Epiphenomenon Multiple Evanescent White Dot Syndrome

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Abstract

Epiphenomenon multiple evanescent white dot syndrome (EpiMEWDS) is considered to be a rare variant of the more common white dot syndrome, multiple evanescent white dot syndrome (MEWDS). Traditional MEWDS has been linked to etiologies including recent viral infection or recent vaccination for a myriad of systemic conditions. In contrast, EpiMEWDS is thought to occur secondary to a concurrent outer retinal, choroidal disease, or both. The established signs of MEWDS include white dots at the level of the outer retina along with foveal granularity, which can result in symptoms such as vision loss, metamorphopsia, central and paracentral scotomas, or any combination of these. EpiMEWDS has a similar presentation but will also present with signs and symptoms of the underlying causative condition. This case report highlights a rare occurrence of EpiMEWDS secondary to an idiopathic choroidal neovascular membrane.

Keywords

outer retinal disease, epiphenomenon multiple evanescent white dot syndrome, multiple evanescent white dot syndrome, fundus auto fluorescence, optical coherence tomography

Initially described by Jampol et al., multiple evanescent white dot syndrome (MEWDS) is considered to be one of the white dot syndromes.[1] The condition manifests as white or white-grey dots at the level of the outer retina with accompanying foveal granularity that represents ellipsoid zone disruption.[1-3] MEWDS tends to occur more so in young females with myopia; males are affected to a much lesser degree.[4]

Although an exact etiology has not been established, the condition is thought to occur due to a previous or concurrent viral infection or secondary to recent vaccination.[1,5,6] Subsequently, the body reacts with an immune response that targets the previously mentioned retinal tissues.

While MEWDS is considered rare, an even rarer form of MEWDS has been recently mentioned in the literature, epiphenomenon multiple evanescent white dot syndrome (EpiMEWDS). The underlying etiology in this condition is likely insult to the outer retinal layers from varying conditions, including choroidal neovascular membranes, leading to subsequent disruption of surrounding outer retinal tissues, resulting in a MEWDS-like presentation.[7,8]

This case report highlights the rare appearance of EpiMEWDS due to an underlying idiopathic choroidal neovascular membrane. A comprehensive review of the condition and comparisons to typical

Suggested citation

Bhakhri R., Alami W., Ittiara S. Epiphenomenon Multiple Evanescent White Dot Syndrome *Can J Optom.* 2026;88(3):69-76.
https://www.doi.org/10.65636/cjo.v88i3.6901

MEWDS are made to aid clinicians in their diagnosis and management plans.

Case Report

A 25-year-old Hispanic male presented with a 3-week history of gradual vision loss and central scotoma OD. Ocular and medical history were unremarkable. The patient reported no recent illness or vaccination. The best corrected visual acuities were 20/50 OD and 20/20 OS. The patient was emmetropic OD and OS with no history of any previous refractive error or refractive correction.

Anterior segment examination and entrance testing were unremarkable OD and OS. Blood pressure was measured at 115/75 mm Hg. The dilated exam revealed subfoveal thickening with subretinal hemorrhage at the macula OD with the remaining retinal findings being unremarkable (Figure 1A).

These findings were highly suspicious for a choroidal neovascular membrane. Examination OS was unremarkable with no evidence of inflammation, edema, hemorrhage, or choroidal neovascularization. Wide field fundus autofluorescence photos OD revealed hyperautofluorescent lesions surrounding the possible choroidal neovascular membrane, indicating possible MEWDS (Figure 1B).

Wide field fundus autofluorescence photos OS were unremarkable. Optical coherence tomography was unremarkable OS, but OD scans showed a choroidal neovascular membrane with adjacent disruption of the ellipsoid zone and retinal pigment epithelium (Figure 1C). These disruptions corresponded with the hyperautofluorescent lesions seen on the fundus autofluorescence photos.

Dr. Raman Bhakhri referred the patient to Dr. Shaun Ittiara, a retinal specialist with a tentative diagnosis of a choroidal neovascular membrane of unknown etiology with possible EpiMEWDS. Differentials at this time for the retinal presentation included infectious and inflammatory etiologies, such syphilis, tuberculosis, sarcoidosis, toxoplasmosis, multifocal choroiditis, and punctate inner choroidopathy.

The patient was sent for appropriate laboratory testing for these conditions.

