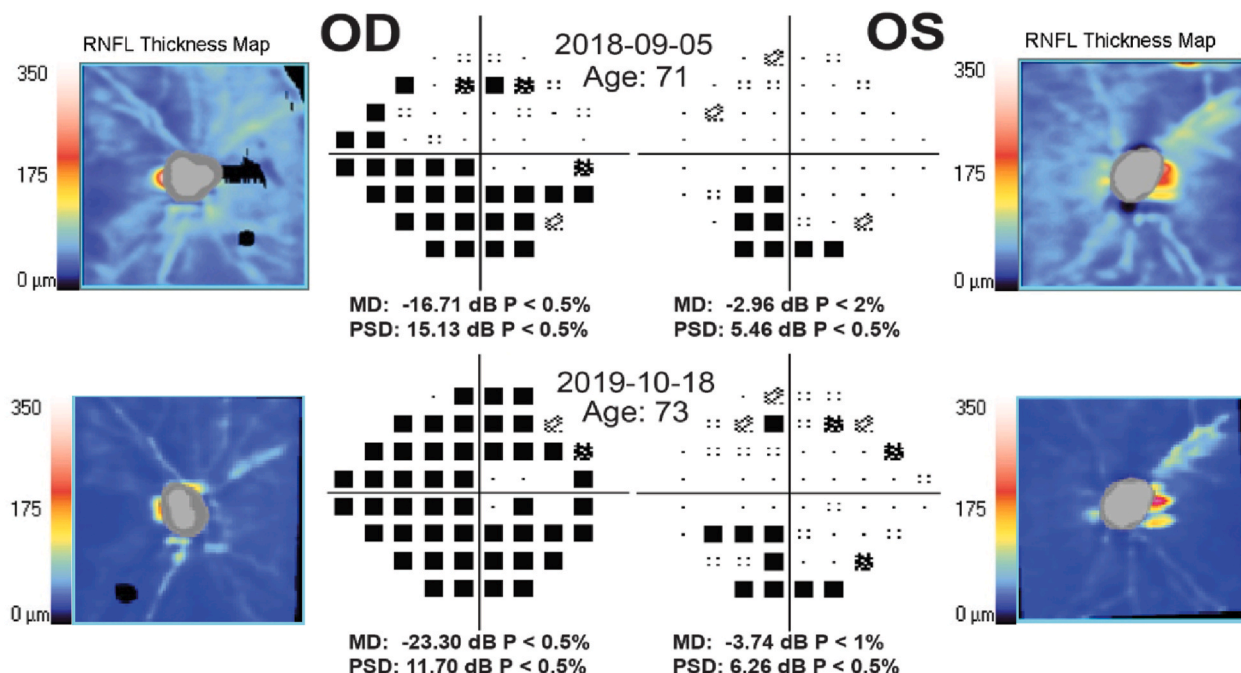
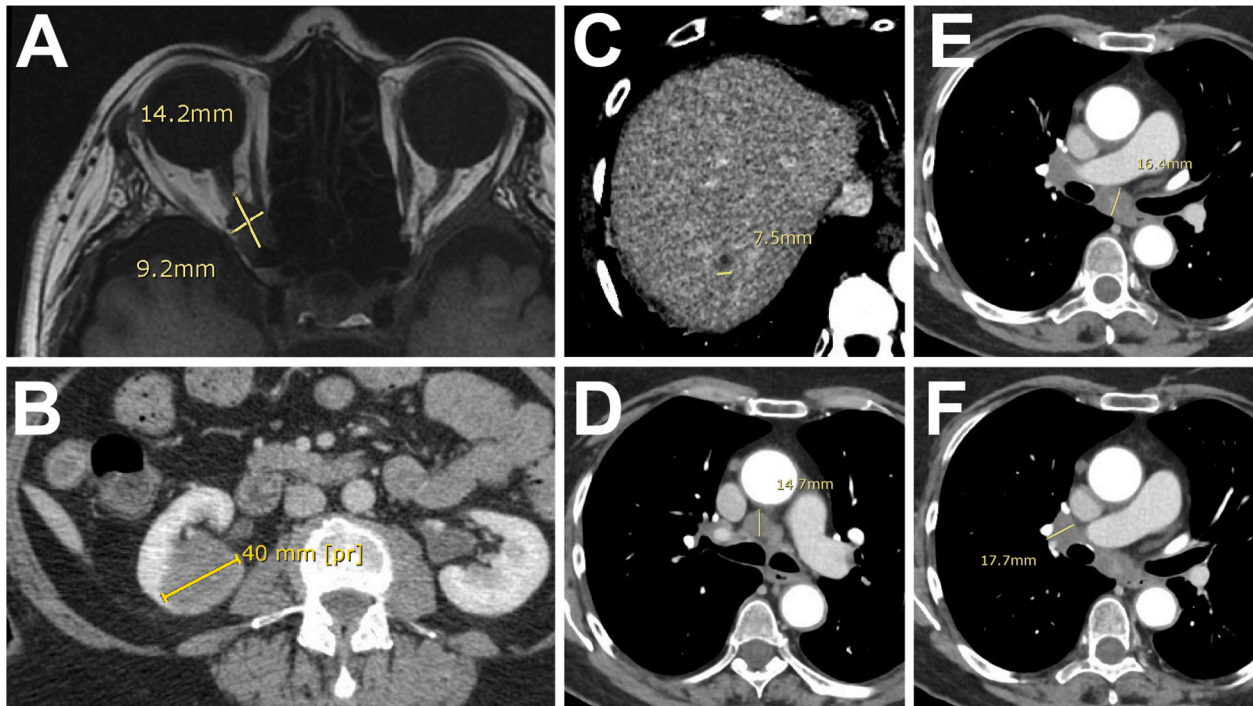


