Bilateral diffuse uveal melanocytic proliferation: A case report and literature review

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Case Report

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Abstract

Background Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic intraocular disease that causes progressive visual loss in patients driven by an IgG factor associated with an underlying malignancy. Characteristic ocular findings include exudative retinal detachment, rapid cataract formation and uveal melanocytic tumors.

Case presentation Here, we presented a patient, whose clinical manifestation was diffusely thickened choroid, shallow anterior chamber, cataract formation and exudative retinal detachment. Histopathologic examination for the biopsies from the choroid during the surgery showed the the tissue might be originated from melanocytes and with the benign biologic behavior. Therefore, the diagnosis for this patient was BDUMP, although there was no obvious history of malignancy until we prepared for this article.

Conclusions This was a rare BDUMP clarified by ophthalmic manifestations and histopathologic examination, without clear history of systematic malignancy.

Introduction

Bilateral diffuse uveal melanocytic proliferation (BDUMP), first described by Machemer[1], is a rare, paraneoplastic intraocular syndrome characterized by multiple, elevated, pigmented uveal lesions, diffuse thickening of the uveal tract and rapidly progressive cataract. It is caused by a diffuse proliferation of benign melanocytes in the uvea, predominantly in the choroid, and is histopathologically unrelated to the primary non-ocular tumor. The typical clinical findings are naevus-like multifocal reddish patches at the level of the retinal pigment epithelium (RPE) which hyperfluoresce on fluorescein angiography (FA)[2]. BDUMP usually occurs in patients with systemic malignant disease, most commonly ovarian carcinoma in women and lung carcinoma in men. Occasionally, it may be associated with gastric adenocacinoma[3], bladder cancer[4], or occur with primary vitreoretinal lymphoma[5, 6].

A review published in 2017 reported that the incidence of BDUMP was significantly increased during the past forty years[7]. After that review published, more than 10 cases of BDUMP were reported in the last three years[4, 6, 8–15], and it was seemed that the incidence of this disease was much higher than before. Consequently, retinal specialists should pay much more attention to this disease and investigate the diagnosis and treatment of BDUMP. Here, we reported a case of BDUMP, with comprehensive ophthalmic examination and detailed pathological examination results.

Case Presentation

A 68-year-old Chinese man was complained by gradual visual loss for more than 9 months in both eyes. A subtotal pneumonectomy had been performed due to the pulmonary benign tumor around half year before he came to our clinic. Increased intraocular pressure (IOP) (around 30 mmHg in both eyes), thickened ciliary body in whole circle and decreased depth of anterior chamber was found in another

clinic about a couple of months before. Best corrected visual acuity (BCVA) was finger count before eyes of both eyes. IOP was 19 mmHg for right eye and 20 mmHg for left eye. Slitlamp examination for the anterior segment of eyes showed obviously tortuous and dilated conjunctival vessels (Fig. S1), significantly decreased depth of anterior segmentation, iris bombe, slight eversion of iris pigment at pupillary margin and cataract (Fig. 1). No sigh of synechia, neovascular membranes of the iris, nor active inflammation was found (Fig. 1). Open angles with pigmentation of the trabecular meshwork was revealed by gonioscopy. Typical exudative retinal detachment was shown by color fundus images in both eyes (Fig. 1), accompanied by naevus-like multifocal reddish patches at the level of the RPE in the superior part of the fundus. These patches were hypoautofluorescent and hyperfluorescent on FA. Ocular coherence tomography (OCT) showed an exudative retinal detachment of the macular with multi hyperreflective elevated lesion of RPE. In order to deepen the anterior chamer, restore the transparency of the refractive media, reattach the retina, and take some choroid for pathologic examination, phacoemulcification, peripheral iridectomy, diagnostic vitrectomy, and silicon oil tamponade was performed on the right eye. During the surgery, vitreous fluid and subretinal fluid was tanken and performed for immunological detection and no specific positive result was found. The hematoxylin-eosin (HE) staining for biopsies from the choroid during the surgery suggested predominantly spindle-shaped melanocytic cell mass and immunohistochemistry staining showed positive for antibodies against S100 (as for melanocytes), whereas negative for antibody against Ki67 (as for proliferation, especially in malignant cells), LCA, PAX-5 and SOX-10 (Fig. 2), in which the mutations are associated with uveal melanoma. The histopathological examination was consistent with melanocyte proliferation, not malignant melanoma. About 1 month after the surgery, the patient felt recovery visual acuity. BCVA was 20/100 for right eye and 20/80 for left eye, and IOP was 21 mmHg for both eyes. The depth of anterior chamber increased and the iris bombe disappeared. The retina reattached and a mass of naevus-like multifocal reddish patches (Fig. 3) were found all around the retina, especially in the mid-peripheral sections. These patches were well consistent with the elevated hyper-reflective mass at the level of RPE (Fig. 3), and also well consistent with hyperfluorescence in auto fluorescence and hypofluorescence in FA. In addition, the OCT showed a multi hyperreflective elevated lesion of RPE with small amount of subretinal fluid.

