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Paraneoplastic acute exudative polymorphous vitelliform maculopathy improved with intravitreal methotrexate

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ABSTRACT

Purpose: To describe a case of acute exudative polymorphous vitelliform maculopathy (AEPVM) treated with intravitreal methotrexate.

Observations: A 58-year-old man with a history of metastatic melanoma developed paraneoplastic acute exudative polymorphous vitelliform maculopathy, refractory to oral prednisone, intravitreal bevacizumab and intravitreal preservative-free triamcinolone. Improvement in vision and resolution of subfoveal fluid was later seen after intravitreal methotrexate therapy.

Conclusions and Importance: AEPVM is a rare and poorly understood retinal disorder that may be idiopathic or may manifest in patients with malignancies. The pathogenic process is thought to be an attack directed against the retinal pigment epithelium (RPE) and photoreceptors. Intravitreal methotrexate may provide benefit when treating AEPVM, especially when trials of steroids and anti-VEGF medications have failed.

1. Introduction

AEPVM was first described by Gass et al. in two healthy individuals.[1] A paraneoplastic form has since been described in eight patients with various cancers including metastatic melanoma and carcinomas of the lung, breast, or colon.[2–4] AEPVM is characterized by bilateral vision decline from multifocal, subretinal, vitelliform macular lesions associated with multiple serous retinal detachments.[1,2] The pathophysiology is not fully understood, although an autoimmune or paraneoplastic process directed against the retinal pigment epithelium and photoreceptors has been postulated.[2] Cases have been reported showing improvement in vision in the idiopathic form from systemic steroids and in the paraneoplastic form from intravitreal aflibercept.[1,4,5]

2. Report of a case

A 58 year old male was referred in September 2018 for a 3-week history of blurry vision in both eyes (OU). He was diagnosed with cutaneous melanoma in May 2015. He was found to have subsequent metastatic disease to the lung and liver in July 2017. He then started a 9 month course of pembrolizumab before discontinuation due to drug-induced colitis around March 2018. On September 7, 2018, trametinib and dabrafenib were started for the melanoma. The patient reported that the blurry vision began within 1–2 weeks prior to the initiation of trametinib and dabrafenib. After persistent blurring he was referred for ophthalmologic assessment.

At his initial presentation to us on September 21, 2018, his Snellen visual acuity was 20/60 in the right eye (OD) and 20/30 in the left eye (OS). Exam revealed multiple oblong, yellow-white, subretinal lesions within the macula OU. Fluorescein and indocyanine angiography showed very faint hyperfluorescent linear lesions and numerous faint multifocal hypercyanescent lesions in the macula (Fig. 1). These lesions were hyperautofluorescent on fundus autofluorescence (Fig. 1). Optical coherence tomography showed numerous areas of serous retinal detachments mixed with subretinal solitary deposits and intraretinal cystic fluid (Fig. 1).

A complete serologic work up was initiated showing no obvious infectious or non-infectious causes for these findings. Oral prednisone 60 mg daily was started with a weekly 10 mg taper. At three-week follow-up, the patient was on prednisone 30 mg daily and reported no improvement in vision. The OCT showed minimally improved subretinal fluid OU (Fig. 2). On October 11, 2018, a trial of intravitreal bevacizumab and preservative-free triamcinolone was given OD and the prednisone taper was continued. Two weeks later, the patient still

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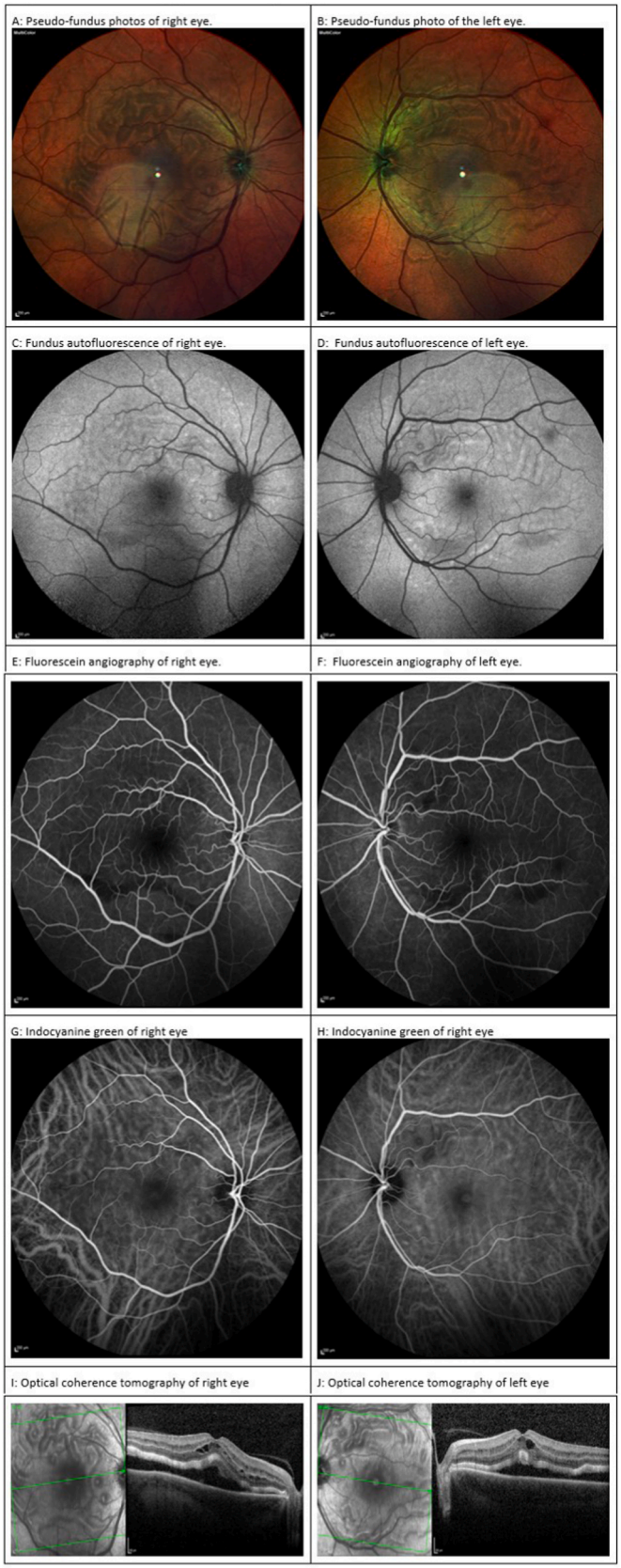