Fig. 1. Visual field mean deviation plots and retinal nerve fiber layer thickness maps before and after rapid atypical visual field progression.



**Fig. 2.** A) MRI of orbits demonstrating the right orbital apex mass, B) CT imaging of the abdomen demonstrating renal midpole mass, and C) hepatic lesion, CT thorax demonstrating enlargement of the D) paratracheal, E) subcarinal and F) hilar mediastinal lymph nodes.

performed, and the surgical site was healthy with no concerning findings. Immediately following the orbital biopsy the patient was assessed in the eye clinic. Vision in the right eye was NLP with an IOP of 12 mmHg, and vision in the left eye was 20/20. The appearance of the fundus and optic nerve were unchanged compared to preoperative assessment. Pathology revealed fibrous tissue containing multinucleated giant cells and scattered, ill-defined, poorly formed, non-caseating granulomata (Fig. 3B). Acid fast bacilli and fungal organisms were not identified with histochemical stains, and there was no evidence of vasculitis or malignancy.

Subsequent CT thorax demonstrated multiple significantly enlarged mediastinal lymph nodes in the right paratracheal, right hilar and subcarinal regions (Fig. 2D–F). A normal CT thorax was reported 5 years earlier. An endoscopic ultrasound-guided *trans*-esophageal fine needle aspiration biopsy of the subcarinal lymph node similarly revealed non-necrotizing granulomatous inflammation (Fig. 3B and C).

Cumulatively, the patient's constitutional symptoms, biopsy findings and CT imaging suggested a systemic inflammatory process – likely sarcoidosis. Bloodwork was ordered at this time and demonstrated leukopenia ( $3.8 \times 10^9$  cells/L; ref:  $4\text{--}10 \times 10^9$  cells/L), lymphopenia ( $0.6 \times 10^9$  cells/L; ref:  $1\text{--}4 \times 10^9$  cells/L), anemia (Hb 110 g/L; ref: 115–160 g/L) and an elevated erythrocyte sedimentation rate (52 mm/hour; ref:  $\leq 20$  mm/hour). Serology was negative for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and rheumatoid factor. Angiotensin converting enzyme (ACE) levels were initially normal at 13U/L (ref: 9–63U/L), however, after one month follow-up were measured low at 3U/L (ref: 9–63U/L). Liver enzymes were presently normal; however, while the patient was on interferon therapy 5 years earlier, with symptoms of cough, myalgias and fatigue, elevations were evident in aspartate transaminase (AST) 144 U/L (ref:  $\leq 32$  U/L), alkaline phosphatase (ALP) 107 U/L (ref: 35–104 U/L) and lactate dehydrogenase (LDH) 298 U/L (ref:  $\leq 240$  U/L).

