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An atypical case of acute posterior multifocal placoid pigment epitheliopathy with recurrent strokes

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ABSTRACT

Purpose: To report an atypical case of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) with central nervous system (CNS) vasculitis and recurrent strokes.

Observations: A 57 year-old female presented with APMPPE after a febrile illness and rash. She developed an acute infarct on magnetic resonance imaging. Computed tomography angiography of the cerebral vasculature was normal. Cerebrospinal fluid (CSF) analysis and an extensive serum lab workup were also unremarkable. She was treated with high-dose corticosteroids and eventually transitioned to methotrexate. A month after being on treatment she developed a second stroke. A cerebral angiogram was obtained and did not show evidence of CNS vasculitis. The methotrexate was eventually stopped and the prednisone was tapered. Approximately 3 months later she developed a third stroke and worsening APMPPE-associated maculopathy in both eyes. She was eventually started on oral cyclophosphamide.

Conclusions & importance: Although rare, CNS vasculitis is a known complication of APMPPE. This case is atypical given the development of multiple recurrent strokes, lack of inflammatory evidence on CSF analysis, and normal imaging of the cerebral vasculature. This report highlights the need for a high level of clinical suspicion for CNS vasculitis with APMPPE despite noncontributory cerebral angiographic imaging and normal CSF analysis.

1. Introduction

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE), first described by Gass[1] in 1968, is a rare but self-limited posterior uveitis that affects the choriocapillaris, retinal pigment epithelium (RPE), and outer retina. It occurs primarily in otherwise healthy young adults, affecting men and women equally. Both eyes are affected in either a simultaneous or sequential fashion.[2,3]

Most patients present with an acute painless decrease in central vision. Large, creamy yellow-white placoid lesions are seen in the posterior pole. These lesions fade and are replaced by geographic RPE changes over the course of weeks. In the acute setting, fluorescein angiography and indocyanine green angiography often show early hypofluorescence related to choroidal nonperfusion. The visual prognosis is often favorable with most patients achieving a final visual acuity of approximately 20/40 or better.[2–4]

The pathophysiology of APMPPE is not fully understood but may involve a primary vasculitis of the choroid. The inflammation disrupts choroidal perfusion and the subsequent ischemia damages the overlying RPE and outer retina.[5] It has been proposed that the inflammatory process could be due to a delayed-type hypersensitivity reaction. This theory has been supported by the presence of a flu prodrome in up to 50% of patients and the association with human leukocyte antigens (HLA) DR2 and B7.[6]

Neurologic involvement is uncommon but can include cerebrospinal fluid (CSF) pleocytosis, headaches, cerebral vasculitis, aseptic meningitis, meningoencephalitis, cranial nerve six palsy, optic neuritis, hearing loss, cavernous sinus thrombosis, and peripheral neuropathy.[5]

2. Case report

A 57 year-old female presented with headaches and a central scotoma in the right eye after a febrile illness with erythema multiforme. Incidentally, the patient reported that her visual symptoms began two days after viewing the solar eclipse with appropriate eye protection. Snellen visual acuity was 20/30 in the right eye. Fundus examination, fluorescein angiography, and spectral domain ocular coherence tomography (SD-OCT) were consistent with a diagnosis of APMPPE (Fig. 1,

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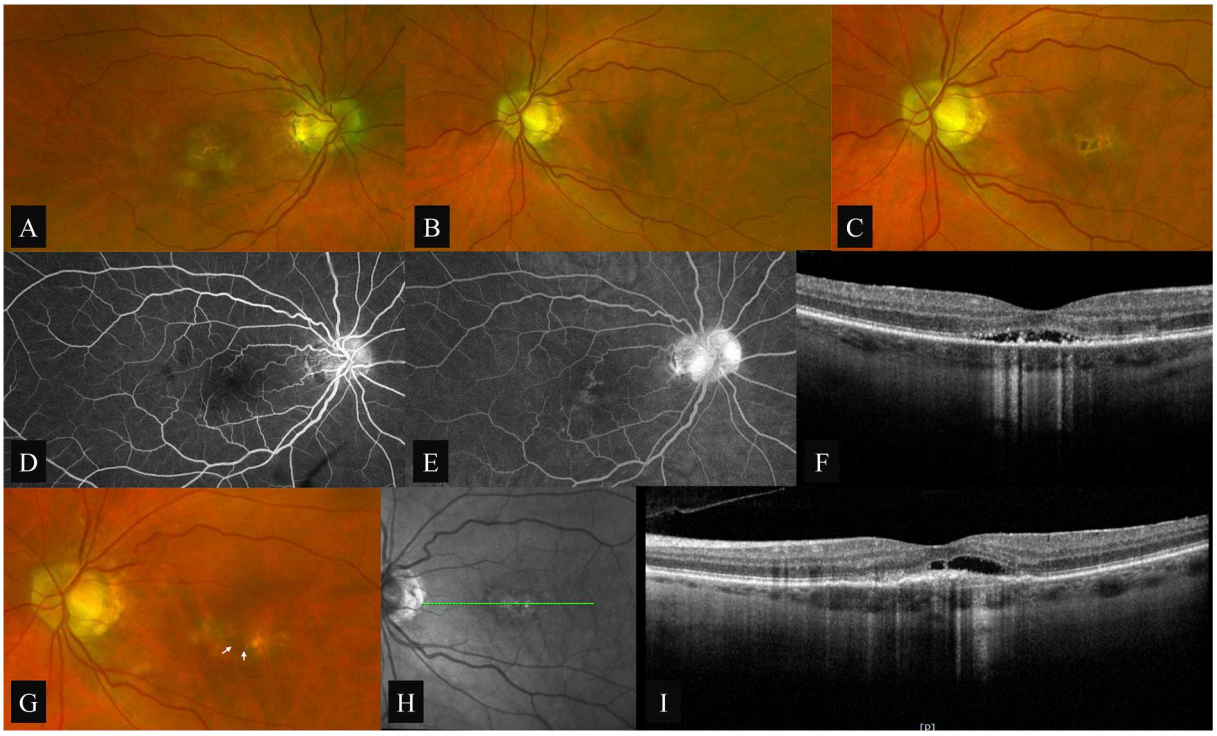

