AMERICAN ACADEMY OF OPHTHALMOLOGY®

A Multiple Evanescent White Dot Syndrome–like Reaction to Concurrent Retinal Insults

Maria Vittoria Cicinelli, MD,[1,2,3,*] *Omar Mohamed Hassan, MD,*[1*] *Manjot K. Gill, MD,*[1] *Debra Goldstein, MD,*[1] *Maurizio Battaglia Parodi, MD,*[2,3] *Lee M. Jampol, MD*[1]

Purpose: To describe a clinical picture resembling classic multiple evanescent white dot syndrome (MEWDS) potentially triggered by previous or concurrent, apparently unrelated, ocular events and to provide a literature review of similar presentations.

Design: Retrospective chart series and literature review.

Participants: Consecutive patients diagnosed with MEWDS at the Feinberg School of Medicine, Northwestern University, Chicago, Illinois, and the IRCCS San Raffaele Scientific Institute, Milan, Italy, between July 2019 and June 2020.

Methods: Charts of patients were reviewed. Ophthalmic history, best-corrected visual acuity, spectral-domain OCT results, OCT angiography results, fundus autofluorescence results, ultra-widefield fluorescein angiography results, and indocyanine green angiography results were collected. A PubMed-based search was carried out for similar presentations using the terms *MEWDS* and *white spot syndromes*.

Main Outcome Measures: An ocular history positive for previous or concurrent ocular events in patients with MEWDS was sought in our cohort and the existing literature.

Results: Five eyes of 4 patients (2 females; age range, 16–81 years) were included. The first eye had a history of bilateral Best vitelliform dystrophy and unilateral choroidal neovascularization. The second eye had angioid streaks complicated by choroidal neovascularization and underwent prior thermal laser photocoagulation. The third eye had a history of high myopia and a scleral buckle procedure for retinal detachment. The fourth patient had bilateral idiopathic retinochoroiditis. We identified 16 case reports from 5 previous publications that support a MEWDS-like reaction to previous ocular insults.

Conclusions: We suggest a MEWDS-like reaction may be elicited by ocular events in a subset of susceptible patients. We hypothesize that damage to the outer retina may play a role in triggering the local inflammatory response. *Ophthalmology Retina 2021;5:1017-1026 © 2020 by the American Academy of Ophthalmology*

Multiple evanescent white dot syndrome (MEWDS), first described in 1983, is a distinct entity defined as a unilateral or, rarely, bilateral self-limiting inflammatory disease, typically characterized by female gender, young to middle-age predilection, and flu-like prodromal symptoms.[1] Fluorescein angiography (FA) and indocyanine green angiography (ICGA) reveal characteristic dots and spots.[2,3] The dots are correlated with linear and vertical aggregations centered at the ellipsoid zone (EZ) on OCT. The spots are larger outer retinal abnormalities (>200 μm) that are hypofluorescent and sometimes confluent on late ICGA[2,3] and correlate with discontinuities or disruption of the EZ on OCT.[4] Foveal granularity, disc edema, and vitreous cells also may be present.[5]

Although this is the classic presentation, reports have described MEWDS occurring in conjunction with other, apparently unrelated, ocular diseases, either concurrently or over the course of follow-up.[6–12] Similar to classic MEWDS, the lesions are evanescent and have a similar appearance on multimodal imaging. However, the patients do not fit the classic clinical findings, the demographics, or the natural course of the disease seen in MEWDS. Herein, we present 4 patients with MEWDS that occurred concurrently or after retinal insult in the same eye. We speculate that the presence of a coexistent retinal disease may not be incidental, but rather a predisposing factor or a trigger for a local inflammatory reaction with clinical features overlapping those of classic MEWDS. Furthermore, we provide a review of the literature for similar presentations.

Methods

All patients were seen at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois, and the IRCCS San Raffaele Scientific Institute in Milan, Italy, between June 2019 and October 2020. The study was exempted from review by the institutional review board and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was not