The orbital apex biopsy and optic nerve decompression were well tolerated and there was no significant post-operative pain. Unfortunately, post-operative vision had decreased to no light perception in the right eye from a preoperative visual acuity of 20/30–1 OD. The left eye

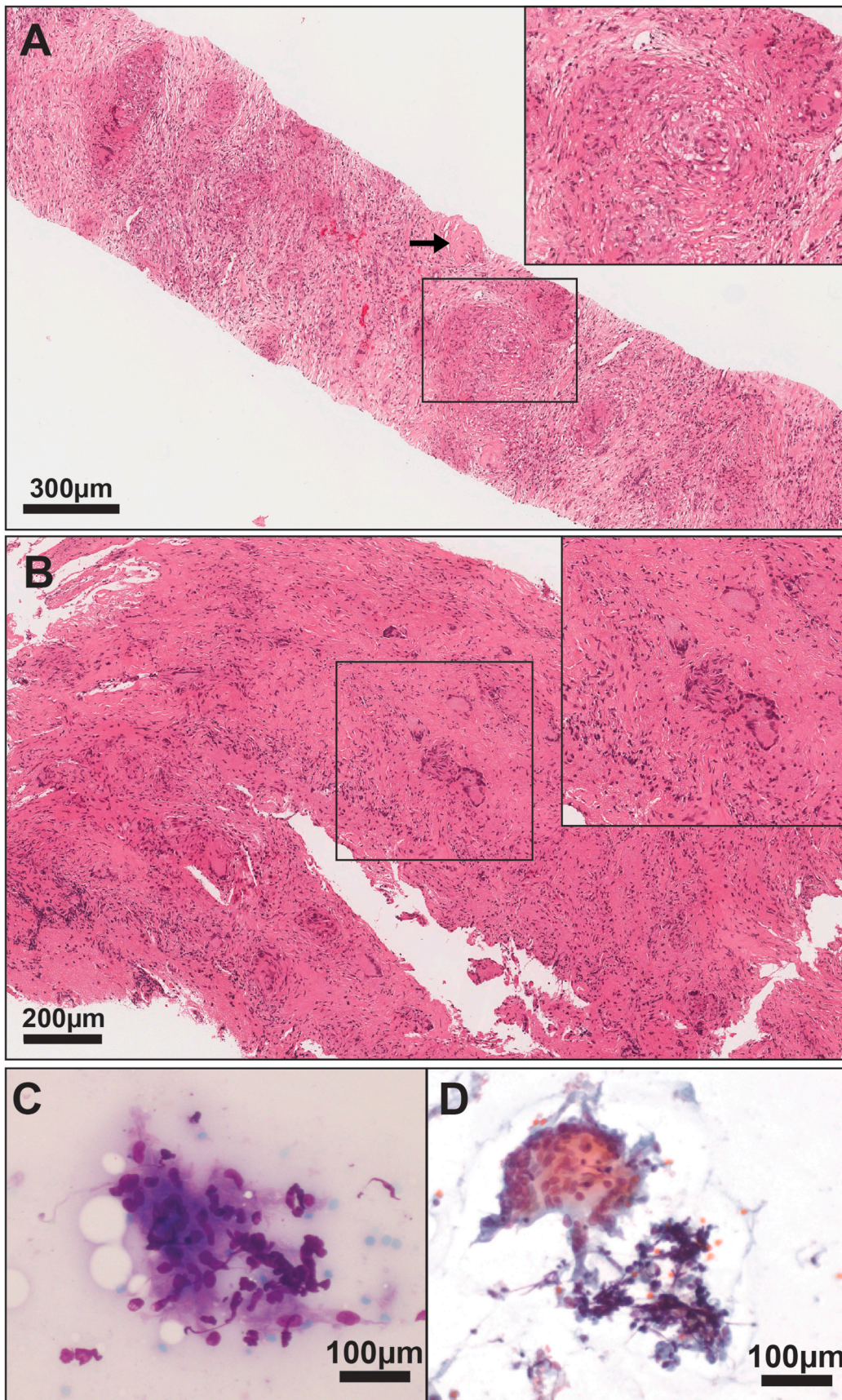
remained stable at 20/20–1. Nonetheless, the patient was satisfied with her decision to undergo definitive diagnostic biopsy, despite the associated vision loss, as she had been spared an unnecessary glaucoma filtration surgery as well as possible cancer diagnosis and treatment. She had nearly always appreciated the visual function of her right eye to be low due to longstanding amblyopia and glaucoma progression. The patient understood and accepted that the medical team, which included an ophthalmologist, otolaryngology – head and neck surgeon, internal medicine specialist, and oncologist required pathological tissue diagnosis to guide appropriate management. A diagnosis of systemic sarcoidosis with extra-pulmonary involvement was confirmed and the patient responded well to appropriate treatment with oral glucocorticoids. Considering that the patient now has monocular vision, with glaucoma progression in the functional eye, increased monitoring for an intraocular pressure response to glucocorticoid treatment courses will be critical to preserving this patient's remaining visual function.

