Multiple evanescent white dot syndrome and panuveitis: a case report

Kazuomi Mizuuchi, Wataru Saito, Kenichi Namba and Susumu Ishida

Abstract
Aim: To report a patient with multiple evanescent white dot syndrome (MEWDS) complicated by iridocyclitis and vitritis.
Case description: A 70-year-old woman developed multiple subretinal white dots, iritis, and diffuse vitreous opacity. Angiographic and macular morphological features were consistent with those of MEWDS. Inflammatory findings including the white dots improved following only topical dexamethasone within 1 month after the initial visit. Best-corrected visual acuity recovered to 1.0 with restored photoreceptor structure.
Conclusion: The presence of iridocyclitis and vitritis, atypical to MEWDS, indicates the concurrent development of panuveitis associated with MEWDS. These results suggest that MEWDS is a clinical entity of uveitis.
Keywords: Choroiditis, Iridocyclitis, Multiple evanescent white dot syndrome, Panuveitis, Vitritis

Background
Multiple evanescent white dot syndrome (MEWDS) is a unilateral inflammatory disease characterized by multiple subretinal white dots extending from the posterior pole to the mid-periphery, which spontaneously resolve with no scarring. In eyes with MEWDS, anterior chamber and/or anterior vitreous cell infiltration can occur; however, the grade of inflammation is usually mild [1]. We herein report a rare case of MEWDS complicated by iridocyclitis with diffuse vitreous opacity.

Case report
A 70-year-old woman presented with a month-long history of blurred vision and photopsia of her left eye. She had medical history of well-controlled systemic hypertension and hyperlipidemia and had no particular family history.

Her best-corrected visual acuity (BCVA) was 1.0 OD and 0.3 OS with mild hyperopia. The right eye was normal except for incipient cataract. Slit-lamp examination revealed 1+ flare and 1+ cells in the anterior chamber together with the infiltration of anterior vitreous cells OS. Her left fundus was hazy due to 2+ diffuse vitreous opacity; and multiple subretinal white dots could thus be barely observed at the mid-periphery (Fig. 1a).

Corresponding to the white dots, fluorescein angiography (FA) showed hyperfluorescence as well as at the peripapillary area in the late phase (Fig. 1b) and indocyanine green angiography (ICGA) revealed no abnormal findings in the initial phase (Fig. 1c) but numerous hypofluorescent dots were visible not only at the white dots but also diffusely around the posterior pole including the optic disc vicinity in the late phase (Fig. 1d). Optical coherence tomography (OCT) showed diffuse loss of the ellipsoid zone (EZ) at the macula OS (Fig. 1e). Goldmann perimetry revealed a ring scotoma of 50 × 70 degrees OS. Single-flash electroretinography showed a reduced amplitude of the a-wave OS. Screening tests were negative for the detection of syphilis, tuberculosis, and sarcoidosis. The patient was followed up with only topical 0.1% betamethasone under a diagnosis of presumed MEWDS OS, although the presence of vitritis was
atypical for MEWDS. Five days later, the number of the white dots, anterior chamber inflammation, and diffuse vitreous opacity were reduced. Seventeen days after the first visit, her BCVA improved to 1.0. Hyperfluorescence on FA and hypofluorescent dots on ICGA initially observed almost disappeared (Fig. 2a, b). Three weeks after the first visit, macular EZ loss improved (Fig. 2c), followed by the regression of diffuse vitreous opacity and subretinal white dots OS (Fig. 2d). Electroretinography and perimetry normalized after 3 months. Brain magnetic resonance imaging and systemic computed tomography revealed no abnormal findings. There were no recurrences of intraocular inflammation until 63 months after the initial visit. Her BCVA maintained at 1.0 OD and 0.9 OS.

**Discussion**

We encountered a case of atypical MEWDS complicated by iridocyclitis with diffuse vitreous opacity. The presence of blurred vision with photopsia, unilateral multiple subretinal white dots, features of FA, ICGA, and OCT at the acute stage was consistent with the features of MEWDS. Moreover, resolution of the white dots with no scaring, recovery of OCT, angiographic, and electroretinographic findings, and favorable visual prognosis with no recurrence of intraocular inflammation for a long-term follow-up period supported a diagnosis of MEWDS. On the other hand, the presence of intraocular inflammation with vitritis, the onset at the advanced age, and the development in a hyperopic eye were atypical for MEWDS.
Diseases masquerading as MEWDS are considered as the differential diagnosis of this case [2]. In the present case, ICGA showed initial normal and late numerous dot-shaped hypofluorescent appearances extending from the peripapillary area and posterior pole to the mid-periphery containing funduscopically visible white dots, which rapidly resolved with no scarring. The features were characteristic of MEWDS [3] and were inconsistent with those of white dot syndrome other than MEWDS including multifocal choroiditis and birdshot chorioretinopathy (hypofluorescence from the initial phase and the development of scar lesions with time corresponding to exudates). Syphilitic chorioretinitis was denied from negative infectious serology. In patients with intraocular lymphoma, the recurrence of ocular involvement is common and the survival rate is poor [4], even if ocular lesions initially respond with systemic corticosteroid treatment. In our case, favorable visual and systemic prognosis with no recurrence of intraocular inflammation for a long-term follow-up period is incompatible with the clinical course of intraocular lymphoma, although vitreous biopsy was not performed. Similarly, cancer-associated retinopathy is unlikely to be considered, although anti-retinal antibodies were not examined.