https://doi.org/10.1016/j.oret.2020.12.007
ISSN 2468-6530/21

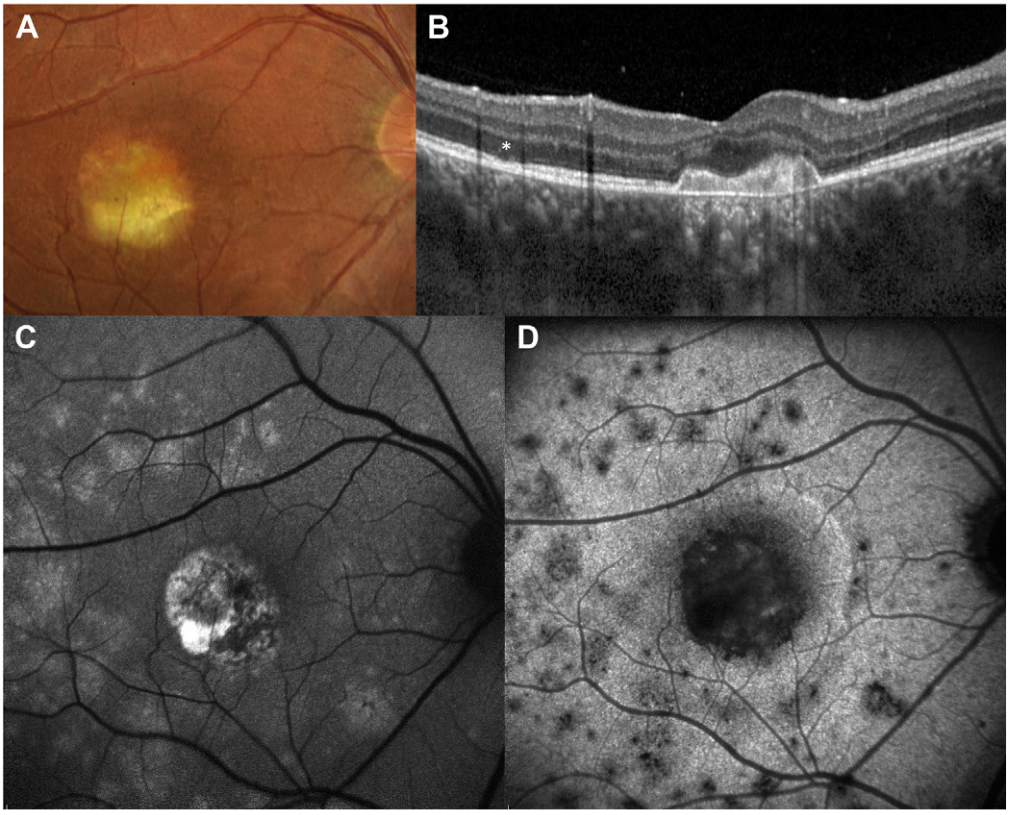

Figure 1. Images from a 19-year-old man with genetically proven Best vitelliform dystrophy and associated choroidal neovascularization in the right eye. **A**, Color fundus photograph of the right eye showing macular vitelliform material and subretinal fibrosis. **B**, OCT image revealing subfoveal hyperreflective material and temporal, focal alterations in the ellipsoid zone (asterisk). **C**, Fundus autofluorescence image showing multiple, partially confluent, hyperautofluorescent spots at the posterior pole and an irregular area of hyperautofluorescence in the macula. **D**, Late-phase indocyanine angiography image revealing a greater number of hypofluorescent dots surrounding the macula.

required due to the limited retrospective nature of the study. Data collection included age, gender, medical history, ophthalmic history, Snellen best-corrected visual acuity (BCVA), refraction, slit-lamp examination, and ophthalmoscopy. Multimodal imaging included spectral-domain (SD) OCT and short-wavelength (488-nm) fundus autofluorescence (FAF; HRA+OCT Spectralis [Heidelberg Engineering, Heidelberg, Germany]), green-light (787-nm) FAF (California [Optos, Dunfermline, United Kingdom]), ultra-widefield FA and ICGA (HRA+OCT Spectralis [Heidelberg Engineering] or California [Optos]), and ultra-widefield pseudocolor fundus imaging (California [Optos]). OCT angiography was collected when available. The diagnosis of MEWDS was made by an experienced clinician (L.M.J.) based on patient signs, symptoms, and multimodal imaging findings. Workup for infectious and inflammatory systemic diseases (including syphilis, tuberculosis, and sarcoidosis) showed negative results for all patients. A PubMed-based search was carried out for similar presentations using terms such as *MEWDS* and *white spot syndrome*. All studies published in English up to August 2020 were reviewed.

Case Reports

Patient 1. A 19-year-old man with a history of genetically proven bilateral Best vitelliform dystrophy and unilateral choroidal neovascularization (CNV) in the right eye sought treatment for visual deterioration and floaters in the right eye. The patient previously had received intravitreal anti−vascular endothelial growth factor agents. The BCVA had dropped from 20/25 to 20/40. Fundus examination revealed amorphous vitelliform material and subretinal fibrosis in the macula, as well as faint, yellow, deep retinal lesions scattered in the posterior pole (Fig 1A). The SD OCT images showed a central hyperreflective lesion with backscattering; some attenuation of the EZ was noted temporally, along with a thick choroid (Fig 1B). The FAF images revealed confluent hyperautofluorescent spots corresponding to the yellow lesions and mottled hypoautofluorescence and hyperautofluorescence in the macula (Fig 1C). Fluorescein angiography showed wreath-like hyperfluorescent lesions in the posterior pole and late macular staining, whereas multiple hypofluorescent spots, more numerous than those on fundus examination or FAF, were noted on ICGA (Fig 1D). The patient was treated with 50 mg/day oral corticosteroids with a slow taper; the symptoms faded, BCVA improved to 20/32, and no recurrence was noted over 4 months of follow-up.

Patient 2. An 81-year-old woman sought treatment for cloudy vision in the right eye 2 weeks after uneventful cataract extraction surgery and intraocular lens implantation. Her ocular history was positive for idiopathic angioid streaks in both eyes and laser retinopexy for retinal tears in the right eye. Macular SD OCT imaging performed elsewhere before cataract surgery showed a retinal pigment epithelium (RPE) detachment with shallow subretinal fluid suggestive of CNV. The BCVA was 20/40 on the first postoperative day, but dropped to counting fingers by the next week. The patient then was referred to us. Fundus photography revealed chorioretinal atrophy in the temporal peripapillary area and faint, discrete, deep yellowish lesions along the major vascular arcades (Fig 2A, asterisks). Fundus autofluorescence revealed

