Bilateral Diffuse Uveal Melanocytic Proliferation (BDUMP)

89-year-old male presents with multiple choroidal nevi, both eyes

Jacob R. Hayes, BS; Jeffrey D. Welder, MD (../bio/authors/Welder-Jeffrey.htm); H. Culver Boldt, MD (http://www.medicine.uiowa.edu/dept_primary_apr.aspx?appointment=Ophthalmology%20and%20Visual%20Sciences&id=boldtc)

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Chief Complaint

Several new choroidal nevi

History of Present Illness

An 89-year-old male was referred to the University of Iowa retina service for evaluation of multiple choroidal nevi which were noted incidentally almost a year after starting intravitreal ranibizumab and aflibercept for exudative age-related macular degeneration. He had no known history of cancer, but was formerly a heavy smoker.

He reported anorexia, an unintentional weight loss of 30 pounds over the prior 6 months, and a mild chronic cough. In the month prior to his ocular examination, a colonoscopy and upper endoscopy were performed and were normal with the exception of diverticulosis.

Past Ocular History

- Exudative age-related macular degeneration (AMD) in both eyes (OU): Treated with 6 anti-vascular endothelial growth factor (anti-VEGF) injections over the prior year OU

- Cataract surgery OU

Past Medical History

- Hypertension
- Gastroesophageal reflux disease
- Hyperlipidemia
- Diverticulosis
- Cardiac valve replacement

Family History

- Sister with macular degeneration
- Brother with an unknown cancer

Social History

- Former smoker (50 pack years), but no tobacco for the last 50 years

Review of Systems

- Negative except as noted in the HPI

Ocular Examination

	Right (OD)	**Left (OS)**
Visual Acuity	20/30-2	20/25+1
Pupils	No afferent pupillary defect	No afferent pupillary defect
Visual Fields	Full	Full
Extraocular Motility	Full	Full
Tonometry	10 mmHg	12 mmHg
Amsler Grid	Normal	Normal
Slit lamp exam		
Lids/Lashes	Marked lower lid ectropion	Mild lower lid ectropion
Conjunctiva/Sclera	Dilated episcleral vessels but no abnormal pigment	Dilated episcleral vessels but no abnormal pigment
Cornea	Clear	Clear
Anterior chamber	Deep and quiet	Deep and quiet

Iris	Normal architecture	Normal architecture
Lens	Intraocular lens	Intraocular lens with 1+ posterior capsular opacification
Vitreous	Posterior vitreous detachment; no anterior vitreous cells	Posterior vitreous detachment; no anterior vitreous cells
Fundus	See Figure 1	See Figure 1

