Category: Retinal Disorders

Clinical characteristics of Multiple Evanescent White Dot Syndrome with poor visual prognosis in Japanese patients

Takayuki Tanaka, MD, PhD, Michiyuki Saito*, MD, PhD, Satoru Kase, MD, PhD, Zhenyu Dong, MD, PhD, Ryo Ando, MD, PhD, Kenichi Namba, MD, PhD, Kiriko Hirooka, Yui Yamashita, Susumu Ishida, MD, PhD

Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Correspondence to: Michiyuki Saito, MD, PhD

Department of Ophthalmology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Nishi 7, Kita 15, Kita-Ku, Sapporo 060-8638, Japan

Phone: +81-11-706-5944, Fax: +81-11-706-5948,

E-mail: s.michiyuki@med.hokudai.ac.jp

Key Message:

What is known

・Recent reports characterized the clinical aspects of primary and secondar multiple evanescent white dot syndrome (MEWDS), but the visual prognosis of these variants is only slowly unfolding.

New information

・Secondary MEWDS associated with foveal involvement of active chorioretinal lesions had significantly poorer visual acuity at the initial visit and showed a trend toward poorer visual acuity at the final visit compared to primary MEWDS.

・In both simple and multiple linear regression analyses, foveal involvement of active chorioretinal lesions was associated with poorer visual outcomes.

・The presence of foveal active chorioretinal lesions in MEWDS may be associated with poorer visual prognosis.

38

Abstract

Purpose: Multiple evanescent white dot syndrome (MEWDS) typically resolves spontaneously and is expected to have a favorable visual prognosis. Therefore, the initial manifestations of MEWDS have yet to be well studied. This study aimed to investigate the clinical characteristics of primary and secondary MEWDS patients and evaluate factors responsible for poor visual prognosis.

Methods: The medical records of 36 patients diagnosed with MEWDS between 2004 and 2021 at Hokkaido University Hospital were retrospectively reviewed. The study evaluated patient demographics, clinical characteristics, and multimodal imaging findings. The clinical factors involving final logMAR best-corrected visual acuity (BCVA) were analyzed. In addition, clinical characteristics of secondary MEWDS cases with poor visual prognosis were investigated.

Results: Twelve of the 36 patients (33.3%) had active chorioretinal lesions distinct from MEWDS lesions, resulting in a prevalence of secondary MEWDS of 33.3%. Four patients presented with foveal active chorioretinal lesions (11.1%). Retinal atrophy developed in these lesions in all four cases during the follow-up period. Compared to primary MEWDS, secondary MEWDS with foveal involvement of active chorioretinal lesions was associated with significantly worse visual acuity at the initial visit (p = 0.004), and

showed a trend toward poorer visual acuity was also observed at the final visit ($p = 0.11$). In simple linear regression analysis, coexisting foveal involvement of active chorioretinal lesions was significantly associated with worse final logMAR BCVA ($p = 0.002$). In multiple stepwise linear regression analysis, coexisting foveal involvement ($p < 0.001$) and male sex ($p = 0.03$) remained independently associated with poorer visual outcomes. **Conclusions:** The presence of foveal active chorioretinal lesions in MEWDS may be associated with poorer visual prognosis.

Keywords:

Multiple evanescent white dot syndrome (MEWDS), Primary MEWDS, Secondary MEWDS

Statements and Declarations:

Competing interest: The authors have no conflicts of interest to declare.

Funding: This work received no funding from any organization.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of Hokkaido University Hospital (Approval ID: 021-0050).

Informed consent: For this type of study, formal consent is not required.

Author contributions: T.T. and M.S. substantially contributed to the present study. K.H. and Y.Y. contributed to data collection. S.K., Z.D., R.A., and K.N. commented on previous manuscript versions. S.I. contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: None.

