• Review Article •

Multiple evanescent white dot syndrome and presentations similar to multiple evanescent white dot syndrome in other disorders: a narrative review

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Received: 2024-07-11 Accepted: 2025-01-02

Abstract

● Multiple evanescent white dot syndrome (MEWDS) is an inflammatory fundus disease primarily affecting the outer retina. It is characterized by transient yellow-white dots on the outer retina. Although the exact pathogenesis remains unclear, the progress in multimodal imaging (MMI) has enhanced our understanding of MEWDS. Most cases of MEWDS are idiopathic, lacking a definite cause, and can spontaneously recover; these are what we term classic MEWDS. Consequently, MEWDS is often referred to as the "common cold of the retina". Simultaneously, patients with other disorders may present with varying degrees of manifestations similar to MEWDS. The resemblance in clinical or imaging findings can lead to misdiagnosis and inappropriate treatment. These MEWDS - like presentations are actually caused by other systemic or ocular disorders with diverse mechanisms. Thus, they differ from classic MEWDS in certain aspects. Using the keywords "MEWDS-like" and "Secondary MEWDS", we searched for all relevant studies published in the PubMed database from January 2021 to January 2024. Subsequently, we retrospectively summarized the clinical and imaging characteristics of MEWDS, along with the manifestations in other diseases that resembled those of MEWDS, and compared classic MEWDS with these similar presentations. Based on our review, we classified such similar presentations under other conditions into two categories and summarized their features for differential diagnosis. We recommend paying close attention to patients suspected of having MEWDS, as there may be more serious systemic or ocular disorders that require prompt treatment.

● **KEYWORDS:** classic multiple evanescent white dot syndrome; epiphenomenon multiple evanescent white dot syndrome; multiple evanescent white dot syndrome; multimodal imaging; secondary multiple evanescent white dot syndrome

DOI:10.18240/ijo.2025.09.20

Citation: Liu ZY, Zhang H, Sun XL. Multiple evanescent white dot syndrome and presentations similar to multiple evanescent white dot syndrome in other disorders: a narrative review. *Int J Ophthalmol* 2025;18(9):1777-1789

INTRODUCTION

Multiple evanescent white dot syndrome (MEWDS) is a well-known acute inflammatory fundus disease. It's characterized by transient multifocal yellow-white dots on the outer retina[1-2]. With the development of multimodal imaging (MMI), we get a deeper understanding of MEWDS, including the primary site and mechanism[1,3-6]. Now the features of MEWDS have been well described[1-2]. The majority of MEWDS cases are idiopathic with spontaneous recovery.

In previous reports, many patients were misdiagnosed with MEWDS due to presenting symptoms akin to it[7-9]. For instance, in the early stage of the systemic disease like syphilis or tuberculosis, patients may have presentations similar to MEWDS. However, they were ultimately diagnosed with conditions other than MEWDS[10-11]. In addition, the word "MEWDS-like" appeared recently[11-13]. There's also the recent usage of the term "MEWDS-like" to describe symptoms similar to those of MEWDS, seen in other fundus diseases such as multifocal choroiditis (MFC) and choroidal neovascularization (CNV), *etc*[1-2]. Studies have proved that MEWDS-like reactions are secondary reactions caused by coexisting pathology[1]. Unlike classic MEWDS, this secondary reaction has identifiable causes.

MEWDS is considered to be a common cold of retina, requiring no treatment[1]. However, conditions that mimic

MEWDS may be due to more serious diseases which should be detected and treated promptly[1].

We reviewed the features of MEWDS and presentations similar to MEWDS seen in other conditions. These similar presentations have distinct clinical or MMI findings. Based on our view, these presentations similar to MEWDS can be divided into two categories—masqueraders of MEWDS and secondary MEWDS. We made a comparison between them and classic MEWDS. Additionally, we conducted a search on the PubMed database using the keywords "MEWDS-like" and "Secondary MEWDS" and reviewed all relevant studies published between January 2021 and January 2024. We recommend further examination for patients presenting symptoms similar to MEWDS to ensure accurate diagnosis and timely treatment.

MULTIPLE EVANESCENT WHITE DOT SYNDROME

Epidemiology MEWDS primarily affect young to middle-aged myopic females. In some reports, up to 75% of the patients are women[14]. Most patients are between 20-40 years old although patients over 60 years old have been reported[7,15-16]. Nearly half of the patients have prodromal flu-like episode before onset[14-15,17]. MEWDS seems to have no geographical or racial tendency and most cases are unilateral[7,14]. Some patients have simultaneous or sequential involvement of both eyes[1,7,18-19]. Researchers have reported a unique cluster of seven cases presented in 3mo[20].

Etiology and Pathogenesis The exact etiology is unknown, therefore most cases of MEWDS are considered to be idiopathic. Because of the prodromal flu-like episode, it is suspected to be related with virus infection[15,21]. The patients may have vaccination history or previously diagnosed autoimmune disorder[7,22]. So MEWDS is considered to be an inflammatory disease related to autoimmunity and genetic susceptibility[15,23].

Since first described by Jampol *et al*[24] in 1984, there are a variety of perspectives on the primary site of the disease. MEWDS was initially considered as a primary disorder of choriocapillaris because of the hypofluorescence on indocyanine green angiography (ICGA) like other inflammatory choriocapillaropathies[2,25-27]. But studies using MMI including optical coherence tomography angiography (OCTA) found the perfusion of choroidal capillaries was normal[28]. MEWDS probably is a primary pathology of retinal pigment epithelium (RPE) or photoreceptor[29-30]. Recent studies have shown that MEWDS primarily affects the outer segments of photoreceptors and the inner segments have been relatively reserved[30-32].