(caption on next column)

Fig. 1. Pseudo-fundus photos (A, B) showed multiple subretinal deposits and vitelliform lesions localized mainly around the temporal superior and inferior arcades and within the macula of both eyes. Fundus autofluorescence (C, D) showed these lesions to be hyper-autofluorescent centrally with a surrounding halo of hypo-autofluorescence. Fluorescein angiography (E, F) showed late linear areas of hypofluorescence corresponding to areas of solid subretinal deposits. Indocyanine green angiography (G, H) showed these lesions to be hypercyanescent. Optical coherence tomography (I, J) showed numerous areas of serous retinal detachment with foveal involvement and intraretinal cystic fluid in both eyes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reported no subjective improvement, and the OCT continued to show a large amount of subretinal fluid under the fovea OU (Fig. 2). Observation was recommended to see if the continued oncologic treatments would improve his macular fluid. Six weeks later, the patient reported considerable improvement in his systemic tumor burden on trametinib and dabrafenib. His vision remained unimproved OD. OCT macula showed persistent subretinal fluid OU (Fig. 2). On December 6, 2018, a trial of intravitreal methotrexate 400 mcg OD was offered and the patient accepted. He followed up 3 months after with reports of improvement in vision after the injection. Vision OD improved from 20/60 to 20/30 while the untreated left eye stayed stable around 20/25. OCT revealed almost complete resolution of subfoveal fluid OD but only mild improvements OS (Fig. 2). The patient reported that his melanoma continued to be controlled on systemic immunotherapy.

3. Discussion

We report a case of paraneoplastic acute exudative polymorphous vitelliform maculopathy (AEPVM) improved from intravitreal methotrexate therapy. AEPVM is a rare disease characterized by acute vision changes and vitelliform retinal lesions and associated with multiple serous retinal detachments.[2] The most common primary neoplasm associated with AEPVM is cutaneous or choroidal melanoma, though association with other carcinomas has also been documented.[6] The main accepted hypothesis for the pathogenesis of AEPVM is RPE dysfunction causing an overload of lipofuscin seen on autofluorescence. Autoantibodies against the primary tumor may cross-react with antigens found on RPE cells.[7]

In our patient, oral steroids along with intravitreal bevacizumab and triamcinolone were tried but failed to show improvement. However, intravitreal methotrexate not only improved the vision in the right eye but also almost completely resolved the subretinal fluid when compared to the untreated left eye which still showed large amounts of subretinal fluid on OCT. We therefore submit that the addition of intravitreal methotrexate should be considered in helping to expedite the resolution of subretinal fluid in cases of paraneoplastic AEPVM in conjunction with medically treated and controlled systemic metastatic disease via its concentrated anti-inflammatory effects locally. We think both factors are likely important in this regard, and it may be that the other anti-inflammatory agents may have been beneficial if given in the time course of this patient's regimen of immunotherapy, with better control of tumor burden realized at the time of methotrexate administration than the formerly given medications.