Introduction:

Multiple evanescent white dot syndrome (MEWDS) is a rare self-limiting retinal disease without residual structural abnormalities, first described by Jampol LM et al in 1984 [1]. Classically, a young adult myopic woman presents with photopsia, an enlarged blind spot or visual impairment, and multiple white spots scattered throughout the fundus. The exact pathogenesis of MEWDS is still unknown. However, since the disease often occurs secondary to a viral infection or vaccination, it is thought to be caused by some type of immune abnormality [2–5].

Recently, it has become an established concept that MEWDS can also be triggered by any insults that disrupt the retinal pigment epithelium (RPE)/Bruch's membrane complex [6–8]. Essilfie J et al. reported two forms of MEWDS [6]. One occurs in the absence of previous or current chorioretinal disease and is called primary MEWDS. The other results from a chorioretinal disease that disrupts the RPE/Bruch's membrane complex and is called secondary MEWDS or EpiMEWDS. Recent reports have shown that secondary MEWDS is mostly caused by multifocal choroiditis (MFC) or punctate inner choroidopathy (PIC), in addition, patients with myopic choroidal neovascularization (CNV) and pseudoxanthoma (PXE) are also at relatively high risk of developing secondary MEWDS [6–10]. Although MEWDS typically has a favorable

visual prognosis with spontaneous resolution and no residual structural abnormalities, it is occasionally associated with a poor visual prognosis. There are few reports on the clinical characteristics of primary and secondary MEWDS. However, the visual prognosis of these variants is slowly unfolding. The aim of this study is to clarify the demographic characteristics of patients with primary and secondary MEWDS, the causative chorioretinal diseases associated with secondary MEWDS, and the predictive factors that may influence visual prognosis.

Methods:

Patients and Diagnosis

The present study is a single-center retrospective study of consecutive cases of MEWDS patients who visited Hokkaido University Hospital from April 2004 to March 2021, before COVID-19 vaccination began in Japan. This study was approved by the institutional review board of Hokkaido University Hospital (approval ID: 021-0050) and adhered to the tenets of the Declaration of Helsinki. Data from medical records included patient age, sex, history of systemic autoimmune disease, presence of photopsia and prodromal flu-like symptoms, and ophthalmic treatment at the onset of MEWDS.

Patients underwent a comprehensive ophthalmic examination including refractive error, best-corrected visual acuity (BCVA), slit-lamp biomicroscopy and fundus photography, and multimodal imaging analysis including fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and blue-light fundus autofluorescence (BAF). The presence of anterior vitreous cells and foveal granularity were also reviewed from the medical records. If the ophthalmic findings of foveal granularity were not described, they were assessed by two ophthalmologists using fundus photographs. These findings were used to determine the diagnosis of MEWDS.

MEWDS was diagnosed in patients fulfilling the following criteria [1, 11–13]: (1) acute onset of unilateral or bilateral visual symptoms, including visual acuity loss, visual field loss, blurred vision, and photopsia; (2) fundus examination showing numerous small gray-white spots located at the level of the RPE or in the deep retina with a diameter of 100 to 200 μm or more that disappear spontaneously within a few weeks; (3) FA showing early hyperfluorescence and late staining in areas corresponding to the gray-white spots; (4) ICGA showing late hypofluorescence in areas corresponding to the gray-white spots; and (5) OCT showing disruption of the ellipsoid zone (EZ) and interdigitation zone (IZ) in areas corresponding to the gray-white spots.

Patients without available early- and late-phase images on FA and ICGA were excluded from this study. Patients who did not undergo spectral-domain OCT (SD-OCT) or swept-source OCT (SS-OCT) at the onset of MEWDS were also excluded.

Secondary MEWDS was diagnosed when an active chorioretinal lesion different from MEWDS lesions was present at the onset, based on multimodal imaging findings, including FA, ICGA, BAF, and OCT.

To compare the final logMAR BCVA, only patients who were followed for more than three months after the onset of MEWDS were included. Patients who developed new chorioretinal lesions or underwent ocular surgery during the follow-up period were excluded from the analysis.