Clinical Manifestation The most common symptoms include acute blurred vision, photopsia, enlarged blind spot or scotomas. Floaters, dyschromatopsia and metamorphopsia may also be presented[33-35]. Patients often have no inflammatory sign in anterior chamber. There may be trace vitreous cells with varying degree of disc edema and congestion[18,32,36]. Some patients may present with relative afferent pupillary defect. In addition, a few patients may present with special performance like periorbital pain[35,37-38].

Imaging Findings

Color fundus photography Color fundus photography shows well-defined yellow-white lesions in the outer retina, mostly distribute near the optic disc or around the macula and spread to the mid-periphery[2,14,39]. Including small dots (<200 μm) and larger spots (≥200 μm)[40]. There are orange or white granules in the macula. There may be congestion or edema of optic disk, vascular sheathing and leakage[1,41].

Fundus autofluorescence Fundus autofluorescence (FAF) is more likely to show the lesions than physical examination[2]. The hyperautofluorescence of spots is attributed to the damage of the photoreceptors. The loss of photopigment screen leads to the unmasking of RPE autofluorescence[42]. The spots will gradually resolve after the acute phase, making the hyperautofluorescent dots more apparent. The dots co-localize with hyperreflective materials on optical coherence tomography (OCT), overlying the spots and presenting only where there are spots. The nature of dots remains poorly understood[30,43]. Some studies indicated that the hyperautofluorescence of dots is a result of increased fluorophores such as degenerated photoreceptor material, for example, the precursors of A2E[40]. At the same time, the impaired clearance of RPE accelerates their accumulation[40].

Fundus fluorescein angiography and indocyanine green angiography Fundus fluorescein angiography (FFA) shows a "wreath-like" pattern of hyperfluorescent lesions. Typical cases have featured "dots & spots" on FFA[40]. The hyperfluorescent area on FFA in thought to be the result of choroidal transmission through disruption of the overlying photoreceptor and RPE (window defects)[39]. After the acute inflammation, there may be hyperfluorescent "Jampol dots"[32], which probably represent the atrophy of RPE.

Classic MEWDS shows patchy or geographic hypofluorescence on late ICGA. For a time it's thought to represent hypoperfusion of choriocapillaris, but this theory has been overturned[29]. Some suggest that it's due to the reduced ICG uptake by damaged RPE and the accumulation of inflammatory materials, and these materials have no affinity for ICG[44-45].

Optical coherence tomography and optical coherence tomography angiography OCT shows the disruption of outer retina, disturbance and attenuation of ellipsoid zone (EZ) and interdigitation zone (IZ)[2,29,45]. The disruption of EZ co-localizes with larger spots. Dots are hyperreflective materials over the spots, sometimes they display as linear aggregation

Table 1 Features of ASPPC, TBSLC, PVRL and CAR for differential diagnosis

Items	Typical fundus manifestation	MMI features	Systematic examination
ASPPC	1) Large placoid yellow lesions in the posterior pole, involve the macula; 2) More serious signs of inflammation than MEWDS like vitritis and retinitis; 3) There may be small creamy yellow retinal precipitates.	1) Loss of EZ on OCT, RPE thickening and irregularity with hyperreflective excrescences; 2) Hyperfluorescence and vascular staining or leakage on FFA; Flow deficiency within choroidal capillary on OCTA.	Serological tests, including treponemal and non-treponemal tests.
TBSLC	1) Serpiginous lesions with pigmentary changes, leaving atrophic area and hyperpigmentation after acute stage; 2) The shape of the lesions is irregular than MEWDS; 3) More serious signs of inflammation than MEWDS like vitritis and retinitis.	1) Choriocapillaris flow deficit areas on OCTA; 2) Mixed hyperfluorescent and hypofluorescent areas on FFA. As the lesions heal, there is well-defined hypofluorescence on late ICGA; 3) Outer retinal irregularity and disruption on OCT, with residual pigment clumping and outer retinal atrophy on healed lesions.	1) Tuberculin skin test; 2) interferon-gamma release assays; chest X-ray.
PVRL	Vitreous haze and cell, optic nerve edema, retinal detachment, RPE abnormalities and cream-colored lesions.	1) Vitrous cells, RPE nodularity, sub-RPE deposits and outer retinal hyperreflectivities on OCT; 2) "Leopard pattern" on FFA and FAF; Mixed hyperautofluorescent and hypoautofluorescent areas on FAF; 3) RPE changes on FFA including granularity and staining.	Imaging examination of central nervous system; diagnostic vitrectomy for biopsy; aqueous humor cytokines detection.
CAR	1) There may be no visible fundus changes in the early stage; 2) Retinal pigment changes, optic disc atrophy and thinner vessels in the late stage.	Atrophy of the photoreceptor layer on OCT and it's difficult to repair than MEWDS.	1) Electrophysiology; 2) detection of serum antibodies; systematic examination

ASPPC: Acute syphilitic posterior placoid chorioretinitis; TBSLC: Tubercular serpiginous-like choroiditis; PVRL: Primary vitreoretinal lymphoma; CAR: Cancer associated retinopathy; MMI: Multimodal imaging; MEWDS: Multiple evanescent white dot syndrome; EZ: Ellipsoid zone; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; FFA: Fundus fluorescein angiography; OCTA: Optical coherence tomography angiography; ICGA: Indocyanine green angiography; FAF: Fundus autofluorescence.

extending through the external limiting membrane into the outer nuclear layer (ONL)/outer plexiform layer (OPL)[11,46]. The contribution of OCTA to diagnosis is limited because most cases haven't significant abnormality on OCTA[47].

Treatment and Prognosis MEWDS is self-limited and will recover spontaneously within 2mo with rare recurrence[15]. Worse presenting vision, young age and disc hyperfluorescence on FFA might be possible causes of incomplete vision recovery[2,48]. MEWDS rarely leaves permanent effects[35]. CNV is a rare complication of MEWDS and may lead to vision impairment.