The localization and origin of subretinal white dots in MEWDS is still controversial. Studies using fundus autofluorescence have revealed hyper-autofluorescence corresponding to the white dots at the acute stage of MEWDS, suggesting impairment of the retinal pigment epithelium [5]. Previous studies showed hypo-reflective lesions at the level of the photoreceptors but no abnormal findings at the choriocapillaris on en face OCT with flow preservation at the choriocapillaris on OCT angiography corresponding to the white dots [6, 7]. These observations may indicate that the photoreceptor is primarily affected in MEWDS. In eyes with MEWDS, multiple hypofluorescent dots observed on ICGA suggest
the involvement of hypoperfusion in the choriocapillaris [3]. In white dot syndromes other than MEWDS, such as serpiginous choroiditis, multifocal choroiditis (MFC) and panuveitis, and acute posterior multifocal placoid pigment epitheliopathy (APMPPE), OCT angiography demonstrated the reduction of choriocapillaris flow [7], suggesting the choroid as a susceptible lesion targeted in these diseases. On the other hand, contradictory results on OCT angiography (i.e., reduced versus preserved flow void at the choriocapillaris) have been reported in eyes with MEWDS [6–8]. Moreover, most recent studies using OCT angiography demonstrate that flow void at the choriocapillaris corresponding to the white dots of MEWDS may at least lie not only in the photoreceptors but also in the RPE and choriocapillaris. Further studies with large number of cases, using OCT angiography, are needed to verify the involvement of circulatory disorder of the choriocapillaris in MEWDS.

In parallel with these angiographic analyses, we have recently demonstrated two distinct but relevant manifestations of the choroid at the acute stage of MEWDS: “choroidal thickening with reduced blood flow”, both of which correlated with visual function [11, 12], suggesting a close link between choroidal circulatory disturbance and visual impairment in MEWDS. Moreover, we identified the inner layer of the choroid as a changeable area responsible for whole choroidal thickening seen at the acute stage of this disease [13], indicating a possibility of the choriocapillaris as the primary focus of MEWDS. The combination of choroidal thickening with impaired circulation would strongly suggest the involvement of choroiditis in the pathogenesis of MEWDS, according to our previous analyses of uveitic diseases such as Vogt-Koyanagi-Harada disease [14] and white dot syndromes including serpiginous choroiditis, punctate inner choriodopathy (PIC), and APMPPE [15–17].

Consistently, a recent case series of MEWDS revealed a negative correlation between reduced intraocular pressure (IOP) and elevated aqueous flare at the acute stage, suggesting the potential role of subclinical cyclitis in compromising aqueous humor production and thus lowering IOP in eyes with MEWDS [18]. The present case developed severer iridocyclitis and vitritis than typical MEWDS does, possibly because inflammation uncommonly extended not only to the choroid but to the whole uvea. MEWDS would reasonably be to our atypical case what PIC is to ‘MFC and panuveitis’, a spectrum disorder with identical etiology but greater severity [19]. Therefore, our atypical case may be called ‘MEWDS and panuveitis’, suggesting that MEWDS is a clinical entity of uveitis.

Abbreviations
MEWDS: Multiple evanescent white dot syndrome; BCVA: Best-corrected visual acuity; FA: Fluorescein angiography; ICGA: Indocyanine green angiography; OCT: Optical coherence tomography; MFC: Multifocal choroiditis; APMPPE: Acute posterior multifocal placoid pigment epitheliopathy

Acknowledgements
None.

Authors’ contributions
KM acquired the data and drafted the manuscript. WS conceptualized the study, acquired the data, and drafted the manuscript. KN and SI drafted the manuscript and analyzed and interpreted the patient data. All authors read and approved the final manuscript.

Funding
No funding or grant support.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate
This case report was exempt from approval of the ethics committee of Hokkaido University Hospital.

Consent for publication
The consent for publication was obtained from the study patients.

Competing interests
The authors declare that they have no competing interests.