Figure 1: *Color fundus photography*

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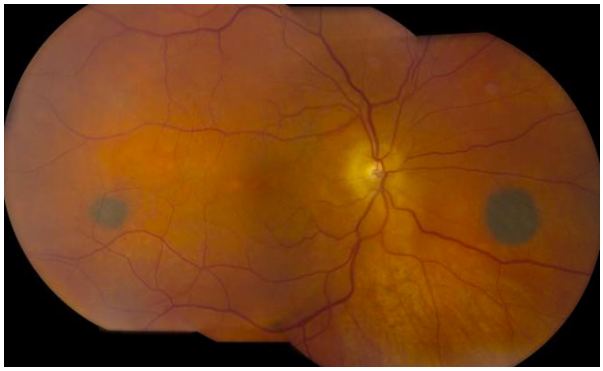
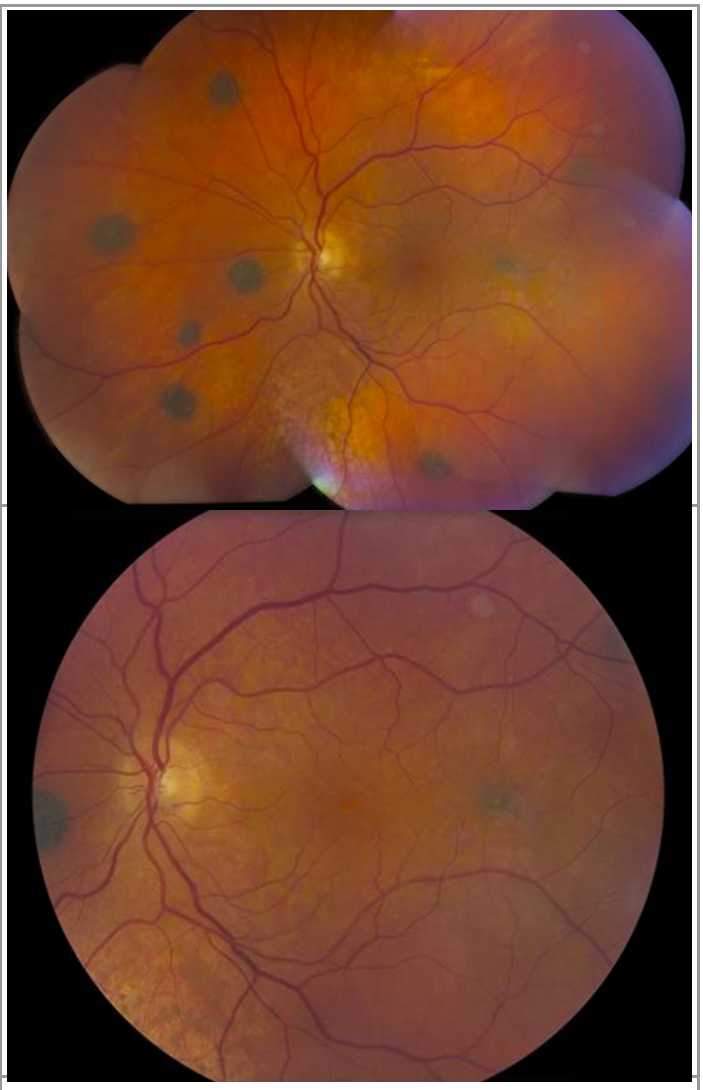
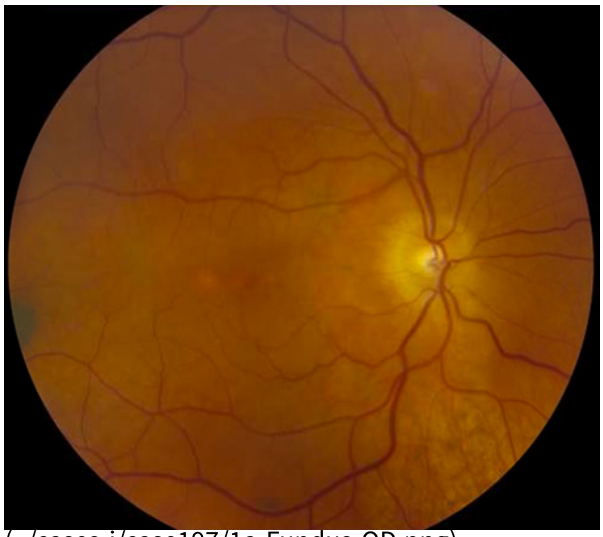
<tr><td>  </td><td rowspan="2">  </td></tr>
<tr><td> 
(../cases-i/case197/1a-Fundus-OD.png)</td></tr>
<tr><td>right eye: Mild non-geographic atrophy in the fovea. Hyperpigmented region temporal to the macula and nasal to the disc. Minimal orange nummular patches around the disc with pigmented epithelium stippling/atrophy inferior to disc.