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Paraneoplastic Vitelliform Retinopathy: Clinicopathologic Correlation and Review of the Literature

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Abstract

Traditionally the paraneoplastic retinopathies have been classified into two groups: melanoma-associated retinopathy (MAR) and cancer-associated retinopathy (CAR). MAR occurs in individuals with metastatic cutaneous or uveal melanoma and is characterized by nyctalopia, photopsias, and variable vision loss. In most cases, the fundus is essentially normal in appearance. More recently, there have been multiple reports of a MAR-like retinopathy with associated detachments of the retinal pigment epithelium (RPE) and neurosensory retina. Such a clinical presentation has been termed *paraneoplastic vitelliform retinopathy*. In the present report, we describe an 80-year-old male with metastatic cutaneous melanoma who developed paraneoplastic vitelliform retinopathy. For the first time, histopathology from enucleation specimens provides a clinicopathologic disease correlation with focal abnormalities in the inner nuclear and outer plexiform layers.

Keywords

paraneoplastic vitelliform retinopathy; melanoma; uveal; cutaneous; MAR; CAR; autoantibodies; retina; autoimmune; retinopathy

I. Introduction

Paraneoplastic retinopathies result from autoantibodies directed against tumor antigens that cross-react with retinal antigens and destroy retinal tissue.¹ While a spectrum exists, the paraneoplastic retinopathies have usually been classified into two groups: cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). CAR is most commonly observed in patients with small cell carcinoma of the lung, but is also associated with breast, gynecologic, and other carcinomas. MAR is typically seen in patients with metastatic cutaneous or uveal melanoma. In contrast to CAR, in which chorioretinal atrophy and other

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fundus changes are visible, MAR often presents with a normal appearing fundus or demonstrates only mild mottling of the retinal pigment epithelium (RPE).^{4,10}

More recently, there have been several reports of a MAR-like retinopathy with associated detachments of the RPE and neurosensory retina.^{5,6,8,9,12,14,16,18} In 2001 Borkowski et al. described 2 cases of a MAR-like syndrome with unusual fundus features.⁶ In the first case, there were oval, white lesions at the level of the RPE, and in a second, there were scattered, well-circumscribed, atrophic lesions in the posterior pole and mid-periphery.⁶ Other groups, including Zacks et al., Jampol et al. (2 cases), and Bianciotto et al. have reported MAR-like presentations with multiple serous retinal detachments.^{18,9,5} Palmowski et al. described a similar retinopathy with multiple RPE detachments.¹⁴ In 2005 Sotodeh et al. reported two cases of a MAR-like retinopathy with serous macular detachments and a third case with small, yellow, curvilinear, vitelliform lesions.¹⁶ This group was the first to use the term *paraneoplastic vitelliform retinopathy*. Since that time, Nieuwendijk et al. and Eksandh et al. have also described similar appearing cases of paraneoplastic vitelliform retinopathy with multiple serous retinal detachments.^{12,8}

We present the clinical features of a patient with metastatic cutaneous melanoma and paraneoplastic vitelliform retinopathy along with optical coherence tomography (OCT) and fluorescein angiography findings. Additional testing included Farnsworth-Munsell 100-hue color vision assessment, Humphrey visual field examination, electroretinography (ERG), electrooculography (EOG), and Western blot of the patient's serum. Histopathology and transmission electron microscopy from postmortem enucleation specimens was also performed. To our knowledge, this is the first case of paraneoplastic vitelliform retinopathy to be presented with accompanying clinicopathologic correlation.

II. Report of a Case

An 80-year-old Caucasian male was referred by a local retina specialist to the Department of Ophthalmic Oncology at the Cole Eye Institute with a diagnosis of possible choroidal metastases. One year previously, a computed tomography for surveillance of an abdominal aortic aneurysm incidentally detected multiple new pulmonary lesions. Histopathology from a right lower lobe pulmonary wedge resection was consistent with metastatic melanoma. The primary site remained obscure. An initial metastatic evaluation with positron emission tomography scan detected widespread disease involving the lungs, liver, and thoracic spine. Two cycles of biochemotherapy with recombinant interferon α -2b and sodium stibogluconate were administered. Pneumonia developed following the second cycle and the disease continued to progress. Given the intolerance to chemotherapy and lack of treatment response, these agents were discontinued. Eight months after diagnosis, he developed brain metastases treated by whole brain radiation. Further management was palliative.