With the typical ocular presentation, accompanied by histopathological examination, the diagnosis was BDUMP.

Discussion

Gass first described the characteristic findings in BDUMP as multifocal red-orange subretinal patches with associated early hyperfluorescence in FA, scattered melanocytic tumors of the uveal tract, exudative retinal detachment, and rapid cataract progression[2]. All these features were present in this patient. As a kind of paraneoplastic syndrome[16], the most common malignant neoplasms associated with BDUMP are ovarian carcinoma in women and pulmonary malignancy in men; other associated diseases include carcinomas of the breast, colon, urinary bladder, gallbladder, pancreas, esophagus, and liver[7]. However,

no clear history of malignancy was found in this patient until now. He only had a history of lobectomy due to pulmonary benign tumor.

When confer to the histopathologic examination, biopsies from the pigmented intra-bulbar lesions showed predominantly spindle-shaped melanocytic cells sometimes with an admixture of epithelial cells, but with no or rare mitotic activity and no atypia[7]. In HE staining for biopsies from the choroid during the surgery, predominantly spindle-shaped melanocytic cell mass was found, which was consistent with the previous studies[17, 18]. The results of immunohistochemistry staining for the biopsy can give us much more useful information about the nature of the tissue. S-100 protein is normally present in cells derived from the neural crest (Schwann cells, and melanocytes), chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells, and keratinocytes. S-100 can be found in melanomas, and in some previous studies, it was used as a biomarker for identify the melanocytes[19]. Here, the positive expression of S-100 demonstrated that the tissue might be originated from melanocytes.

Ki67 is a nuclear protein and its expression is strongly associated with tumor cell proliferation and growth[20, 21]. Therefore, it is widely used in routine pathological investigation as a proliferation marker[21]. Here, the negative expression of Ki67 demonstrated that the benign biologic behavior of the tissue. Gass described the characteristic findings in BDUMP, he divided differential diagnoses to BDUMP in conditions resembling BDUMP before and after development of multifocal pigmented choroidal tumors[2]. Some researchers had reported BDUMP associated with B-cell lymphoma[5] and BDUMP with primary vitreoretinal lymphoma[6]. Therefore, we further investigated the immunohistochemistry staining against LCA, PAX-5 and SOX-10. The PAX-5 gene is a member of the paired box (PAX) family of transcription factors. The PAX proteins are important regulators in early development, and alterations in the expression of their genes are thought to contribute to neoplastic transformation. The PAX-5 gene encodes the B-cell lineage specific activator protein (BSAP)[22] that is expressed at early, but not late stages of B-cell differentiation. Its expression has also been detected in developing central nerve system, therefore, PAX-5 gene product may not only play an important role in B-cell differentiation[23], but also in neural development. The deregulation of PAX-5 gene transcription contributes to the pathogenesis of the lymphomas and up to 97% of the Reed-Sternberg cells of Hodgkin's lymphoma express Pax-5[24]. The SOX-10 gene encodes a member of SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and determination of cell fate. It was reported previously that mutation in SOX-10 gene are associated with uveal melanoma[25]. Because of the negative result for immunohistochemistry staining against LCA, PAX-5 and SOX-10, the possibility of originating from B-cell lymphoma and uveal melanoma was excluded.