</td><td>left eye:Six hyperpigmented regions nasal to disc and temporal to macula and another hyperpigmented area in the inferior midperiphery. Nummular orange lesions temporal to disc and along the inferotemporal arcade. Stippled pigmentation and atrophy inferior to disc.</td></tr>
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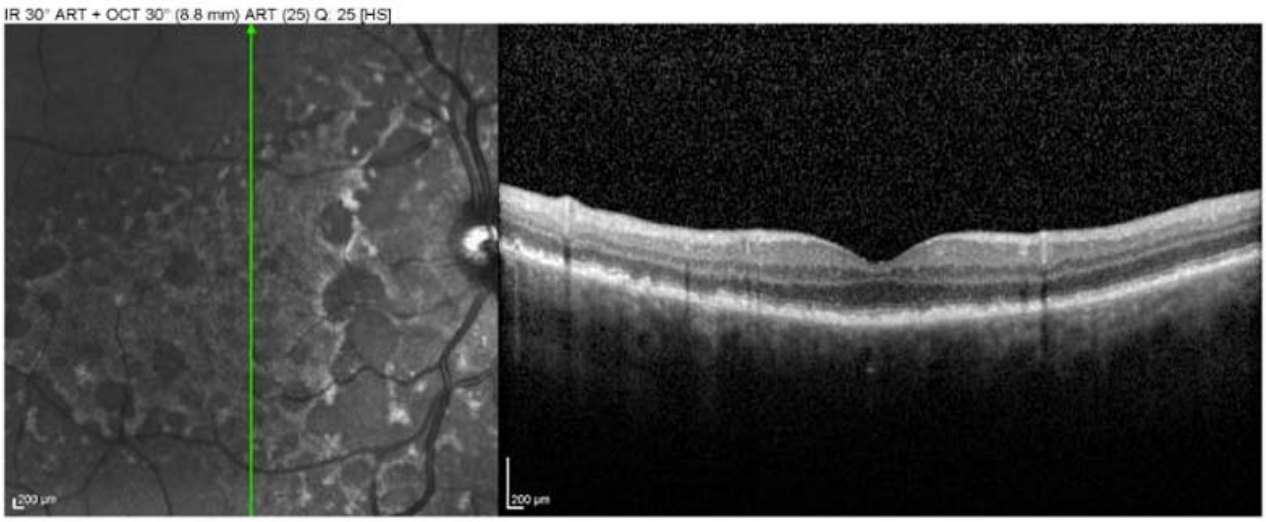
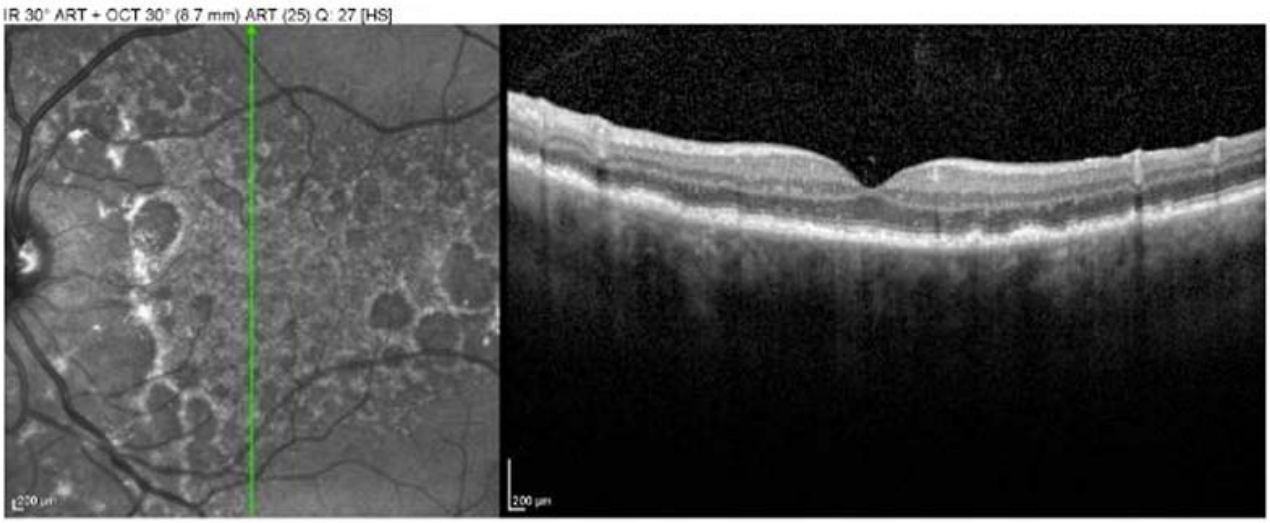
Figure 2: *Optical Coherence Tomography. OD and OS: Irregular retinal pigment epithelial thickening, without subretinal fluid in the macula. Nummular appearance of macula on infrared image.*