Another differential that was considered was a pachychoroid-related choroidal neovascular membrane as a thicker choroid was noted on optical coherence tomography. However, the patient did not have any prior history of any pachychoroidal spectrum disease, no associated risk factors, nor any additional exam findings that can be seen with pachychoroidal conditions (e.g., gravitational tracks suggestive of chronic central serous and pachydrusen). Additionally, pachychoroid neovascular membranes tend to present in patients aged 50 years or older.[9]

The patient was seen the next day by the retinal specialist and received an intravitreal injection of bevacizumab OD, based on insurance approval, at that visit.

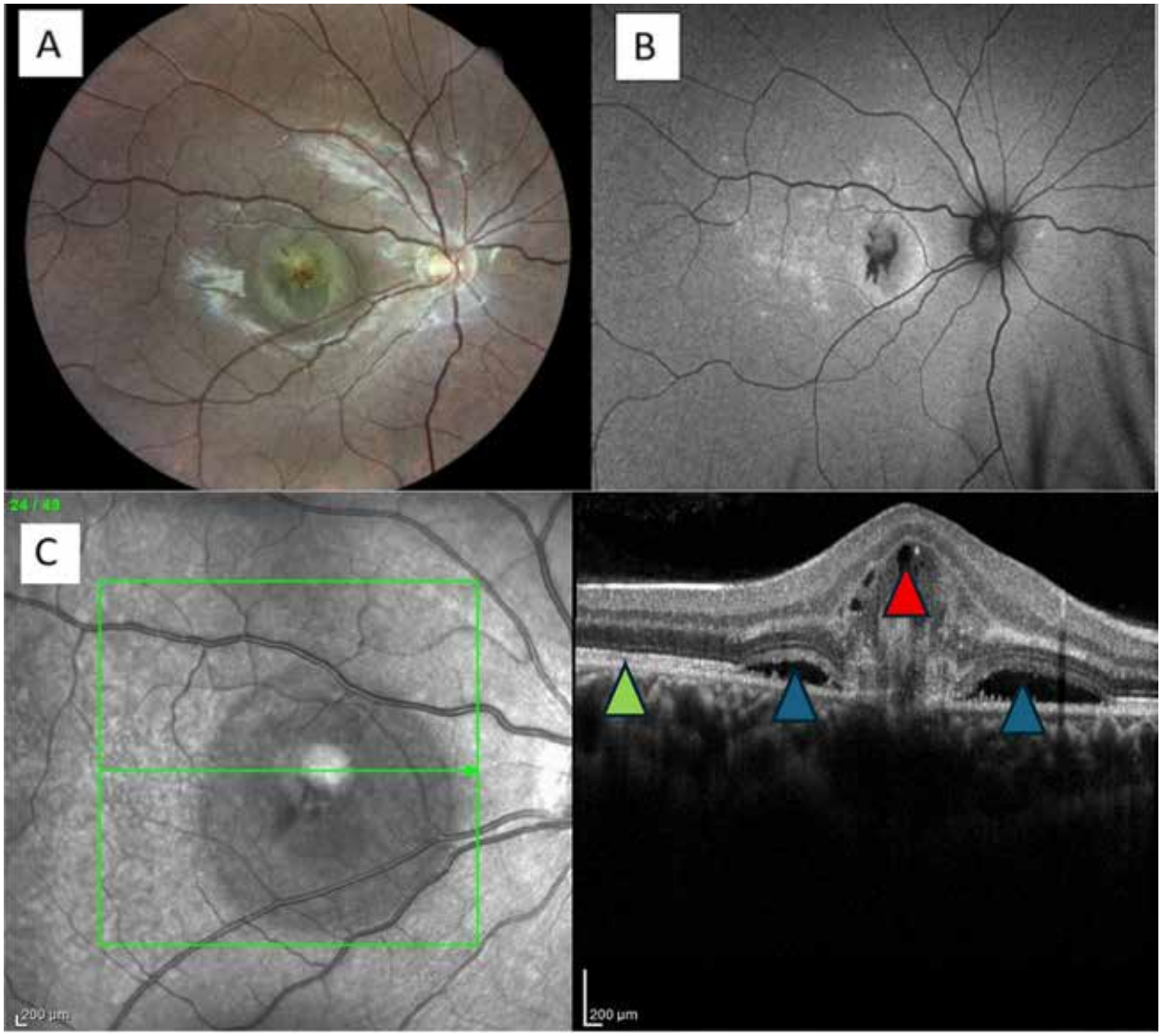
At the 5-week follow-up visit, the visual acuity had improved from 20/50 to 20/25 OD. Substantial resolution of the subretinal thickening and hemorrhaging from the choroidal neovascular membrane was seen on optical coherence tomography as well as recovery of the previously disrupted ellipsoid zone and retinal pigment epithelium (Figure 2A).