Although the exact pathogenesis of BDUMP and mechanism of uveal and dermal melanocytic proliferation in BDUMP remains unclear, cultured melanocyte elongation and proliferation (CMEP) factor from the IgG fraction isolated from serum from patients with BDUMP has been previously found to stimulate melanocytic proliferation[26]. Human melanocytes were grown when exposed to serum or plasma of patients with BDUMP. To show that the proliferation was melanocyte selective, human dermal

fibroblasts, keratinocytes and ovarian cancer cells were also treated with plasma from BDUMP patients. Specific proliferation of cultured melanocytes was found when exposed to patient serum. This observation was further supported by Jansen[27], who reported two cases of BDUMP in whom serum were collected. The serum of the first patient was investigated after plasmapheresis and did not demonstrate proliferation of cultured human melanocytes, while the serum of the second patient was evaluated prior to treatment with plasmapheresis and did induce this proliferation. In theory, CMEP factor should not be present in the serum from the first patient but should be present in the serum from the second patient. Human melanocytes were exposed to serum form patients and only serum from the second patient induced melanocytic proliferation, confirming the ability of a IgG factor in BDUMP patients to induce proliferation.

Conclusion

In summary, the diagnosis of BDUMP of this patient was clarified by ophthalmic manifestations and histopathologic examination, although without clear history of malignancy. The association of tumor load with melanocytic proliferation in this patient supports a role for a diffusible factor produced by the tumor or in response to the tumor that results in melanocytic proliferation. Treatment with surgery developed the visual acuity of this patient only due to cataract extraction, restoration of refractive interstitial transparency, and the treatment of the exudative retinal detachment.

Abbreviations

Bilateral diffuse uveal melanocytic proliferation
BDUMP
retinal pigment epithelium
RPE
fluorescein angiography
FA
intraocular pressure
IOP
Best corrected visual acuity
BCVA
Ocular coherence tomography
OCT
hematoxylin-eosin
HE
cultured melanocyte elongation and proliferation
CMEP

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication

The manuscript is approved by all authors for publication

Availability of data and materials

A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interest

The authors declare that they have no competing interests.

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Author's contributions

Nianting Tong and Liangyu Wang have made substantial contribution to the draft of the work and will do the further revision for the manuscript. They contributed equally for this work. Nan Wang has mad substantial contributions to the acquisition, analysis, and interpretation of the data for this work. Zhanyu Zhou has mad substantial contributions to the conception and design of the work.

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Authors' information

Not applicable

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Figure S1 Legend

Figure S1 This was the photos from anterior segment examination, which showed obviously tortuous and dilated conjunctival vessels (A-D for right eye showing temporal, superior, inferior, and nasal side respectively; E-H for left eye showing temporal, superior, inferior, and nasal side respectively).

