

Case Report

Bilateral Diffuse Uveal Melanocytic Proliferation in a Woman with Metastatic Scalp Squamous Cell Carcinoma Treated with Cemiplimab

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Keywords

Bilateral diffuse uveal melanocytic proliferation · Anti-PD-1 · Cemiplimab · Plasmapheresis · Scalp squamous cell carcinoma

Abstract

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic intraocular syndrome that causes progressive visual loss in patients driven by an IgG factor associated with an underlying malignancy. The IgG factor – cultured melanocyte elongation and proliferation – was found in the IgG fraction of the serum of BDUMP patients. It has been shown to be involved in melanocytic proliferation. In this case report, we describe the first case of BDUMP related to metastatic cutaneous squamous cell carcinoma (cSCC) of the scalp. A 61-year-old woman complained of decreased vision in both of her eyes, while being treated with cemiplimab (an anti-PD-1 therapy) for metastatic cSCC. Fundus examination showed hypopigmented lesions in a leopard pattern and pigmentary clumps in both eyes. Further imaging confirmed the diagnosis of BDUMP. The patient was successfully treated with plasmapheresis. During follow-up, cataract progressed in both eyes, and she underwent cataract surgery with visual acuity improvement to 20/20. BDUMP is a challenging diagnosis especially in patients treated with anti-PD-1 immunotherapy as it can be confused with drug-related effects. It is

crucial to distinguish between the cases in order to allow the appropriate treatment which includes continuation of systemic anti-PD-1 for the underlying malignancy and plasmapheresis therapy for BDUMP.

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Introduction

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic intraocular syndrome, with around 60 cases reported [1, 2]. As first described by Gass et al. [3] in 1990, BDUMP is characterized by multiple, elevated, pigmented uveal lesions, diffuse thickening of the uveal tract, and rapidly progressive cataract. The mechanism of uveal and dermal melanocytic proliferation in BDUMP is not clear. However, a cultured melanocyte elongation and proliferation factor from the IgG fraction of the serum of BDUMP patients has been shown to be involved in melanocytic proliferation [4].

BDUMP is mainly associated with primary endocrine carcinomas; female urogenital (69% of all female cases) and male lung carcinomas (52% of all male cases) are the most common related carcinomas. Other sporadic-related carcinomas reported to date include carcinomas of the colon, urinary bladder, pancreatic, esophageal, breast, hepatocellular, Bartholin gland, gallbladder, and renal cell, as well as central nervous system lymphoma [1]. We describe the first case of BDUMP related to metastatic squamous cell carcinoma (SCC) of the scalp in a patient treated with cemiplimab, an anti-programmed cell death protein 1 (PD-1) checkpoint inhibitor.

Case Report

A 61-year-old woman with a known metastatic cSCC of the scalp was referred to the ophthalmology clinic due to decreased vision in both eyes for 3 months. Eighteen months earlier, the patient was diagnosed with skin SCC in her right occipital scalp. She underwent wide local excision along with neck dissection; however, shortly after surgery, her disease progressed with new nodal and lung metastases. Systemic chemotherapy (cisplatin and 5-fluorouracil) was commenced, followed by cetuximab, but her disease continued to rapidly progress. At this point, there was extensive involvement of her right neck and axilla, base of skull, mediastinum, and lungs (Fig. 1a). Treatment was changed to cemiplimab, a recombinant human IgG4 monoclonal antibody that blocks the PD-1 receptor. A near-complete response was seen clinically and per imaging after 4 months (Fig. 1b).

A year and a half after her initial cSCC diagnosis and 4 months under cemiplimab treatment, the patient presented to the ophthalmology clinic with bilateral vision deterioration lasting several months. Her best-corrected visual acuity was 20/30 in both eyes. Clinical examination revealed a normal intraocular pressure, normal anterior segment, and mild nuclear sclerosis in both eyes. On fundusoscopic examination, hypopigmented lesions in a leopard pattern and pigmentary clumps were present in both eyes (Fig. 2a). Fundus autofluorescence imaging showed multiple scattered hypoautofluorescent lesions interspersed within areas of hyperautofluorescence in a symmetric pattern in both eyes in the macula and temporal to the macula (Fig. 2b). Spectral-domain enhanced-depth imaging optical coherence tomography revealed choroidal folds, pronounced and diffuse abnormalities at the level of the RPE, with alternating hyperreflective and irregular thickening, subretinal fluid, and scattered hyperreflective spots in the retina and choroid (Fig. 2c). The patient was diagnosed with BDUMP and referred to therapeutic plasma exchange (therapeutic plasmapheresis) with albumin, while

