

Paraneoplastic Vitelliform Retinopathy in Metastatic Cutaneous Melanoma: A Case Series

Parisa Taravati¹, Kathryn Pepple and Russell Van Gelder

Department of Ophthalmology, University of Washington, Seattle, Washington, USA

Corresponding author: Parisa Taravati, University of Washington Medicine Eye Institute - Box 359608, 325 Ninth Avenue, Seattle, WA 98104, USA; Tel: 206-616-1768; Fax: 206-685-9315; E-mail: taravati@uw.edu

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Abstract

Paraneoplastic vitelliform retinopathy is a rare condition associated with metastatic melanoma. Like melanoma-associated retinopathy (MAR), it can cause nyctalopia and progressive vision loss; however, unlike MAR, the fundus shows multifocal, yellow-orange vitelliform lesions beneath the neurosensory retina and at the level of the retinal pigment epithelium, as well as areas of subretinal fluid in the macula. The treatment of paraneoplastic vitelliform retinopathy is aimed at the underlying metastatic melanoma but unfortunately has a poor prognosis, with most patients succumbing to their disease. We report two cases of paraneoplastic vitelliform retinopathy in patients with metastatic cutaneous melanoma.

Keywords: Paraneoplastic; Vitelliform; Melanoma; Retinopathy; Metastasis

Introduction

Melanoma-associated retinopathy (MAR) is a well-recognized paraneoplastic syndrome resulting from the non-metastatic, immunologic effects of cutaneous melanoma on the retina. It often causes progressive vision loss and nyctalopia, and it may also cause shimmering, flickering, or pulsating photopsias. Although the retina may appear normal in a large proportion of patients, MAR has also been described to cause retinal pigment epithelial changes, optic nerve pallor, retinal vessel attenuation, retinal periphlebitis, and vitreous cells. Electroretinogram findings often show a reduced B wave with normal dark-adapted A wave [1,2]. The mechanism has been determined to be due to the production of autoantibodies against a melanoma antigen that cross-reacts with bipolar cells of the retina [3].

More recently, however, there have been reports of a paraneoplastic MAR-like condition causing a vitelliform retinopathy, with detachments of the neurosensory retina and retinal pigment epithelium. These cases have been reported not only in metastatic cutaneous melanoma, but also metastatic choroidal melanoma [4-16]. We report two cases of paraneoplastic vitelliform retinopathy in metastatic cutaneous melanoma.

Case Report

Case 1

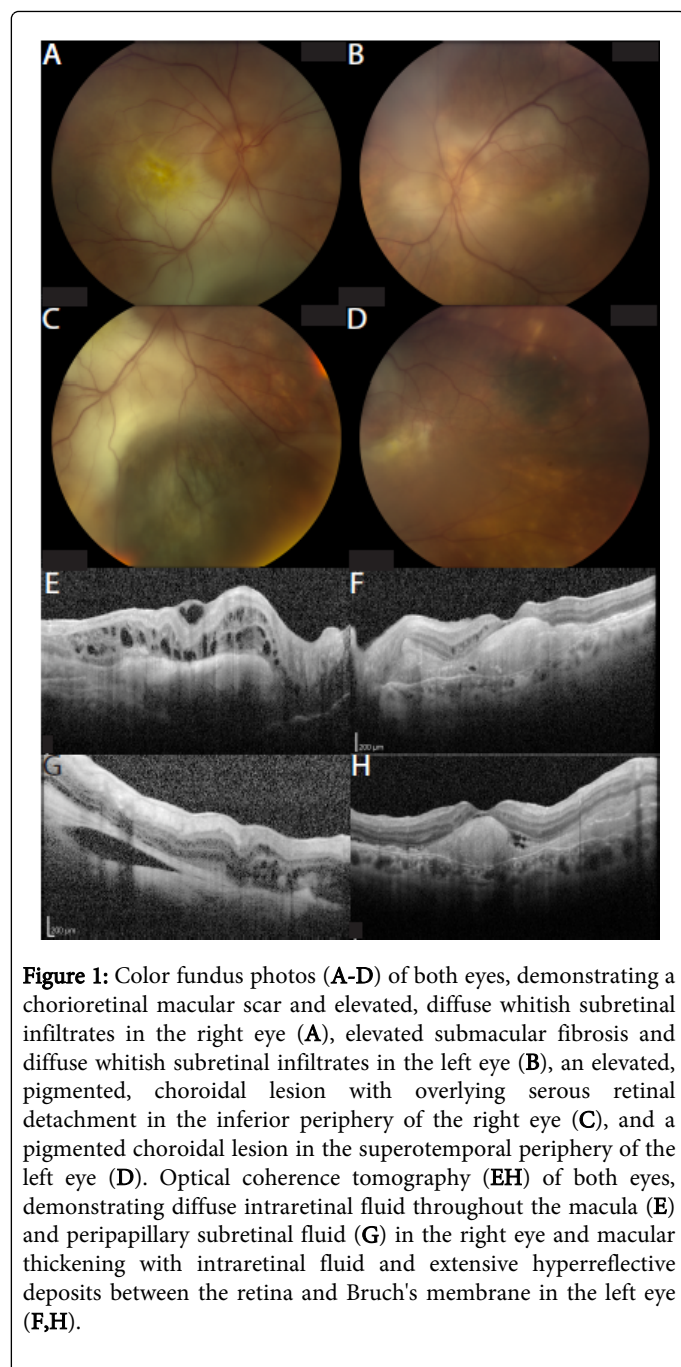
An 89-year-old female was referred to the Uveitis service for evaluation of bilateral vitritis and retinitis. Her symptoms began one year prior to presentation, when she was diagnosed with cutaneous melanoma, which was excised. One month later, she experienced abruptly decreased vision in both eyes. At that time, she was found to have bilateral vitritis and exudative age-related macular degeneration. She was treated with bilateral aflibercept injections (a total of five injections in the right eye and twelve injections in the left eye), but

