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Bilateral diffuse uveal melanocytic proliferation: Report of a novel optical coherence tomography finding and clinical response to plasmapheresis

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ABSTRACT

Purpose: To describe a novel optical coherence tomography (OCT) finding in a case of bilateral diffuse uveal melanocytic proliferation (BDUMP) and to report the clinical response to plasmapheresis.

Observations: We report the case of a 54-year-old man who was being treated with adjuvant immune checkpoint inhibitors for metastatic renal cell carcinoma. He had suffered from bilateral progressive vision loss without ocular pain. At presentation in the retina clinic, visual acuity was counting fingers bilaterally. Examination revealed characteristic findings suggestive of a peculiar paraneoplastic intraocular syndrome called BDUMP. Multiple choroidal nevi-like melanocytic tumors were noted bilaterally. The diagnosis was confirmed using multimodal imaging with fluorescein angiography and fundus autofluorescence, which revealed a typical leopard pattern. Ultrasonography revealed choroidal thickening extending to the ciliary body. OCT showed multiple pockets of serous retinal detachment (SRD) and bacillary layer detachment (BALAD), a newly recognized and rarely described manifestation of the disease. The clinical response to plasmapheresis was robust with resolution of the BALAD and SRD and improvement of the vision to 20/30 in both eyes at the seven-month follow-up.

Conclusions and importance: BALAD is a newly recognized manifestation of BDUMP. Early recognition of this paraneoplastic syndrome and prompt initiation of plasmapheresis has the potential to improve and stabilize vision.

1. Introduction

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic ocular disorder that was first described by Machemer in 1966.[1] It is most commonly associated to urogenital carcinomas in women and lung carcinomas in men, but it can occur with a wide variety of tumors.[2] Gass et al. described the cardinal features of the disease in 1990, namely the presence of multiple orange-red subretinal patches showing early hyperfluorescence on fluorescein angiography (FA), multiple elevated uveal melanocytic tumors with diffuse choroidal thickening, serous retinal detachment (SRD), and rapidly progressive cataracts.[3] The exact pathogenesis of this disease remains unclear; however, a possible explanation is the secretion by the primary solid tumor of a serum factor that selectively causes choroidal melanocyte proliferation.[4] Hence, plasmapheresis has been proposed as a potential therapeutic modality to remove this circulating serum factor, with variable success.[5–10]

Recently, Mehta et al. coined the term "bacillary layer detachment" (BALAD) to describe a particular pattern of intraretinal cystoid space (CS) in which the photoreceptor layer splits at the level of the myoid portion of the inner segments.[11] This separation leaves the remaining inner segment myoids and ellipsoids as well as the outer segments attached to the retinal pigment epithelium (RPE).[11] The finding of BALAD has been reported in patients with various inflammatory pathologies, including Vogt-Koyanagi-Harada (VKH) disease, toxoplasma retinochoroiditis, posterior scleritis, and, more recently, BDUMP.[12–16] To the best of our knowledge, no previous reports describe the clinical response to plasmapheresis in patients with BALAD associated with BDUMP.

Abbreviations: BDUMP, Bilateral diffuse uveal melanocytic proliferation; BALAD, Bacillary layer detachment; OCT, Optical coherence tomography; SRD, Serous retinal detachment; ICIs, Immune checkpoint inhibitors.

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2. Case report

A 54-year-old man was referred to our ophthalmology clinic because he had a suspected ocular adverse event from immune checkpoint inhibitors (ICIs). The patient had noticed a bilateral progressive painless decline in vision that started two weeks prior. He had metastatic clear cell renal cell carcinoma (RCC) for which he had undergone radical nephrectomy six months earlier. Four months prior to presentation, he was started on adjuvant immunotherapy using a combination of ipilimumab and nivolumab. Good response to treatment was noted with regression of the metastatic disease in the lungs and abdominal lymph nodes.