Received: 30 June 2020 Accepted: 15 October 2020
Published online: 29 October 2020

References
1. Uy HS, Chan PS (2002) Multiple evanescent white dot syndrome. In: Foster CS, Vitale AT (eds) Diagnosis and treatment of uveitis. W. B. Saunders, Philadelphia, pp 767–771
2. Russell JF, Pichi F, Scott NL, Hartley MJ, Bell D, Agaval A et al (2020) Masqueraders of multiple evanescent white dot syndrome (MEWDS). Int Ophthalmol 40:627–638
3. Obana A, Kusumi M, Maki T (1996) Indocyanine green angiographic aspects of multiple evanescent white dot syndrome. Retina 16:97–104
4. Klimova A, Heissigerova J, Rihova E, Blichova M, Pytlik R, Spicka I et al (2018) Combined treatment of primary vitreoretinal lymphomas significantly prolongs the time to first relapse. Br J Ophthalmol 102:1579–1585
5. Hashimoto H, Kishi S (2015) Ultra-wide-field fundus autofluorescence in multiple evanescent white dot syndrome. Am J Ophthalmol 159:98–106
6. Pichi F, Srivastava SK, Chessel S, Lembo A, Lima L, Neri P et al (2016) En face optical coherence tomography and optical coherence tomography angiography of multiple evanescent white dot syndrome: new insights into pathogenesis. Retina 36(Suppl 1):S178–S188
7. Pichi F, Sarraf D, Arepalli S, Lowner CY, Cunningham ET Jr, Neri P et al (2017) The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. Prog Retin Eye Res 59:178–201
8. Wang JC, Lains J, Sobrin L, Miller JB (2017) Distinguishing white dot syndromes with patterns of choroidal hypoperfusion on optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina 48:638–646
9. Tang W, Guo J, Liu W, Xu G (2020) Quantitative analysis of retinal and choriocapillaris vascular density of multiple evanescent white dot syndrome by optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol 258:1697–1707
10. Kang HG, Kim YT, Kim M, Byeon SH, Kim SS, Koh HJ et al (2020) Expanding the clinical Spectrum of multiple evanescent white dot syndrome with overlapping multifocal Choroiditis. Ocul Immunol Inflamm. https://doi.org/10.1080/09273948.2020.1795206 Epub ahead of print
11. Hashimoto Y, Saito W, Saito M, Hasegawa Y, Mori S, Noda K et al (2016)
  Relationship between choroidal thickness and visual impairment in multiple
  evanescent white dot syndrome. Acta Ophthalmol 94:e804–e806
12. Hashimoto Y, Saito W, Saito M, Hirooka K, Mori S, Noda K et al (2015)
  Decreased choroidal blood flow velocity in the pathogenesis of multiple
  evanescent white dot syndrome. Graefes Arch Clin Exp Ophthalmol 253:
  1457–1464
13. Hashimoto Y, Saito W, Hasegawa Y, Noda K, Ishida S (2019) Involvement
  of inner choroidal layer in choroidal thinning during regression of multiple
  evanescent white dot syndrome. J Ophthalmol 2019:6816925
14. Hirooka K, Saito W, Namba K, Takemoto Y, Mizuuchi K, Uno T et al (2015)
  Relationship between choroidal blood flow velocity and choroidal thickness
  during systemic corticosteroid therapy for Vogt-Koyanagi-Harada disease.
  Graefes Arch Clin Exp Ophthalmol 253:609–617
15. Takahashi A, Saito W, Hashimoto Y, Saito M, Ishida S (2014) Impaired
  circulation in the thickened choroid of a patient with serpiginous
  choroiditis. Ocul Immunol Inflamm 22:409–413
16. Hirooka K, Saito W, Hashimoto Y, Saito M, Ishida S (2014) Increased macular
  choroidal blood flow velocity and decreased choroidal thickness with
  regression of punctate inner choroidopathy. BMC Ophthalmol 14:73
17. Hirooka K, Saito W, Saito M, Hashimoto Y, Mori S, Noda K et al (2016)
  Increased choroidal blood flow velocity with regression of acute posterior
  multifocal placoid pigment epitheliopathy. Jpn J Ophthalmol 60:172–178
18. Ito Y, Ito M, Ueno S, Karoka K, Takeuchi J, Kominami T et al (2020) Changes
  in intraocular pressure and aqueous flare in eyes with multiple evanescent
  white dot syndrome. Jpn J Ophthalmol 64:378–384
19. Ahnood D, Madhusudhan S, Tsaloumas MD, Waheed NK, Keane PA,
  Denniston AK (2017) Punctate inner choroidopathy: a review. Surv
  Ophthalmol 62:113–126

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in
published maps and institutional affiliations.