Measurement of central choroidal thickness

At baseline, central choroidal thickness (CCT) was measured below the fovea using enhanced depth imaging OCT (EDI-OCT) or SS-OCT. The distance from the inner border of the hyperreflective line corresponding to Bruch's membrane to the outer border of the choroid was manually measured as CCT using EDI-OCT and SS-OCT horizontal scanning images through the fovea. Two graders independently graded the OCT images

in a masked fashion, masked to the clinical information of the subject, and the average of the two gradings was used for analysis.

Statistical Analysis

All data were analyzed using the R statistical package (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria). BCVA was converted to the logMAR value for statistical comparisons. Statistical comparisons of numerical variables were performed using the Mann–Whitney U test. The Wilcoxon signed-rank test was used to compare initial and final logMAR BCVA. Simple linear regression analysis and multiple stepwise linear regression analysis with the multiple imputation method were used to determine baseline factors associated with final logMAR BCVA. For the multiple imputation method, the pooled of the 20 imputed datasets were analyzed, and the pooled analysis results were provided by the mice package 3.16.0. Statistical significance was set at a *p*-value <0.05.

Results:

Demographic and Clinical Characteristics

A total of 36 patients were included in the study; 72.2% (n = 26) were female and 27.8% (n = 10) were male. All patients had unilateral disease. Demographic and clinical characteristics of the patients are shown in Table 1. The mean age at presentation was 33.6±13.0 years (range: 14 to 70 years; median: 32.5 years). According to the medical records, the presence or absence of photopsia was described in 27 patients, of whom 19 (70.4%) had photopsia. Similarly, a prodromal flu-like symptom was described in 17 patients, of whom 3 (17.6%) had flu-like symptoms. None of the patients had COVID-19 infection. None of the patients had a history of systemic autoimmune disease.

The mean initial logMAR BCVA was 0.40±0.48 (range: -0.08 to 1.70; median: 0.22). The mean spherical equivalent refractive error was -6.69±3.03 diopters (range: -12.0 to 0.88 diopters; median: -7.00 diopters) in 35 patients, excluding one patient with a history of laser-assisted in situ keratomileusis. On slit lamp examination, the presence or absence of anterior vitreous cells was described in 32 patients; 26 (81.3%) had them; the presence or absence of foveal granularity was investigated in 35 patients by reviewing the medical records and fundus photographs; 24 (68.6%) were positive; one case could not be evaluated because it was not documented in the medical records and the resolution

of the fundus photograph was low. BAF was performed in 22 patients, all of whom (100%) had hyperautofluorescence corresponding to MEWDS lesions. Late staining of the optic disc was observed in all 36 patients. Four patients received systemic oral or intravenous corticosteroid treatment.

None of the patients had foveal chorioretinal atrophy at the onset of MEWDS; however, extrafoveal chorioretinal atrophy was observed in 3 of the 36 patients (8.3%) at the onset of MEWDS. The chorioretinal atrophy in 1 of these 3 patients closely resembled atrophic scars due to PIC/MFC. In addition, BAF revealed hyperautofluorescence in MEWDS lesions, whereas hypoautofluorescence in active chorioretinal lesions and chorioretinal atrophy effectively distinguished MEWDS lesions (Figure 1 F).

Characteristics of secondary MEWDS

In our case series, we found that active chorioretinal lesions coexisted with MEWDS lesions. Figure 1 shows a representative case of secondary MEWDS associated with foveal active chorioretinal lesions. 4 of the 36 patients had foveal active chorioretinal lesions (11.1%) and 10 had extrafoveal active chorioretinal lesions (27.8%) that were different from MEWDS lesions at the initial visit. Two cases had active chorioretinal lesions at both the fovea and extrafovea, resulting in 12 of 36 patients with concomitant

209 active chorioretinal lesions (33.3%). The prevalence of secondary MEWDS was 33.3%.
210 All extrafoveal active chorioretinal lesions demonstrated early and late hyperfluorescence
211 on FA and early and late hypofluorescence on ICGA. In lesions that could be imaged by
212 OCT, hyperreflectivity and thickening of the RPE, and/or disruption of the RPE/Bruch's
213 membrane complex were observed.