In view of the spontaneous recovery, anti-inflammatory or immunosuppressive therapy is not recommended unless there are sight-threatening complications[35]. In some cases, the complicated CNV regressed following intravitreal anti-vascular endothelial growth factor (anti-VEGF)[49-50] but it is unclear whether the administration of anti-VEGF could prompt the resolution of MEWDS.

PRESENTATIONS SIMILAR TO MEWDS IN OTHER DISORDORS

Masqueraders of MEWDS Many other systematic/ocular diseases may be misdiagnosed as MEWDS since part of their presentations are similar to MEWDS[11]. These systematic/ocular diseases are regarded as masqueraders of MEWDS. The patients have presentations similar to MEWDS in different degrees. But such presentations will change with the development of real systematic/ocular diseases. And the presentations similar to MEWDS will disappear after the treatment of systematic/ocular diseases, which is different from classic MEWDS. We summarized the diseases that are most commonly misdiagnosed as MEWDS and list their characteristics for differential diagnosis (Tables 1 and 2).

Infectious Conditions

Ocular syphilis Ocular syphilis is a great masquerader as many symptoms and signs can mimic other eye disorders[51]. Acute syphilitic posterior placoid chorioretinitis (ASPPC) is the most relevant type[51]. Moraes *et al*[52] reported a 31-year-old white man presented with bilateral foveal granularity and gray-white dots scattered in the posterior pole, corresponding to EZ disruption on OCT. But his symptoms still did not improve after 6mo. Funduscopy showed an outer retinal placoid lesion and systemic tests suggested a positive result for syphilis[52]. Similarly, Azar *et al*[10] reported a case of a 59-year-old man presented with painless visual impairment of both eyes after minimal flu-like symptoms. Signs on MMI were particularly like MEWDS. But a full examination suggested ASPPC as the final diagnosis. In above cases, the ophthalmological manifestations improved significantly after penicillin treatment. ASPPC is easily confused with MEWDS but can be distinguished. Studies found ASPPC may have choriocapillaris perfusion flow voids or defects on OCTA[53-56]. In addition, ASPPC might have more obvious inflammatory manifestations like vitritis or retinal vasculitis. And the damage of outer retina is more serious than MEWDS. Presentations similar to MEWDS has also been reported in syphilitic outer retinitis. In the report from Russell *et al*[11], two patients with syphilitic

Table 2 Characteristics of other WDS diseases for differential diagnosis

Items	Typical fundus manifestation	MMI characteristics
MFC/PIC	1) Multiple well-defined yellow-white chorioretinal lesions; 2) Progressive chorioretinal atrophy and scarring; 3) Inflammatory reaction is obvious than MEWDS.	1) Atrophy of outer retina and inner choroid with punched-out scars; 2) Acute lesions exhibit early hypofluorescence with late hyperfluorescent staining on FFA; 3) Atrophic lesions appear as window defects on FFA and hypoautofluorescence on FAF; 4) ICGA shows hypofluorescent lesions; 5) The performance of CNV.
APMPPE	Yellow, creamy placoid lesions in the posterior pole, often in various stages.	1) OCT shows hyperreflectivity of outer retina in the early stages. Disruption of outer retina and RPE atrophy in the resolved areas; (2) FFA shows early hypofluorescence and late hyperfluorescence. Hypoautofluorescence on FAF. Hypoperfused areas on OCTA corresponding to the hypofluorescent areas on ICGA.
SC	1) Serpentine lesions with chronic and progressive sub-retinal infiltrates; 2) Geographic scarring. Atrophy involving the choriocapillaris and RPE.	1) Active lesions have hyperreflectivity and thickening of outer retina, disruption of photoreceptor layers; 2) FFA shows early hypofluorescence and late hyperfluorescence. The old lesions have window defects and staining on FFA; 3) The inactive lesions appear as well defined hypofluorescence on ICGA and hypoautofluorescence on FAF.
BCR	1) Oval or circular creamy lesions with a birdshot style; 2) Retinal vasculitis and/or CME presentation.	1) OCT shows outer retinal disruption and atrophy of choroid; 2) FA reveals unique “quenching” of BCR; 3) The atrophic area shows hypoautofluorescence on FAF.
AZOOR	1) Fundus appearance may be normal; 2) Followed retinal vessels attenuate and pigmentary changes like retinitis pigmentosa.	1) Thinning or atrophy of the outer retina on OCT; 2) characteristic trizonal pattern on MMI.
ARPE	Multiple cluster yellow-white pigmentary alteration near the macular.	1) FFA shows cluster hypofluorescent lesions with hyperfluorescent margins; 2) OCT reveals hyperreflectivity of RPE, discontinuity of the outer retina, residual RPE atrophy.

WDS: White dots syndrome; MMI: Multimodal imaging; MFC: Multifocal choroiditis; PIC: Punctate inner choroidopathy; MEWDS: Multiple evanescent white dot syndrome; FFA: Fundus fluorescein angiography; FAF: Fundus autofluorescence; ICGA: Indocyanine green angiography; CNV: Choroidal neovascularization; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; OCTA: Optical coherence tomography angiography; SC: Serpiginous choroiditis; BCR: Birdshot chorioretinopathy; CME: Cystoid macular edema; AZOOR: Acute zonal occult outer retinopathy; ARPE: Acute retinal pigment epitheliitis.

outer retinitis presented with widespread presentations like MEWDS.