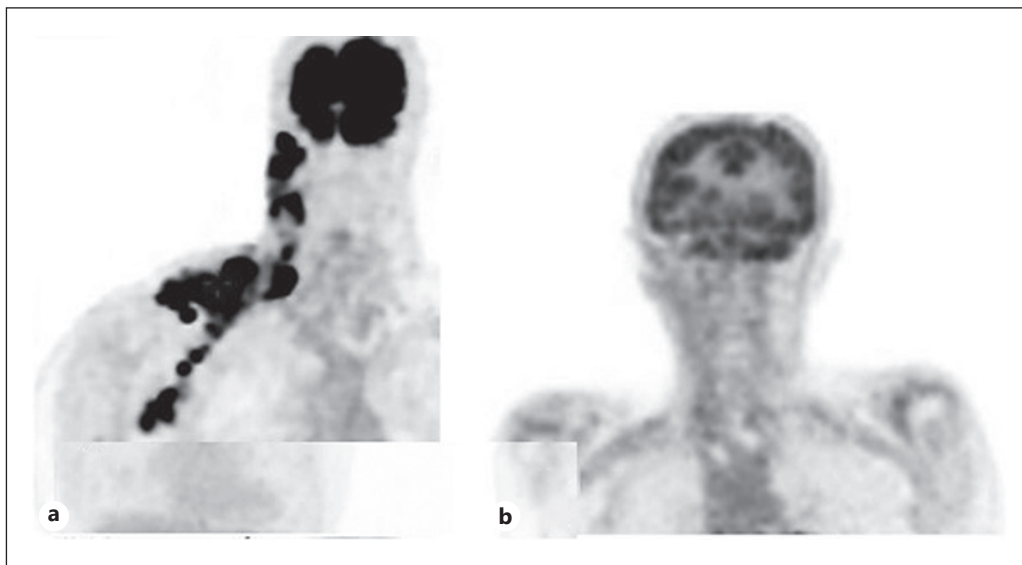


Fig. 1. **a** Head and neck PET-CT demonstrating metastatic SCC of the scalp. **b** Disease remission 4 months after cemiplimab. SCC, squamous cell carcinoma.