Fig. 1. Clinical presentation (A–F) with recurrence 9 months later (G–I). Fundus photographs of the right (A) and left eye (B) at initial presentation. In the right eye there are multiple creamy, yellow-white placoid lesions within the macula. The left eye is not yet affected. Two weeks later the left eye becomes involved (C). Fluorescein angiogram (FA) of the right eye at initial presentation shows blockage in the early phase (D) followed by late staining (E). Spectral domain ocular coherence tomography (SD-OCT) of the right eye at initial presentation (F) demonstrates subretinal fluid and ellipsoid zone disruption. Fundus photograph (G), near-infrared photography (H), and SD-OCT (I) of the left eye 9 months later showing recurrence with small subretinal hemorrhage (G, arrowheads) and new subretinal fluid (I). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

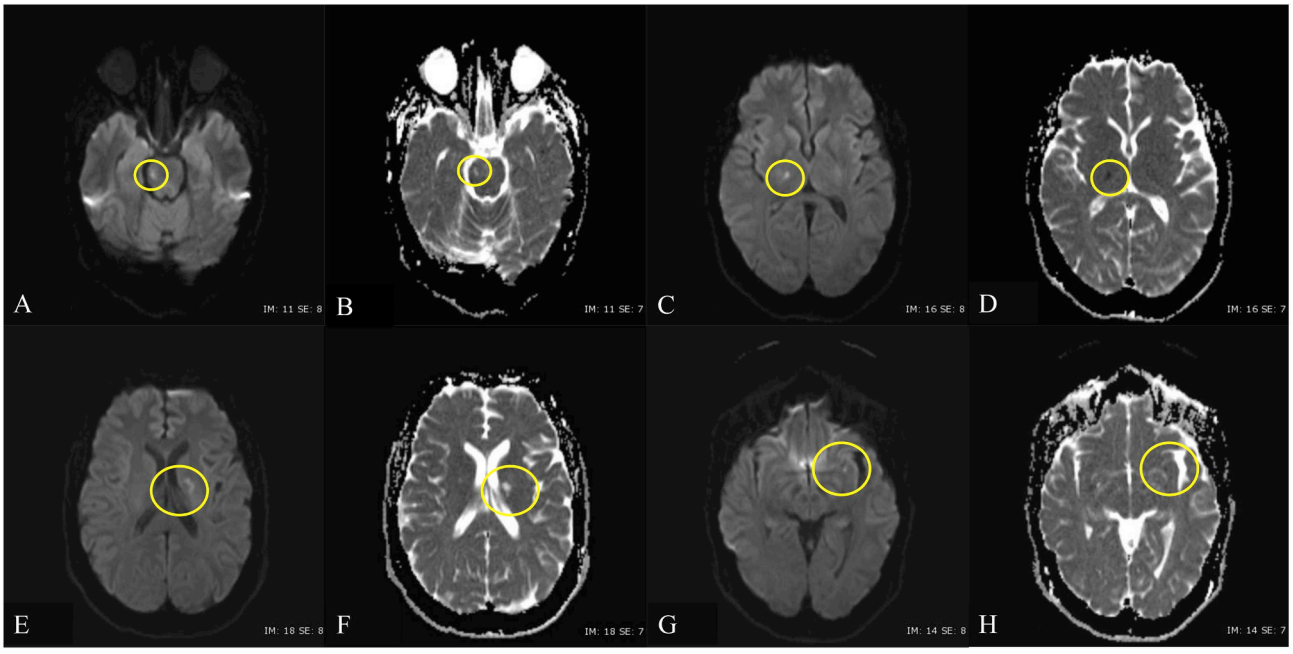

Fig. 2. Magnetic resonance imaging (MRI) - initial (A-D) and follow up (E-H). A focal, chronic infarct in the right lateral aspect of the upper pons appears hyperintense on both diffusion-weighted imaging (DWI) (A) and apparent diffusion coefficient (ADC) map (B). An acute infarction in the right thalamus is demonstrated by the combination of a hyperintense signal on DWI (C) and marked hypointense signal on ADC (D). Follow up imaging shows interval development of two new infarcts (E-H). A chronic infarct is seen within the genu and anterior limb of the left internal capsule (E–F). It appears hyperintense on both DWI (E) and ADC map (F). A more acute punctate infarct is seen within the left anterior subinsular region (G–H). The combination of hyperintense signal on DWI (G) and hypointense signal on ADC (H) indicates an acute process.

Table 1
Recurrent strokes in APMPPE-associated CNS vasculitis.

Case Report	Year Reported	Gender	Age (years)	Number of Strokes	CSF Studies	Neuroimaging
Smith et al.[10]	1983	M	25	2	WBC 100 cells/μL Protein 30 mg/dL	**CT with contrast**: right occipital infarct **Cerebral angiogram**: segmental narrowing, occlusion of right posterior cerebral artery
Weinstein et al.[12]	1988	M	23	2	WBC 19 cells/μL Protein 33 mg/dL	**MRI**: hemorrhagic infarct of right occipital lobe, infarct of left basal ganglia **Cerebral angiogram**: multiple arterial abnormalities suggestive of arteritis