On initial examination, spectacle-corrected visual acuity was 20/25 in the right eye and 20/20 in the left eye. Anterior segment examination was normal. Spectral-domain optical coherence tomography (OCT) revealed bilateral diffuse thickening of the RPE as well as multiloculated dome-shaped SRDs involving the macula (Fig. 1A&B). The pockets of SRD did not show a gravitating appearance, similar to what is observed in mitogen-activated protein kinase (MEK) inhibitor-associated retinopathy.[17] An adverse event of ICIs was suspected and, as such, the immunotherapy was halted in an aim to preserve vision. Adjuvant sunitinib, a multitargeted receptor tyrosine kinase inhibitor, was started to manage the risk of tumor recurrence. At the one-month follow-up, the vision had declined to 20/50 in the right eye and 20/100 in the left eye. At that time, OCT demonstrated persistent SRDs, increasing RPE nodularity and outer retinal disorganization (Fig. 1C&D). The patient was referred to the retina clinic for further investigation.

Two months after initial presentation, the vision had decreased to counting fingers in both eyes. Fundus examination revealed bilateral SRDs, multiple choroidal nevi-like pigmented melanocytic tumors and diffuse mid-peripheral RPE stippling and atrophy (Fig. 2A&B). Fundus autofluorescence showed a nummular pattern of hypoautofluorescence and increased autofluorescence (Fig. 2C&D), with a reciprocating pattern on FA (Fig. 2E&F). This characteristic finding has been described as a leopard or giraffe pattern.[18] B-scan ultrasonography of the right eye showed choroidal thickening (Fig. 3A) which extended into the ciliary body (Fig. 3B). Considering the findings together, we established a diagnosis of BDUMP associated with RCC. At that time, OCT of the right eye showed a large intraretinal CS containing amorphous hyperreflective material with a foveal-splitting BALAD (Fig. 4A&C). OCT of the left eye showed a nasal BALAD and a foveal SRD (Fig. 4B&D).

Plasmapheresis was initiated three times per week with 5% human serum albumin as replacement serum. After three sessions, vision and OCT appearance rapidly improved (Fig. 5A&B). At the completion of 18 sessions of plasmapheresis, the pockets of fluid resorbed, leaving outer retinal atrophy and diffuse RPE changes on OCT (Fig. 5C&D). At latest follow-up seven months after presentation, the vision had significantly improved to 20/30 in both eyes and 1+ cortical and posterior subcapsular cataracts were noted bilaterally. The patient was maintained on weekly treatments to manage the risk of ocular relapse.

3. Discussion

BDUMP is a rare paraneoplastic intraocular syndrome characterized by the proliferation of benign uveal melanocytes in the setting of non-ocular tumors.[2] Our case demonstrated several of the cardinal features of BDUMP as described by Gass et al., including a typical fluorescence pattern on FA, multiple uveal melanocytic tumors with diffuse choroidal thickening and bilateral fluid accumulation.[3] However, cataracts did not progress rapidly and only appeared seven months after initial presentation. Our patient's primary malignancy was metastatic RCC, which has been reported only once in the literature, according to a recent review.[2] The same review noted the use of plasmapheresis in 10 of the 59 identified BDUMP cases over the past four decades with reported beneficial outcomes in six cases.[2] In our case, the clinical response to plasmapheresis was drastic, with gradual resolution of the BALAD and SRD and improvement in visual acuity. We elected to maintain the patient on weekly plasmapheresis to preserve visual function, based on our current understanding of the disease and previous anecdotal evidence on the recurrence of fluid after cessation of treatment.[9]

The number of reported cases of BDUMP has increased over the past two decades.[2] Improved identification of this disease with multimodal imaging has probably contributed to this trend. Longer patient survival attributed to novel treatment approaches and targeted cancer drugs like ICIs is another factor.[19] Our patient was receiving adjuvant immunotherapy using a combination of two ICIs – ipilimumab and nivolumab – that target immune checkpoints on T cells to restore antitumor autoimmunity. Ipilimumab targets the cytotoxic T-lymphocyte antigen

