Melanoma-associated retinopathy, a form of paraneoplastic retinopathy associated with metastatic cutaneous or ocular melanoma, is suspected to be caused by antiretinal antibodies. Patients with melanoma-associated retinopathy typically present with a sudden onset of shimmering, flickering, or pulsating photopsias, visual field defects, progressive visual loss, and/or night blindness.1

Electrophysiologic testing reveals abnormalities with melanoma-associated retinopathy, which are diagnostic even in the absence of clinical fundus findings. Herein we describe a case of a patient with melanoma-associated retinopathy who was treated with the immune checkpoint inhibitor pembrolizumab for metastatic melanoma and who presented with “smokelike” vision, photopsias, nystagmata, and, importantly, fundus findings atypical of melanoma-associated retinopathy or paraneoplastic vitelliform retinopathy.

Report of a Case

A patient was referred with a 7-month history of nystagmata and smokelike vision in both eyes and atypical fundus findings. The patient had received a diagnosis of malignant melanoma (stage IIIa) of the back 19 months prior to presentation, which had been surgically excised but recurred 6 months after surgery. The melanoma was metastatic to lymph nodes, both lungs and the brain. The brain was treated with the use of a gamma knife 6 months later. Concurrently, the patient first experienced visual symptoms and was seen by an ophthalmologist, who did not report any fundus changes; however, visual fields were notably abnormal. Shortly thereafter, the patient started receiving pembrolizumab with an excellent response in the brain and elsewhere. However, night vision worsened, and the patient noticed smokelike vision. A follow-up examination at the outside ophthalmologist’s office 2 months prior to referral and first presentation to us revealed previously undescribed, subtle fundus lesions in the right eye.

On presentation, best-corrected visual acuity was 20/20 OD and 20/25 OS, with no afferent pupillary defect. The results of slitlamp biomicroscopy and applanation pressures were normal. A moderate degree of vitritis was noticed in both eyes. Both optic nerves had a cup to disc ratio of 0.1 with slightly blurred temporal disc margins and some pallor that was more obvious in the left eye. The macula appeared bilaterally normal. In the retinal periphery, multiple choriretinal scars and pigment clumps were present that were much more abundant and extensive in the right eye than the left eye (Figure 1 and Figure 2). On fluorescein angiograms, these lesions showed early and late hyperfluorescence consistent with “window defects” caused by atrophy of the retinal pigment epithelium and hypofluorescent spots caused by pigment clumps (Figure 3). Spectral-domain optical coherence tomographic B-scans of the macula revealed no abnormalities in either eye. Humphrey perimetry and Goldmann perimetry (ie, visual field testing) were performed, revealing pronounced...
Figure 1. Fundus Photography and Optical Coherence Tomography of Fundus Lesions in the Right Eye

Color fundus photography montage (A-C) and infrared en face (D and F) and spectral-domain optical coherence tomographic (SD-OCT) B-scans (Spectralis HRA+OCT, Heidelberg Engineering) (E and G) of the patient's right eye. Chorioretinal lesions can be seen in the peripheral retina. The green arrows indicate the location of the SD-OCT B-scans.
scotomata in the central visual field of both eyes, as well as advanced visual field constriction. The electroretinogram showed a predominant b-wave loss and nondetectable, isolated, dark-adapted rod b-wave response, characteristically found in patients with melanoma-associated retinopathy. The patient tested positive for antiretinal autoantibodies against the 23-kDa (not reactive to recoverin), 30-kDa (carbonic anhydrase II), 34-kDa, 40-kDa (aldolase), 42-kDa, 46-kDa (enolase), and 136-kDa proteins. Based on the patient’s history, clinical findings, and electroretinographic findings, a diagnosis of melanoma-associated retinopathy was made. The decision was made to continue the pembrolizumab treatment. During 15 weeks of follow-up, best-corrected visual acuity was stable in both eyes. The chorioretinal lesions did not change in size, but a gradual loss of pigmentation was noted.