Ocular tuberculosis Ocular tuberculosis can masquerade as other disorders like retinoblastoma, vasculitis, or atypical ocular toxoplasmosis[57-59]. Nicolau *et al*[60] described a patient with presumed ocular tuberculosis masquerading as MEWDS. The patient presented with sudden blurred vision and paracentral scotoma of the left eye. Fundus exam revealed deep retinal gray-whitish dots predominantly in the upper nasal quadrant. FAF showed hyperautofluorescent lesions, corresponding to the hyperfluorescence on FFA. Some lesions had a “wreath-like” appearance. OCT showed disruption of EZ corresponding to the lesions on FAF. All of the above are consistent with MEWDS. The tuberculin skin test was positive and his family members had a history of tuberculosis. After 5mo of anti-tuberculosis treatment, visual acuity improved and white dots resolved. FAF and FFA exams were also improved. Khochtali *et al*[61] described a patient with latent tuberculosis presented like MEWDS in the left eye. ICGA and OCTA findings suggested choriocapillaris ischemia, which is atypical in MEWDS. After treatment of latent tuberculosis, visual acuity had improved and white dots had completely resolved.

Ocular tuberculosis has varied clinical phenotypes, tubercular serpiginous-like choroiditis is easy to be confused with MEWDS because of the multifocal yellow-white lesions[62]. Chest radiography and tuberculin test could indicate tuberculosis infection[63]. Antituberculosis treatment can effectively inhibit tuberculosis associated ocular symptoms[64-66].

Other infectious conditions Punctate outer retinal toxoplasmosis (PORT) is a rare variant of ocular presentation after toxoplasma infection. The characteristic manifestation of PORT is multiple gray-white lesions in deep retina and RPE layer, probably with mild vitritis. Toxoplasma infection displays a geographical variation, and part of PORT patients have bilateral involvement[67]. Multiple punctate lesions may be mistakenly regarded as the lesions of MEWDS without further examination[59,68-70]. Parasite DNA detection is helpful to make a definitive diagnosis. Bartonella neuroretinitis and human immunodeficiency virus retinopathy have also been reported with presentations like MEWDS[7,11].

Neoplastic Conditions

Primary vitreoretinal lymphoma Primary vitreoretinal lymphoma (PVRL) is a rare tumor originating from the vitreoretinal tissue and is the most common type of intraocular lymphoma[71-73]. In previous studies, PVRL is another common disease presenting with features like MEWDS besides syphilis[7,11]. Russell *et al*[11] reported two patients with PVRL misdiagnosed as MEWDS. The grey-white spots in outer retina corresponded to EZ disruption, and the lesion had a wreath-like pattern on FFA. PVRL was confirmed several years later. With the treatment of PVRL, the ocular symptoms disappeared[11].

Although the early stage of PVRL may be similar to MEWDS, most cases can be identified by clinical features or imaging findings. Detection of aqueous humor cytokines can be used for the monitoring of PVRL[74].

Cancer Associated Retinopathy Cancer associated retinopathy (CAR) is a rare type of paraneoplastic retinopathy[75]. Patients may have symptoms similar to MEWDS like painless vision loss and photopsias[76]. In previous report of CAR, hyperautofluorescent lesions distributed in peripapillary region and extended along the major vessels, sparing the central macula. The lesions corresponded to photoreceptor layer loss and hyperreflective ONL on OCT[77]. CAR should be considered when patients with tumor history present with features like MEWDS. Patients suspected of CAR should be further examined to detect systematic tumors as soon as possible.

Autoimmune or Inflammatory Conditions The autoimmune or inflammatory diseases that need to be differentiated from MEWDS most is white dot syndrome (WDS) diseases. Actually, the relationship between WDS and MEWDS is unclear[15,42,78-79]. Due to similar demography and clinical performance, MEWDS used to be one of the WDS diseases, along with MFC, Acute zonal occult outer retinopathy (AZOOR), Acute posterior multifocal placoid pigment epitheliopathy, *etc*.

In fact, it is not appropriate to regard them as the masqueraders of MEWDS without further examination. After our further understanding of these diseases, many cases were identified as secondary MEWDS followed by WDS disease (we described these conditions in the next section). However, the mechanism, treatment and prognosis of MEWDS are different from other WDS[1,42]. So, it is necessary to distinguish them.

Multifocal choroiditis MFC is an inflammatory fundus disease involving the choroid, RPE, and outer retina, with many common features with MEWDS. Russell *et al*[11] described a 38-year-old myopic woman of MFC masquerading as MEWDS. There were multiple gray outer retinal lesions easily visualized on FAF. OCT through the lesions showed EZ disruption and hyperreflective materials of the outer retina. The lesions were hyperfluorescent with intermix hypofluorescence on ICGA and resolved after oral prednisone. She had a final diagnosis of MFC. It's not appropriate to classify MFC as a masquerader of MEWDS as the relationship between the MFC and MEWDS is still controversial[37,80-82].

Acute zonal occult outer retinopathy AZOOR is an inflammatory disorder with outer retinal dysfunction. In the report by Russell *et al*[11], a 42-year-old woman showed bilateral gray-white spots and a large annular ring at the disk margin in left eye. The lesions were hyperautofluorescent. ICGA showed hypofluorescent lesions on the late stage. OCT showed the disruption of EZ, with high reflection of ONL. Thus, a diagnosis of MEWDS was made. Three months later the lesion remained unresolved and the patient was diagnosed with AZOOR eventually. In the acute phase of AZOOR, the periphery of the lesion sometimes exhibit as punctate hyperautofluorescent dots similar to MEWDS[83].

The characteristic trizonal pattern can help in the diagnosis of AZOOR. In addition, AZOOR may lead to irreversible visual field defects and obvious abnormality on retinal electrophysiological examination.

Other WDS diseases Acute posterior multifocal placoid pigment epitheliopathy sometimes may be misdiagnosed as MEWDS[11]. Most of WDS cases can be identified by the characteristic fundus findings [84-85]. We list some distinguishing features of WDS diseases (Table 2). MFC and punctate inner choroidopathy (PIC) can be considered as same kind of disease to be identified with MEWDS.