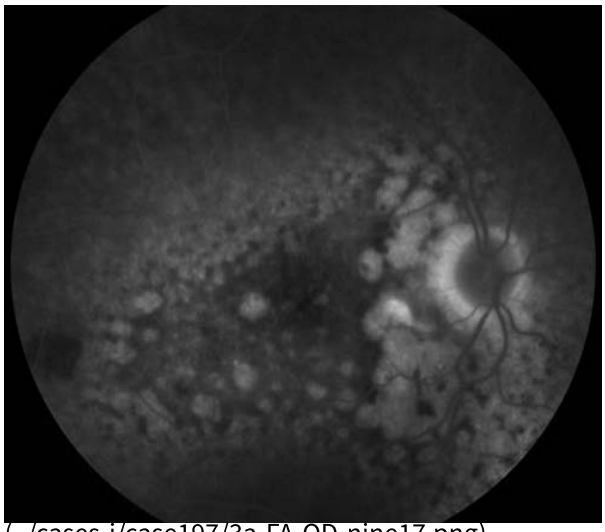


Right eye

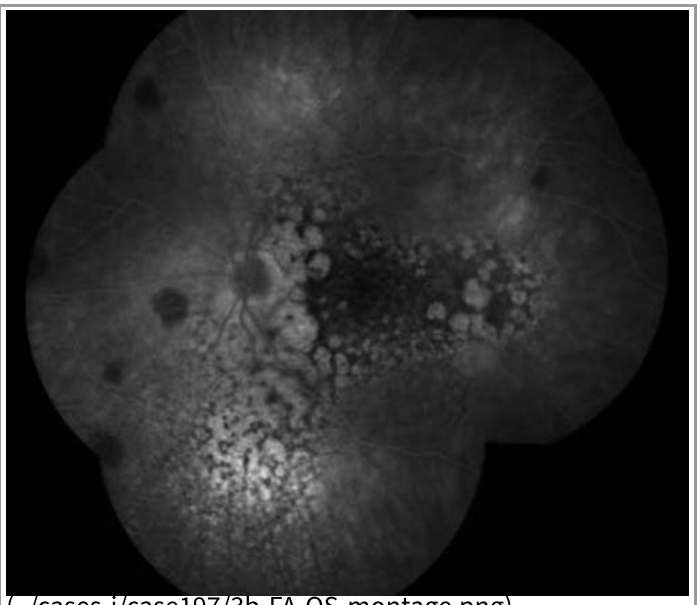


Left Eye

***Figure 3**: Fundus fluorescein angiography*



(../cases-i/case197/3a-FA-OD-nine17.png)



(../cases-i/case197/3b-FA-OS-montage.png)

Right eye: *Multifocal nummular areas of transmission defect with surrounding blockage from increased choroidal pigmentation throughout the macula and inferior to the disc. Focal choroidal hypofluorescence temporal to macula.*	***Left eye:*** *Multifocal nummular areas of transmission defect with surrounding blockage from increased choroidal pigmentation throughout the macula and inferior to the disc. Multifocal areas of choroidal blockage nasal to the disc and superotemporal to the disc.*

Clinical course

The patient was diagnosed with bilateral diffuse uveal melanocytic proliferation (BDUMP). Multiple choroidal nevi in the presence of chronic cough and unintentional weight loss in a former smoker were highly suspicious for possible malignancy; consequently the patient underwent a metastatic evaluation. The evaluation revealed Stage 3B adenocarcinoma of the lung. Unfortunately, his lung cancer progressed despite treatment and eventually chemotherapy was discontinued. He continued to receive bilateral anti-VEGF injections for exudative age-related macular degeneration, and had stable to improved visual acuity 7 months after presentation (20/30-2 OD and 20/20 OS). Ten months after his original presentation to the eye clinic, his vision had mildly decreased in each eye to 20/40. One month later, he died.