progressed to central macular scarring. She was noted to have bilateral vitreous cells, diffuse retinal whitening, and a serous retinal detachment overlying a dark subretinal mass in the right eye. The patient was referred for further evaluation and management of these findings.

On examination, visual acuity without correction was hand motions in the right eye and 20/200 in the left eye, and there was no improvement of vision with pinhole. Intraocular pressures were 12 mm Hg in the right eye and 15 mm Hg in the left eye. There was a relative afferent pupillary defect in the right eye. Confrontation visual fields showed no detection in any quadrant in the right eye and generalized constriction in the left eye. Ocular motility was full in both eyes. The anterior segment exam was significant for a mild bilateral corneal subepithelial haze and bilateral pseudophakia, but the anterior chamber was quiet. In the right eye, dilated fundus examination was significant for mild vitritis, a chorioretinal macular scar, and elevated, diffuse whitish subretinal infiltrates, multiple hypopigmented chorioretinal scars in the periphery, and a large, elevated, pigmented, choroidal lesion with overlying serous retinal detachment inferiorly. In the left eye, dilated fundus exam revealed mild vitritis, diffuse whitish subretinal infiltrates, elevated submacular fibrosis, a pigmented choroidal lesion along the superotemporal arcade, and multiple chorioretinal scars in the periphery (Figure 1).

B-scan ultrasonography of the right eye confirmed a choroidal lesion with homogeneous echogenicity and overlying serous retinal detachment. Optical coherence tomography (OCT) of the macula showed diffuse intraretinal fluid throughout the macula and peripapillary subretinal fluid in the right eye and macular thickening with intraretinal fluid in the left eye (Figure 1).

Chest x-ray was significant for a right perihilar mass measuring 3.4 cm, likely representing an enlarged lymph node. Computed tomography (CT) of the chest showed small nodules in her lungs and throat, concerning for metastatic disease. At the time of this report, treatment for systemic melanoma had not yet been initiated. Liver function tests were normal.