214 Regarding foveal active chorioretinal lesions, three patients demonstrated early and
215 late hyperfluorescence on FA and early and late hypofluorescence on ICGA (Figure 2,
216 patients 1, 3, and 4). One patient exhibited early hyperfluorescence, late fluorescence
217 leakage on FA, and slight hyperfluorescence in both the early and late phases on ICGA
218 (Figure 2, patient 2). These foveal active chorioretinal lesions resulted in retinal atrophy
219 during the follow-up period (Figure 2, patients 1 to 4). Figure 2 presents fundus
220 photographs, FA and ICGA images at early- and late-phases, and OCT findings at
221 baseline and the final visit in four patients with secondary MEWDS associated with foveal
222 active chorioretinal lesions. Among the four patients with foveal active chorioretinal
223 lesions, Patient 2 received a combination therapy of intravitreal bevacizumab (1.25 mg),
224 sub-tenon’s triamcinolone acetonide (40 mg), and oral corticosteroids; Patient 4 was
225 treated with oral corticosteroids alone.
226

Comparison of LogMAR BCVA and CCT between Primary MEWDS and Secondary MEWDS

Secondary MEWDS was also divided into two subgroups: a fovea-involving subgroup and a fovea-sparing subgroup, according to the location of the active chorioretinal lesion, compared to primary MEWDS. The mean initial logMAR BCVA for the 36 patients in the primary MEWDS, secondary MEWDS all patients, secondary MEWDS fovea-involving subgroup, and fovea-sparing subgroup were 0.29±0.33 (range: -0.08 to 1.10; median: 0.22; n = 24 eyes), 0.63±0.66 (range: -0.08 to 1.70; median: 0.61; n = 12 eyes), 1.32±0.45 (range: 0.82 to 1.70; median: 1.37; n = 4 eyes), and 0.29±0.44 (range: -0.08 to 1.10; median: 0.11; n = 8 eyes), respectively. Comparing each secondary MEWDS group to the primary MEWDS, only the fovea-involving secondary MEWDS subgroup had significantly worse visual acuity than the primary MEWDS ($p = 0.003$).

The mean final logMAR BCVA for the 28 patients followed for more than three months in the primary MEWDS, secondary MEWDS all patients, secondary MEWDS fovea-involving subgroup, and fovea-sparing subgroup were -0.09±0.06 (range: -0.18 to 0.05; median: -0.08; n = 17 eyes), 0.04±0.29 (range: -0.18 to 0.82; median: 0.00; n = 11 eyes), 0.22±0.44 (range: -0.18 to 0.82, 0.11; n = 4 eyes), and -0.07±0.09 (range: -0.18 to 0.05; median: -0.08; n = 7 eyes), respectively. No statistically significant differences

245 in final logMAR BCVA were observed between the primary MEWDS group and each of
246 the secondary MEWDS subgroups. Although the *p* value for the comparison between the
247 primary group and the fovea-involving secondary MEWDS subgroup was 0.11,
248 suggesting no statistical significance, a trend toward poorer visual outcomes was
249 observed. The mean follow-up duration for these 28 patients was 28.4 ± 28.0 months
250 (range: 3–132 months; median: 19 months).