The patient had a history of dry macular degeneration and was therefore followed at regular intervals by a retina specialist. One year after being diagnosed with metastatic melanoma, he developed new, bilateral fundus lesions that had not been present 6 months prior. On examination, his best corrected visual acuity was 20/30 in the right eye and 20/25 in the left eye. Anterior segment examination revealed mild nuclear sclerosis bilaterally. There were no cells in the anterior chamber or vitreous. On dilated fundus examination, multiple yellow to white lesions were noted scattered throughout the posterior pole and mid-periphery of both eyes. These were nummular, flat, and well-demarcated and appeared clinically to be located within the deep retinal layers (Figure 1A). Small hard drusen and granular RPE changes, consistent with mild dry macular degeneration, were present in the macula of both eyes.

On fluorescein angiography, there was blockage of fluorescence and absence of late staining corresponding to the clinically observed location of the lesions (Figure 1B).

Autofluorescence of these lesions was present. Spectral domain optical coherence tomography (SD-OCT) showed that the lesions were located within the outer plexiform layer (Figure 1C). SD-OCT also effectively excluded the possibility of choroidal involvement in all of the lesions and therefore the diagnosis of choroidal metastases. Additional studies including 30-2 Humphrey visual field testing and Farnsworth-Munsell 100-hue color vision testing were normal. ERG showed a mild reduction in both the a-wave and the b-wave amplitudes for both scotopic and photopic waveforms suggestive of involvement of both rods and cones. An electrooculogram demonstrated a pathologically reduced Arden ratio (1.27 OD, 1.49 OS, >1.9 normal) consistent with RPE dysfunction.

As the patient was asymptomatic and had good visual acuity, the decision was made to monitor the fundus lesions with periodic observation. He was admitted to the hospital several weeks later with painful spinal metastases, pneumonia, and sepsis and died approximately 1 month following ophthalmic examination. The patient's family was approached for eye donation and provided their consent for postmortem enucleation for research purposes. Within 4 hours, both globes were enucleated and immediately fixed in 10% formalin solution.

III. Western Blot

A sample of serum collected approximately 1 week prior to death was analyzed by Western blot at the Ocular Immunology Laboratory (Casey Eye Institute, Oregon Health & Science University, Portland, OR). The serum was tested against human retinal proteins (HRE) and human retinal pigment epithelium (RPE) proteins. The serum had high titers of retinal autoantibodies against a 30-kDa protein present in retina and RPE, which was determined to be carbonic anhydrase II (CAII). There was also subtle reactivity with an unknown 35-kDa RPE protein (Figure 2).

IV. Histopathology

Further pathological analysis of the enucleated globes (an intact left eye and a portion of right eye) was performed at the Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD. Gross sectioning of the left globe most closely correlated with the clinical features appreciated by ophthalmoscopy and is therefore presented. The left globe measured 24.5 × 24.0 × 24.0 mm and was sectioned in a horizontal plane via the papillary/optic nerve axis. On gross pathology, two round, yellow to white lesions were barely visualized along the inferior arcade temporal to the macula (Figure 3A). These corresponded to those observed clinically with indirect ophthalmoscopy. Microscopically these lesions demonstrated focal retinal edema and loss of nuclei, likely the bipolar cells in the inner nuclear layer (Figure 3B). There was atrophy and splitting of the inner nuclear layer. The lesions extended from the inner nuclear layer mostly toward the outer plexiform layer and much less to the outer nuclear layer (Figure 3C). No active inflammation or evidence of malignant melanoma was observed. Similar histopathologic findings were observed in the right eye (Figure 3D).

V. Transmission Electron Microscopy

Electron microscopy of the enucleated globes was performed at the Histology Core, National Eye Institute, National Institutes of Health, Bethesda, MD. Tissue was double-fixed in buffered formalin (10%) and osmium tetroxide (0.5%), dehydrated, and embedded into Spurr's epoxy resin. Ultrathin sections (90 nm) were made and double-stained with uranyl acetate and lead citrate, and viewed using a JEOL JEM 1010 transmission electron

microscope. Electron micrographs show that the inner nuclear layer was the most affected retinal tissue in both eyes; it showed thinning and atrophy, which seemed to originate from the inner nuclear layer and extend to the outer plexiform and outer nuclear layers, resulting in focal degeneration, edema, and atrophy (Figure 4A). No active inflammation or melanoma cells were observed.