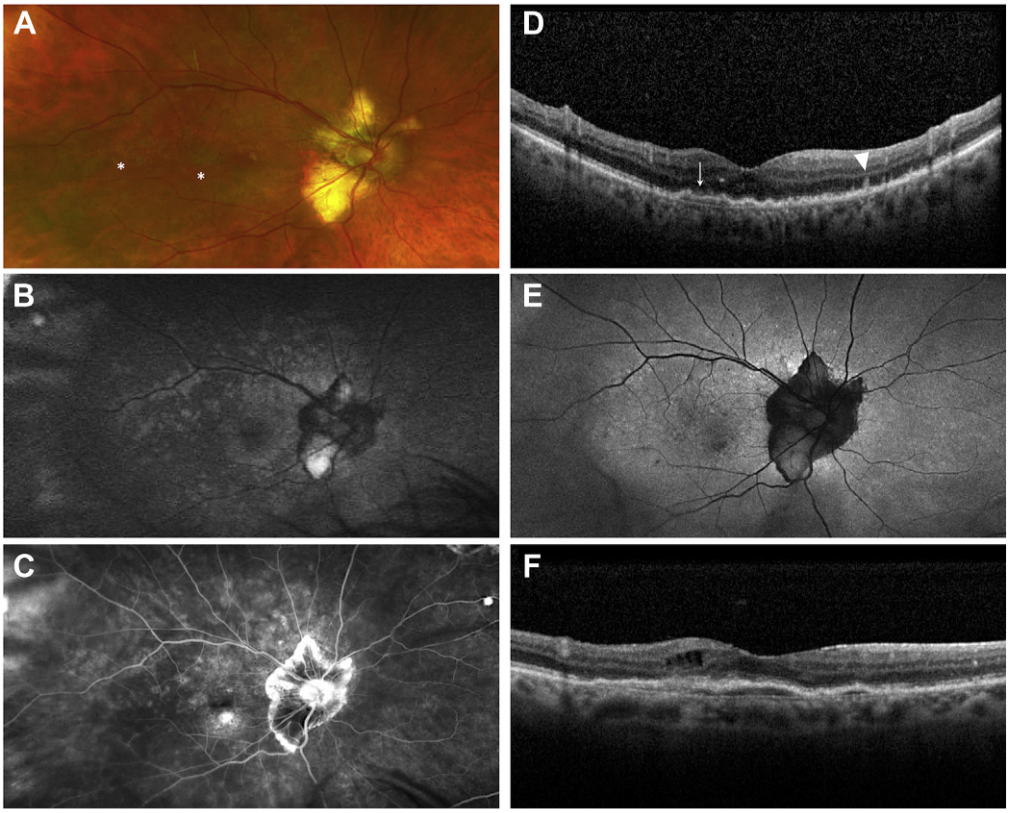

Figure 2. Images from an 81-year-old woman with angioid streaks, choroidal neovascularization, previous laser retinopexy to retinal tears, and multiple evanescent white dot syndrome-like reaction in the right eye. **A**, Color fundus photograph of the right eye showing chorioretinal atrophy radiating from the optic nerve and discrete, deep yellow lesions along the major vascular arcades (asterisks). **B**, Fundus autofluorescence image showing peripapillary hypoautofluorescence and multiple, hyperautofluorescent, partially confluent spots along the vascular arcades and in the macula. **C**, Fluorescein angiography image revealing early window defect and late staining at the edges corresponding to peripapillary atrophy, hyperfluorescent wreath-like lesions, and late leakage in the macula. **D**, OCT image obtained at 1 week after cataract surgery visit revealing disruption of the external limiting membrane (ELM) and the ellipsoid zone (EZ), a subfoveal retinal pigment epithelium detachment—probable type 1 neovascularization (arrow)—and vertical hyperreflective excrescences from the EZ pointing toward the outer nuclear layer (arrowhead). **E**, Fundus autofluorescence image obtained 1 month after presentation showing resolution of the hyperautofluorescent lesions. **F**, Horizontal OCT scan revealing slightly increased pigment epithelium detachment, intraretinal cysts temporally to the fovea, and extrafoveal restoration of the ELM and EZ. The vertical lesions have disappeared.

hyperautofluorescent, partially confluent spots surrounding the optic disc and the main temporal vascular arcades (Fig 2B). Fluorescein angiography showed wreath-like hyperfluorescent lesions with late staining, macular leakage, and window defects in the peripapillary region (Fig 2C); a few punched-out posterior pole chorioretinal lesions also were revealed on FA. Spectral-domain OCT revealed disruption of the external limiting membrane and the EZ, in addition to the previously noted RPE fibrovascular detachment (Fig 2D). Within 1 month, the hyperautofluorescent spots faded (Fig 2E); OCT imaging showed restoration of the EZ layer and some intraretinal cysts (Fig 2F). The CNV was treated with intravitreal injections of anti–vascular endothelial growth factor agents.

Patient 3. A 38-year-old woman had a history of high myopia (−9.25 diopters [D] in the right eye and −10.25 D in the left eye) and rhegmatogenous retinal detachment in the left eye repaired with scleral buckle 14 years previously. She reported floaters in the left peripheral vision of 1 week's duration. Best-corrected visual acuity was 20/20 in the right eye and 20/30 in the left eye. Fundus examination of the left eye showed cells in the vitreous, heavily pigmented demarcation lines from the previous retinal detachment, and deep, creamy, large lesions surrounding the disc. Smaller white lesions were seen in the posterior pole and the mid periphery (Fig 3A). The large lesions were consistent with multifocal choroiditis (MFC), and the smaller lesions resembled those of MEWDS. The MEWDS-like lesions were hyperautofluorescent on FAF (Fig 3B), hyperfluorescent on FA (Fig 3C), and hypofluorescent on both early- and late-frame ICGA (Fig 3D). On SD OCT, they corresponded to multiple foci of outer retinal disruption, with loss of segmentation at the level of the EZ and the external limiting membrane. Vertical extensions into the outer nuclear layer also were noted (Fig 3E). The patient initially was observed, and both types of lesions gradually resolved. She returned 4 months later with new central photopsia and visual distortion. Fundus autofluorescence revealed recurrence of diffuse hyperautofluorescence; an SD OCT scan through the macula revealed a new parafoveal RPE elevation with no intraretinal or subretinal fluid. OCT angiography showed no evidence of CNV; the patient was started on 60 mg oral prednisone and was tapered slowly. On follow-up, a new RPE elevation appeared, with OCT angiography revealing a large CNV network (Fig 3F). Intravitreal injections of anti–vascular endothelial growth factor agent were administered, and oral steroid treatment was restarted; BCVA at last follow-up was 20/40.

