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Bilateral Diffuse Uveal Melanocytic Proliferation in the Setting of Ovarian Cancer

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Abstract

Purpose: To describe a case of bilateral diffuse uveal melanocytic proliferation in the setting of metastatic ovarian cancer. **Methods:** A single case was analyzed and a literature review of treatment efficacy performed. **Results**: A 64-year-old woman presented to ophthalmology in July 2022 for evaluation of blurred vision in the setting of ovarian cancer and a possible reaction to chemotherapy. A comprehensive workup led to the diagnosis of bilateral diffuse uveal melanocytic proliferation. Treatment to potentially preserve the patient's vision comprised a sub-Tenon triamcinolone injection and plasmapheresis. **Conclusions:** Plasmapheresis did not improve the visual acuity (VA) in the patient's right eye; however, 6 months after the last treatment, the VA in the left eye improved from 20/50 to 20/30, corresponding to a decrease in macular edema. Given the rarity of bilateral diffuse uveal melanocytic proliferation, its uncertain pathogenesis, and its varied responses to treatment, it is imperative to establish a diagnostic management and treatment algorithm to improve visual outcomes.

Keywords

bilateral diffuse uveal melanocytic proliferation, ophthalmology, cancer-associated retinopathy, serous retinal detachment, plasmapheresis

Introduction

Bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic syndrome associated with a nonocular systemic malignancy. Characteristics include multiple round or oval red patches in the fundus, multifocal early hyperfluorescence correlating with fundus lesions on fluorescein angiography (FA), scattered pigmented and nonpigmented uveal melanocytic tumors with diffuse choroidal thickening, exudative retinal detachment (RD), and rapidly progressing cataracts.[1] Malignancies associated with bilateral diffuse uveal melanocytic proliferation include ovarian, lung, gallbladder, uterine, kidney, pancreatic, breast, esophageal, and colorectal cancers.[2]

Since Machemer first described the syndrome in 1966, reports of cases of bilateral diffuse uveal melanocytic proliferation have been quite rare in the literature, with 4.4 cases a year reported between 2012 and 2017.[3] The mean age of onset has been reported to be 64 years, with a mean duration of 1 year between the onset of ocular symptoms and death.

In 44% of cases, patients presented with a previously diagnosed primary tumor.[4] The typical disease presentation consists of loss of vision before the diagnosis of systemic malignancy; however, clinical presentations have been reported that do not include all diagnostic features, such as cataracts and exudative RD.[5]

On short-wavelength fundus autofluorescence, a leopard-spot pattern corresponds with the inverse pattern of hyperfluorescence and hypofluorescence on FA. Retinal pigment epithelium (RPE) aggregations with irregularity on optical coherence tomography (OCT), subretinal fluid (SRF) accumulation and subsequent detachments, glaucoma, a shallow anterior body chamber, dilated episcleral vessels, ciliary body cysts, iridocyclitis, and iridodonesis have been observed, in addition to the 5 signs described by Gass et al.[4] Management of bilateral diffuse uveal melanocytic proliferation consists of treating the primary malignancy and metastases as well as plasmapheresis to eliminate the potential causative agents.[2]

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We present a case of bilateral diffuse uveal melanocytic proliferation associated with stage IIIc ovarian cancer. Electrophysiology testing was used at the onset of disease. We also report the outcomes of plasmapheresis treatment and review the literature regarding the efficacy of reported treatments.

Case Report

A 64-year-old woman presented with a history of significant bloating, early satiety, constipation, and straining with bowel movements 3 years before presenting to ophthalmology. She also reported an unintentional weight loss of 20 pounds. A computed tomography-guided biopsy showed poorly differentiated carcinoma involving minute fragments of adipose tissue. Immunostaining showed that the tumor cells were positive for CAM 5.2, PAX8, and p53 and negative for CDX2, INSM1, and GATA3. Four months after initial presentation, the patient had extensive debulking. Pathology showed stage IIIC high-grade clear cell ovarian adenocarcinoma.

Five months after presentation, weekly bevacizumab and paclitaxel were started and continued for 14 months, followed by a 6-month chemotherapy holiday. During this same time, the patient may have received durvalumab or olaparib in a clinical trial; however, this was uncertain because of the study's protocol. Bevacizumab and paclitaxel were resumed after her involvement in the clinical trial. Seven months later, she stopped bevacizumab and continued with paclitaxel only.