Comu et al.[11]	1996	F	23	2	WBC 60 cells/μL Protein 45 mg/dL	**MRI #1**: bilateral parieto-occipital, left basal ganglia, splenium infarcts **MRI #2 (during prednisone taper)**: right parietal infarcts **Cerebral angiogram**: normal
O'Halloran et al.[9]	2001	M	16	2	WBC 28 cells/hpf Protein 85 mg/dL IgG 5.7 mg/dL	**MRI #1**: meningeal enhancement, right frontal and parietal lobe encephalomalacia **MRI #2**: biparietal hemorrhages **Cerebral angiogram**: superior sagittal sinus thrombosis
O'Halloran et al.[9]	2001	F	38	4	IgG index 0.77 Oligoclonal bands 4	**MRI**: enhancing lesion at left midbrain-pontine junction, two small periventricular white matter T2 lesions
Bugnone et al.[15]	2006	F	20	2	Not performed	**MRI**: acute infarct in head of right caudate nucleus, chronic infarct in corpus callosum
Luneau et al.[7]	2009	M	43	2	WBC 253 cells/mm^3 Protein 57 mg/dL	**MRI #1**: ischemia in the distribution of right middle cerebral artery **MRI #2 (after cyclophosphamide discontinued)**: new parietal infarct **Cerebral angiogram**: mild stenosis and dilation of branches of right middle cerebral artery and anterior cerebral artery
Matamala et al.[13]	2013	M	15	2	WBC 13 cells/mm^3 Protein 21 mg/dL	**MRI #1**: bilateral ischemic lesions in lenticular nuclei and corona radiata **MRI #2**: ischemic lesion in head of right caudate nucleus **Cerebral angiogram**: diffuse stenosis of intracranial arteries
Tsuboyama et al.[14]	2018	M	64	2	Not performed	**MRI #1**: bihemispheric multifocal infarcts **MRI #2**: extensive multifocal infarcts **Cerebral angiogram**: arterial beading of posterior cerebral arteries, superior cerebellar arteries, and middle cerebral arteries; mild stenosis of right vertebral artery
Tsuboyama et al.[14]	2018	M	55	2	WBC 21/hpf Protein 40 mg/dL	**MRI #1**: right cerebellar infarcts **MRI #2 (during steroid taper)**: bilateral basal ganglia and internal capsule infarcts **Cerebral angiogram**: irregularities in right proximal vertebral artery and superior cerebellar artery; aneurysm of left anterior cerebral artery
Present case	2019	F	57	3	No abnormalities	**MRI #1**: acute right pons infarct **MRI #2**: right thalamocapsular infarct **MRI #3**: acute punctate infarct in left subinsular white matter, remote infarct in left internal capsule **CTA**: normal **Cerebral angiogram**: normal

A-B, D-F).