251 A total of 32 patients had SS-OCT or EDI-OCT imaging available at the initial
252 visit. In these patients, the mean initial CCT in the affected eye in the primary MEWDS,
253 secondary MEWDS all patients, secondary MEWDS fovea-involving subgroup, and
254 fovea-sparing subgroup were 204±86 μm (range: 53 to 375 μm; median: 202 μm; n = 21
255 eyes), 224±55 μm (range: 148 to 333 μm; median: 210 μm; n = 11 eyes), 244±40 μm
256 (range: 209 to 280 μm; median: 244 μm; n = 4 eyes), and 212±62 μm (range: 148 to 333
257 μm; median: 192 μm; n = 7 eyes), respectively. No statistically significant differences in
258 CCT were observed between any of the secondary MEWDS subgroups and the primary
259 MEWDS group.

260

261 **Changes in logMAR BCVA from baseline to final visit**

The changes in logMAR BCVA from baseline to final visit for the 28 patients followed for more than three months are shown in the scatter plots (Figure 5A). These data indicate that visual outcome was poor in two of the cases with foveal involvement of active chorioretinal lesions (Figure 5A, triangle marks). In all 28 patients, the mean initial logMAR BCVA was 0.44±0.52 (range: -0.08 to 1.70; median: 0.45), and it significantly improved to -0.04±0.19 (range: -0.18 to 0.82; median: -0.08) at the final visit (Figure 5B, $p < 0.001$). When stratified by sex, the six male patients had a mean initial logMAR BCVA of 0.38±0.38 (range: –0.08 to 0.82; median: 0.31), with no statistically significant improvement at the final visit (0.09±0.36; range: –0.08 to 0.82; median: –0.08; $p = 0.07$; Figure 5B). In contrast, the 22 female patients demonstrated a significant improvement in visual acuity, with mean logMAR BCVA improving from 0.45±0.56 (range: –0.08 to 1.70; median: 0.30) to –0.07 ± 0.10 (range: –0.18 to 0.22; median: –0.08; $p < 0.001$) (Figure 5B). Among the six male patients, primary MEWDS, fovea-involving secondary MEWDS, and fovea-sparing secondary MEWDS were diagnosed in four, one, and one patient, respectively. Among the 22 female patients, 13 had primary MEWDS, three had fovea-involving secondary MEWDS, and six had fovea-sparing secondary MEWDS.

Analysis of factors associated with final logMAR BCVA

In addition, 28 eyes from 28 patients followed for more than three months were analyzed to identify baseline clinical factors associated with final logMAR BCVA. In simple linear regression analysis, coexisting foveal involvement of active chorioretinal lesions was significantly associated with worse final logMAR BCVA (p = 0.002). In multiple stepwise linear regression analysis, coexisting foveal involvement ($p < 0.001$) and male sex ($p = 0.03$) remained independently associated with poorer visual outcomes (Table 3).

Discussion:

The present study investigated the characteristics and clinical findings of patients with primary and secondary MEWDS. The epidemiologic features observed in our cohort were consistent with previous reports, demonstrating a predominance of myopic eyes and female patients [14–16].

The main results of this study are I) Compared to primary MEWDS, secondary MEWDS with foveal involvement of active chorioretinal lesions was associated with significantly worse visual acuity at the initial visit ($p = 0.003$), and showed a trend toward poorer visual acuity was also observed at the final visit (p = 0.11). II) Two patients with foveal involvement of active chorioretinal lesions exhibited a poor visual prognosis. III) In

simple linear regression analysis, coexisting foveal involvement of active chorioretinal lesions was significantly associated with worse final logMAR BCVA (p = 0.002). In multiple stepwise linear regression analysis, coexisting foveal involvement (p < 0.001) and male sex (p = 0.03) remained independently associated with poorer visual outcomes.

In this study, we first describe that secondary MEWDS with foveal involvement of active chorioretinal lesions was associated with significantly worse visual acuity at the initial visit, and showed a trend toward poorer visual acuity was also observed at the final visit. Figure 2 shows four cases of secondary MEWDS associated with foveal involvement of active chorioretinal lesions. Retinal atrophy developed in these lesions in all four cases during the follow-up period. Among them, Patients 1 and 3 had a poor visual prognosis, with logMAR BCVA at the final visit of 0.82 and 0.22, respectively. Three of the four patients were suspected to have complicated PIC/MFC (Patients 1, 3, and 4) and the other was suspected to have complicated CNV (Patient 2). In addition, all cases with extrafoveal involvement of active chorioretinal lesions were suspected to have PIC/MFC.