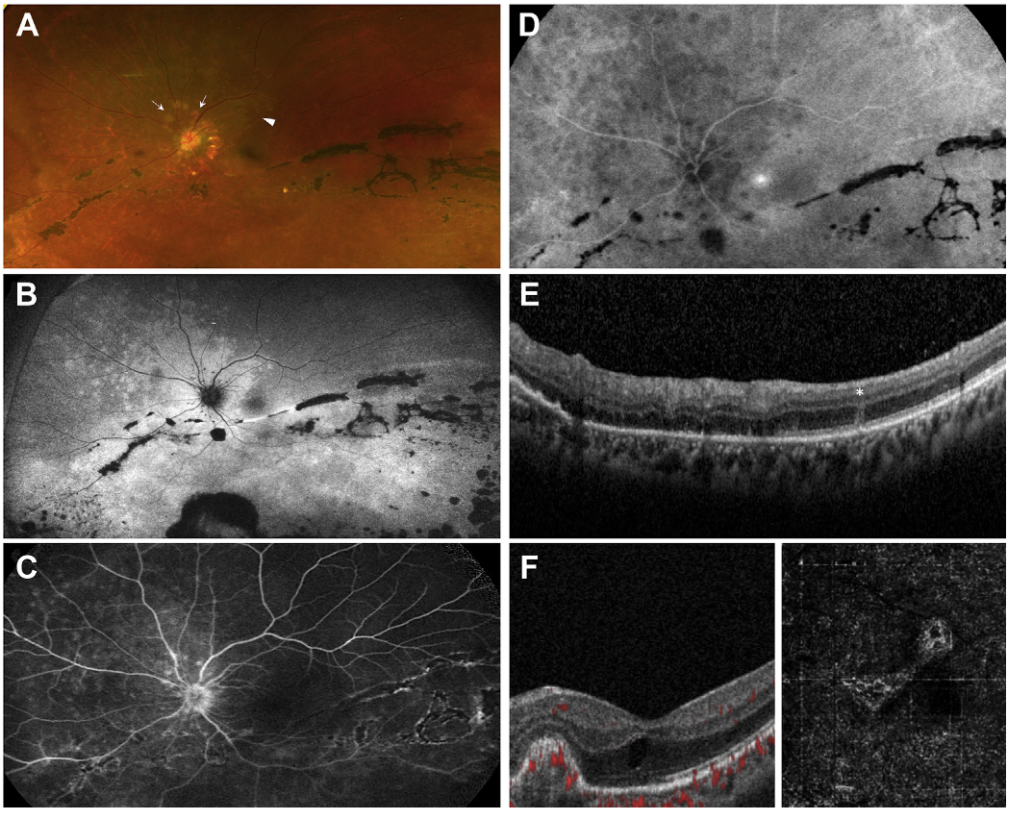

Figure 3. Images from a 38-year-old woman with pathologic myopia, a previous scleral buckle procedure for rhegmatogenous retinal detachment, and multiple evanescent white dot syndrome–like reaction in the left eye. **A**, Color fundus photograph showing pigmented demarcation lines across the posterior pole. Multiple large, circumpapillary, creamy lesions (arrows) and smaller, midperipheral white lesions (arrowhead) are visible. **B**, Fundus autofluorescence image revealing discrete hyperautofluorescence in the nasal midperiphery, confluent peripapillary hyperautofluorescence, and inferior pigmentary changes from the previous retinal detachment. **C**, Fluorescein angiography image revealing hyperfluorescent lesions corresponding to the fundus autofluorescence alterations and staining of some peripapillary lesions. **D**, Indocyanine green angiography image showing numerous dark lesions corresponding to the superonasal peripapillary and mid-peripheral regions. **E**, Horizontal OCT image passing superior to the optic nerve revealing diffuse alterations of the ellipsoid zone and the external limiting membrane extending into the outer nuclear layer. **F**, Structural OCT angiography image through the fovea showing an area of retinal pigment epithelium elevation with red flow pixels; en face OCT angiography shows a large choroidal neovascular network.

Patient 4. A 16-year-old boy sought treatment for visual disturbances and photopsia of the left eye. Best-corrected visual acuity was 20/20 in the right eye and 20/50 in the left eye. Slit-lamp biomicroscopy revealed 2+ anterior chamber cells and 2+ vitreous cells bilaterally. Ophthalmoscopy revealed multiple chorioretinal scars in the periphery of both eyes (Fig 4A, B). Multimodal imaging demonstrated partially confluent hyperautofluorescence on FAF (Fig 4C, D), hyperfluorescent peripapillary spots and periphlebitis on FA (Fig 4E, F), and EZ disruption with vertical protrusions on SD OCT (Fig 4G, H, asterisks). The patient was observed, but the peripheral atrophic chorioretinal scars increased in number at the 1-month follow-up. Because the systemic workup for infectious diseases showed negative results, the patient was diagnosed with idiopathic retinochoroiditis and was started on oral prednisone, followed by adalimumab.