Other conditions Russell *et al*[11] described a 28-year-old retinal phlebitis patient masquerading as MEWDS. Levine *et al*[8] reported a 23-year-old female with sarcoidosis after gastrointestinal viral illness and the MMI findings were similar to MEWDS. However, OCTA showed flow deficit of choroidal capillary, which is not typical in MEWDS. In addition, presentation similar to MEWDS may also occur in macular diseases[7].

Secondary MEWDS "MEWDS-like" reaction is being reported by more and more researchers[2,29,46]. Briefly, the presentations similar to MEWDS appeared in patients with other disorders. As described by Jampol and Becker[23], classic MEWDS is idiopathic and can resolve spontaneously[2,29,46]. The biggest difference between classic MEWDS and MEWDS-like reaction is that MEWDS-like reaction has a definite etiology. So MEWDS-like reaction is regarded as secondary MEWDS, which looks like classic MEWDS on clinical manifestations and imaging findings, including characteristic "dots & spots" and spontaneous resolution[2,29,46].

Discovery of secondary MEWDS Gliem *et al*[86] found 5% of patients with pseudoxanthoma elasticum would experience a specific acute retinopathy. Symptoms include different degrees of visual loss, hazy vision, scotoma, *etc*. All patients with this acute retinopathy revealed characteristic fundus features with evanescent outer retinal whitish dots at the posterior pole, corresponding to hyperautofluorescence on FAF, hyperfluorescence on FFA, and loss of EZ on OCT. Electroretinography showed variable reduction of amplitudes. Anti-retinal or anti-RPE autoantibodies were positive in some patients[86]. The performance shares some similarities with MEWDS, so it is regarded as a "MEWDS-like" reaction. MEWDS mainly affects otherwise healthy individuals, but MEWDS-like reaction occurs under the presence of other

Table 3 Summary of reports of "MEWDS-like" or secondary MEWDS

History or coexisting conditions associated with "MEWDS-like" or secondary MEWDS	Patients (*n*)	Eyes (*n*)	Report and year
Chorioretinitis (including MFC/PIC)	61	64	Cicinelli *et al*[36], 2021; Essilfie *et al*[45], 2022; Serrar *et al*[46], 2022; Meng *et al*[15], 2023; Ong *et al*[91], 2023; Chen *et al*[77], 2017
CNV	15	16	Cicinelli *et al*[36], 2021; Burke *et al*[13], 2022; Serrar *et al*[46], 2022; Desira *et al*[12], 2024
Myopia and lacquer cracks	7	7	Ong *et al*[91], 2023; Essilfie *et al*[45], 2022; Ong *et al*[91], 2023
Surgery/photocoagulation	3	3	Essilfie *et al*[45], 2022; Ong *et al*[91], 2023; Mirzania *et al*[93], 2023
AS	1	1	Ong *et al*[91], 2023
CSC	1	1	Ong *et al*[91], 2023
SO	1	1	Cicinelli *et al*[1], 2023
Chorioretinal scarring	5	5	Serrar *et al*[46], 2022; Ong *et al*[91], 2023
Other conditions	11	12	Duong *et al*[33], 2022; Wiley *et al*[18], 2022; Serrar *et al*[46], 2022

MEWDS: Multiple evanescent white dot syndrome; MFC: Multifocal choroiditis; PIC: Punctate inner choroidopathy; CNV: Choroidal neovascularization; AS: Angioid streaks; CSC: Central serous chorioretinopathy; SO: Sympathetic ophthalmia.

eye disorders. For example, MEWDS-like reaction can occur simultaneously or successively with choroiditis, or present in eyes with Best disease or history of vitreoretinal surgery[2,29,46]. This may be a coincidence but also gives us a question: although they seem to be unrelated, is there a potential connection between coexisting diseases and MEWDS-like reaction.

Cicinelli *et al*[36] described the features of MEWDS-like patients with an ocular history positive for previous or concurrent ocular events. They put forward a hypothesis that MEWDS-like reaction is a secondary reaction caused by coexisting diseases as an epiphenomenon MEWDS, it has independent progression and resolution and doesn't affect the course and prognosis of coexisting diseases. Their hypothesis was further proved by Meng *et al*[15]. They described the MEWDS-like reaction caused by MFC/PIC. They found the course of MEWDS-like reaction were independent from the MFC/PIC and the occurrence of MEWDS-like lesions would not affect the coexisting MFC/PIC[15].

MEWDS-like reaction has a definite cause, which is different from classic MEWDS[15]. So researcher began to take it as the secondary form of MEWDS[15]. Many conditions are associated with secondary MEWDS. For example, angioid streaks (AS) of pseudoxanthoma elasticum patients, ocular trauma and subretinal hemorrhage, *etc*[87-89]. In 2022, Essilfie *et al*[45] summarized the features of MEWDS-like reaction under other disorders of posterior segment. These seemingly unrelated conditions have a common pathological feature-the disruption of RPE-Bruch's membrane-choriocapillaris (RPE-BM-CC) complex. For this reason, classic MEWDS without specific etiology, described by Jampol *et al*[24], can be considered as primary MEWDS, while the MEWDS-like reaction secondary to the damage of RPE-BM-CC complex is secondary MEWDS[45].

We conducted a search using the PubMed database, employing the keywords "MEWDS-like" and "secondary MEWDS", studies published between January 2021 and January 2024 were reviewed, and we summarized them in Table 3.

Nature of secondary MEWDS Secondary MEWDS is often found with inflammatory chorioretinopathies[46]. In the cases of MEWDS secondary to CNV, chorioretinal inflammatory lesions can present simultaneously with MEWDS or before or after the onset of MEWDS[81]. This suggests the inflammatory environment is an important factor to induce the reaction. Fung *et al*[88] described a case of MEWDS developed ten weeks after a traumatic subretinal hemorrhage in a 24-year-old female. The author hold that blunt ocular trauma might resulted in secondary MEWDS due to the exposure of choroidal antigens. Considering the temporal relationship between the traumatic event and secondary MEWDS, dehemoglobinized blood could be the inciting event as well[88].