Repeat fundus autofluorescence photos revealed complete resolution of the hyperautofluorescent dots, which corresponded to healed outer retinal disruption on optical coherence tomography (Figure 2B).

The previously ordered lab work had returned negative for all requested testing. With negative lab results for infectious or inflammatory conditions, no history of recent illness or vaccination, a fundus presentation not resembling multifocal choroiditis nor punctate inner choroidopathy, multimodal imaging results, and an unremarkable ocular history, the patient was diagnosed with EpiMEWDS secondary to an idiopathic choroidal neovascular membrane.

The patient received 3 more bevacizumab injections over the course of 9 months, with examination findings remaining stable over this time. The patient continues to be followed with his last examination showing no evidence of an active choroidal neovascular membrane.

Figure 1: Initial images of patient's right eye

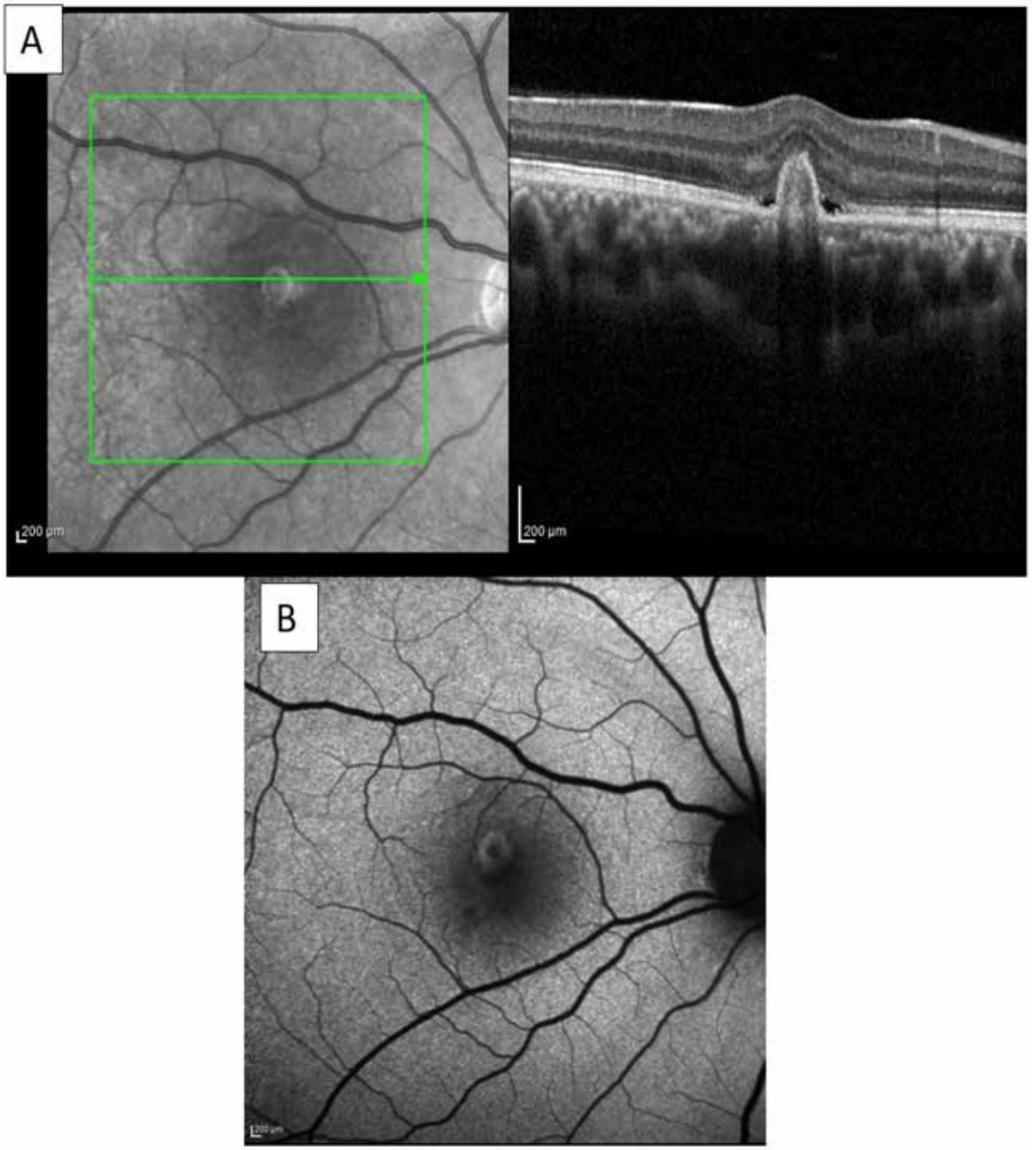


A: Fundus photo showing subretinal fluid and thickening with subretinal hemorrhage in the right eye indicative of a choroidal neovascular membrane.

