American Journal of Ophthalmology Case Reports 32 (2023) 101934

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Metastatic squamous cell carcinoma masquerading as acute retinal necrosis

Effie Z. Rahman [a,b,*], Pooja Shah [a,c], Rajiv Shah [a]

[a] Department of Ophthalmology, Atrium Health Wake Forest Baptist School of Medicine, Winston-Salem, NC, 27157, USA
[b] Retina Consultants of Texas, Retina Consultants of America, Bellaire, TX, USA
[c] Department of Ophthalmology, University of North Carolina Chapel Hill, Chapel Hill, NC, 27517, USA

ARTICLE INFO

Keywords:
Retinal metastases
Acute retinal necrosis
Squamous cell carcinoma
Surgical intraocular tumor debulking

ABSTRACT

Purpose: To describe a case of retinal and optic nerve metastases masquerading as acute retinal necrosis secondary to primary squamous cell carcinoma of the lung.
Observations: A 66-year-old male with a history of Stage IV lung cancer, actively on chemotherapy, presented with right eye vision loss, an afferent pupillary defect, and partial visual field deficiencies. Exam revealed vitritis, macula-involving infiltrative retinitis, optic neuritis, and vasculitis of the right eye. The patient was treated empirically for acute viral retinitis with intravitreal foscarnet and ganciclovir injections and oral acyclovir and trimethoprim-sulfamethoxazole. A diagnostic pars plana vitrectomy with vitreous biopsy, intravitreal antivirals and silicone oil fill was performed. The resulting cytology was positive for malignant squamous cell carcinoma.
Conclusions and importance: We present a unique case of primary squamous cell carcinoma metastasizing to the retina and optic nerve which masqueraded as an acute viral retinitis. To date, there have not been any reported cases on Pubmed or Google Scholar at publication time of known squamous cell carcinoma metastases to the retina that demonstrated interval growth leading to emergent elevations in intraocular pressure (IOP). This case demonstrates the importance of considering metastasis when encountering an atypical acute retinal necrosis case, as well as bring awareness to the possibility that elevated IOP may be the first sign of interval metastases, despite surgical debulking, in cases involving known tumor metastases to the retina.

1. Introduction

Metastatic carcinoma of the eye is the most common type of intraocular malignant neoplasm. Lung cancer in males and breast cancer in females are the most common primary cancers preceding intraocular metastases. Choroidal metastases are quite common.[1] However, retinal metastases represent just 1% of intraocular metastases.[2] With variance in clinical presentation, diagnoses can be challenging and cause delays in treatment or result in inadequate treatment approaches.[3,4] The under-recognition of intraocular metastases is problematic as its presence is a poor prognostic indicator for survival.[5] The following case is one of the few reported occurrences of both retinal and optic nerve metastases presenting as acute retinal necrosis. This is a unique case of known interval increased tumor load that led to elevated intraocular pressure (IOP) despite surgical debulking of a primary squamous cell carcinoma.

2. Case report

A 66-year-old male presented in November 2020 for evaluation of a retinal infiltrate in his right eye (OD). He reported worsening vision OD two months prior. He was diagnosed with Stage IV lung cancer in September 2019 with primary metastasis to the bone. He was previously treated with chemotherapy including pembrolizumab 200 mg, Paclitaxel IV 100 mg/m^2, carboplatin IV, and pembrolizumab 200 mg IV for one year. At presentation, his chemotherapy regiment included docetaxel 75mg/m^2, ramucirumab 10 mg/kg IV and pegfilgrastim 6 mg subcutaneously. His past medical history includes rheumatic fever at nine-years-old, chickenpox, hypothyroidism, and hypertension. His other medications includes albuterol and Incruse Ellipta (umeclidinium) inhalers, bupropion, dexamethasone, levothyroxine, lisinopril, nystatin, olanzapine, penicillin V potassium, and pravastatin. He was a former smoker who stopped tobacco use in 2016 and previously worked in the tire industry.

On initial examination, the patient's best corrected visual acuity (BCVA) was 20/60-2 OD and 20/20-2 OS. IOPs were 14 OD and 19 OS.