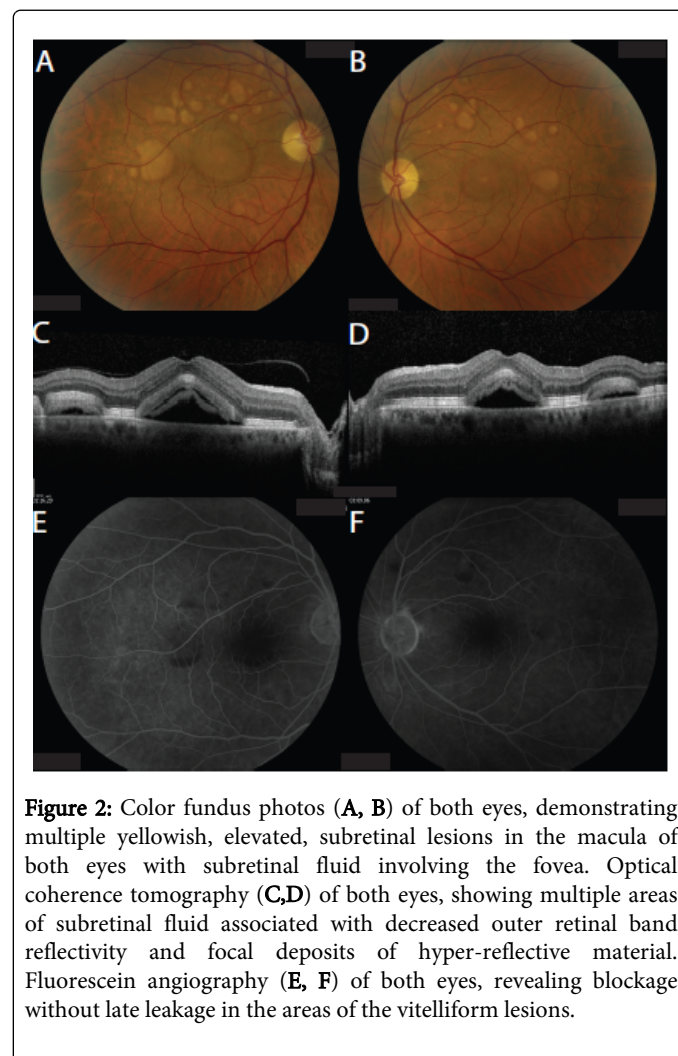


The patient's retinal appearance was felt to be consistent with paraneoplastic vitelliform retinopathy secondary to metastatic cutaneous melanoma. Additionally, the pigmented choroidal lesions were thought to represent metastatic disease.

Case 2

A 71 year old male was referred the Uveitis service for evaluation of an "atypical white dot syndrome." Symptoms began two months prior to presentation with acute recognition of bilateral visual changes described as "seeing brown circles." He denied eye pain, redness, flashes, or floaters or other systemic symptoms with the exception of an intermittent left-sided headache. Initial exam by a local retina

specialist identified bilateral macular vitelliform deposits and a superotemporal rhegmatogenous retinal detachment in the left eye. The retinal detachment was successfully repaired with a pneumatic retinopexy and cryotherapy. The patient was referred for further evaluation of the unusual vitelliform deposits.



On examination, visual acuity without correction was 20/70 improving with pinhole to 20/40 in the right eye, and 20/60 improving to 20/30 by pinhole in the left eye. His intraocular pressures were 16 mm Hg in the right eye and 20 mm Hg in the left eye. There was no relative afferent pupillary defect. Motility and confrontation visual fields were full in both eyes. The anterior segment exam was unremarkable except for the presence of trace nuclear cataracts bilaterally. No evidence of current or prior inflammation was noted. Fundus exam revealed multiple yellowish, elevated, subretinal lesions in the macula of both eyes (right>left) with subretinal fluid involving the fovea (Figure 2). There was no associated hemorrhage, drusen, or retinal pigment epithelium (RPE) atrophy. The peripheral retina of the right eye was unremarkable, and the left eye had scarring consistent with the previous retinal detachment repair. OCT showed multiple areas of subretinal fluid associated with decreased outer retinal band reflectivity and focal deposits of hyper-reflective material (Figure 2). No sub-RPE or choroidal lesions were present. Fluorescein angiography revealed blockage without late leakage in the areas of the

lesions (Figure 2). A full field electroretinogram (ERG) showed mild decreases in cone amplitudes with loss of oscillations and normal rod responses. An electrooculogram (EOG) revealed an abnormally low Arden ratio in both eyes, 1.58 on the right and 1.41 on the left.

In addition, a chest X-ray was performed, which identified a large paraspinal mass. This was confirmed by chest CT that also identified thoracic lymphadenopathy. Upon further questioning, the patient reported a history of resection of a stage IB cutaneous melanoma from his back 7 years prior. Biopsy of the paraspinal mass confirmed the diagnosis of metastatic melanoma.

The retinal findings were felt to be due to paraneoplastic vitelliform retinopathy from metastatic cutaneous melanoma.