B: Fundus autofluorescence imaging revealing areas of hyperautofluorescence concentrated around the choroidal neovascular membrane, with additional areas of involvement noted distant from the lesion (yellow circles).

C: Optical coherence tomography of the right eye showing intraretinal (red arrowhead) and subretinal fluid (blue arrowheads) secondary to a choroidal neovascular membrane. Adjacent disruption/ inflammation of the ellipsoid zone/retinal pigment epithelium (green arrowhead) corresponds to the hyperautofluorescence seen in the fundus auto fluorescence photos indicating epi-multiple evanescent white dot syndrome.

Figure 2: Five-week follow-up images of patient's right eye



A: Repeat optical coherence tomography 5 weeks after initial bevacizumab injection showing substantial resolution of the intra and subretinal fluid corresponding to reduction in choroidal neovascular membrane size. Restoration of the previously inflamed ellipsoid zone/retinal pigment epithelium is also appreciated.

B: Repeat fundus autofluorescence showing complete resolution of the previous hyperautofluorescent lesions.

Discussion

This rare case corresponds to recent literature findings of a condition termed EpiMEWDS (or at times, secondary MEWDS).[7,8] Traditional MEWDS (or primary MEWDS) has been thought of as a transient retinal condition that typically results in a unilateral presentation of white dots and foveal granularity in young females with myopia, with a preceding history of viral infection or vaccination.[1,3,10] This can include vaccinations from Epstein-Barr virus, hepatitis A and B, human papilloma virus, and recently severe acute respiratory syndrome coronavirus (COVID-19).[2,5,6,11-14] It has also been suggested that unknown genetic factors combined with exposure to environmental factors, like those viruses, may make a person more susceptible to developing MEWDS.[4,15] Symptoms can include vision loss, photopsias, and paracentral or central scotomas. Fortunately, the condition resolves without intervention within a few weeks of onset.[16,17]

EpiMEWDS also tends to present in young females with myopia more so than males; however, it is thought to present secondary to other retinal or choroidal diseases, namely those that affect the outer retina.[7]

Most cases in the literature have described EpiMEWDS like lesions occurring concurrently in patients with multifocal choroiditis and punctate inner choroidopathy.[7,18,19] These conditions all share a possible underlying association as they are grouped together under the spectrum of white dot diseases. More specifically, they all involve some sort of immune-mediated inflammation of the retinal pigment epithelium and underlying choroid.[20]

Although even rarer, conditions outside of the white dot diseases (but with a similar capability of affecting the outer retina) have also been noted to induce EpiMEWDS. This includes cases of ocular toxoplasmosis, Candida endophthalmitis, tubercular serpiginous choroiditis, ocular syphilis, pseudoxanthoma elasticum, high myopia, radiotherapy for retinoblastoma, focal scleral nodules, and previous vitreoretinal surgery for retinal detachments.[21-25]

The literature also describes choroidal neovascular membranes as a possible cause, with underling etiologies being Best disease (or vitelliform macular dystrophy), punctate inner choroidopathy, multifocal choroiditis, and central serous chorioretionathy.[7,18] Idiopathic choroidal neovascular membranes have also infrequently been linked to EpiMEWDS.[7,26] In these cases, patients tended be young and, despite an extensive systemic and ocular workup, no evident cause was noted. The condition was then classified as an idiopathic choroidal neovascular membrane secondary to unknown and subclinical inflammatory causes.[27,28]

Our case mirrors those cases as the patient was young (i.e., 25 years old) with all testing for a possible cause for the choroidal neovascular membrane returning normal.