* Corresponding author. Retina Consultants of Texas, Houston, TX, 77401, USA.
E-mail addresses: ezrmd@retinaconsultantstexas.com (E.Z. Rahman), pmshah@ad.unc.edu (P. Shah), rajshah@wakehealth.edu (R. Shah).

https://doi.org/10.1016/j.ajoc.2023.101934
Received 5 April 2023; Received in revised form 17 September 2023; Accepted 26 September 2023
Available online 28 September 2023

He had an afferent pupillary defect OD. Visual fields were full OS and he had partial outer superior temporal, inferior temporal, and inferior nasal deficiencies OD. His external exam was normal OU. He had minimal vitritis OD and 1+ nuclear sclerosis OU on slit lamp exam. Fundus examination OD demonstrated an infiltrative retinitis affecting the macula. There were small amounts of heme and necrosis nasally as well as along the superior and inferior quadrants (Fig. 1A). Fundus OS demonstrated small, inactive chorioretinal scars (Fig. 1B). The initial differential diagnosis included acute retinal necrosis, fungal endophthalmitis, toxoplasmosis, tuberculosis, cytomegalovirus, progressive outer retinal necrosis, inflammatory reactions to mitogen-activated protein kinase (MEK) inhibitors, lymphoma, and both primary and metastatic cancer. Labs were ordered to rule out Lyme disease, syphilis and sarcoidosis. The patient received intravitreal injections OD of Foscarnet 1.2 mg and Ganciclovir 2.0 mg for suspected herpes zoster and simplex viruses in the setting of a previous history of chickenpox and immunosuppression from chemotherapy. A vitreous tap OD was performed and the vitreous was sent for polymerase chain reaction (PCR) analysis including herpes zoster, herpes simplex 1 and 2, toxoplasmosis and both bacterial and fungal cultures.

Initial labs were significant for a red blood cell count of 4.13 and hemoglobin of 12.3, red cell distribution width of 18.7, monocyte absolute of 1.0, bicarbonate of 22, total protein of 5.9, interleukin-2 receptor (CD25) of 964.1, and angiotensin converting enzyme of 6. Negative labs included enzyme immunoassay, human immunodeficiency virus antibody-antigen combination, rapid plasma regain/microhemagglutination assay for Treponema pallidum antibodies, interferon-gamma release assay, hepatitis panel, fungitell (1,3)-b-D-Glucan assay, lysozyme and Lyme disease antibody. PCR for qualitative toxoplasma gondii, herpes simplex virus 1 and 2, cytomegalovirus, and varicella zoster virus were also within normal limits.

On follow-up two days later, the patient's BCVA decreased to 20/200 OD. His examination was unchanged except for a possible inferior and nasal serous detachment. Optos-wide field photography showed a yellow infiltrative lesion nasally with associated atrophy and a possible serous detachment OD. Due to lack of improvement from the initial visit, the patient was started on sulfamethoxazole-trimethoprim 160 mg two times daily and valacyclovir 2000 mg three times daily for empiric varicella zoster and ocular toxoplasmosis treatment, despite a negative PCR. On follow-up 6 days later, his BCVA improved to 20/100 OD, but his examination was otherwise unchanged. Optical coherence tomography (OCT) showed inner retinal cystic changes and a lamellar hole OD, with no outer retinal atrophy (Fig. 2A). OCT OS was within normal limits (Fig. 2B). Optos fundus photography showed persistent nasal retinitis OD with no abnormal findings OS. His examination and imaging demonstrated an atypical appearance for a viral infection, given that acute retinal necrosis should demonstrate outer retinal layer loss. Since antiviral injections had not yielded improvement, a prompt pars plana vitrectomy with undiluted vitreous biopsy and silicone oil tamponade was recommended. The patient's medication regimen was decreased to sulfamethoxazole-trimethoprim 160 mg twice daily and valacyclovir 2000 mg twice daily due to the patient's difficulty with medications.

3. Results

A 23-gauge pars plana vitrectomy with undiluted vitreous biopsy, perfluorocarbon, air-fluid exchange, laser retinopexy, and 5000 centistoke silicone oil (SO) OD was performed (Fig. 3A and B). Vitreous biopsy tested negative for interleukin-6, interleukin-10, T-cell gene rearrangement, fungitell, Viracor-IBT, B cell clonality, mycobacterium tuberculosis complex and for Ebstein Barr virus and toxoplasma gondii PCR. Cytology was positive for malignant cells, consistent with squamous cell carcinoma.