Ultrastructural damage within the outer plexiform layer included extensive homogenous deterioration of the synapses characterized by empty vacuoles, disintegrated mitochondria with fragmented inner membrane, disorganization and stacking of filaments, and apoptotic bodies. The adjacent cells in the inner and outer nuclear layers demonstrated various degrees of cytoplasmic breakdown (Figure 4A and Figure 4B).

VI. Review of the Literature

a. Demographics

The clinical features in the present case are similar to those described in previous reports of paraneoplastic vitelliform retinopathy, establishing the clinical diagnosis in our case. The patient was 80, older than the average age of 56 years in all reported cases; however, in the setting of metastatic cutaneous melanoma the diagnosis of paraneoplastic vitelliform retinopathy was consistent. Of 13 reported cases, including the present patient, approximately equal numbers of males ($n = 6$, 46%) and females ($n = 7$, 54%) were affected. The majority ($n = 8$, 62%), had metastatic cutaneous melanoma, while slightly more than a third ($n = 5$, 38%) had metastatic uveal melanoma (Table 1).

b. Symptoms

Most individuals ($n = 8$, 62%) reported some degree of subjective visual loss. Of these patients, best-corrected Snellen visual acuity was variable and ranged from 20/100 or worse ($n = 2$, 25%), 20/50 to 20/80 ($n = 2$, 25%), or better than 20/40 ($n = 4$, 50%). The majority ($n = 9$, 69%) reported both nyctalopia and photopsias. These symptoms are common features of paraneoplastic retinopathies. Both symptoms imply dysfunction of the retinal photoreceptors.

c. Visual Field Testing

Visual field testing has yielded variable results in patients with paraneoplastic vitelliform retinopathy. In reported cases, visual field testing was conducted in only 5 cases (38%). Of these, 2 individuals (40%) had cecocentral scotomas.^{16,8} In these 2 cases, the presence of cecocentral scotoma on visual field testing was consistent with the clinical findings. For example, the patient reported by Sotodeh et al. (case 9) had bilateral serous macular detachments, and the patient described by Eksandh et al. (case 11) was described as having a “vitelliform pseudohypopyon macular appearance.”^{16,8} Visual field testing was normal in the remaining 3 individuals. Similarly, in the present case, no visual field defects were observed.

d. Color Vision Testing

Only one previous case was assessed with formal color vision testing. This patient was found to have 2 errors along the tritan axis on Farnsworth D-15 testing.⁸ In the present case Farnsworth-Munsell 100-hue color vision testing was unremarkable. A third patient described by Sotodeh et al. (case 7) complained of color dullness; however formal color vision assessment was not reported. Symptoms of nyctalopia were reported more frequently ($n = 9$, 69%) than symptoms of reduced color vision ($n = 2$, 15%). This suggests that rod photoreceptors may be affected more severely than cones.

e. Electrophysiology

Paraneoplastic retinopathies are often accompanied by characteristic ERG changes. In MAR, reduction or absence of the dark-adapted b-wave with preservation of the a-wave is characteristic and suggestive of bipolar cell dysfunction.⁹ Of the 13 reported cases of paraneoplastic vitelliform retinopathy, ERG was performed in over half (n = 8, 62%). Of the 8 patients who underwent testing, the majority (n = 5, 63%) demonstrated notable findings. Both in the present case and in the patient described by Sotodeh et al. (case 9), the ERG exhibited reduction in both the a-wave and b-wave amplitudes for both scotopic and photopic testing.¹⁶ In the patient described by Palmowski et al., Ganzfeld ERG showed selective reduction of the isolated rod scotopic b-wave amplitude while multi-focal ERG demonstrated a reduced amplitude of the central 4 degrees.¹³ In the case reported by Zacks et al., the full field ERG had a non-detectable rod response to a 0.5 Hz blue stimulus and a cornea-negative mixed cone-rod response to a 0.5 Hz white stimulus. The cone response to a 30 Hz white flicker was normal in both amplitude and implicit time.¹⁸ Borokowski et al., reported reduction in the b-wave amplitude under both dark-adapted and light-adapted conditions.⁶