### 3. Discussion/conclusion

Sarcoidosis is an infiltrative, granulomatous disease that can affect any organ system. Although it can occur at any age, it is often seen in adults 40–55 years old but has peak incidence at 50–60 years in women.<sup>7</sup> Incidence is highest in individuals of African American descent, 18–71 cases per 100,000, and in Scandinavian countries, 11–60 cases per 100,000.<sup>1,2,4</sup> The lowest incidence occurs in Asian and Hispanic communities with 1–5 cases per 100,000 individuals. Most patients present with general fatigue and/or breathing difficulties with subsequent discovery of pulmonary changes, however nearly 50% of patients diagnosed with sarcoidosis are asymptomatic.<sup>2</sup> In terms of non-ophthalmic manifestations, this patient had baseline chronic cough and fatigue which were initially attributed to rapid glaucoma medication escalation secondary to significantly accelerated visual field progression. These symptoms contributed to glaucoma medication compliance issues which supported an initial suspicion of accelerated glaucomatous progression.

The symptoms of cough and fatigue which can be secondary to





**Fig. 3.** A) Hematoxylin and eosin-stained slide of the kidney biopsy showed diffuse involvement by non-necrotizing granulomatous inflammation. Arrow indicates sclerosed glomerulus. Box indicates enlarged image of non-necrotizing granulomata. B) Hematoxylin and eosin-stained slide of the right orbital apex mass biopsy revealed fibrous tissue containing multinucleated giant cells, ill-defined and poorly formed non-necrotizing granulomata composed of epithelioid histiocytes, and a mixed population of lymphocytes. Box indicates enlarged image of non-necrotizing granulomata. C) Non-necrotizing granulomata in a mixed lymphoid background stained with DiffQuik and D) Papanicolaou stains. Samples were acquired from an enlarged mediastinal lymph node by endoscopic ultrasound-guided transesophageal fine needle aspiration biopsy.



certain classes of anti-glaucoma medications are also consistent with systemic manifestations of sarcoidosis. Instead, this patient presented with symptoms secondary to a single, unilateral offending mass at the orbital apex. Given the history of cutaneous melanoma with a prematurely aborted 1-month course of interferon therapy,<sup>8</sup> a metastatic lesion was considered in the differential diagnosis. However, metastasis to the eye is rare in cutaneous malignant melanoma and it is estimated that only 0.5–1% of intraocular metastases originate from a cutaneous primary tumor.<sup>9</sup> Intra-orbital metastases occur even less frequently than those to the globe.<sup>10,11</sup>

It should be emphasized that the diagnosis of sarcoidosis requires histological confirmation. Pathological examination of the involved tissue confirmed the presence of non-necrotizing granulomatous inflammatory lesions in the orbital apex, kidney, and mediastinum. A diagnosis of sarcoidosis was considered to be most likely when the pathological findings were considered in the context of the imaging and clinical findings, which included mediastinal lymphadenopathy, leukopenia, and a small uncharacterized hepatic lesion, all in the absence of another systemic explanation. Most specifically, lymphadenopathy noted in CT imaging of the thorax presents in 75–90% of patients with sarcoidosis.<sup>2</sup>