Three years after her initial presentation, the patient presented to ophthalmology for evaluation of blurred vision in the setting of ovarian cancer and a possible reaction to chemotherapy. Cataract extraction with intraocular lens implantation had been performed at an outside institution. Her best-corrected visual acuity (BCVA) at presentation was 20/30 OD and 20/50 OS. OCT showed an exudative/serous RD and a poor ellipsoid zone in both eyes. Fundus photography with autofluorescence photographs and OCT images taken on initial presentation are shown in Figure 1.

The differential diagnosis in this patient with a history of cancer and chemotherapy included cancer-associated retinopathy (CAR), toxic retinopathy caused by a chemotherapeutic agent, and bilateral diffuse uveal melanocytic proliferation. Toxic retinopathy was initially presumed to be caused by a reduced response on electroretinography (ERG); however, the development of the characteristic giraffe-spot or leopard-spot pattern and serous RDs is a hallmark of bilateral diffuse uveal melanocytic proliferation and, once manifested, lead to an accurate diagnosis.

Table 1 shows the results of the visual-evoked potentials, which were first done in September 2022. Regular pattern-reversal visual-evoked potentials were recorded monocularly, elicited by monochromatic checkerboard stimuli to an approximately 2-degree (8 × 8), approximately 1-degree at 5 minutes (16 × 16), 33 minutes (32 × 32), 16 minutes (64 × 64), and 8 minutes (128 × 128) pattern at 100% contrast and 2 Hz (active at occipital lobe electrode, reference at forehead reference, ground at left earlobe), fully compliant with the latest edition of the International Society for Clinical Electrophysiology of Vision standard. Two runs were recorded from each eye to show reproducibility, and the records were averaged and printed if reproducibility was present. Flash visual-evoked potentials were also done. Delayed flash stimulation and normal pattern stimulation were observed in both eyes.

Table 2 shows the results of the multifocal ERG, also done in September 2022 and performed binocularly according to the latest revision of the International Society for Clinical Electrophysiology of Vision standard to a 61-hexagon, 60-degree stimulus. Dawson, Trick, and Litzkow electrodes were used with the patient wearing her own refraction. In both eyes, fixation was good and findings included delayed implicit time and central loss. Table 3 shows the results of the regular full-field ERG, which was also done in September 2022 and complied with the latest update of the International Society for Clinical Electrophysiology of Vision standard. Both pupils dilated well in the dark to an 8.0 mm diameter. There was a decreased and delayed ERG response, although the dark-adapted rod response appeared to be normal.

A sub-Tenon triamcinolone injection was given to address the serous RD; however, no improvement was seen on follow-up. A review of the current literature in March 2023 resulted in the initiation of plasmapheresis 3 times weekly. The first week consisted of 3 sessions on 3 consecutive days with albumin replacement. The next 4 weeks consisted of 15 plasmapheresis sessions with fresh frozen plasma replacement every other day.

Although the patient moved from the geographic area, her electronic medical records were available. Six months after the last plasmapheresis treatment, her distance BCVA decreased from 20/70 to 20/150 OD and improved from 20/50 to 20/30 OS. A repeat positron emission tomography/computed tomography scan showed progression of her metastatic ovarian cancer with enlarging cervical, thoracic, and abdominopelvic lymph nodes; enlarging peritoneal nodules; and metastasis to the left adrenals. Treatment was continued with gemcitabine and cisplatin; however, the patient had no improvement in vision with plasmapheresis and declined further treatment given her guarded visual and survival prognosis.

Conclusions

The rarity of bilateral diffuse uveal melanocytic proliferation makes determining its exact pathogenesis difficult. At present, there are 3 proposed prevalent mechanisms involved. The first is the synchronous growth of the uveal melanocytes and visceral carcinoma as a result of a shared unknown oncogenic stimulus. The second proposed mechanism is uveal melanocytic proliferation from an unknown stimulus released by the primary extraocular tumor. The final mechanism is the coincidental development of visceral carcinoma and bilateral diffuse uveal melanocytic proliferation resulting from an unknown genetic predilection.[1,5,6] Miles et al[2] used serum analysis and melanocyte cultures to