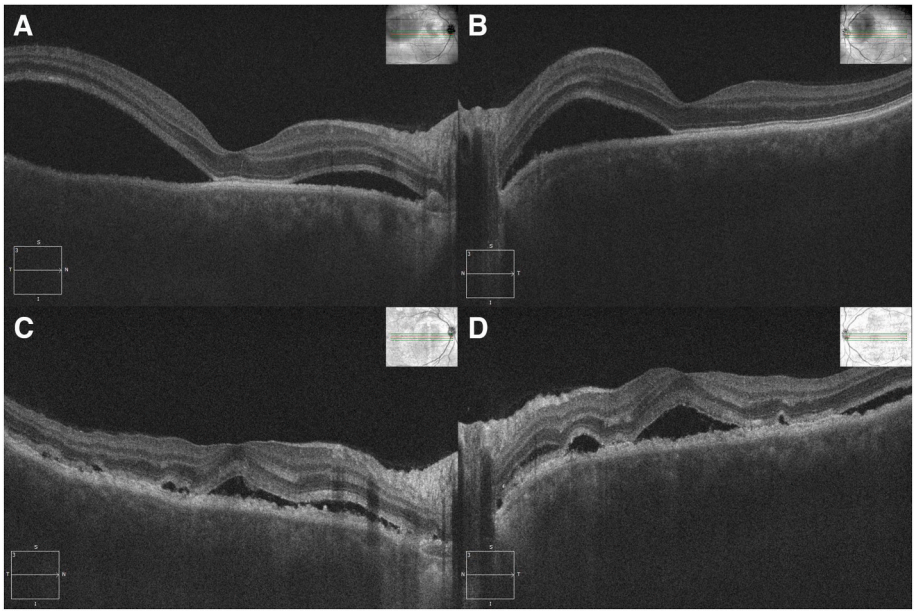

Fig. 1. Spectral-domain optical coherence tomography (OCT) at presentation and at the one-month follow-up. (A, B) There is diffuse thickening of the retinal pigment epithelium (RPE) as well as multiloculated dome-shaped serous retinal detachments (SRDs) involving the macula in both eyes. (C, D) The pockets of SRD became shallow but confluent, with increasing RPE nodularity and outer retinal layer disorganization.