Review of the Literature

Our review of the literature identified 16 case reports from 5 previous publications that support a MEWDS-like reaction to previous or concurrent ocular insults. The color fundus photographs, FAF, OCT, FA, and ICGA imaging presented in these reports are consistent with the proposed diagnosis (Table 1). We also identified 10 eyes of 9 patients from 5 publications that possibly show a MEDWS-like reaction; however, because of incomplete information or inability to exclude other plausible conditions, we are uncertain if they describe the same phenomenon (Table 2).

Discussion

Our 4 patients featured fundus and imaging characteristics consistent with MEWDS occurring in conjunction with posterior segment abnormalities (Best vitelliform dystrophy, angioid streaks, previous laser retinopexy, retinal detachment surgery, and an undetermined retinochoroiditis) as well as recent cataract surgery. All 4 patients demonstrated evanescent lesions associated with the inflammatory spots and permanent retinal changes. Three eyes had unilateral disease and 1 eye had bilateral MEWDS lesions. Because of the differences in the clinical settings from cases of classic MEWDS, we refer to this collection of signs as a MEWDS-like reaction. Although the co-occurrence of other diseases featuring macular damage (e.g., idiopathic CNV, secondary CNV, or Best vitelliform dystrophy) and MEWDS in a single eye could be coincidental, we suspect a possible

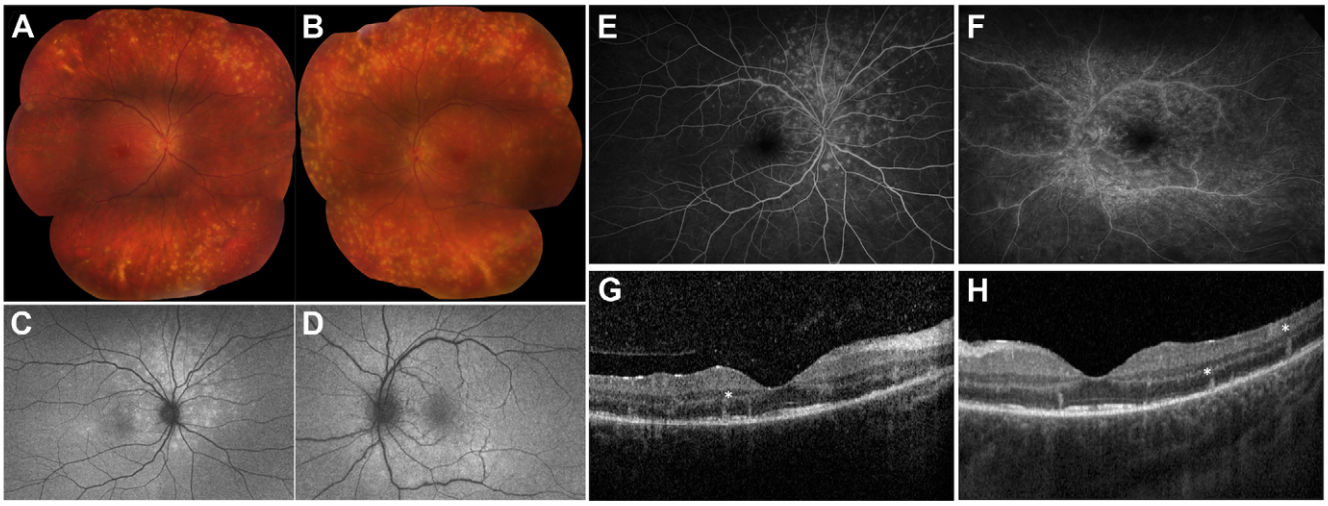

Figure 4. Images from a 16-year-old male with idiopathic retinochoroiditis and bilateral multiple evanescent white dot syndrome–like reaction. **A**, **B**, Color fundus photographs revealing multiple peripheral lesions, macular and peripapillary white spots, and foveal granularity in both eyes. **C**, **D**, Fundus autofluorescence showing partially confluent hyperautofluorescence in the peripapillary area, most of which is visible in the right eye. **E**, **F**, Fluorescein angiography imaging significant for late hyperfluorescent spots in both the (**E**) right eye and (**F**) left eye; periphlebitis more evident in (**F**) the left eye. **G**, **H**, OCT image revealing vitreous cells, ellipsoid zone, and external limiting membrane disruption and vertical hyperreflective excrescences from the ellipsoid zone in (**G**) the right eye and (**H**) the left eye (asterisks).

association between macular RPE or Bruch's membrane disruption and the acute inflammatory event.

Patient 1 demonstrated Best vitelliform dystrophy with a previously treated CNV. Previous examples of MEWDS-like reaction apparently related to CNV have been reported.[8,9] In particular, Bryan et al[8] described 2 patients with a history of a previous macular insult in a case series of MEWDS occurring after the onset of MFC, one of whom had Best disease and a macular fibrotic scar. The other patient had idiopathic CNV treated with thermal laser therapy (Table 1).[8] Mathis et al[9] described 6 patients with CNV with varying primary diagnoses, all of whom demonstrated a MEWDS-like reaction concurrently or after the diagnosis of CNV (Table 1). In their report, the authors attributed the onset of MEWDS-like features to a proinflammatory milieu created by the presence of the CNV. Consistent with our patient 1, the association between Best vitelliform dystrophy and a MEWDS-like reaction has been reported previously.[12]

Patient 2 showed angioid streaks complicated by CNV. The association between angioid streaks and posterior segment inflammation has been described previously.[7,13] Marchese et al[14,15] reported 2 young patients with pseudoxanthoma elasticum and coinciding features of MEWDS and MFC. Gliem et al[7] reported 9 cases of acute outer retinopathy in patients with pseudoxanthoma elasticum with some clinical characteristics resembling MEWDS (Table 1). The authors suggested that the alteration of Bruch's membrane, the RPE, and the outer retina that occurs with angioid streaks was most likely the trigger of the acute retinopathy.[7] Notably, similar to patients 1 and 2, at least 3 patients extracted from the Gliem et al's[7] series had a history of CNV. Although fibrovascular proliferation is a common complication of angioid streaks, it also may have a causative role in the onset of an inflammatory MEWDS-like reaction.