Figures

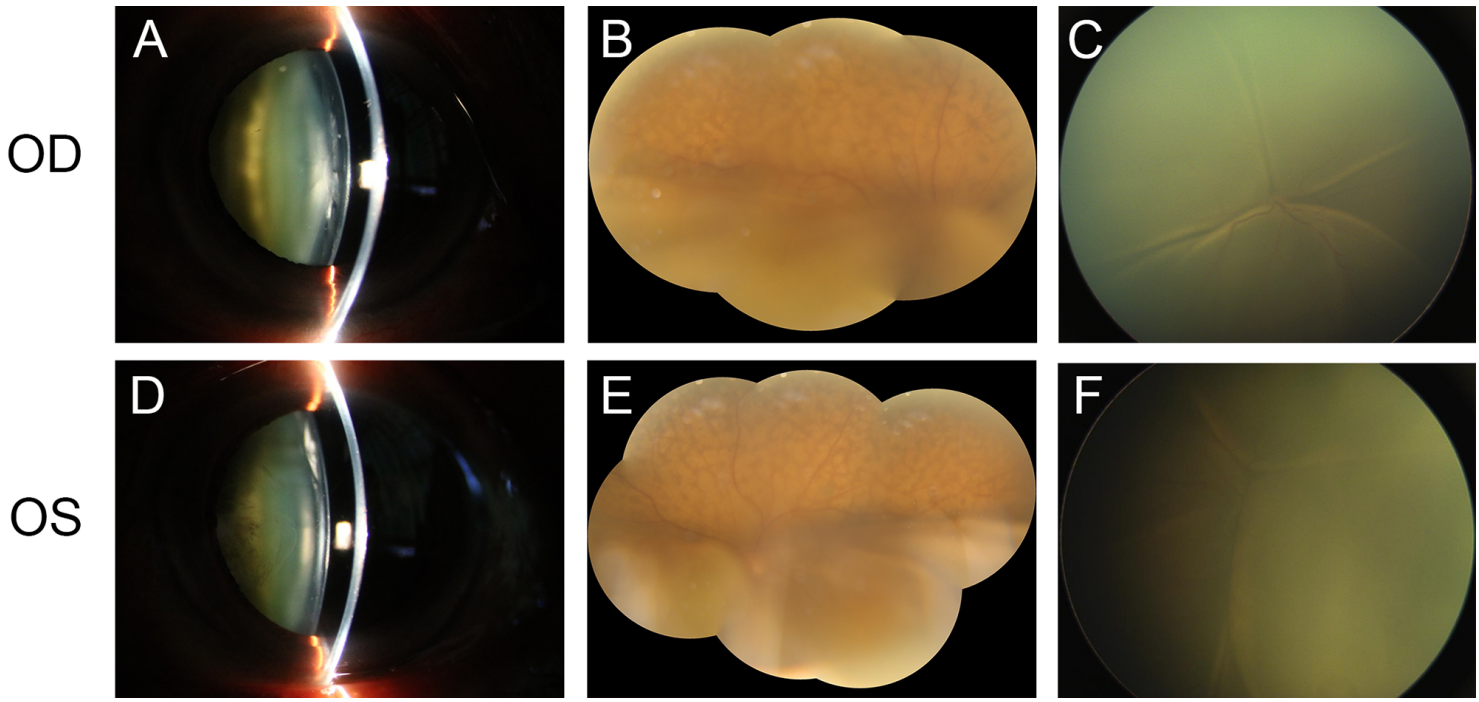

Figure 1

This was the main clinic manifestation for the patient before the surgery. A showed the obvious cataract in the right eye of this patient. B showed the exudative retinal detachment in the inferior part of the retina, accompanied by naevus-like multifocal reddish patches in the superior part of the fundus. Total retinal detachment was found in the posterior pole of the retina when the patient was in supine position (C). D-F showed the similar clinic manifestation for the left eye.

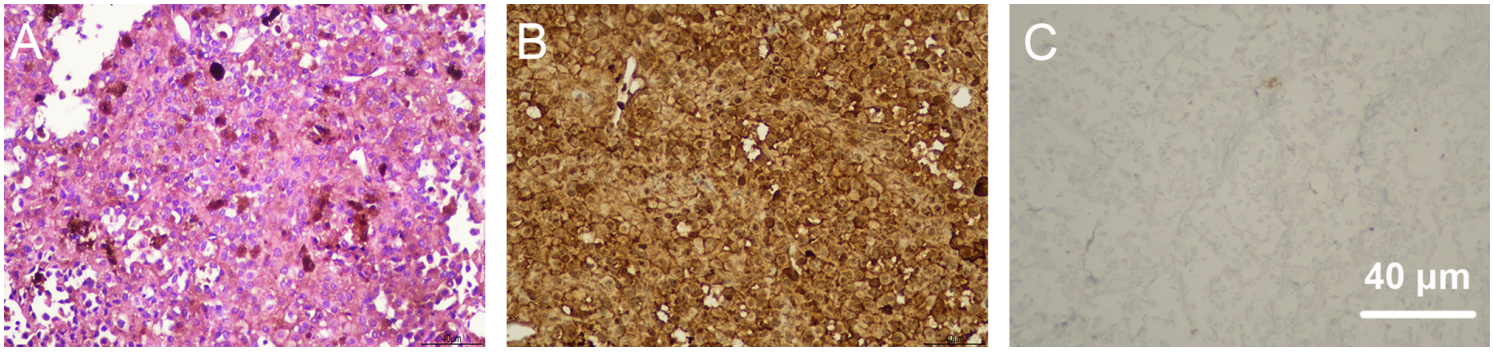

Figure 2

This was the pathologic examination for biopsies from the choroid during the surgery. A was hematoxylin-eosin (HE) staining for biopsies and showed predominantly spindle-shaped melanocytic cell mass. Immunohistochemistry staining showed positive for antibodies against S100 (B) while negative for antibodies against Ki67 (C).