Secondary, in simple linear regression analysis, coexisting foveal involvement of active chorioretinal lesions was significantly associated with worse final logMAR BCVA. In multiple stepwise linear regression analysis, coexisting foveal involvement and male sex remained independently associated with poorer visual outcomes. Six of the 28

316 patients followed for more than three months were male. One of these male patients had
317 secondary MEWDS with foveal involvement of active chorioretinal lesions, and
318 experienced poor visual outcomes, which may have contributed to the male sex being
319 identified as a poor prognostic factor for visual outcome. Additionally, the finding that
320 male patients had worse visual outcomes may be coincidental due to the small sample
321 size and the disproportionate number of female patients in the primary MEWDS group.

322 Regarding CCT in MEWDS cases, Kang HG et al. reported that a comparison
323 between the MEWDS-alone group and the PIC/MFC-complicated group revealed
324 significantly thicker choroidal thickness at baseline in both the affected and fellow eyes
325 of the PIC/MFC-complicated group [9]. In the present study, CCT in the affected eye was
326 not significantly different between any of the secondary MEWDS subgroups and primary
327 MEWDS, suggesting no association between choroidal thickness and secondary MEWDS.
328 Further investigation of the differences in CCT between patients with primary MEWDS
329 and secondary MEWDS is warranted.

330 As an angiographic test, we used both FA and ICGA in the diagnostic criteria of
331 MEWDS. However, BAF, a noninvasive and clinically convenient diagnostic tool,
332 detected MEWDS lesions as hyperautofluorescent spots more clearly than FA and ICGA
333 in all 22 patients examined. BAF can detect MEWDS lesions even when gray-white spots

334 are obscured. Since active chorioretinal lesions appear as hypoautofluorescence on BAF,
335 it is also helpful in the diagnosis of secondary MEWDS. Previously, BAF has been
336 reported to aid in the diagnosis of MEWDS [17–19], although the number of cases in
337 these studies was limited. The present study is the first report to demonstrate the
338 usefulness of BAF in the diagnosis of MEWDS in a relatively large number of cases.
339 These results suggest that cases with foveal hypoautofluorescence on BAF may have a
340 poor visual prognosis, because foveal involvement of an active chorioretinal lesion is
341 associated with worse visual outcomes.

342 This study has some limitations. First, PIC/MFC and CNV complications were not
343 accurately evaluated because OCT angiography was not used in this study. It may not be
344 easy to differentiate between PIC/MFC and CNV [20], although multimodal imaging
345 analysis plays a critical role in the differentiation. Second, this is a single-center,
346 retrospective study, which limits the number of cases studied. Further research on
347 secondary MEWDS is warranted.

348 In conclusion, this study showed poor visual prognosis of patients with secondary
349 MEWDS associated with foveal involvement of active chorioretinal lesions. We believe
350 that the presence of active chorioretinal lesions at the fovea determine poor visual
351 prognosis. In addition, treatment may not be necessary for patients with primary MEWDS

352 because spontaneous resolution can be expected. In secondary MEWDS, on the other
353 hand, treatment would have to be tailored to the actual pathology of the MEWDS-
354 triggering pathology. Hence, CNV would be treated with anti-vascular endothelial growth
355 factor therapy and inflammatory disease with steroids. Appropriate treatment for the
356 underlying pathology of the MEWDS-triggering is important.
357

References

1. Jampol LM, Sieving PA, Pugh D, et al (1984) Multiple evanescent white dot syndrome. I. Clinical findings. Arch Ophthalmol 102:671–4. https://doi.org/10.1001/archopht.1984.01040030527008