Patient 3 demonstrated outer retinal dots and spots 14 years after rhegmatogenous retinal detachment repaired with a scleral buckle. In reviewing the literature, we identified other patients diagnosed with overlapping features of MEWDS and MFC after retinal detachment in the same[16,17] or the fellow[18] eye. One of the 2 cases of retinal detachment followed by an MFC has been attributed to a hypersensitivity reaction to the scleral buckling material.[16] In light of our hypothesis, it may be that the retinal insult at the time of the detachment and the consequent surgical repair played a role in triggering a local inflammatory response. Other reports may support this theory; features resembling MEWDS and MFC have been described in association with other types of globe trauma, including laser photocoagulation for peripheral retinal tears,[19] choroidal rupture,[6] penetrating injuries,[20] or surgery for orbital lymphangioma (Table 1).[8] Fung et al[6] reported a case of a 24-year-old woman with blunt trauma to the right eye complicated by a choroidal rupture who demonstrated grayish deep retinal dots and spots 10 weeks after the initial insult. Foveal granularity, mild vitreitis, hyperemia and edema of the optic nerve head, and retinal vasculitis also were noted. Fluorescein angiography and ICGA imaging showed features consistent with MEWDS, and SD OCT imaging showed overlapping characteristics between MEWDS and MFC. Given the temporal and geographic sequence with the traumatic event, the authors conjectured that the exposure of choroidal antigens or dehemoglobinized blood was the inciting trigger contributing to the fundus manifestations.

Patient 4 showed concurrent features of MEWDS and an undiagnosed retinochoroiditis. We initially reported the

Table 1. Literature Review of Plausible Examples of Multiple Evanescent White Dot Syndrome–like Reaction to Other Primary Retinal Conditions

Authors	Year	No. of Patients	Age (yrs)	Gender	Underlying Retinal Disease	Visual Acuity (Snellen)		Presenting Symptoms	Duration of Multiple Evanescent White Dot Syndrome–like Reaction	Treatment	Additional Comments
						At Time of Multiple Evanescent White Dot Syndrome–like Reaction	*Last Follow-up*				
Fung et al	2012	1	24	F	Choroidal rupture	20/50	N/A	Scotoma and floaters	8 wks	Oral steroids	Angiographic leakage, vitreitis, papillitis, and vasculitis
Gliem et al	2019	9	19–55 (range)	8 F, 1 M	PXE	20/30–HM	20/20–20/320	Reduced vision, metamorphopsia, scotomas, dark spots, glare, haze	From 1 mo to prolonged course	Steroids and anti-VEGF agents (3/9); anti-VEGF only (1/9); steroids only (1/9); none (4/9)	Vitreitis documented in 6/9 eyes; at least 4 eyes presented with CNV
Pece et al	2016	1	20	F	Angioid streaks	20/100	20/25	Reduced vision	2 wks	None	MEWDS developed in the eye with angioid streaks complicated by CNV
Bryan et al	2002	Patient 1	34	F	MFC	N/A	N/A	Reduced vision, photopsias	"Several months"	None	
		Patient 2	29	F	Best disease, MFC	20/200	N/A	Reduced vision, photopsias	2 mos	None	MEWDS developed in the eye complicated by CNV
		Patient 3	32	F	MFC, CNV, macular laser	20/40	20/20	Visual disturbance	4 wks	None	MEWDS developed in the eye complicated by CNV
		Patient 4	29	F	MFC	20/50	20/20	Visual disturbance	4 wks	None	
Mathis et al	2017	Patient 2	33	F	PIC, CNV	CF		N/A	2 mos		FA, ICGA, FAF, and OCT consistent with MEWDS

CF = counting fingers; CNV = choroidal neovascularization; F = female; FA = fluorescein angiography; FAF = fundus autofluorescence; HM = hand movements; ICGA = indocyanine green angiography; M = male; MEWDS = multiple evanescent white dot syndrome; MFC = multifocal choroiditis; N/A = not available; PIC = punctate inner choroidopathy; PXE = pseudoxanthoma elasticum; VA = visual acuity; VEGF = vascular endothelial growth factor.