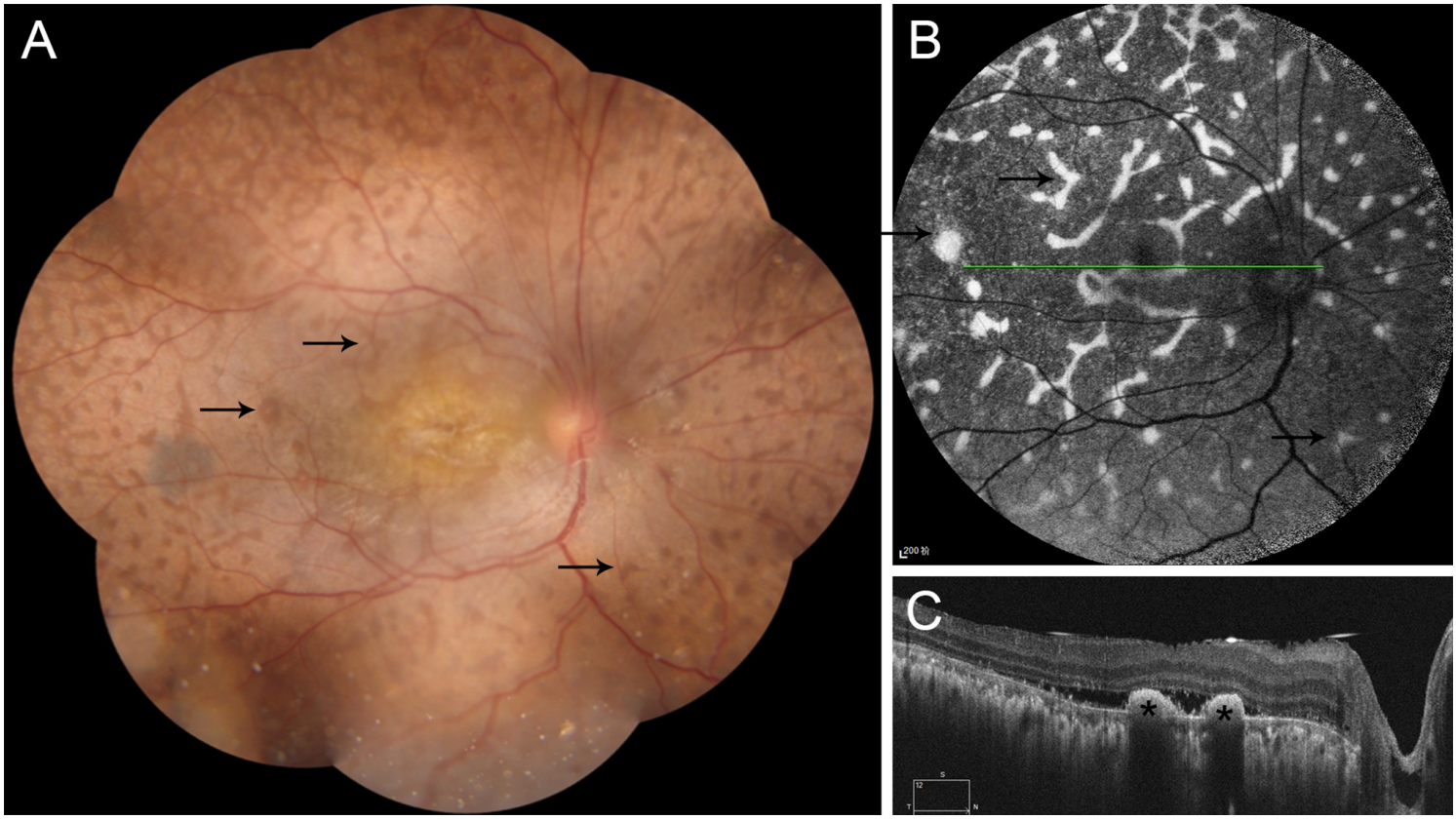

Figure 3

This was the main clinic manifestation for the patient before the surgery. A showed a mass of giraffe-like multifocal reddish patches (arrow) in the retina. These patches were well consistent with increased autofluorescence (B, arrow) and also well consistent with multi hyperreflective elevated lesion of retinal pigment epithelium (C, asterisk) in ocular coherence tomography.

Supplementary Files

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