Variability in ERG responses in reported cases of paraneoplastic vitelliform retinopathy was likely secondary to reporting as well as by methodology, including the type of ERG performed. The more commonly observed reduction in the b-wave amplitude implies that there is selective destruction of bipolar cells. EOG was performed in just over a third of patients (n = 5, 38%). Of these a pathologically reduced Arden ratio was seen in 2 cases (40%), including the patient described by Eksandh et al. and the present case.⁸ EOG was normal in the remaining 3, suggesting normal functioning of the RPE.^{12,13,16}

f. Autoantibodies

Autoantibodies that cross-react with and destroy retinal proteins has been demonstrated in a variety of paraneoplastic retinopathies. For example in CAR, autoantibodies directed against α -enolase, recoverin, heat shock cognate protein (HSC70), and others have been found.^{17,7,3} In contrast, MAR has historically been associated with autoantibodies directed against retinal bipolar cells¹¹ but other autoantibodies have also been identified. Nine of 13 cases (69%) were tested for autoantibodies to retinal proteins either by Western blot or by immunohistochemistry and 8 (89%) had detectable levels of retinal autoantibodies most commonly directed against bipolar cells (n = 4, 44%); but also antibodies targeted to carbonic anhydrase II (CAII), interphotoreceptor retinoid binding protein (IRBP), Bestrophin, α -enolase, myelin basic protein, and rod outer segment proteins (Table 2).^{5,8,13,16}

The role of anti-CAII autoantibodies in paraneoplastic retinopathies has not been fully elucidated. Anti-CAII autoantibodies have the capacity to induce cellular damage by impairing CAII cellular function through inhibition of the catalytic activity of CAII in a dose dependent manner.² This causes decreased intracellular pH and increased intracellular calcium, which results in decreased retinal cell viability.² Thus, anti-CAII autoantibodies can decrease retinal cell survival. Immunohistochemistry has revealed the presence of autoantibodies directed against CAII in multiple locations within the retina, including the outer segments of photoreceptors, the inner nuclear layer, and the ganglion cell layer.²

VII. Histopathology and Electron Microscopy

Histopathology revealed focal retinal edema and atrophy predominantly involving the inner nuclear layer with extension to the outer plexiform layer and outer nuclear layers. These findings were corroborated by transmission electron microscopy. These findings are histopathologically distinct from other disorders that may have a similar clinical appearance.

In Best disease RPE and photoreceptor cell atrophy occurs in the macula, and there is accumulation of abnormal lipofuscin in residual RPE cells. In our case of paraneoplastic vitelliform retinopathy, there were no increases of lipofuscin deposits in the RPE cells. Additionally, the lesions in this case were scattered throughout the posterior pole, not just limited in the macula.

VIII. Conclusion

Paraneoplastic retinopathies are rare, making them difficult to classify. When MAR was first described in the 1980s, it was characterized by nyctalopia, photopsias, variable visual loss, and an essentially normal appearing fundus. More recent accounts of MAR-like syndromes combined with neurosensory detachments of the retina or well-circumscribed lesions in the outer layers of the retina or at the level of the RPE may represent a subset of MAR or perhaps a new, clinically distinct entity. The presence of detectable autoantibodies directed towards malignant melanoma that cross-react with retinal and RPE antigens implicates an autoimmune pathogenesis. For the first time, histopathology and transmission electron microscopy demonstrates retinal damage to the inner nuclear, outer plexiform, and outer nuclear layers, which most likely results from an autoimmune process. Systemic or local immunosuppression resulted in clinical improvement in 30 patients with autoimmune retinopathy after 3 to 89 months follow-up.¹⁹ The possibility also exists that the disorder could in part be treatment-related. Immunomodulatory therapies, including the use of adjuvant interferon- α , are more commonly being used in advanced cases of metastatic melanoma. Other autoimmune phenomenon associated with the use of interferon- α , including vitiligo, have been described.¹⁵ While rare, the presence of vitelliform lesions signals a poor prognosis, with most individuals succumbing to metastatic disease within months of diagnosis.

IX. Method of Literature Search

A PubMed literature search was conducted for studies related to paraneoplastic vitelliform retinopathy published between January 1, 2001 and January 1, 2011. Key words including “paraneoplastic vitelliform,” “paraneoplastic retinopathy,” “melanoma associated retinopathy,” “MAR,” “cancer associated retinopathy,” and “CAR” were employed to identify studies of interest. A total of eight publications were identified and included along with the present case in this review.

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Figure 1.