Table 2. Literature Review of Possible Examples of Multiple Evanescent White Dot Syndrome–like Reaction to Other Primary Retinal Conditions

Authors	Year	No. of Patients	Age (yrs)	Gender	Underlying Retinal Disease	Visual Acuity (Snellen)		Presenting Symptoms	Duration of Multiple Evanescent White Dot Syndrome–like Reaction	Treatment	Additional Comments
						At Time of Multiple Evanescent White Dot Syndrome–like Reaction	*Last Follow-up*				
Golshani et al	2017	2 (bilateral)	67	F	Retinal tears treated with laser retinopexy	Right eye: 20/40 Left eye: 20/80	Both eyes: 20/20	Reduced vision and floaters	4 wks (right eye) and 8 wks (left eye)	None	No signs of vasculitis or optic nerve staining on FA; ICGA not provided; VRL not fully excluded
Mathis et al	2019	14	30.5 ± 10.9 (mean ± SD)		Ocular toxoplasmosis	20/50	20/30	N/A	32 d	Steroids and antibiotics	Satellite dark dots on ICGA present in 48.1% of patients
Mathis et al	2017	Patient 1	22	F	Choroidal atrophy, CNV	20/40	20/43	N/A	1 mo		Only FAF provided, showing hyper-FAF signal; OCTA or FA confirm presence of CNV
		Patient 3	15	F	PIC, CNV	20/20	N/A	N/A	2 mos	Anti-VEGF	
		Patient 4	40	M	CSCR, CNV	20/40	N/A	N/A	1 mo	Anti-VEGF	
		Patient 5	49	F	PIC, CNV	20/40	N/A	N/A	1 mo	Anti-VEGF	
		Patient 6	35	M	PIC, CNV	20/80	N/A	N/A	1 mo	Anti-VEGF	
Park et al	1997	1	23	M	Best disease	20/140	20/60	Blurred vision	1 mo	None	FAF and color fundus photography consistent with MEWDS; no ICGA or OCT provided
Vance et al	2011	1	27	F	Toxoplasmosis	20/20	20/20	Pressure behind the eye, headache, upper respiratory symptoms	4 wks	Atovaquone	FA, OCT, and color fundus photography consistent with MEWDS; no ICGA or FAF provided

CNV = choroidal neovascularization; CSCR = central serous chorioretinopathy; F = female; FA = fluorescein angiography; FAF = fundus autofluorescence; ICGA = indocyanine green angiography; M = male; MEWDS = multiple evanescent white dot syndrome; N/A = not available; PIC = punctate inner choroidopathy; SD = standard deviation; VA = visual acuity; VEGF = vascular endothelial growth factor; VRL = vitreoretinal lymphoma.

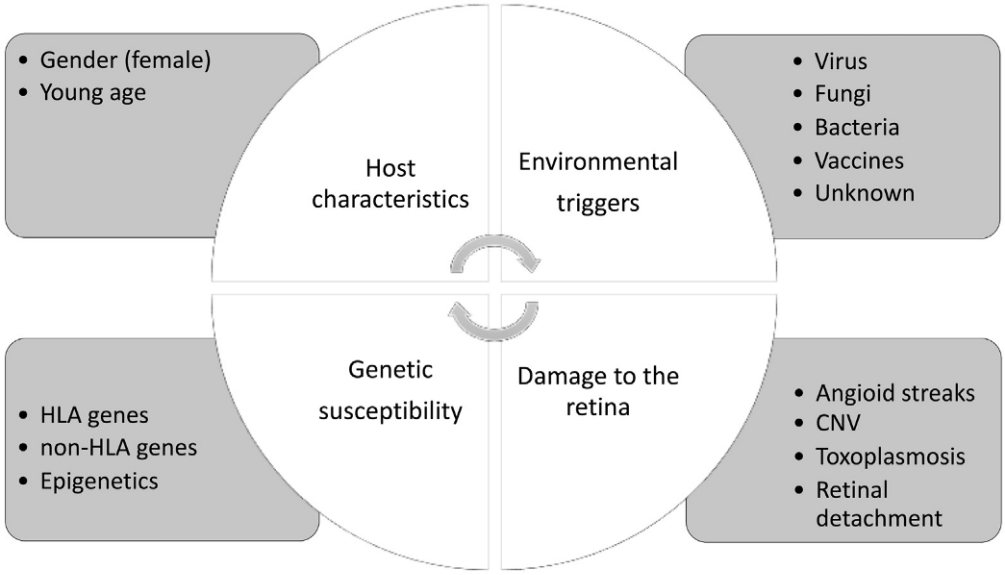

Figure 5. Diagram showing possible pathogenesis of multiple evanescent white dot syndrome–like reaction seen in association with other retinal diseases. CNV = choroidal neovascularization; HLA = human leukocyte antigen.

coexistence of features of MEWDS and MFC[21]; more recent evidence has supported this association.[8,22–24] Although MFC and MEWDS represent different entities, each with a specific prognosis and therapeutic response, some patients may demonstrate symptoms and fundus characteristics of both conditions. For this reason, some authors have suggested that MFC and MEWDS may share some similarities in their pathogenesis.[23] Furthermore, the occurrence of 2 or more different inflammatory diseases belonging to the spectrum of white spot syndromes simultaneously or on longitudinal observation (namely, acute zonal occult outer retinopathy and MEWDS[25] and acute posterior multifocal placoid pigment epitheliopathy and MFC[26]) has been described and may reinforce the partial overlap of diseases in this group.[27]

The pathogenesis of MEWDS is unknown, but we and others have hypothesized an immune-mediated mechanism involving the presence of both immunogenic triggers and a permissive host genetic susceptibility.[28] We hypothesized a genetic link between systemic autoimmune diseases and white spot syndromes,[29] and we identified an increased prevalence of systemic autoimmunity in patients with white spot syndromes and in their first- and second-degree relatives.[28] Nevertheless, because of the rarity of white spot syndromes, apart from a sporadic association with human leukocyte antigen (HLA)-B51,[30] a clear link between autoimmune susceptibility and a specific genotypic signature (such as polymorphisms in the human leukocyte antigen loci or immune regulatory pathways) has not been established. Systemic fungal,[31] bacterial,[32] and viral[33–35] infections, as well as vaccines[35–37] also have been implicated among the possible triggers of MEWDS.