After discussion with the patient's medical oncologist, further chemotherapy and repeat metastatic work up was recommended. The patient was started on Tagrisso 80 mg daily for targeted therapy as well as nivolumab 360 mg IV adipilimumab 1 mg/kg IV. Multiple brain metastases were noted on repeat brain and orbit magnetic resonance imaging (MRI), prompting multiple rounds of radiation including two separate sessions of right frontal lobe Gamma Knife of 2000 cGy and left frontal lobe Gamma Knife of 2000 cGy. On post-operative week two, the patient's BCVA worsened to light perception (LP), and fundus photos OD demonstrated persistent infiltration superior and inferior to the nerve (Fig. 4A and B).

On follow up twelve weeks postoperatively, the patient presented with increased IOP to 44 mm mercury. Both examination and fundus photos OD demonstrated a new, large subretinal mass on his dilated fundus exam. The patient had a shallow anterior chamber due to silicone oil displacement forward. There was no neovascularization of the iris or angle on exam.

The patient was scheduled for urgent surgical debulking the same day. During vitrectomy, a clear change in his exam was noted. There was a new, large subretinal and intraretinal mass which was debulked with the cutter. Given the limited view to the posterior pole, a combined 23-gauge PPV with surgical debulking and phacoemulsification with lens implantation was performed. Silicone oil was removed and a retinectomy was performed with reinsertion of 5000 centistoke SO.

Ongoing discussion with the patient's oncology team lead to the discovery of further brain metastases. Following the patient's second surgery, a right frontal craniotomy was performed followed by a left frontal craniotomy 6 months later. The patient also underwent radiation to the right orbit of 3000 cGy in 300 cGy daily fractions. Despite this, the patient was found to have recurrent lesions in his MRI at the end of 2022 and was given palliative whole brain re-irradiation 3000 cGy in 300 cGy

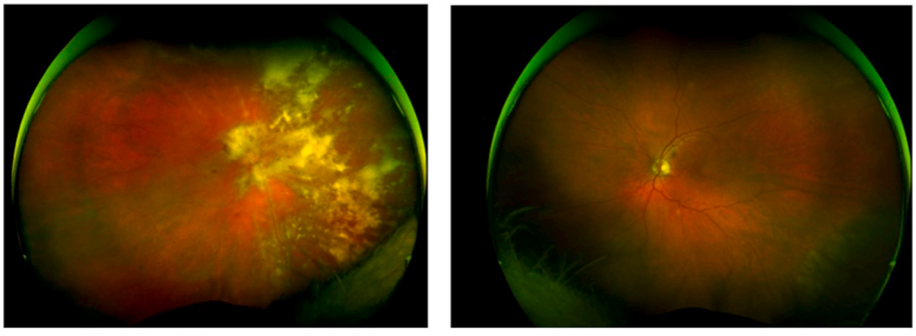

Fig. 1. Fundus photographs of both eyes at presentation
Ultra-wide field fundus photographs of the right (A) and left (B) eyes. A) Yellow appearing infiltrative retinitis involving the inferior, superior and temporal retina. There is a yellow appearing mass emanating from the optic nerve and a questionable inferior retinal detachment. B) two small half-disc diameter nummular lesions are noted inferiorly and superiorly. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

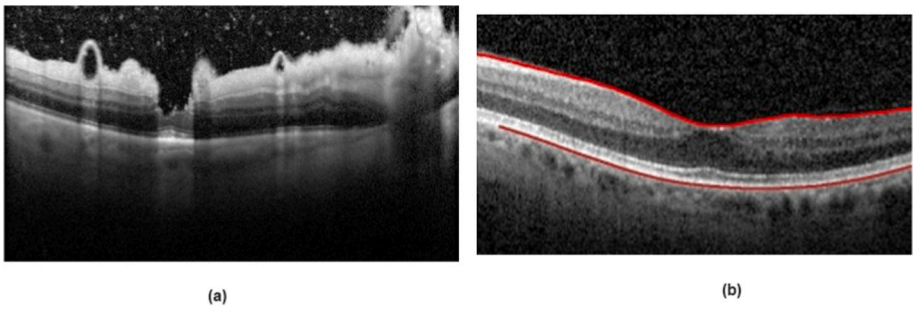

Fig. 2. Optical coherence tomography (OCT) of both eyes at presentation
A) OCT of right eye demonstrating inner retinal cystic changes. Note that the outer retinal layers remain preserved and there is no sign of outer retinal atrophy. B) OCT of left eye appears within normal limits.