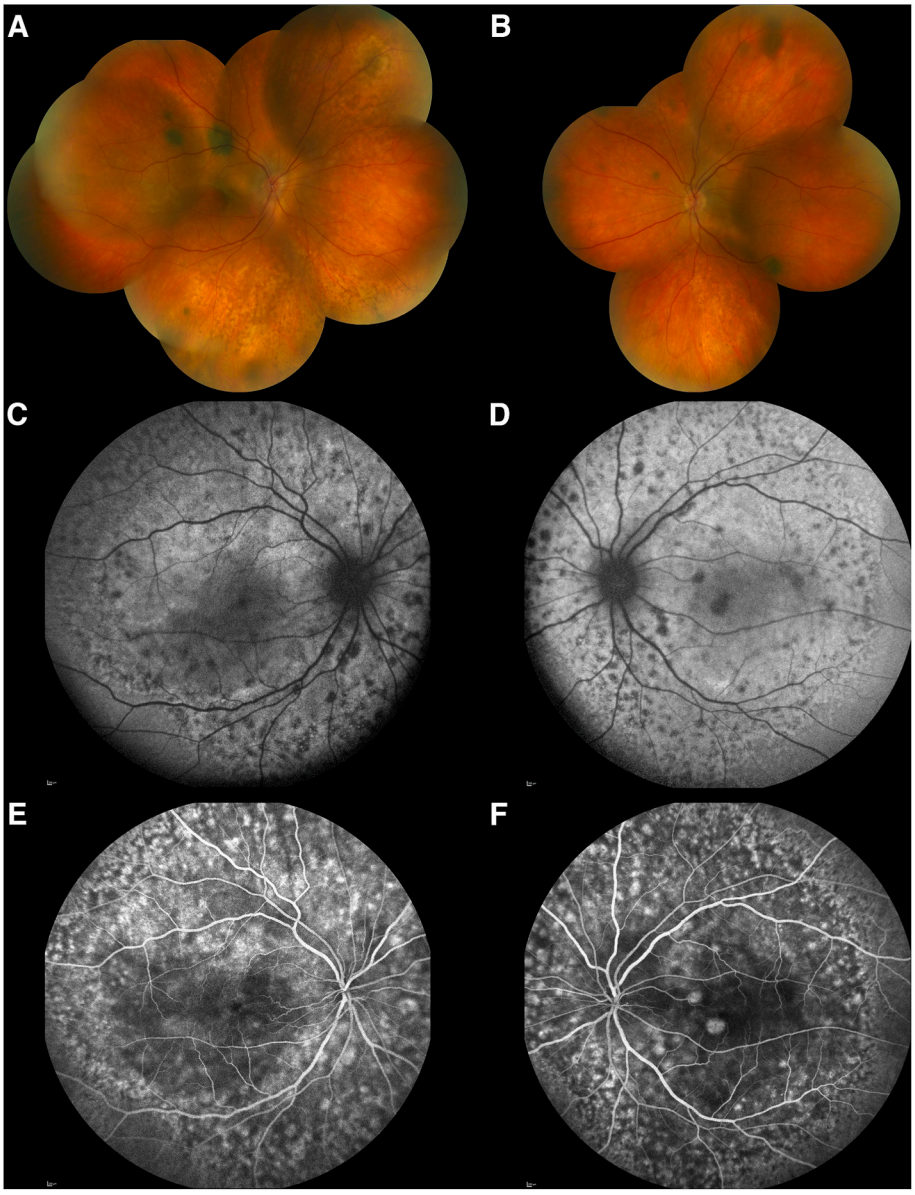

Fig. 2. Multi-modal imaging. (A, B) Color fundus photographs showing multiple choroidal nevi-like melanocytic tumors in both eyes and, diffuse mid-peripheral retinal pigment epithelial (RPE) stippling and atrophy (more prominent in the right eye). (C, D) Blue light fundus autofluorescence demonstrated a nummular pattern of hypoautofluorescence surrounded by a large area of increased autofluorescence in both eyes. (E, F) A reciprocating pattern is seen on late-phase fluorescein angiography that reveals window-defect hyperfluorescence of multiple nummular RPE atrophic lesions with mild staining. This characteristic finding has been described as a leopard or giraffe pattern. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

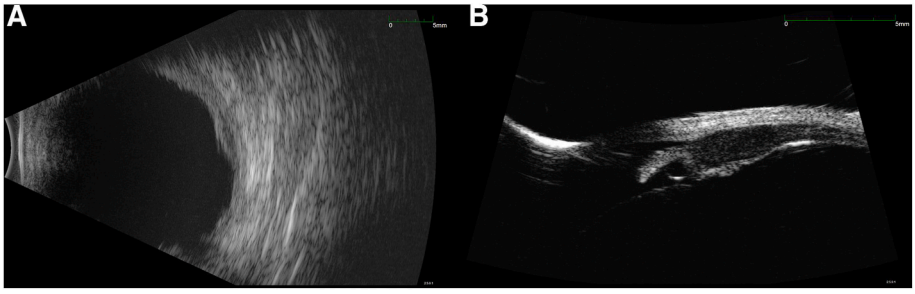

Fig. 3. Diagnostic ultrasound of the right eye. (A) 10 MHz posterior B-scan showing choroidal thickening. (B) 40 MHz ultrasound biomicroscopy B-scan showing ciliary body thickening.

(CTLA-4) and nivolumab binds the anti-programmed death 1 (PD-1) receptor.[20] When used in combination, ICIs have shown increased efficiency in RCC and other cancers at the expense of toxicity, mainly in the form of immune-related adverse events (irAEs), stemming from an excessively activated immune system.[20,21]

Ocular irAEs typically occur within weeks to months of starting therapy but are rare, affecting only 1% of patients.[22,23] An ocular irAE was suspected in our patient since the initial clinical picture resembled MEK inhibitor-associated retinopathy that also shows dome-shaped SRDs.[24] Uveal effusion syndrome with serous choroidal detachment and intraretinal fluid, VKH-like syndrome, and birdshot-like chorioretinopathy have also been reported with ICIs.[20,25,26] In our case, during