2. Jampol LM, Becker KG (2003) White spot syndromes of the retina: A hypothesis based on the common genetic hypothesis of autoimmune/inflammatory disease. Am J Ophthalmol 135:376–379. https://doi.org/10.1016/S0002-9394(02)02088-3

3. Ng CC, Jumper JM, Cunningham ET (2020) Multiple evanescent white dot syndrome following influenza immunization - A multimodal imaging study. Am J Ophthalmol Case Rep 19:. https://doi.org/10.1016/J.AJOC.2020.100845

4. Zecevic AA, Vukovic D, Djurovic M, et al (2023) Multiple Evanescent White Dot Syndrome Associated with Coronavirus Infection: A Case Report. Iran J Med Sci 48:98–101. https://doi.org/10.30476/IJMS.2022.95007.2632

5. Gargouri MA, Yousfi N, Toutain J, et al (2023) Multiple Evanescent White Dot Syndrome Following COVID-19 mRNA Vaccination. Ocul Immunol Inflamm 31:1240–1244. https://doi.org/10.1080/09273948.2022.2127782

6. Essilfie J, Bacci T, Abdelhakim AH, et al (2022) ARE THERE TWO FORMS OF MULTIPLE EVANESCENT WHITE DOT SYNDROME? Retina 42:227–235. https://doi.org/10.1097/IAE.0000000000003288

7. Ong AY, Birtel J, Agorogiannis E, et al (2023) Topographic patterns of retinal lesions in multiple evanescent white dot syndrome. Graefes Arch Clin Exp Ophthalmol 261:2257–2264. https://doi.org/10.1007/S00417-023-06032-1

8. Cicinelli MV, Hassan OM, Gill MK, et al (2021) A Multiple Evanescent White Dot Syndrome–like Reaction to Concurrent Retinal Insults. Ophthalmol Retina 5:1017–1026. https://doi.org/10.1016/j.oret.2020.12.007

9. Kang HG, Kim TY, Kim M, et al (2022) Expanding the Clinical Spectrum of Multiple Evanescent White Dot Syndrome with Overlapping Multifocal

Choroiditis. Ocul Immunol Inflamm 30:81–89. https://doi.org/10.1080/09273948.2020.1795206

10. Gliem M, Birtel J, Müller PL, et al (2019) Acute Retinopathy in Pseudoxanthoma Elasticum. JAMA Ophthalmol 137:1165–1173. https://doi.org/10.1001/JAMAOPHTHALMOL.2019.2910

11. Ie D, Glaser BM, Murphy RP, et al (1994) Indocyanine green angiography in multiple evanescent white-dot syndrome. Am J Ophthalmol 117:7–12. https://doi.org/10.1016/S0002-9394(14)73008-9

12. Obana A, Kusumi M, Miki T (1996) Indocyanine green angiographic aspects of multiple evanescent white dot syndrome. Retina 16:97–104. https://doi.org/10.1097/00006982-199616020-00002

13. Marsiglia M, Gallego-Pinazo R, De Souza EC, et al (2016) Expanded clinical spectrum of multiple evanescent white dot syndrome with multimodal imaging. Retina 36:64–74. https://doi.org/10.1097/IAE.0000000000000685,

14. Ramakrishnan MS, Patel AP, Melles R, Vora RA (2021) Multiple Evanescent White Dot Syndrome: Findings from a Large Northern

California Cohort. Ophthalmol Retina 5:850–854. https://doi.org/10.1016/j.oret.2020.11.016

15. Bosello F, Westcott M, Casalino G, et al (2022) Multiple evanescent white dot syndrome: Clinical course and factors influencing visual acuity recovery. British Journal of Ophthalmology 106:121–127. https://doi.org/10.1136/bjophthalmol-2020-317357

16. Asano T, Kondo M, Kondo N, et al (2004) High prevalence of myopia in Japanese patients with multiple evanescent white dot syndrome. Jpn J Ophthalmol 48:486–489. https://doi.org/10.1007/S10384-004-0107-6