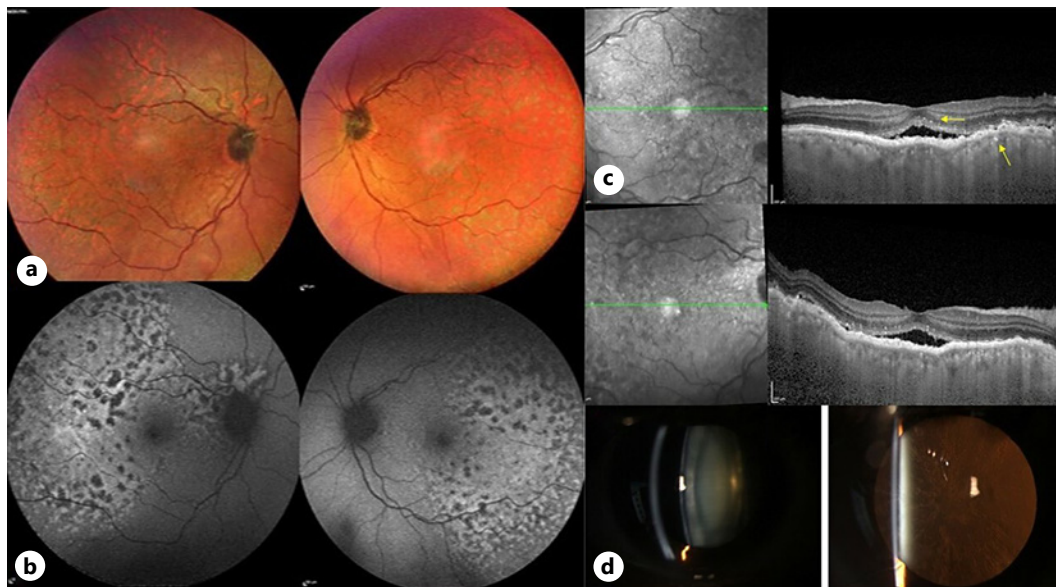


Fig. 2. **a** Funduscopy multicolor picture showing irregular, pigmented lesions with widespread multifocal patches of well-circumscribed areas of RPE hypopigmentation in a leopard pattern; FAF imaging showing multiple scattered hypoautofluorescent lesions interspersed within areas of hyperautofluorescence (**b**); SD-OCT showing choroidal folds, irregularity of the RPE, with RPE elevation and thickening, subretinal fluid, and scattered hyperreflective spots in the retina and choroid (**c**); slit lamp image of the RE showing advanced nuclear and posterior subcapsular cataract (**d**).

treatment with cemiplimab was continued. After 3 cycles, complete resolution of the SRF was noticed. Overall, she underwent 9 cycles of therapeutic plasmapheresis. During follow-up, the cataract progressed and VA decreased to 20/60 in the right eye and 20/40 in the left eye (Fig. 2d), and the patient underwent cataract surgery. At the last follow-up, 12 months after

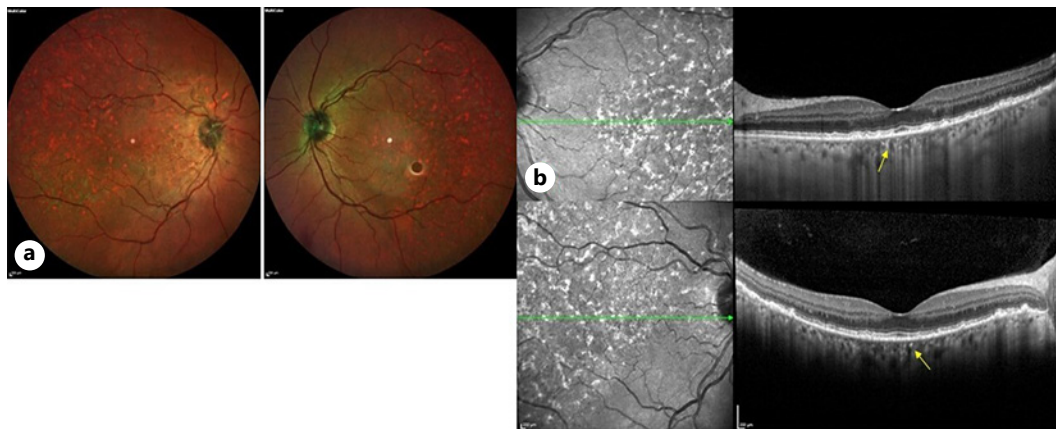


Fig. 3. **a** Fundusoscopic multicolor picture, 9 months after plasmapheresis treatment, showing the hypopigmented lesions in a leopard pattern. **b** SD EDI OCT 9 months after final plasmapheresis treatment showing resolution of choroidal folds, flattening and only mild irregularity of the RPE with absorption of all subretinal fluid. Note less hyperreflective spots in the retina and choroid.

completing the plasmapheresis treatment, best-corrected visual acuity improved to 20/20 in both eyes, there was no subretinal fluid, the choroidal folds resolved, and the RPE flattened and appeared less irregular (Fig. 3). The patient continued treatment with cemiplimab for 15 months with full regression of her primary disease (Fig. 1b). At the last follow-up, 3 months after cemiplimab cessation, there was no systemic disease recurrence.