Melanoma-Associated Retinopathy
Melanoma-associated retinopathy is part of the spectrum of autoimmune retinopathies, a group of rare diseases often characterized by the presence of antiretinal antibodies. The disease was first postulated to be paraneoplastic by Berson and Lessell. The autoimmune response in melanoma-associated retinopathy is often directed mainly against bipolar cells, although antibodies against a variety of different antigens in the retina have been identified in the serum of patients with melanoma-associated retinopathy. Vitritis, although not a necessary finding for the diagnosis of melanoma-associated retinopathy, has been described in the literature. Although for many of the patients with melanoma-associated retinopathy, the fundus appears normal, depigmentation with no to little pigment deposition, optic disc pallor, and attenuation of the retinal vessels have been reported. Borkowski et al described 2 cases of melanoma-associated retinopathy with unusual fundus findings. One of the patients had small, deep, white, round lesions on the posterior pole involving the retinal pigment epithelium and the outer retina (prior to advent of optical coherence tomography), whereas the other patient had diffuse loss of pigment in the fundus and well-

Figure 2. Fundus Photography and Optical Coherence Tomography of Fundus Lesions in the Left Eye

Color fundus photography montage (A and B) and infrared en face (C) and spectral-domain optical coherence tomographic (SD-OCT) B-scan (D) of the patient’s left eye. Note the depigmented lesions with pigment clumping in the center in the enlarged segment of the color fundus photograph (B). The green arrows indicate the location of the SD-OCT B-scan.
circumscribed chorioretinal atrophic lesions throughout the posterior pole and midperiphery. This patient, however, developed fundus changes dissimilar to the ones described in Borkowski et al.4 Multiple scars, mostly atrophic, were seen that differed from the lesions previously described by their location (retinal periphery with preservation of the macula) and by the presence of pigment clumps (Figures 1 and 2). The lesions also differed from the paraneoplastic vitelliform lesions seen in patients with metastatic melanoma.5

Pembrolizumab

The development of novel drugs known as checkpoint inhibitors has improved survival rates among patients with metastatic melanoma.6-8 It has been known that tumor cells evade immune recognition by different mechanisms, including immunosuppression, by expression of specific proteins such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed death ligand-1 (PD-L1). PD-L1 binds to programmed death 1 (PD-1), which is present on the surface of activated T cells, thereby downregulating their activity. Checkpoint inhibitors are immunomodulatory antibodies that enhance the activity of the immune system by blocking these proteins. Pembrolizumab and nivolumab, both of which are monoclonal anti–PD-1 antibodies, have been shown to have marked clinical efficacy and have recently been approved by the US Food and Drug Administration. Despite invaluable clinical benefits, careful patient care is required because the disinhibition of the immune system can cause a number of potentially life-threatening inflammatory adverse effects, known as immune-related adverse events. The most common immune-related adverse event reported among patients treated with checkpoint inhibitors is skin toxicity. Other adverse effects include gastrointestinal symptoms such as diarrhea, as well as hepatotoxicity or endocrine toxicity. Ocular adverse effects have been reported as well, often associated with damage to other organ systems.9-12 Audemard et al13 reported a case of melanoma-associated retinopathy and melanoma-associated vitiligo in a 70-year-old female patient whose skin depigmentation and visual acuity worsened when she received treatment with ipilimumab. They reported focal vessel dilatation and mild perivascular sheathing and leakage on fluorescein angiograms.13 However, the lesions did not resemble the ones seen in our patient.

These case reports illustrate the necessity of a close and thorough follow-up of patients treated with immune checkpoint inhibitors. Particularly for patients with a predisposition to autoimmunity, there is concern that treatment with checkpoint inhibitors can trigger the exacerbation and onset of clinically active autoimmune disease and associated complications. This may be what occurred in our patient, presenting a clinical resemblance to idiopathic multifocal choroiditis.

The fundus lesions found in this patient are not typical of melanoma-associated retinopathy or paraneoplastic vitelliform retinopathy, which is also seen with melanoma. It is possible that these lesions are an atypical form of melanoma-associated retinopathy. Another plausible hypothesis, based on the chronology of the onset of symptoms and sequential fundus lesions, is that the patient developed melanoma-associated retinopathy initially and only later developed the fundus findings, possibly caused by “unleashed” autoimmunity triggered by the treatment with pembrolizumab. Seemingly, this would indicate the likely presence of antiretinal antibodies before the onset of pembrolizumab treatment. The retinal lesions were not present when the patient first complained of visual symptoms, and thus the chorioretinal lesions may have been related to the use of pembrolizumab.
REFERENCES