Discussion

A review of the literature shows that there are eight previously-reported cases of paraneoplastic vitelliform retinopathy associated with metastatic cutaneous melanoma [4,6,10,12,14,17] seven cases associated with metastatic choroidal melanoma, [5,7,9,11,14-16] one case associated with metastatic visceral melanoma, [8] and two cases associated with metastatic melanoma with unknown primary source [7,18]. There is one reported case of paraneoplastic vitelliform retinopathy associated with carcinoma in a patient with a history of breast and lung cancer but no sign of melanoma on systemic evaluation [19].

Both of our cases were associated with cutaneous melanoma. As with all of the other reported cases of paraneoplastic vitelliform retinopathy, our cases were associated with metastatic disease. Most patients experience nyctalopia, though, as in our cases, they can experience other symptoms, such as decreased vision, haloes, photopsias, or metamorphopsia. All cases have been reported to be bilateral (except in patients whose fellow eye had previously been enucleated due to choroidal melanoma). Typical fundus findings show multifocal, yellow-orange vitelliform lesions beneath the neurosensory retina and at the level of the RPE. There is often associated subretinal fluid in the macula. Fluorescein angiography, which was performed in our second case, typically shows blockage without leakage in the areas of the vitelliform lesions. As with our cases, OCT can show multiple areas of subretinal fluid, as well focal deposits of hyper-reflective material overlying the RPE. EOG was performed in seven previously-reported cases, and of these cases, four reported abnormal Arden ratios, ranging from 1.1 to 1.7 [4,5,10,11,14,15,18]. This is consistent with the EOG results of our second case.

Several of the previously-reported cases of vitelliform retinopathy associated with metastatic melanoma have demonstrated the presence of anti-retinal antibodies, supporting a paraneoplastic etiology [4,5,12,18]. Two of these cases demonstrated anti-RPE antibodies [5,18]. The first case showed a serum sample positive for autoantibodies against bestrophin-1, a 68 kDa RPE protein affected in Best macular dystrophy. However, genetic testing was not consistent with Best macular dystrophy, as it did not show any evidence of mutations in the VMD2 gene, which encodes the bestrophin-1 protein. The serum sample also showed a low titer of autoantibodies against α -enolase but not recoverin, which are commonly associated with cancer-associated retinopathy (CAR) [5]. CAR is usually seen in patients with small-cell carcinoma of the lung. The second case showed a serum sample not only positive for MAR antibodies, but also positive for anti-RPE autoantibodies against peroxiredoxin 3 isoform b (PRDX3), a 26.1 kDa protein. This case also did not show any

mutations in the VMD2 gene [18]. Another case showed high serum titers of autoantibodies against carbonic anhydrase II (CAII), which is a 30-kDa protein present in the retina and RPE [4]. Finally, one case showed serum autoantibodies against bipolar cells, which has been demonstrated in MAR [12].

There is one report of the histopathology of vitelliform retinopathy associated with metastatic cutaneous melanoma. In this case, although there were no clinical signs of choroidal metastasis (via fundus examination, fluorescein angiography, or ultrasonography), histopathology revealed a flat, pigmented, cellular infiltrate composed of spindle-shaped and epithelioid cells in the choroid consistent with metastatic choroidal melanoma. Overlying the tumor were multiple, small RPE detachments. The authors argue that the histopathology in this case supports a local, subclinical metastasis as the cause of the vitelliform lesions rather than a paraneoplastic entity. Another proposed explanation was that the choroidal metastasis developed after the development of paraneoplastic vitelliform lesions [17]. Our first case showed two clinically visible metastatic lesions, and whether the vitelliform lesions were present prior to choroidal metastases or developed as a result of the choroidal metastases is unclear.

Unfortunately, the presence of vitelliform retinopathy in a patient with metastatic melanoma is generally associated with a poor prognosis, with most patients succumbing to their metastatic disease. There is, however, a report of a patient who responded well to the oral treatment of his melanoma with the alkylating agent, temozolomide. Treatment of his systemic disease resulted in resolution of the subretinal fluid and improvement of visual acuity, though the vitelliform deposits still increased in size [18].

As paraneoplastic vitelliform retinopathy is a rare condition, it is unknown at present whether any acquired vitelliform retinopathy should warrant a full neoplastic workup. However, this condition should be considered in any patient with vitelliform lesions and a history of prior malignancy, even if the malignancy was previously considered to be in remission. A thorough systemic evaluation should be performed for metastatic disease, and treatment is aimed at the underlying malignancy.

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