Discussion

We describe the first case of BDUMP secondary to cSCC, in a patient treated with cemiplimab (an anti-PD-1 therapy) for her metastatic cSCC. The patient, a 61-year-old female, fits the epidemiological profile of BDUMP patients described in the literature (female 60% and age 50–80) [1]. The patient presented with all 5 characteristic signs of the disease described by Gass et al. [3], including multiple subretinal round patches in the RPE, multiple elevated pigmented and nonpigmented uveal melanocytic lesions with early fluorescence of these lesions on FA, diffuse choroidal thickening, subretinal fluid, and rapid cataract development. BDUMP is a challenging diagnosis especially in patients treated with anti-PD-1 therapies (cemiplimab) as these drugs may cause ocular side effects including serous retinal detachment and Vogt-Koyanagi-Haradai-like syndrome [5]. It is crucial to distinguish BDUMP from ocular manifestations secondary to the use of immunotherapy as it is of utmost importance to continue systemic immunotherapy treatment of the underlying systemic disease (Table 1). The continuation of immunotherapy treatment whilst on plasmapheresis enables control of the systemic as well as the ocular disease. Treatment with plasmapheresis is based on the rationale of removing certain proteins such as circulating antibodies from the bloodstream. Cultured melanocyte elongation and proliferation factor is an IgG fraction of circulating antibodies found in the serum of patients with BDUMP. This protein has been found to cause in vitro melanocytic proliferation [6]. Different plasmapheresis protocols have been described ranging from 3 treatments per week for 1 week to 3 treatments per week for 7 months [7, 8]. The treatment was shown to be highly effective in maintaining favorable ocular disease outcome [7–12]. Our patient underwent overall 9 treatments during a 1-month period. After 1 month, all the subretinal fluid was absorbed, and we began to see an improvement in the RPE structure. In addition, she underwent a successful

Table 1. Main differentiating features between BDUMP and PD-1 immunotherapy-related effects, specifically VKH-like effect of cemiplimab

	BDUMP	Anti-PD-1 immunotherapy-related effects (VKH-like)
Lens	Rapidly progressive nuclear and posterior subcapsular cataract	None described
Fundus	Irregular, pigmented lesions with widespread multifocal patches of well-circumscribed areas of RPE hypopigmentation in a leopard pattern	Retinal vasculitis (occlusive or not), with its consequent exudation, hemorrhage, or macular edema; “sunset glow” fundus
FAF	Multiple scattered hypoautofluorescent lesions interspersed within areas of hyperautofluorescence in a leopard pattern compatible with the fundus findings	Larger areas of hyperautofluorescence and hypoautofluorescence suggestive of multifocal areas of regressed exudative retinal detachment
OCT	Choroidal folds, irregularity of the RPE, with RPE elevation and thickening, subretinal fluid, and scattered hyperreflective spots in the retina and choroid	Choroidal folds, subretinal fluid with multiple septae
FA	Reticular pattern of hypofluorescence surrounded by a background of choroidal hyperfluorescence creating a characteristic mosaic with hyperfluorescent patches	Early hypofluorescence and late hyperfluorescence in the areas of retinal pigment epithelial changes, consistent with multifocal exudative retinal detachments

BDUMP, bilateral diffuse uveal melanocytic proliferation; anti-PD-1, anti-programmed cell death protein 1.

cataract surgery in both eyes with visual acuity improvement. Our case is the first case of BDUMP related to SCC of the scalp and has the longest follow-up as compared to previously published BDUMP cases. Twelve months after last plasmapheresis treatment, the patient demonstrated a favorable ocular result; VA was excellent in both eyes, there was no recurrence of subretinal fluid, no evidence of choroidal folds, and RPE appearance improved. Thanks to the quick diagnosis of BDUMP, an appropriate treatment with plasmapheresis was given while maintaining systemic treatment with cemiplimab that achieved complete response of her metastatic cSCC. Theoretically, the filtration process of plasmapheresis could lower the desired antibody levels of the cemiplimab, and this phenomenon was not described in the literature. However, due to the short-term treatment schedule of plasmapheresis (1 month) and the devastating visual loss, we planned for the patient to receive cemiplimab during and after the last plasmapheresis treatment. The systemic effect of cemiplimab was not compromised in this case, as seen on the last oncologic follow-up and PET-CT.

Statement of Ethics

The subject has given her written informed consent to publish the case (including publication of images); this study has been granted an exemption from requiring ethical approval by the Institutional Review Board (IRB) of the Tel Aviv Medical Center, Israel.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Etti Katzburg conceived and designed, collected the data, and wrote the manuscript. Dinah Zur conceived and designed, contributed data, and revised the manuscript. Orit Gutfeld contributed data and revised the manuscript. Ilya Kirshner contributed data and revised the manuscript. Zohar Habot-Wilner conceived and designed, collected the data, and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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