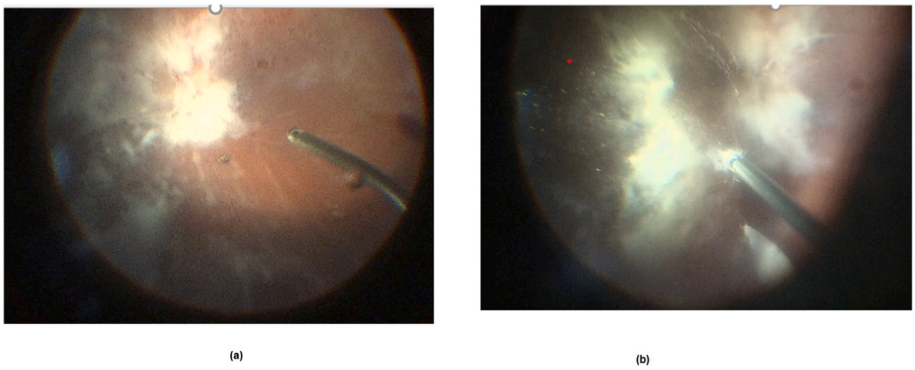

Fig. 3. Intraoperative photos
A) Clear view at the beginning of surgery. White-creamy intraretinal lesions were noted throughout the posterior pole. The optic nerve is not visible due to the overlying ocular nerve metastases and surrounding intraretinal metastases. The retina appears detached inferiorly. B) The retina was noted to be fragile and friable with necrotic pieces circulating throughout the vitreous cavity.

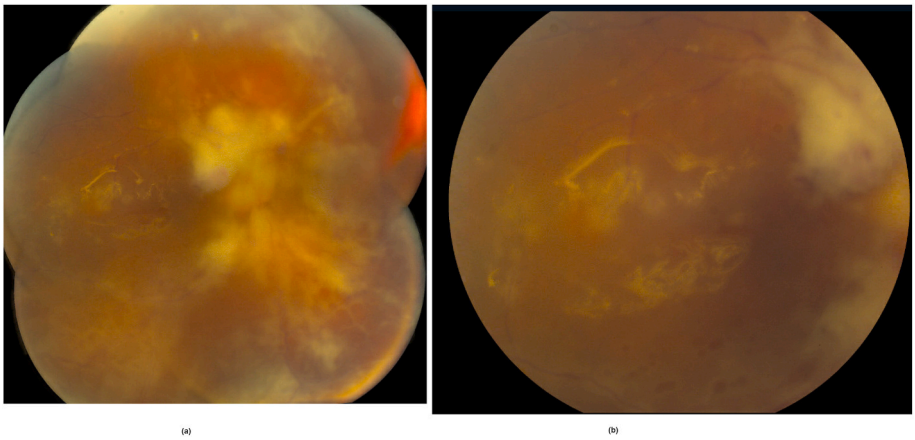

Fig. 4. Postoperative Photographs of the Right Eye
A) Montage fundus photograph of the right eye following pars plana vitrectomy with 5000 centigrade silicone oil fill. The retina appears flat. The optic nerve and posterior pole are indistinct due to the presence of white infiltrative intraretinal and optic nerve metastases. B) fundus photograph of the right eye focusing on the macula. Macula appears flat. Irregular borders of the white infiltrative intraretinal metastases are visible temporal to the macula overlying the posterior pole. No obvious subretinal masses are present at this time.

daily fractions. Following radiation, the patient was started on a new chemotherapy regiment including nivolumab 360 mg IV and ipilimumab 1 mg/kg IV. For two years following his initial surgery, the patient's vision was maintained at LP; however, following his last radiation session, his vision deteriorated to no light perception. The patient developed ocular pain and was enucleated 26 months after his initial presentation.