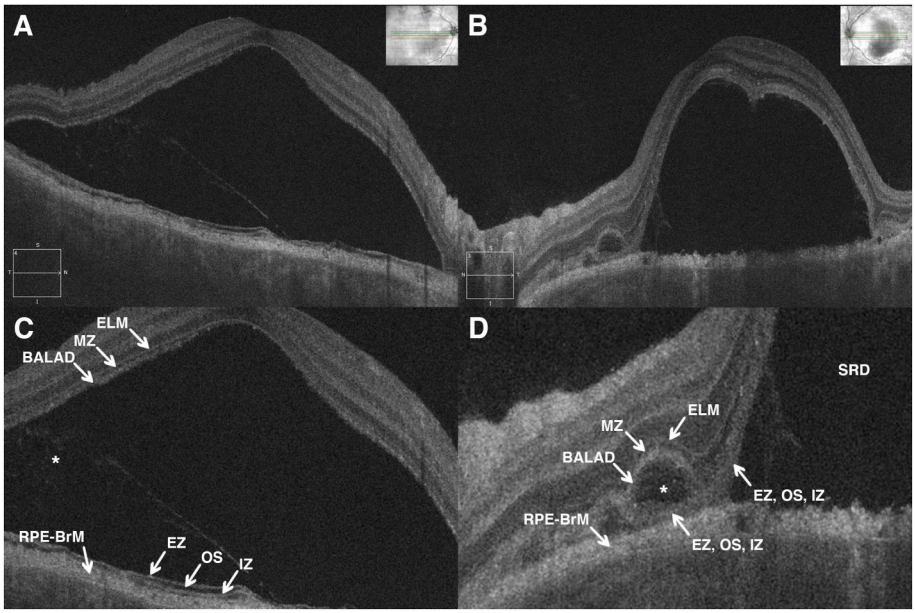

Fig. 4. Spectral-domain OCT at the diagnosis of bilateral diffuse uveal melanocytic proliferation (BDUMP) with magnified views highlighting the areas of interest. (A, C) In the right eye, there is a large intraretinal cystoid space (CS) containing fluid with amorphous hyperreflective material (white asterisk), with a foveal-splitting bacillary layer detachment (BALAD). The external limiting membrane (ELM) is the hyperreflective line running anterior to the CS. Posterior to the ELM lies the hyporeflective myoid zone (MZ) that has split, producing a BALAD and leaving remnants of the MZ, ellipsoid zone (EZ), outer segments (OS), and interdigitation zone (IZ) attached to the RPE/Bruch's membrane complex. (B, D) In the left eye, the scan shows a localized CS created by the BALAD containing amorphous material (white asterisk) adjacent to an area of SRD that shows lower reflectivity. The ELM and remnants of the MZ run anterior to the CS while the EZ, OS, and IZ form the base of the CS created by the BALAD. These separate layers are indistinguishable on this scan. In the area of the SRD, the fluid accumulates under the EZ, OS, and IZ, representing a SRD (true neurosensory retinal detachment). In both eyes, there is diffuse choroidal thickening with loss of choroidal vascular details which is suggestive of infiltration.

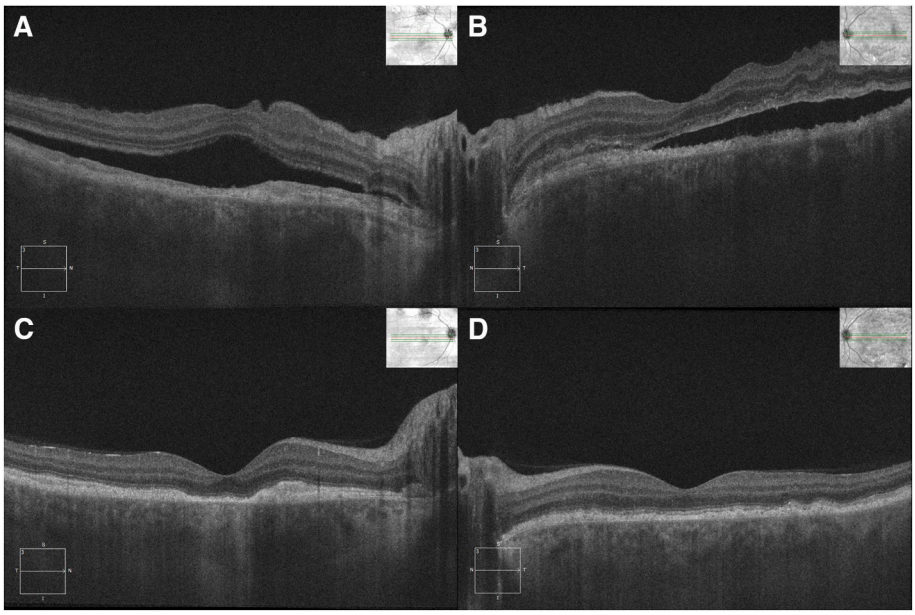

Fig. 5. Spectral-domain OCT during follow-up after the initiation of plasmapheresis. (A, B) After three sessions of plasmapheresis, diffuse RPE thickening remained in both eyes. In the right eye, there is less fluid in the intraretinal CS created by the BALAD. In the left eye, the nasal BALAD has resolved and there is improvement in the SRD. (C,D) Following 18 cycles of plasmapheresis, the pockets of fluid resorbed, leaving outer retinal atrophy, diffuse RPE thickening, and nodularity.