Discussion

Presentation

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic syndrome resulting in severe vision loss and benign proliferation of choroidal melanocytes. The melanocytes are histopathologically unrelated to the non-ocular tumor. The condition was first reported in 1966 by Machemer, and there are approximately 31 reported cases in the literature (1-3,8).

Typically, BDUMP presents as bilateral vision loss in an adult patient between the ages of 50 and 80 years old. In 85% of cases, pigmented choroidal lesions are observed. Bilateral exudative retinal detachment and rapid cataract formation often follow the initial vision loss. Surgical removal of cataracts and resolution of associated retinal detachment with treatment of systemic malignancy may improve vision to a limited degree (if these conditions are present), but patients nonetheless have a very guarded prognosis as a result of the presence of systemic malignancy. The etiology of retinal detachment is unclear, but it is thought that a poorly-functioning retinal pigment epithelium (RPE) and breakdown of the blood-retina barrier are involved. The etiology of rapid cataract formation (as rapid as 3 months) has been hypothesized to result from ciliary body involvement, leading to inadequate aqueous volume, poor nutrient composition, or release of toxins (1).

In nearly half of the cases of BDUMP there is a history or known diagnosis of non-ocular malignancy at the time of diagnosis of BDUMP (2). In the other half of cases, the primary systemic malignancy is discovered subsequent to the diagnosis of BDUMP, as was the case in our report. BDUMP is associated with multiple visceral cancers including lung, colon, pancreatic, gallbladder, ovarian, uterine, and cervical. Gynecologic cancers (i.e. ovarian carcinoma) are the most prevalent systemic tumors associated with BDUMP in women. In men, the most frequent causative cancers are pancreatic and lung. BDUMP has no known gender predilection (1).

Pathogenesis

The pathogenesis of BDUMP is currently unknown; however, a feature that may point to its pathogenesis is the development of hyperpigmentation at other, non-ocular sites in the body. Approximately 26% of BDUMP patients have pigmented lesions of the skin and mucous membranes. In addition, acanthosis nigricans is associated with many of the same visceral adenocarcinomas that occur with BDUMP. As such, one hypothesis for the pathogenesis of BDUMP is that the primary non-ocular tumor releases endocrine factors which lead to proliferation of uveal melanocytes and systemic hyperpigmentation. This idea has biologic plausibility, because

the cancers known to cause BDUMP are tumors that are well-known to cause other paraneoplastic syndromes through factor release. In addition, certain BDUMP patients have simultaneous development of paraneoplastic states such as hypercoagulability and hypercalcemia (1).

Another hypothesis for the pathogenesis suggests that anti-retinal autoantibodies may be in part responsible for destruction of photoreceptors (1,3).

Diagnosis and Testing

Gass in 1990 (6) described the five cardinal ocular signs that accompany vision loss in patents with BDUMP:

- Multiple, round or oval, subtle, red patches at the level of the retinal pigment epithelium in the posterior fundus
- A striking pattern on fluorescein angiography of multifocal areas of early hyperfluorescence corresponding with these patches
- Development of multiple, slightly elevated, pigmented and nonpigmented uveal melanocytic tumors, as well as evidence of diffuse thickening of the uveal tract
- Exudative retinal detachment
- Rapid progression of cataracts

The differential for BDUMP includes choroidal metastases of skin melanoma and choroidal nevi associated with neurofibromatosis I (7). BDUMP should be considered in the differential of patients with pigmented fundus lesions, especially when presenting bilaterally, with bilateral vision loss, and a history of non-ocular tumors (2).

Though BDUMP has a clinical presentation similar to uveal melanoma, the two may be easily distinguished because choroidal melanoma is typically focal and dome or mushroom-shaped. Diffuse choroidal melanoma is more similar to BDUMP, but does not involve the entire uveal tract and is unilateral (1).