There can be consideration given to the fact that the patient was formerly on pembrolizumab as well which has been seen to cause inflammatory changes in the eye,[8] and has also been a medication used during another documented case of AEPVM.[9] The authors of this case describe a patient developing AEPVM days after starting vemurafenib, which was subsequently stopped due to ocular symptoms, all the while on pembrolizumab among other forms of therapy. These authors also considered whether pembrolizumab could be a cause of the condition, however the patient had been on this therapy for some time and the condition improved over four months while still on the medication, which should seemingly argue against it being causative. However in

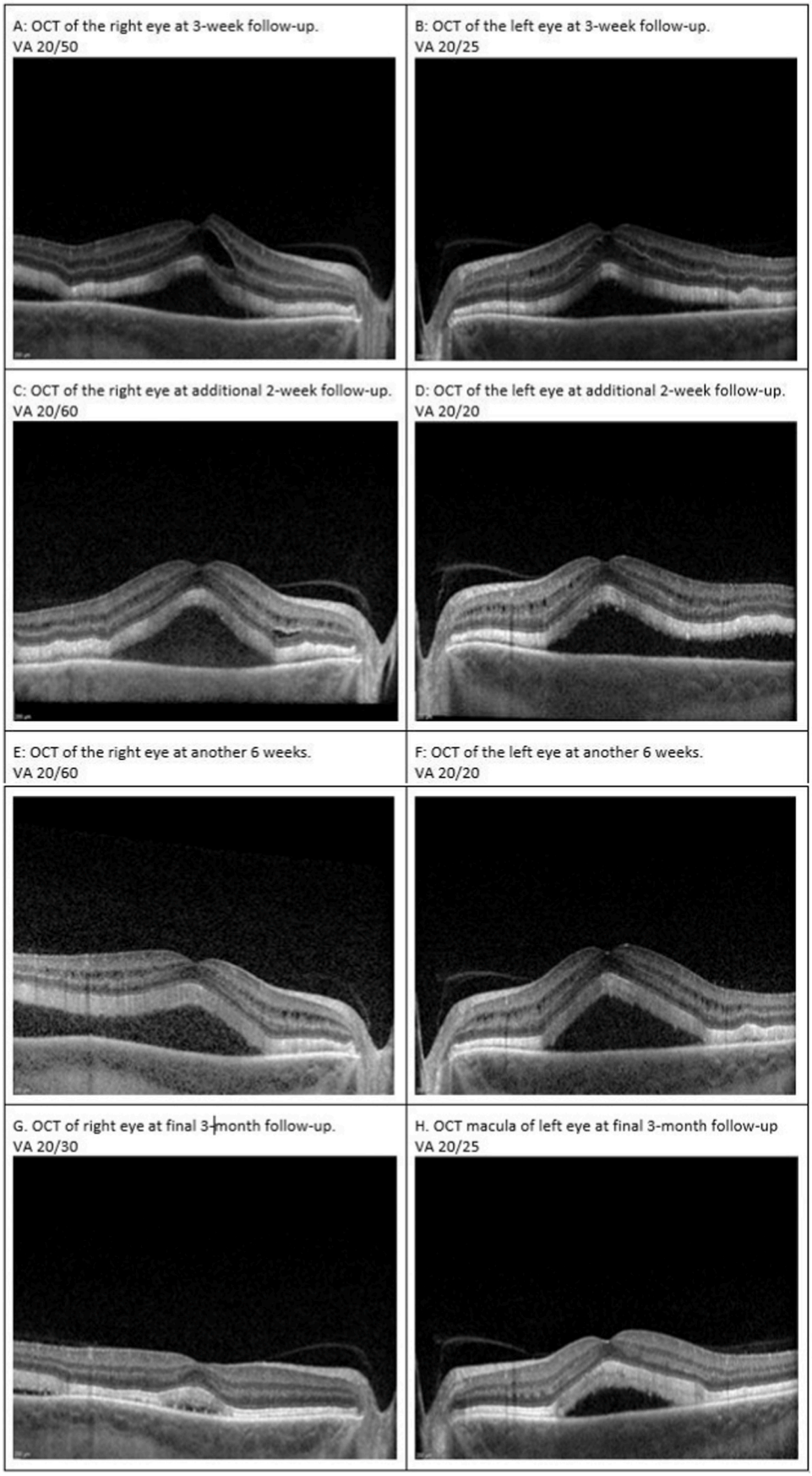

Fig. 2. OCT of the macula showed no significant change with oral prednisone at 2-week follow-up (A, B). Subsequent trial of intravitreal bevacizumab and preservative-free triamcinolone in the right eye also showed no improvement at the next 3-week follow-up (C). Left eye had persistent fluid without further treatment (D). Observation while the patient was treated systemically for his metastatic melanoma also showed no improvement after an additional 6 weeks (E, F). Ultimately, intravitreal methotrexate showed a near complete resolution of subfoveal fluid in the right eye at the final 3-month follow-up (G) compared to the mild improvement in the untreated left eye (H).

their case, tumor burden worsened and the patient ultimately died one month after ocular symptoms resolved, so it is possible this case and ours may represent unique entities. We believe it is unlikely that pembrolizumab contributed to our patient's findings as the medication was discontinued six months prior to symptom onset, and our patient also did not respond to initial attempts at anti-inflammatory therapy, which have been shown to improve other forms of pembrolizumab-associated ocular changes.

In summary, we present a patient with metastatic melanoma who manifested findings suggestive of AEPVM that showed significant improvement in vision and subretinal fluid through adjuvant intravitreal methotrexate therapy along with medically-induced control of his systemic malignancy.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain and personal identifying information.

Disclosures

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Authorship

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

Declaration of competing interest

I confirm that none of the authors have any conflicts of interest in the publication of this manuscript. There are no financial disclosures and no funding or support was received for this study.

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