According to the theory by Essilfie *et al*[45], coexisting chorioretinal disorders lead to the damage of RPE-BM-CC complex then cause secondary MEWDS as an epiphenomenon (epi MEWDS), which is parallel to the primary pathology. How does the disruption of RPE-BM-CC complex trigger secondary MEWDS? According to a presumption proposed by Abdelhakim *et al*[90], disruption of the RPE-BM-CC complex damages the retinal barrier to expose the outer retinal antigens, leading to the loss of immune privilege. When the outer retinal antigens are recognized by the immune system, autoantibodies will be produced, triggering an autoimmune response, leading to temporal inflammatory manifestations. The autoantibodies in some secondary MEWDS patients supported the autoimmune process in secondary MEWDS[86].

In previous studies, secondary MEWDS was most associated with MFC/PIC[15,45]. The mechanism of MEWDS secondary to MFC/PIC remains unclear. By the above theory, the inflammatory reaction in MFC/PIC can disrupt the RPE-BM-CC complex and lead to secondary MEWDS. Meng *et al*[15] found the abnormalities of the RPE-BM-CC complex always

Table 4 Comparison between classic and secondary MEWDS

Items	Classic MEWDS	Secondary MEWDS
Demography	Young to middle-aged women, with no geographical or racial tendency	Most are young women, older than primary MEWDS
History	Low to moderate myopia	Disorder or manifestation that disrupt RPE-BM-CC complex, myopia may be higher than classic MEWDS
Etiology	Unclear, may be related to the viral infection	Disruption of RPE-BM-CC complex
Symptoms	Blurred vision, photopsia, enlarged blind spot, scotomas with or without prodromal flu-like episode	Presentations of coexisting disorder, with visual symptoms like classic MEWDS
Representative fundus findings	Macular granularity, yellow-white lesions in outer retina, characteristic dots & spots on FAF and angiography, EZ interruption and hyperreflective material on OCT, mild inflammatory sign	Findings like classic MEWDS on MMI, with coexisting disorder, inflammatory response may be severe than classic MEWDS
Distribution	In the posterior pole, most centered on the optic disc or macula	Smaller than classic MEWDS, starting from the site or quadrant of coexisting pathology, lower symmetry than classic MEWDS
Laterality	Most are unilateral, also can be bilateral	Depend on the coexisting disorder
Prognosis	Spontaneous resolution in 2mo generally without sequelae, rarely recurrence	Spontaneous resolution like classic MEWDS, the prognosis and recurrence are influenced by coexisting disorder

MEWDS: Multiple evanescent white dot syndrome; RPE-BM-CC: Retinal pigment epithelium-Bruch's membrane-choriocapillaris; FAF: Fundus autofluorescence; EZ: Ellipsoid zone; OCT: Optical coherence tomography; MMI: Multimodal imaging.

appeared before or simultaneously with the onset of secondary MEWDS. In addition, as a common complication of MFC/PIC, CNV is also an important factor to promote secondary MEWDS by inflammatory environment[81].

Characteristics of Secondary MEWDS Secondary MEWDS is different from classic MEWDS in many aspects[46,91]. Serrar *et al*[46] compared classic MEWDS and MEWDS secondary to coexisting PIC/MFC, Best disease, *etc*. They found that the proportion of women, spherical equivalent, subfoveal choroidal thickness and best-corrected visual acuity at baseline were similar in both groups, but patients with secondary MEWDS were older and had higher inflammatory scores. The lesions of secondary MEWDS were significantly smaller and less symmetrical with respect to both horizontal and vertical axis[46]. A study in 2023 demonstrated different topographic distributions of two forms of MEWDS[91]. In most cases of classic MEWDS, the lesions were centered on the optic disc or macula. Consistent with previous view[46], secondary MEWDS usually centered on the lesion that presumably triggered the MEWDS episode then extend to other areas.

We compare the features of classic and secondary MEWDS (Table 4). It can be argued that secondary MEWDS is equivalent to classic MEWDS plus the coexisting pathology. Similar with the classic MEWDS, secondary MEWDS also has characteristic "dots & spots", and the evolution of lesions is relatively independent, with spontaneous resolution without sequelae[2,29,46]. The difference is secondary MEWDS has the fundus presentation of the coexisting pathology. A more severe inflammatory response may occur when MEWDS is secondary to severe choroiditis, while the inflammatory response of the classic MEWDS is very mild[46]. When the primary pathology is chronic and likely recurrent, secondary MEWDS may occur simultaneously with the recurrence[81]. If the primary pathology is unilateral, secondary MEWDS tends to take place in the ipsilateral eye[36]. The prognosis of secondary MEWDS is related to the underlying pathology. If the underlying pathology has no significant effect on vision, the vision prognosis will not be particularly bad even if secondary MEWDS occurs.

DISCUSSION

Classic MEWDS have no definite cause and can resolve spontaneously. But according to our summary, patients with disorders other than MEWDS may also have similar presentations to MEWDS. Such presentations can be divided into two states—masqueraders of MEWDS or secondary MEWDS. They are different from classic MEWDS. Their main features are listed in Table 5.