Approximately 2 weeks later the left eye became involved (Fig. 1, C). Subretinal fluid was present on SD-OCT. She received intravitreal bevacizumab and triamcinolone acetonide. Magnetic resonance imaging (MRI) showed a small subacute infarct in the right pons (Fig. 2, A-B). Computed tomography angiography (CTA) was unremarkable. CSF analysis did not show a leukocytic pleocytosis, elevated protein level, or evidence of viral meningitis. An extensive autoimmune and infectious work-up was unremarkable except for a mildly elevated C-reactive protein. The diagnostic work-up included antineutrophil cytoplasmic antibodies, antinuclear antibody, angiotensin converting enzyme, and chest x-ray. Serologies and CSF analysis were performed for herpes simplex, varicella zoster, and cytomegalovirus. Of note the patient was HLA DR2 negative.

She was treated with a three-day course of intravenous solumedrol followed by high-dose oral prednisone. A month after being on treatment the patient developed acute left-sided paresthesia and was found to have a right thalamic stroke (Fig. 2, C-D). She was restarted on high-dose steroids and transitioned to methotrexate as a slow steroid taper was initiated. A cerebral angiogram was obtained a month later and did not show evidence of small- or large-vessel vasculopathy. The methotrexate was eventually stopped due to poorly tolerated side effects and the prednisone was slowly tapered.

Three months after being off all immunosuppressants a routine MRI was performed which showed two new subclinical infarcts (Fig. 2, E-H). Approximately 2 weeks later the patient developed worsening APMPPE-associated maculopathy in both eyes. Fundus examination and OCT demonstrated a small submacular hemorrhage with new subretinal fluid in the left eye (Fig. 1, G-I). The left eye was treated with intravitreal bevacizumab and triamcinolone acetonide. High-dose steroids were restarted and the patient was eventually transitioned to oral cyclophosphamide.

3. Discussion

CNS vasculitis is a rare complication of APMPPE. A recent review by Algahtani et al.[5] found 28 documented cases of APMPPE-associated cerebral vasculitis. Recurrent strokes in the setting of APMPPE is extremely uncommon.[7]

The case presented here is atypical in a number of ways. First, our patient was a 57 year-old female. While APMPPE affects men and women equally, neurologic involvement has been found to be more common in men with an average age of approximately 30 years.[5]

Secondly, the CSF analysis did not show a lymphocytosis or elevated protein level. In the review by Algahtani et al.,[5] lumbar puncture was performed in 64.3% of cases and was abnormal (either pleocytosis or elevated protein) in 77.8%. Given the presence of a subacute pons infarct on MRI and the fact that lumbar puncture was performed early on in the work-up of our patient, we would have expected an abnormal CSF.

Third, the neuroimaging performed in this case did not show evidence of cerebral vasculopathy. The initial CTA was likely not sensitive enough to identify small vessel vasculitic changes. For this reason conventional angiography is often needed.[8] Catheter cerebral

angiography has been abnormal in many cases of APMPPE-associated cerebral vasculitis.[5,7,9–14] In a review by Luneau et al.[7] 90% of the angiograms showed a small vessel vasculopathy. However, nearly half of the reviewed cases did not document an angiogram so those findings are unknown. Despite the greater sensitivity of catheter angiography, its ability to detect disease in vessels less than 500 μm may still be limited.[16] This is highlighted by the well-documented cases of primary CNS vasculitis with a positive brain biopsy but normal angiogram.[17] The angiogram in our case was performed a month after the second stroke so the diagnostic yield may have been limited by the month of immunosuppressive therapy.

Finally, our case adds to the handful of documented cases of recurrent cerebral infarction with APMPPE (Table 1).[7,9–15] Consistent with other reported cases, our patient developed a new infarct during steroid tapering or de-escalation of immunosuppressive therapy. Most cases of recurrent cerebral vasculitis have documented an abnormal CSF.[7,9–14] Furthermore, only one other case of recurrent stroke has reported a normal cerebral angiogram.[11]

Complications from APMPPE-associated cerebral vasculopathy can cause long-term disability or even be fatal.[5] In a patient with APMPPE and evidence of cerebral infarction on MRI, there should be a high clinical suspicion for CNS vasculitis. An underlying vasculitic process should not be ruled out on the basis of a normal CSF composition and negative CTA. Although more invasive, a catheter cerebral angiogram may be useful early in the evaluation, before immunosuppressive treatment potentially confounds the results. As outlined by Salvarani et al., treatment should begin with high-dose glucocorticoids. The addition of cyclophosphamide has been shown to decrease disease recurrence in primary CNS vasculitis. After induction therapy, transition to a maintenance regimen with methotrexate, azathioprine, or mycophenolate is recommended.[18] The addition of low-dose aspirin, as was done in this case, has also been suggested.[16]

Patient consent

Written consent to publish case details was obtained from the patient.

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Authorship

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

Declaration of competing interest

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Appendix A. Supplementary data

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