Elevated serum ACE often occurs in sarcoidosis.<sup>3,4</sup> The International Guidelines for the diagnosis of sarcoidosis propose serum ACE levels as a diagnostic and prognostic marker,<sup>12</sup> however sensitivity and specificity are rather poor – 41.4% sensitivity and 89% specificity. Approximately 50% of patients with sarcoidosis present with normal lab values.<sup>13</sup> In cases of sarcoidosis with ocular involvement, serum ACE is reported to be a more specific and sensitive biomarker with 84% sensitivity and 95% specificity.<sup>14</sup> While the patient did not have an elevated serum ACE, it is noteworthy that the patient was receiving long-term ACE inhibitor therapy which is known to artificially depress serum ACE levels in patients with sarcoidosis thereby reducing its utility as a biomarker.<sup>15</sup>

A notable past exposure for this patient was a short course of interferon alfa-2b therapy after melanoma excision. Fatigue, transiently elevated liver enzymes, myalgias and cough all arose shortly after commencement of interferon therapy, resulting in early treatment cessation after one month, and persisted to some degree for five years thereafter. Prior exposure to immunomodulating agents is a risk factor for developing drug-induced sarcoid-like reactions (DISR) for as long as ten years after cessation of any duration of therapy.<sup>2,16</sup> There are no clinical, radiological or laboratory findings that distinguish DISR from primary sarcoidosis, however DISR usually resolves after discontinuation of the offending medication.<sup>16</sup>

This patient's exposure to interferon alfa-2b was remote, relatively brief, and discontinuation did not result in remission of sarcoid disease, making DISR an unlikely etiology. However, it remains of note that interferons are one of the most frequently associated pharmacological agents associated with the development of DISR.<sup>16</sup> There are 557 reported cases of interferon-associated sarcoidosis in the WHO pharmacovigilance database (VigiBase)<sup>17</sup> – approximately three times the number of reports expected when compared to similar drugs according to a conservative (lower end of 95% CI) disproportionality analysis method developed by the Uppsala Monitoring Center.<sup>18</sup> Interferon-associated sarcoidosis with ocular involvement, to the best of our knowledge, has been reported in the literature four times previously.<sup>17,19</sup>

Ing et al. reported a case of sarcoidosis masquerading as a meningioma prior to biopsy and reviewed 17 other similar cases.<sup>20</sup> Over two thirds of the 18 cases were suspected to have optic nerve sheath meningioma or optic nerve glioma and no patients were diagnosed with systemic sarcoidosis prior to biopsy. Ing et al. emphasized the virtual impossibility of distinguishing between optic nerve sarcoid and optic nerve sheath meningioma without a definitive tissue biopsy. Nonetheless, it is important to make this distinction as the implications of sarcoidosis and cancer are very different for management and patient wellbeing.

A key takeaway from this case of an orbital apex sarcoid lesion in an established glaucoma patient is the challenge of securing the diagnosis. Sarcoidosis is rare; even more so are sarcoid manifestations creating intra-orbital mass effects and an associated acceleration of glaucoma-like visual field progression. This is especially true in a patient who had self-reported non-compliance issues. Cough and fatigue, common glaucoma medication side effects, contributed to this patient's non-compliance; however, these symptoms overlap with and in retrospect may have represented early constitutional symptoms characteristic of sarcoidosis. Neuroimaging is not routinely performed for primary open angle glaucoma patients with advancing visual field defects and elevated intraocular pressures, unless there is evidence of vertically aligned visual field defects or the patient is younger than 50 years of age, neither of which applied in this patient's case.<sup>21–24</sup>

Fortunately, clinical suspicion prompted the imaging necessary to discover the orbital apex and other masses, thus sparing the patient unnecessary glaucoma filtration surgery and possible radiation/chemotherapy. An interdisciplinary team that worked collaboratively to secure the orbital apex, renal and mediastinal lymph node biopsies combined with subsequent histopathological analyses was pivotal to rule out a primary optic nerve tumor or secondary melanoma metastasis. These diagnostic measures allowed for treatment to be directed appropriately toward the patient's sarcoid disease, spared the patient unnecessary glaucoma surgery and/or radiation/chemotherapy, and had dramatic implications for the patient's prognosis. The patient was grateful for the care involved and appreciative of the commitment of the interdisciplinary team to investigating and managing this unexpected diagnosis appropriately.

#### Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing. This report does not contain any personal identifying information.

#### Statement of ethics

Written informed consent was obtained from the patient prior to publication of her relevant de-identified medical information. This work was conducted in accordance with the World Medical Association Declaration of Helsinki. The Western University Office of Research Ethics considers de-identified reports on less than five ( $n < 5$ ) patients to be exempt from Research Ethics Board review.

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#### Declaration of competing interest

The authors have no conflicts of interest to declare.

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#### Appendix A. Surgical Note for *Trans-nasal Orbital Apex Biopsy*

**PREOPERATIVE DIAGNOSIS:** Lesion right posterior orbit causing optic nerve compression.

**POSTOPERATIVE DIAGNOSIS:** Lesion right posterior orbit causing optic nerve compression, await final pathology, preliminary intraoperative report suggesting granulomatous lesion.

## PROCEDURES:

1. Right optic nerve decompression and biopsy of right posterior orbit.
2. Stereotactic neuronavigation.

**SURGEON:** Dr. Brian Rotenberg.

**ANAESTHETIST:** Dr. Rosemary Craen

**CLINICAL NOTE:** The patient was referred to me by the Ophthalmology Team for consideration of biopsy of a lesion of her posterior orbit causing optic nerve compression and visual loss. This lesion has been slowly growing over time. The diagnosis was unclear based on imaging, but there was a concern regarding malignancy and possible metastatic melanoma. The patient was consented for the aforementioned procedure, stressing to her the possible risks of visual loss, diplopia and blindness as part of the surgery. She was placed on the Emergency Room list, and the case took place after 1700 hours today.

**SURGICAL NOTE:** The patient was identified and brought to the Operating Room. General anaesthesia was administered using orotracheal intubation. Preoperative Ancef 2 g and hydrocortisone 100 mg was given intravenously. We obtained 3 dimensional MRI sequences for stereotactic neuronavigation. The Mayfield frame was hooked up with 3-point fixation, and image-guided apparatus and verified as being accurate to within 1 mm and used throughout the case to assist in navigating into critical structure of the posterior orbit. We then decongested the nose and visible landmarks infiltrated with 1% lidocaine and 1:100,000 epinephrine to a total of 5 mL. Inferior turbinate outfractured and middle turbinate medialized. Wide maxillary antrotomy created. Infraorbital nerve was identified. A complete anterior and posterior ethmoidectomy performed, boundaries being base of skull and lamina papyracea. Sphenoidotomy performed. Within the sphenoid sinus the pituitary gland, clivus, carotid artery and optic nerve were all identified. The microdebrider was used to verify the placement of the carotid artery. We now traced the optic nerve from the optic foramen posteriorly to the orbital apex anteriorly and, marking this out, we used a high-speed diamond bur to drill away all bone covering the orbital apex and optic nerve. We now used the navigation to decisively verify the placement of these structures and then localize the location of the lesion, that being in the orbital apex. This was marked off and then incised with a sickle blade from anterior to posterior. This nicely decompressed the optic nerve. Upon entering the dura, we could see what appeared to be unusual whitish irregular appearing tissue. The medial rectus and oblique muscles were not clearly seen. The optic nerve was now decompressed. Biopsies were taken for frozen section, and these returned as showing granulomatous lesion with no signs of malignancy. We then took a secondary specimen for permanent. By this time, we had nicely decompressed the entire length of the optic nerve to take the pressure off of the nerve. We also had lesional tissue that now could be analyzed by Pathology. Therefore, the goal of surgery had been accomplished. We washed out the incision and the posterior orbital apex with bacitracin-infused Tis-U-Sol. There was no particular bleeding seen. We placed a few squares of Gelfoam along all cut edges of dura and covered this in a layer of Tisseel. We now obtained intranasal hemostasis. NasoPore packing was placed. A Meroceel patty covered in Bactroban was placed on the floor of the nose. The patient was reversed from anaesthesia and transferred to PACU in stable condition. She will be admitted overnight for observation. Because of the suspicion of granulomatous disease, we will order a panel of blood work to check for various vasculitis and granulomatous disorders.

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