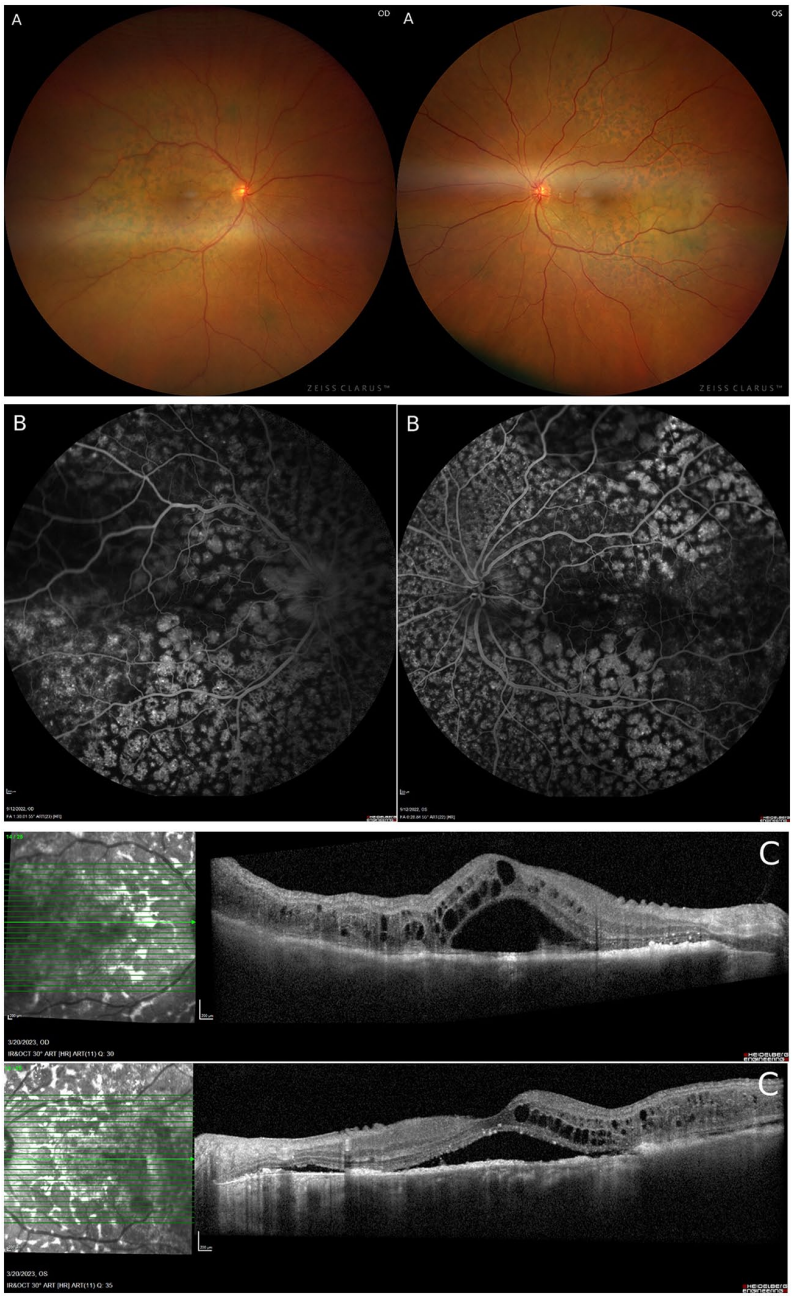

Figure 1. (A) Color fundus photographs of the patient's right eye and left eye are shown on initial presentation. The classic presentation of reticulated hyperpigmented patches (leopard or giraffe spots) are present. The darkened retinal pigment epithelium (RPE) is surrounded by gross orange pigment lipofuscin. (B) Fluorescein angiography shows early hyperfluorescence corresponding to the areas of giraffe-like hyperpigmentation with areas of blockage. (C) Optical coherence tomography of the right eye and left eye shows the presence of exudative retinal detachments involving both macula with intraretinal fluid and subretinal fluid, hypertrophy and atrophy of the RPE, and choroidal thickening.

show that the portion enriched with immunoglobulin G contains cultured melanocyte elongation and proliferation factor, which drives melanocytic proliferation in patients with bilateral diffuse uveal melanocytic proliferation. This finding suggests that immunoglobulins secreted by the cancer cells or the immune system are responsible for disease progression. This rationale explains the use of plasmapheresis to remove the serum factor that selectively stimulates uveal melanocytes.

Mets et al[7] were the first to describe the use of plasmapheresis to treat bilateral diffuse uveal melanocytic proliferation, reporting an increase in VA from 20/40 OD and 20/50 OS to 20/20 OD and 20/25 OS after 17 sessions; however, vision

Table 1. Visual-Evoked Potential Results.[a]

Stimulus: Check (Minutes)	Right Eye		Left Eye	
	Amplitude	Timing	Amplitude	Timing
8×8	Normal	Normal	Normal	Normal
16×16	Normal	Normal	Normal	Normal
32×32 (33')	Normal	Normal	Normal	Normal
64×64 (16')	Decreased	Normal	Decreased	Normal
128×128	Decreased	Normal	Decreased	Borderline
Flash VEP	Normal	Delayed	Normal	Delayed

Abbreviation: VEP, visual-evoked potential.
[a]VEP showed delayed flash stimulation, and normal pattern stimulation was observed in both eyes.