Classic MEWDS may represent a MEWDS-like reaction to a viral trigger, although this is unproven. However, the MEWDS-like reaction we describe herein should be distinguished from other ocular inflammatory conditions. A clinical syndrome with features similar to those of MEWDS-like reaction has been described in infectious diseases involving the posterior segment, even in the absence of outer retinal damage.[38] Multiple hyperautofluorescent mid-peripheral and posterior pole spots have been reported in patients with syphilitic outer retinitis; the hyperfluorescence in syphilitic outer retinitis has been related to the infection-related EZ disruption, with a different mechanism compared with classic MEWDS.[24] An atypical MEWDS-like reaction featuring macular granularity, multiple deep white dots, blurred optic disc margins, and disruption of the EZ on OCT has been reported in a woman with latent tuberculosis with no evident signs of ocular disease.[39] Finally, Mathis et al[40] reported 14 eyes with hyperautofluorescent lesions on FAF, EZ disruption on SD OCT, and hypofluorescent spots on late ICGA in patients with acute ocular toxoplasmosis that disappeared after the resolution of the acute infection (Table 1). The authors hypothesized that this clinical picture corresponded to a transient disorder of the outer retina, triggered by the local infectious or inflammatory environment.[40]

In this report, we add a further interpretation of the pathogenesis of MEWDS-like findings, suggesting that previous or concurrent ocular damaging events may trigger a local, nonspecific inflammatory reaction with characteristics resembling those of classic MEWDS.[38] The primary event in the pathogenesis of this MEWDS-like reaction is uncertain. Because the patients included in our literature review all featured damage at the level of RPE–Bruch's membrane, perhaps the loss of outer retinal integrity with exposure to new retinal antigens plays a role (Fig 5). Nonetheless, a MEWDS-like reaction must be differentiated from the retinal disruption occurring in patients with other idiopathic conditions, such as punctate inner choroidopathy (PIC) or MFC. PIC- or MFC-related

retinal disruption is characterized by a classic sub-RPE lesion extending into the outer retina on OCT and diffuse hyperautofluorescence on FAF with variable patterns[41]; often it is transient, but can be associated with zonal or diffuse chorioretinal atrophy in rare cases.[41,42] A MEWDS-like reaction, however, shows distinguishable dots and spots on FA and ICGA, characteristic EZ changes on SD OCT, and discrete posterior-pole and mid-peripheral lesions on FAF. We acknowledge that PIC- or MFC-related outer retinal disruption and MEWDS-like reactions may share a similar pathway, implying an inflammatory involvement of the photoreceptors and the breakdown of the outer blood−retinal barrier. Nevertheless, we believe that the 2 conditions are distinguishable clinically, and we apply the term *MEWDS-like reaction* to the other circumstances described in this review, rather than PIC or MFC. Further longitudinal observations could clarify how PIC- or MFC-related outer retinal disruptions and MEWDS-like reactions are related.

Despite the small size of our series, our hypothesis may add additional insights to the pathogenesis of MEWDS and expand the spectrum of the possible causative events. We suggest that a MEWDS-like reaction may be triggered, in a susceptible subset of subjects, by previous or concurrent distinct events involving damage to the outer retina. The identification of genetic predisposition and the molecular basis of this response would help to shed further light on the understanding of this disease.

Acknowledgments. The authors thank Gregory L. Fenton, MD, for referring one of the included patients to the Northwestern Memorial Group.

Footnotes and Disclosures

Originally received: August 11, 2020.
Final revision: December 13, 2020.
Accepted: December 14, 2020.
Available online: December 22, 2020. Manuscript no. ORET-2020-674.

[1] Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

[2] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy.

[3] Department of Ophthalmology, IRCCS San Raffaele Scientific Institute, Milan, Italy.

*Both authors contributed equally as first authors.

Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form. The author(s) have made the following disclosure(s): M.B.P.: Board member − Bayer, Novartis

D.G.: Consultant − AbbVie, Bausch and Lomb, Allergan

HUMAN SUBJECTS: Human subjects were included in this study. The study was exempted from review by the institutional review board. All research adhered to the tenets of the Declaration of Helsinki. Informed consent was not required due to the limited retrospective nature of the study.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Cicinelli, Hassan, Jampol

Analysis and interpretation: Cicinelli, Hassan, Gill, Goldstein, Battaglia Parodi, Jampol

Data collection: Cicinelli, Hassan, Gill, Goldstein, Battaglia Parodi, Jampol

Obtained funding: N/A

Overall responsibility: Cicinelli, Hassan, Gill, Goldstein, Battaglia Parodi, Jampol

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CNV** = choroidal neovascularization; **EZ** = ellipsoid zone; **FA** = fluorescein angiography; **FAF** = fundus autofluorescence; **ICGA** = indocyanine green angiography; **MEWDS** = multiple evanescent white dot syndrome; **MFC** = multifocal choroiditis; **PIC** = punctate inner choroidopathy; **RPE** = retinal pigment epithelium; **SD** = spectral domain.

Keywords:
Multimodal imaging, Multiple evanescent white dot syndrome, Ocular inflammatory disease, White spot syndromes.

Correspondence:
Omar Mohamed Hassan, MD, Department of Ophthalmology, Northwestern University, 645 North Michigan Avenue, Suite 440, Chicago, IL 60611. E-mail: omar.hassan@northwestern.edu.

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