The nature of masqueraders of MEWDS has nothing to do with MEWDS[11]. Because a part of MMI findings look like MEWDS, the masqueraders may be misdiagnosed as MEWDS[91]. Neri and Pichi[92] point out that syphilis is the most common "masquerader"; while acute symptomatic platelet count reduction with purpura (ASPPC) was first proposed in 1990. Later studies showed ASPPC is an inflammatory reaction of the outer retina and inner choroid[93-94]. Thus, we can speculate that the inflammatory reaction is limited and mild in the early stage of ASPPC and might only involve the outer retina. At this time, ASPPC manifests as an inflammatory reaction of the outer retina like MEWDS. With the progression of ASPPC, more severe and unique manifestations appear, which is different from MEWDS[93-94]. It's the same for other masqueraders of MEWDS. This explains why these diseases are easily confused with MEWDS in their early stage[11].

The masqueraders are similar to MEWDS in different degrees. Some have only a part of morphological similarity

Table 5 Comparison between classic MEWDS and presentations similar to MEWDS in masqueraders of MEWDS and secondary MEWDS

Items	Etiology	Course	MMI findings
Classic MEWDS	Idiopathic, no definite cause	Self-limited course, spontaneous resolution	Yellow-white lesions, characteristic dots & spots, outer retinal interruption
Presentations similar to MEWDS under other conditions			
Masqueraders of MEWDS	Systematic/ocular disease, the most common is syphilis	Progress/regress along with systematic/ocular disease	Findings of systematic/ocular disease, including different degrees of similarity with MEWDS
Secondary MEWDS	Disruption of RPE-BM-CC complex	Self-limited course, spontaneous resolution	Findings of classic MEWDS plus coexisting pathology

MEWDS: Multiple evanescent white dot syndrome; MMI: Multimodal imaging; RPE-BM-CC: Retinal pigment epithelium-Bruch's membrane-choriocapillaris.

and some have consistent characteristics on many kinds of examinations[91]. It's related to their different mechanisms. For PVRL, the lymphoma cells are deposited and infiltrated between RPE and Bruch's membrane, makes part of the appearance on OCT like MEWDS[95]. The presentations similar to MEWDS on MMI will change with the real systematic/ocular disease, and this is an obvious difference from classic MEWDS. Such presentations will progress with the aggravation of real disease and improve with the treatment of real diseases. For example, after penicillin treatment for syphilis, the lesions similar to MEWDS caused by syphilis would also disappear[11]. This also reflects that the similar presentation is a part of the masquerader's manifestation. The real disease may need early treatment[11], so it's significant to remember the features of these masqueraders for differential diagnosis. When the presentation of the real disease is atypical in the early stage, we should avoid the preconception of MEWDS diagnosis.

Unlike the masqueraders, secondary MEWDS could be taken as a special form of MEWDS. The biggest difference between classic MEWDS and secondary MEWDS is that classic MEWDS has no definite cause, while secondary MEWDS is caused by the disruption of RPE-BM-CC complex[45]. A variety of pathology/iatrogenic conditions might give rise to secondary MEWDS[81,88-89]. Because of the definite cause, secondary MEWDS is different from classic MEWDS in some respects (Table 4). For example, the lesions of secondary MEWDS tend to appear from the area or quadrant of the coexisting pathology[46,91,96]. These differences also reveal the correlation between coexisting pathology and secondary MEWDS. The self-limited course and characteristic "dots & spots" of secondary MEWDS are the same as classic MEWDS. This suggests the two forms of MEWDS may have some overlapping mechanisms.

The evolution of secondary MEWDS is relatively independent from the coexisting pathology. We think the independence of secondary MEWDS is because of the coexisting pathology is not the direct reason for secondary MEWDS but through the destruction of RPE-BM-CC complex[45]. In addition,

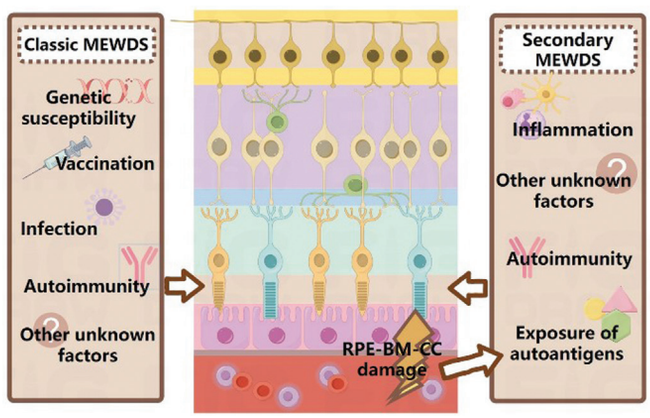

Figure 1 Differences in pathogenesis between classical and secondary MEWDS Factors like infection and genetic susceptibility may play a role in the pathogenesis of classical MEWDS. Secondary MEWDS is related to the destruction of RPE-BM-CC complex. MEWDS: Multiple evanescent white dot syndrome; RPE-BM-CC: RPE-Bruch's membrane-choriocapillaris.

inflammatory factors play a significant role in the triggering of secondary MEWDS[46]. Many reports have described MEWDS secondary to the occurrence of inflammatory CNV[81]. The most reasonable mechanism is the inflammatory environment caused by CNV[97]. And the occurrence of CNV also represents the retinal barrier damage and active inflammation[98]. In previous reports, secondary MEWDS would recovered spontaneously. But the occurrence of secondary MEWDS may be related to the activity of coexisting pathology, indicating that the course and duration of secondary MEWDS may be affected by the coexisting pathology[81]. It still needs to be studied. And if secondary MEWDS could reflect the activity of coexisting pathology to some extent, we should treat the primary disorder actively when secondary MEWDS appeared. Meanwhile, classic MEWDS is regarded as having a close association with autoimmunity. We use a picture to describe the pathogenesis of classic and secondary MEWDS (Figure 1). The occurrence of MEWDS might be initiated by elements like viral infections that can stimulate the body's autoimmune reactions. For instance, when viruses, such as particular ones belonging to the herpes virus family, enter the