Although it is unknown why EpiMEWDS occurs, an initial hypothesis suggests that damage occurs to the tunica Ruyschiana (consisting of Bruch's membrane, the choriocapillaris, and the retinal pigment epithelium) from infectious, inflammatory, idiopathic conditions (as in this case), or any combination of these. This causes the outer retinal blood barrier and ellipsoid zone to lose immune privilege. Further transient outer retinal inflammatory changes follow, leading to or triggering an interaction of the immune system with retinal antigens.[8,18,21,24] These complexes are then hypothesized to induce MEWDS as an epiphenomenon. Evidence for this is seen in the EpiMEWDS lesions being less extensive than MEWDS lesions and being observed in closer proximity to the primary area of chorioretinal involvement rather than being spread diffusely across the retina as seen in primary MEWDS.[7,24]

This was noted in our patient as the areas of focal inflammation were isolated around the choroidal neovascular membrane. As idiopathic choroidal neovascular membranes are thought to be a result of outer retinal and choroidal inflammation and insult,[27,28] it likely followed the previously described process, resulting in the epiphenomenon.

With clinical presentation being subtle or difficult to note with fundus examination, multimodal imaging is essential in helping arrive at an accurate diagnosis. Multimodal imaging findings in EpiMEWDS closely resemble those in MEWDS with minor yet important differences. Both conditions will have outer retinal disruption on optical coherence tomography,

Table 1: Comparison of key clinical features, imaging findings, and management considerations between MEWDS and EpiMEWDS

Feature	MEWDS	EpiMEWDS
Etiology or pathophysiology	Idiopathic, viral, or vaccination exposure leading to outer retinal inflammation	Underlying retinal, choroidal, or both disorders causing a secondary outer retinal inflammation
Laterality	Unilateral	Unilateral
Demographics	Young females	Young females
Symptoms	Reduced vision, photopsias, scotomas	Reduced vision, photopsias, scotomas, plus symptoms associated to underlying cause
Fundus signs	Multiple white dots, foveal granularity	Multiple white dots, foveal granularity but located near primary chorioretinal lesion
Optical coherence tomography findings	Ellipsoid zone disruption	Ellipsoid zone disruption but located near primary chorioretinal lesion
Fundus autofluorescence findings	Hyperautofluorescent lesions corresponding to white dots	Hyperautofluorescent lesions corresponding to white dots but located near primary chorioretinal lesion
Treatment	Observation due to spontaneous resolution; no treatment needed	Observation due to spontaneous resolution; treatment indicated for underlying causative condition
Prognosis	Full recovery in most cases	Full recovery in most cases; underlying cause may still lead to permanent vision loss

EpiMEWDS, epiphenomenon multiple evanescent white dot syndrome; MEWDS, multiple evanescent white dot syndrome.

hyperautofluorescence of the white dots on fundus autofluorescence, and hyperfluorescent dots in a wreath-like pattern on fluorescein angiography.[3,7,17] However, as noted previously, all of these findings for EpiMEWDS should be proximal to the primary area of chorioretinal involvement.[7,24] Additional similarities and distinctions between the two conditions are expanded on in Table 1.

Fortunately, EpiMEWDS follows its own path of progression and resolves spontaneously, similar to MEWDS, without affecting the course of the associated or causative condition.[24] The visual prognosis is variable as definitive treatment is aimed at the underlying causative chorioretinal condition.

Treatment for these conditions can vary but can consist of anti-inflammatory, antimicrobial, or anti-vascular endothelial growth factor therapy based on the specific etiology.[18,21,22,25]

The literature suggests that EpiMEWDS may pose a greater risk for recurrent disease and fellow eye involvement, when compared to primary MEWDS, indicating a possible systemic association.[24] However, another study noted that recurrent and

bilateral forms of EpiMEWDS were not more frequent.[7] With the condition being rare, further research into these statements may be limited.

Conclusion

Clinicians should be cognizant of EpiMEWDS and its association to outer retinal disease even though it is considered unique and rare. Although it presents in a similar fashion to MEWDS, differences can be noted with careful history, examination, and multimodal imaging results.

The prognosis is variable as EpiMEWDS ultimately resolves without treatment. Therefore, definitive treatment should be ultimately directed at the causative outer retinal condition.

Disclosures

Contributors: All authors contributed to the conception or design of the work and the acquisition, analysis, or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

Funding: This case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Competing interests: All authors have completed the ICMJE uniform disclosure forms and declare no conflicts of interest.

Ethical approval: Ethical approval is not required for this article type as it is a case report. Approval for the use of images was provided by the patient.

AI statement: The authors confirm no generative artificial intelligence or AI assisted technology was used to generate content.

Acknowledgements: The authors thank Natalie Bobrowska for her assistance in editing this article.

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