Table 2. Multifocal Electroretinography Findings.[a]

Ring	Right Eye		Left Eye	
	Amplitude	Timing	Amplitude	Timing
Fovea	Borderline	Delayed	Borderline	Delayed
Parafovea	Decreased	Delayed	Borderline	Delayed
Near perifovea	Borderline	Delayed	Borderline	Delayed
Far perifovea	Borderline	Delayed	Borderline	Delayed
Vascular arcades	Borderline	Delayed	Borderline	Delayed

[a]In both eyes, fixation was good and findings include delayed implicit time and central loss.

Table 3. Full-Field (Flash) Electroretinography Findings.[a]

Stimulus	Right Eye		Left Eye	
	Amplitude	Timing	Amplitude	Timing
Dark-adapted 0.01 ERG	Decreased	Normal	Decreased	Normal
Dark-adapted 3.0 ERG	Decreased	Delayed	Decreased	Delayed
Dark-adapted 3.0 OPs	Decreased	Delayed	Decreased	Delayed
Dark-adapted 10.0 ERG	Decreased	Delayed	Decreased	Delayed
Light-adapted 3.0 ERG	Decreased	Delayed	Decreased	Delayed
Light-adapted 3.0 flicker	Decreased	Delayed	Decreased	Delayed

Abbreviations: ERG, electroretinography; OP, oscillatory potentials.
[a]There was a decreased and delayed ERG response, although the dark-adapted rod response appeared to be normal.

declined after cessation of the sessions. There have been varying reports on the efficacy of plasmapheresis treatment. Of 22 reported cases that received plasmapheresis treatment through 2023, 14 had improvement in vision.[8,9] Four cases had a worsening of serous RD despite plasmapheresis treatment.[10,11] In our patient, plasmapheresis appeared successful in improving vision in the left eye; however, there was a significant decline in vision in the right eye. A previous report of regression in vision and a relapse of SRF after cessation of plasmapheresis treatment led to the clinical decision to maintain plasmapheresis treatments to preserve visual function.[12]

In addition to cultured melanocyte elongation and proliferation factor, hepatocyte growth factor and antiretinal autoantibodies have been identified and correlated with the progression of bilateral diffuse uveal melanocytic proliferation. Niffenegger et al[13] suggested that chronic high levels of hepatocyte growth factor plus retinal autoantibodies could be responsible for driving the choroidal nevi growth and damage to the RPE. After this report, it was concluded that there was no correlation between hepatocyte growth factor levels and the growth of cultured melanocytes using plasma fractions from a patient with bilateral diffuse uveal melanocytic proliferation because plasma samples that were hepatocyte growth factor deplete still drove melanocyte proliferation.[10] A serum analysis from bilateral diffuse uveal melanocytic proliferation with underlying gastric adenocarcinoma identified multiple antiretinal antibodies associated with paraneoplastic CAR, supporting the hypothesis that bilateral diffuse uveal melanocytic proliferation is an antibody-mediated paraneoplastic syndrome.[14]

The advances in the discoveries of the role of cultured melanocyte elongation and proliferation factor and other possible mechanisms have led to trials of new treatment modalities. A recently published case report described a favorable outcome with the use of high-dose intravenous immunoglobulin that led to rapid and sustained improvement in the patient's condition.[14] Despite the success in that case, 2 other cases had no improvement with intravenous immunoglobulin treatment. Lentzsch et al[11] attempted a variety of treatments for bilateral diffuse uveal melanocytic proliferation, including triamcinolone injection, antivascular endothelial growth factor injections, weekly plasmapheresis treatment, and 4 intravenous immunoglobulin treatments; however, the patient still had VA loss that progressed from 20/400 OD and 20/25 OS at the initial visit to light perception OD and 20/200 OS at the 30-month follow-up. Another report from Navajas et al[15] described no visual improvement despite treatment with local corticosteroids, plasmapheresis, and intravenous immunoglobulin. Alsoudi et al[16] were the first to report a case of improvement and stabilization of vision with pembrolizumab therapy and an intravitreal dexamethasone implant.

The various serum findings and responses involved in bilateral diffuse uveal melanocytic proliferation bring into question the disease's true pathophysiology. Is there heterogeneity in the factor responsible for the variable responses to treatment? Is the mechanism multifactorial, consisting of a collection of discovered and undiscovered serum-derived factors that stimulate melanocytic growth? Even with an increase in recognition and diagnoses, bilateral diffuse uveal melanocytic proliferation is not well understood and is surrounded by incidental findings and hypotheses. Given its rarity as well as the myriad therapeutic options to treat vision loss, it seems appropriate for a clinical professional society to establish a diagnostic and management algorithm to improve vision outcomes in patients with this paraneoplastic syndrome.

Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

The patient provided informed consent, including permission for publication of all photographs and images included herein.

Declaration of Conflicting Interests

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References

1. Gass JD, Gieser RG, Wilkinson CP, Beahm DE, Pautler SE. Bilateral diffuse uveal melanocytic proliferation in patients with occult carcinoma. *Arch Ophthalmol*. 1990;108(4):527-533.
2. Miles SL, Niles RM, Pittock S, et al. A factor found in the IgG fraction of serum of patients with paraneoplastic bilateral diffuse uveal melanocytic proliferation causes proliferation of cultured human melanocytes. *Retina*. 2012;32(9):1959-1966.
3. Klemp K, Kiilgaard JF, Heegaard S, Norgaard T, Andersen MK, Prause JU. Bilateral diffuse uveal melanocytic proliferation: case report and literature review. *Acta Ophthalmol*. 2017;95(5):439-445.
4. Parakh S, Maheshwari S, Das S, et al. Presumed bilateral diffuse uveal melanocytic proliferation - a case report and review of literature. *Am J Ophthalmol Case Rep*. 2022;27:101582.
5. Pefkianaki M, Agrawal R, Desai P, Pavesio C, Sagoo MS. Bilateral diffuse uveal melanocytic proliferation (BDUMP) associated with B-cell lymphoma: report of a rare case. *BMC Cancer*. 2015;15:23.
6. Margo CE, Pavan PR, Gendelman D, Gragoudas E. Bilateral melanocytic uveal tumors associated with systemic non-ocular malignancy. Malignant melanomas or benign paraneoplastic syndrome? *Retina*. 1987;7(3):137-141.
7. Mets RB, Golchet P, Adamus G, et al. Bilateral diffuse uveal melanocytic proliferation with a positive ophthalmoscopic and visual response to plasmapheresis. *Arch Ophthalmol*. 2011;129(9):1235-1238.
8. Weppelmann TA, Khalil S, Zafrullah N, Amir S, Margo CE. Ocular paraneoplastic syndromes: a critical review of diffuse uveal melanocytic proliferation and autoimmune retinopathy. *Cancer Control*. 2022;29:10732748221144458.
9. Dallinga MG, Bolhuis K, Bins A, de Hoog J. Bilateral diffuse uveal melanocytic proliferation mistaken for nivolumab-induced VKH-like syndrome. *Retin Cases Brief Rep*. 2024;18(3):332-336.
10. Lavine JA, Ramos MS, Wolk AM, et al. Heterogeneity of cultured melanocyte elongation and proliferation factor in bilateral diffuse uveal melanocytic proliferation. *Exp Eye Res*. 2019;184:30-37.
11. Lentzsch AM, Siggel R, Schnorr C, Holtick U, Liakopoulos S. Long-term follow-up of asymmetric bilateral diffuse uveal melanocytic proliferation in a patient with metastasized urothelial carcinoma. *Retin Cases Brief Rep*. 2023;17(2):105-110.
12. Antaki F, Ferreira BG, Sahyoun JY, Hammamji K. Bilateral diffuse uveal melanocytic proliferation: report of a novel optical coherence tomography finding and clinical response to plasmapheresis. *Am J Ophthalmol Case Rep*. 2022;25:101349.
13. Niffenegger JH, Soltero A, Niffenegger JS, Yang S, Adamus G. Prevalence of hepatocyte growth factor and autoantibodies to alpha-HGF as a new etiology for bilateral diffuse uveal melanocytic proliferation masquerading as neovascular age-related macular degeneration. *J Clin Exp Ophthalmol*. 2018;9(4):740.
14. Saba NJ, Hong TJ, Walter SD. Successful adjunctive treatment of bilateral diffuse uveal melanocytic proliferation (BDUMP) with high-dose intravenous immunoglobulin therapy (IVIG). *Retin Cases Brief Rep*. 2023.
15. Navajas EV, Simpson ER, Krema H, et al. Cancer-associated nummular loss of RPE: expanding the clinical spectrum of bilateral diffuse uveal melanocytic proliferation. *Ophthalmic Surg Lasers Imaging*. 2011;42:e103-e106.
16. Alsoudi AF, Parvus MN, Pulido J, et al. Multiplying brown spots. *Retin Cases Brief Rep*. 2024;18(5):642-646.