follow-up, characteristic findings of BDUMP became evident and, considering those cardinal features together, we established a diagnosis of BDUMP rather than an irAE. Despite this determination and in agreement with expert opinion, we believe that the immunotherapy might have played a role in the genesis of BDUMP in our patient through reprogramming of the cell death pathway in the eye (an immune-privileged tissue).[27] Evaluation of our patient's serum for the presence of cultured melanocyte elongation and proliferation factor (CMEP factor) could have provided definitive evidence for BDUMP.[28]

Breazzano et al. were the first to report the occurrence of BALAD in BDUMP, although the finding of BALAD has been previously published without comment by O'Day et al.[12,15] Originally thought to represent a histologic artifact, BALAD has now been described with several macular diseases and seems to occur frequently in VKH disease.[14] Our case demonstrated several OCT hallmarks of BALAD, including colocalization with subretinal fluid (seen in 77.5% of BALADs) and characteristic features of the outer retinal structures.[16] As described in Fig. 4, BALAD has distinguishing findings on OCT that differ from SRD where subretinal fluid accumulates between the neurosensory retina and the underlying RPE. Although the precise location of the detachment is still debated, the current interpretations of this finding in the literature suggest that it occurs at the myoid portion of the inner segments.[11,12,14] This corresponds to the myoid zone (MZ) on spectral-domain OCT based on current consensus.[29] Fluid accumulation and fibrin formation occur

under the external limiting membrane (ELM) and MZ, moving the ellipsoid zone, outer segments, and interdigitation zone posteriorly, leaving these bands attached to the RPE/Bruch's membrane complex. As illustrated in Fig. 4, in both eyes, the ELM was distinguishable at the border of the BALAD (seen in 72% of BALADs) along with an underlying granular band presumably containing fragments of structures of the MZ and regenerating photoreceptor inner and outer segments.[16] The posterior border of the BALAD is probably composed of detached photoreceptor inner and outer segments adherent to the RPE.[16] In the right eye, unlike in the left, under the first hyperreflective band at the floor of the BALAD (the EZ), a second hyperreflective band was detectable corresponding to the IZ (visible in 47.7% of BALADs).[16] No subretinal fluid under the floor of the BALAD was seen in either eye (reported in 50.3% of BALADs).[16] Higher reflectivity compared to subretinal fluid was seen in both eyes (noted in 90.8% of cases).[16]

The configuration of BALAD has been attributed to the convergence of different pathophysiologic mechanisms, including the quick accumulation of fluid in exudative diseases, rapid inner choroidal ischemia and RPE dysfunction, and choroidal hyperpermeability and RPE degeneration.[12] Breazzano et al. also suggest that fibrin formation plays an important role in the creation of a BALAD and that it can dissect into the plane of the bacillary layer with enough exudation.[12] Identifying BALAD in inflammatory conditions using OCT can serve as a distinguishing feature from other noninflammatory diseases associated with subretinal fluid in the macula.[14,26] It can also provide insight into photoreceptor and visual acuity recovery following the resorption of intraretinal and subretinal fluid.[14] Following initiation of plasmapheresis, the BALAD resolved leading to improvement of visual acuity similar to what is seen after initiation of high-dose corticosteroid therapy in VKH.[14]

4. Conclusions

We herein describe a novel OCT finding in BDUMP and report the clinical response to plasmapheresis. Any patient presenting with suspected ocular complications of anticancer immunotherapy should be examined using multimodal imaging as these studies can reveal characteristics findings of BDUMP. Notably, identification of BALAD on OCT can be suggestive of BDUMP. Making this distinction is crucial to orient the systemic therapy and avoid unnecessary discontinuation of immunotherapy. Given the progress in cancer survival, long-term follow-up of patients with BDUMP (with fundoscopy and macular OCT) should be considered to monitor for disease recurrence, especially when plasmapheresis is stopped. At the earliest signs of relapse, findings should be promptly communicated to the treating oncologist to restart plasmapheresis and to ensure optimal management of the underlying malignancy.

Patient consent

Written consent was obtained from the patient. This report does not contain any personal identifying information.

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Authorship

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

Declaration of competing interest

None of the authors has any financial/competing interests to disclose.

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