Management and Prognosis

The presentation of bilateral vision loss is antecedent to the discovery of a primary non-ocular tumor in nearly half the cases (2). The vision in BDUMP patients typically progresses to legal blindness within 1 year of presentation. Survival following the diagnosis of BDUMP is between 8 and 24 months (1,2) and the majority die within three years (7). Death typically occurs due to complications from the underlying systemic malignancy. Management of BDUMP must include extensive workup for occult malignancy and repeated screenings until the underlying malignancy is found.

In the past, treatment for BDUMP involved bilateral enucleation due to the concern for uveal melanoma. External beam radiation has also been used in the past (due to concern for melanoma) without any significant improvement. These therapies are no longer employed. Other therapies including drainage of subretinal fluid and corticosteroids have also been attempted, but failed to demonstrate any significant improvement. (1,3,7,8,10) There is one case in the literature of a patient's exudative retinal detachment improving with periorbital corticosteroid injection (9) but that treatment modality has not been replicated again in the literature.

More recently, plasma exchange (PE) has been suggested as a potential therapeutic approach for BDUMP. Although the mechanism of BDUMP is not yet known, several reports have shown improved visual acuity, resolution of subretinal fluid, and decreased choroidal thickening with the use of PE (3,7,8). Unfortunately, frequent courses of plasma exchange are associated with the possibility of immunosuppression and relapse after PE is completed. Because it is thought by some that BDUMP represents an autoimmune response to cancer, suppression of the response may trigger cancer growth (7,8).

There is some controversy as to the benignity of the melanocytic proliferation seen in BDUMP. Most cases report benign-appearing spindle-shaped cells on histopathology; however, some case reports show the presence of enough malignant melanocytes for a diagnosis of melanoma (4). One study done by Margo (5) showed a lack of p53 immunoreactivity after immunostaining of eight eyes with BDUMP. Since p53 overexpression is common in malignancies such as uveal melanoma, it appears that the melanocytic proliferation in BDUMP may be through a different mechanism. There is no report in the literature of metastasis of uveal tumors seen in BDUMP.

Our case is atypical, due to the preservation of good visual acuity for months after the diagnosis. The use of anti-VEGF agents has not been reported in the literature for the treatment of exudative RD in BDUMP. Consequently, it is not known whether the anti-VEGF therapy the patient received for his exudative AMD may have improved the outcome for his BDUMP. Indeed, his bilateral macular edema, subretinal fluid, and irregularly elevated RPE may have actually been the earliest manifestations of his BDUMP rather than manifestations of exudative AMD.

Diagnosis: Bilateral diffuse uveal melanocytic proliferation (BDUMP)

EPIDEMIOLOGY	SIGNS
• Extremely rare; only ~31 reported cases in the literature • No gender preference • Most common causative malignancy is ovarian carcinoma in women and pancreatic or lung cancer in men	• Multiple subtle red patches at the level of the retinal pigment epithelium in the posterior pole • Multifocal areas of early hyperfluorescence on fluorescein angiography corresponding to the patches • Development of multiple slightly elevated, pigmented and nonpigmented uveal melanocytic tumors with diffuse uveal tract thickening • Exudative retinal detachment • Rapid progression of bilateral cataracts
SYMPTOMS	TREATMENT
• Rapidly-progressive vision loss • Symptoms associated with systemic non-ocular malignancy possible, but not necessary	• Extensive workup for systemic non-ocular malignancy and appropriate treatment of that malignancy • Plasma exchange has been shown to improve visual acuity, resolve subretinal fluid, and decrease choroidal thickening

Differential Diagnosis

- Choroidal melanoma
- Skin melanoma metastases to the choroid
- Choroidal nevi associated with neurofibromatosis 1
- Multiple congenital hypertrophy of the retinal pigment epithelium (CHRPE) lesions associated with Gardner syndrome

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University of Iowa Carver College of Medicine
Department of Ophthalmology & Visual Sciences
200 Hawkins Dr.
Iowa City, IA 52242