4. Discussion

Retinal metastases are rare, and reported cases have variable clinical presentations, often mimicking other retinal conditions. The above case demonstrated findings consistent with retinal detachment, vasculitis, infiltrative retinitis, and acute retinal necrosis, a condition most often caused by VZV infection, which our patient was initially treated for empirically.[6] While there have been no cases of squamous cell

pulmonary carcinoma presenting in this fashion, cases of secondary vitreoretinal lymphoma and esophageal carcinoma metastasizing to the retina have resembled acute retinal necrosis.[4,7] In another similar case, a 62-year-old male with a history of lung cancer presented with decreased vision and clinical features of cyclomegaloviral retinitis. He was treated empirically, but viral cultures were negative. A PPV with a retinal biopsy was performed, and pathology demonstrated sheets of tumor cells with pleomorphic nuclei which stained positive for cytokeratin, consistent with metastatic adenocarcinoma.[8]

Head and neck carcinoma metastasis to the choroid, vitreous, and rarely optic nerve head have also been reported and have an aggressive course, with the average survival time of seven months after diagnosis of ocular metastasis.[9–11] Isolated optic disc metastases are rare, with only 1.2% of intraocular metastases confined to the nerve without involvement of the choroid or retina. These often present unilaterally with central swelling of the disc, flame-shaped hemorrhages, and diffuse enlargement of the optic disc without a distinct nodule.[12] One case of squamous cell carcinoma of the lung presented with vision loss and a milky white tumor of the optic disc extending into the vitreous. MRI of the head and orbits showed heterogeneous thickening throughout the intraorbital optic nerve but was otherwise non-revealing for metastases.[13]

5. Conclusions

The above represents a unique case of pulmonary squamous cell carcinoma metastasizing to the retina and optic nerve, masking as acute retinal necrosis. Moreover, our presentation demonstrating continued tumor growth under oil despite tumor debulking with pars plana vitrectomy, continued systemic chemotherapy, radiation, and surgical intervention has not been reported on Pubmed or Google Scholar. At the time of publication, key words including “retinal metastases”, “acute retinal necrosis”, “squamous cell carcinoma” and “surgical intraocular tumor debulking” did not yield any known cases of squamous cell carcinoma metastases to the retina and optic nerve that demonstrated interval growth, leading to an emergent elevation in IOP. There are many causes for acute elevation in IOP following surgery, including poor compliance with positioning. Occasionally, a patient with SO may inadvertently shallow his anterior chamber and cause subsequent congestion of the angle when positioning supine, or the patient may have undergone mild orbital trauma without recalling the event. The above scenarios may be common causes for our patient’s elevated IOP, with increased tumor burden being a rarer cause. Increased tumor metastases may be difficult to observe initially; however, the patient’s rapid increase in IOP led to this discovery. Though viral retinitis was a plausible cause of acute retinal necrosis in the setting of immunosuppression, this case validates consideration of intraocular metastases in patients who present with atypical retinitis and a history of pulmonary carcinoma. In cases of what may appear to be non-resolving acute retinal necrosis, despite treatment, vitreous and/or retinal biopsies are warranted. In rare cases in which metastatic cancer may have masqueraded as acute retinal necrosis, and acute retinal necrosis has been ruled out, treatment approaches including chemotherapy, cryosurgery, surgical resection, or radiotherapy. These options should be considered in conjunction with oncologists and radiation therapists and guided by the patient’s cancer prognosis.[14] The above case is interesting in that the initial concern for ARN was valid given the patient’s acute unilateral presentation. However, given that the patient did not improve with treatment for ARN, it was imperative that the team consider other options in a prompt manner. In patients with a history of cancer, despite whether in remission or not, it is important to rule out intraocular metastases. In atypical cases, prompt PPV with vitreous biopsy is imperative and is the standard of care. In the rare case in which intraocular metastases are discovered, it is important to communicate efficiently with the patient’s primary oncology team. Options may include radiation to the orbits as well as re-initiating or revising chemotherapy medications depending on the patient’s prognosis.

Patient consent

The patient consenting to the publication of the case in writing.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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