Fundus appearance of paraneoplastic vitelliform retinopathy in an 80 year old man with metastatic cutaneous melanoma (A-1 Right eye; A-2 Left eye). Fluorescein angiography demonstrated blockage of fluorescence (B-1 Right eye; B-2 Left eye). Spectral domain optical coherence tomography revealed high resolution imaging of all retinal layers and confirmed the location of these lesions within the outer plexiform retinal layer (C).

Figure 2.

Western blot of the patient's serum tested against human retinal (HRE) proteins and human retinal pigment epithelium (RPE) proteins, revealed that the serum had a high titer of retinal autoantibodies directed against carbonic anhydrase II (CAII) in retina and RPE.

Figure 3.

Gross pathology demonstrated two faint, round, yellow to white lesions (arrows) along the inferior arcade (A, Left eye), and microscopic examination showed edema (B, asterisks) in the outer plexiform extending to inner and outer nuclear layers, as well as loss of nuclei in the inner nuclear layer (C). Similar histopathologic findings were observed in the right eye (D, arrows). Hematoxylin and eosin (original magnification x 200).

Figure 4.

Transmission electron micrograph showing cross section of the retina with localized damage to the outer plexiform layer and inner and outer nuclear layers. There is severe degeneration of the outer nuclear layer and thinning of the outer plexiform layer with loss of synapses (A). Cross section of the outer plexiform layer illustrating the damage targeted by autoantibodies. Signs of deterioration include stacked filaments (arrowheads), vacuoles/phagosomes (arrows), and disintegrated mitochondria (concave arrowhead) (B).

Demographics and form of metastatic melanoma associated with paraneoplastic vitelliform retinopathy in previously published reports

Table 1

Case	Author	Year	Age	Sex	Disease	Clinical Description
1	Borkowski, et al.	2001	57	M	Cut	Circumscribed, atrophic PP lesions
2	Borkowski, et al.	2001	47	F	Cut	Oval, white lesions in the RPE
3	Zacks, et al.	2001	69	F	Chr	Serous retinal detachments
4	Palmowski, et al.	2002	33	F	Cut	Multiple RPE detachments
5	Jampol, et al.	2004	41	F	Cut; UP	Multiple serous retinal detachments
6	Jampol, et al.	2004	41	F	Chr	Multiple serous retinal detachments
7	Sotodeh, et al.	2005	61	F	Cut	Serous macular detachments
8	Sotodeh, et al.	2005	56	M	Chr	Curvilinear, yellow vitelliform lesions
9	Sotodeh, et al.	2005	59	M	Cut	Serous macular detachments
10	Nieuwendijk et al.	2007	62	F	Chr	Yellow serous retinal detachments
11	Eksandh, et al.	2008	45	M	Chr	Central serous retinal detachment
12	Bianciotto, et al.	2010	74	M	Cut	Multiple serous retinal detachments
13	Current	2010	80	M	Cut; UP	Yellow lesions in the deep retina

M = male, F = female, Cut = metastatic cutaneous melanoma, Chr = metastatic choroidal melanoma, UP = unknown primary, PP = posterior pole, RPE = retinal pigment epithelium

Table 2

Presence of symptoms, ophthalmic testing, and autoantibodies directed against retinal antigens in cases of paraneoplastic vitelliform retinopathy.

Case	Dec Va	N/P	VF	Color	ERG	EOG	Autoantibodies
1	-	+	NP	NP	+	NP	Bipolar cells
2	+	+	NP	NP	NP	NP	Bipolar cells
3	+	+	NP	NP	+	NP	Bipolar cells
4	-	+	-	NP	+	-	Bipolar cells, MBP
5	-	+	NP	NP	NP	NP	NP
6	-	+	NP	NP	NP	NP	NP
7	+	-	NP	NP	NP	-	NP
8	+	+	NP	NP	NP	NP	NP
9	+	-	+	NP	+	NP	ROS protein
10	+	-	-	NP	-	-	None
11	+	+	+	+	-	+	Bestrophin, α-enolase
12	+	-	NP	NP	-	NP	IRBP
13	-	+	-	-	+	+	CAII (retina and RPE)

Dec Va = decreased visual acuity, N/P = nyctalopia and/or photopsias, ERG = electroretinography, VF = visual field testing, Color = color vision testing, MBP = myelin basic protein, ROS = rod outer segment, IRBP = interphotoreceptor retinoid binding protein, CAII = carbonic anhydrase II, NP = testing not performed