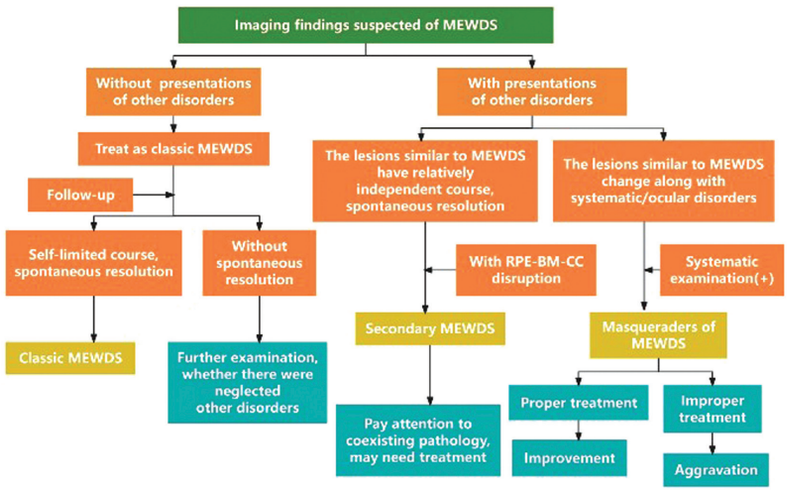

Figure 2 Diagnostic approach for patients with presentations similar to MEWDS Different situations should be taken into account. MEWDS: Multiple evanescent white dot syndrome; RPE-BM-CC: RPE-Bruch's membrane-choriocapillaris.

human body, they may display their antigenic constituents on the surface of retinal cells. In the procedure of identifying these foreign antigens, the body's immune system may erroneously recognize and assault certain antigens of the retina as if they were foreign invaders. The commencement of such autoimmune responses constitutes a vital aspect in the development mechanism of classic MEWDS. thereby leading to retinal lesions. In certain patients, irregularities in immune markers like circulating immune complexes, IgG, IgM, IgA, and antinuclear antibody (ANA) can be found. Case reports have indicated that a 30-year-old women manifested MEWDS two weeks subsequent to contracting COVID-19, which implies that the COVID-19 virus might be triggering certain autoimmune responses[99].

MEWDS used to be an important component of WDS[100-101]. But the mechanism of MEWDS is different from other WDS diseases, and the inflammatory reaction in MEWDS is the least compared with other WDS diseases[29]. We think MEWDS is a primary disorder of photoreceptors, specifically, it primarily affect the outer segments of photoreceptors[102]. There are no sequelae and rare complications after spontaneous recovery, suggesting the inflammation of MEWDS is not enough to cause permanent damage[102]. On the contrary, in the diseases related to RPE damage, there will be pigmentation and permanent loss of function[103]. The study using adaptive optics imaging and en-face OCT reconstructions have proved our speculation[30,32]. There is a long-term dispute on the relationship between MEWDS and MFC about whether they are continuums of the same disease or two distinct entities[15,45]. The recognition of secondary MEWDS can explain this disputation to some extent. The destruction of RPE-BM-CC complex in MFC can lead to secondary MEWDS, and CNV, the most common complication of MFC, will aggravate the destruction of RPE-BM-CC complex and inflammatory reaction, also contribute to the generation of secondary MEWDS. On the contrary, we think MEWDS is unlikely to trigger MFC. Because the inflammation of MEWDS is too slight to involve the choroidal capillaries[28].

According to the mechanism of secondary MEWDS, we can explain the possible mechanism of classic MEWDS. The longer axial of myopic eye changes the fundus structure, makes the RPE-BM-CC complex vulnerable to be damaged, and promotes the invasion of virus, eventually leads to autoimmune and inflammatory reactions[104-105]. Young women are susceptible population of autoimmune disorders. This also explains why most patients with MEWDS are myopic female.

In conclusion, presentations similar to MEWDS may appear under other conditions. Classic MEWDS is an evanescent inflammation of the outer retina with no definite etiology. The masqueraders of MEWDS have morphological similarities with MEWDS, but according to the real diagnosis, they have own etiologies and courses. Secondary MEWDS is a special form of MEWDS, which can be triggered by disruption of RPE-BM-CC complex. Similar as classic MEWDS, secondary MEWDS will recover spontaneously, and also has characteristic "dots & spots" on MMI. However, secondary MEWDS has a definite cause, which is not seen in classic MEWDS. Usually, we regard MEWDS as a common cold of retina, which does not need treatment. But for masqueraders or secondary MEWDS, there may be underlying severe diseases that need to be treated as soon as possible, and we summarized a flow chart of different situations (Figure 2). Consequently, we can depend on the imaging manifestations and integrate them with the existence or non-existence of the related manifestations of other diseases to more comprehensively ascertain whether it is the classic MEWDS or other diseases analogous to MEWDS, thus enhancing the precision of the diagnosis results. We should pay attention to patients suspected

of MEWDS, and be careful to identify the presentations similar to MEWDS.

Although we fully utilized the PubMed database resources in this review, eliminating the necessity of recollecting a substantial amount of data as in traditional research, thereby saving time and cost and enhancing research efficiency, it should be noted that there remain numerous large-scale gene databases currently accessible, such as GWAS Catalog, IEU, UK Biobank, *etc.* and these databases likewise possess abundant gene information and associated phenotypic data. Furthermore, we are able to mine additional potential associated information from these databases.

ACKNOWLEDGEMENTS

Authors' Contributions: Liu ZY and Zhang H collected literatures, conceived the experiments and drafted the manuscript. Sun XL evaluated the literatures, extract data and performed the statistical analysis. All authors read and approved the final manuscript.

Artificial Intelligence Statement Disclosure: The authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Conflicts of Interest: Liu ZY, None; **Zhang H,** None; **Sun XL,** None.

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