17. Furino C, Boscia F, Cardascia N, et al (2009) Fundus autofluorescence and multiple evanescent white dot syndrome. Retina 29:60–63. https://doi.org/10.1097/IAE.0B013E31818C5E04

18. Joseph A, Rahimy E, Freund KB, et al (2013) Fundus autofluorescence and photoreceptor bleaching in multiple evanescent white dot syndrome. Ophthalmic Surg Lasers Imaging Retina 44:588–592. https://doi.org/10.3928/23258160-20131105-08

19. Harada S, Kato K, Matsui Y, et al (2023) Multiple evanescent white dot syndrome in highly myopic eye in which fundus autofluorescence was

427 diagnostically useful: A case report. Medicine 102:E32713.
428 https://doi.org/10.1097/MD.0000000000032713
429 20. Spaide RF, Goldberg N, Freund KB (2013) Redefining multifocal
430 choroiditis and panuveitis and punctate inner choroidopathy through
431 multimodal imaging. Retina 33:1315–24.
432 https://doi.org/10.1097/IAE.0b013e318286cc77
433 21. Hashimoto Y, Saito W, Noda K, Ishida S (2014) Acquired focal choroidal
434 excavation associated with multiple evanescent white dot syndrome:
435 observations at onset and a pathogenic hypothesis. BMC Ophthalmol 14:.
436 https://doi.org/10.1186/1471-2415-14-135
437
438

Figure legends:

Figure 1. A representative case of secondary MEWDS associated with foveal active chorioretinal lesion (a 24-year-old woman, left eye)

A fundus photograph showed gray-white spots due to MEWDS and an atrophic scar lesion at the inferior parafovea, presumed to be caused by PIC/MFC **(A)**. The early **(B)** and late **(C)** FA revealed hyperfluorescences corresponding to MEWDS lesions, foveal active chorioretinal lesion and lesions surrounding the dark pigmented scar at the inferior parafovea. ICGA showed early and late hypofluorescent corresponding to the foveal active choroioretinal lesion and atrophic scar, and late hypofluorescence consistent with MEWDS lesions **(D, E)**. BAF showed multiple hyperautofluorescent spots corresponding to the MEWDS lesions and hypoautofluorescent consistent with the foveal active chorioretinal lesion and atrophic scar **(F)**. OCT revealed extensive disruption of the ellipsoid zone and external limiting membrane and subretinal precipitates corresponding to the foveal active chorioretinal lesion **(G)**.

Figure 2. Fundus photographs, fluorescein angiography, indocyanine green angiography, and optical coherence tomography images from four patients with secondary MEWDS associated with foveal active chorioretinal lesions

Initial fundus photographs, early- and late-phase FA and ICGA, and both initial and final OCT findings (**A-AB**) are presented for Patients 1-4. The OCT images labeled **G, N, U,** and **AB** correspond to the final visit. **Patient 1 (A-G):** Initial logMAR BCVA was 0.82. At 29 months, BCVA remained at 0.82, with near-complete atrophy of the outer retinal layers observed in the fovea **(G)**. **Patient 2 (H-N):** Initial logMAR BCVA was 1.70. At 62 months, BCVA improved to -0.18, with outer retinal irregularities observed in the fovea (**N**). **Patient 3 (O-U):** Initial logMAR BCVA was 1.05. At 32 months, BCVA was 0.22, indicating visual impairment associated with foveal focal choroidal excavation **(U),** which was previously described in our case report on MEWDS [21]. **Patient 4 (V-AB):** Initial logMAR BCVA was 1.70. At 7 months, BCVA improved to 0, with disruption of the EZ and IZ in the fovea **(AB)**.

Figure 3. Changes in logMAR BCVA from the initial to final examinations in 28 patients who were followed for more than three months.

(A) The scatter plot illustrates the relationship between the initial and final logMAR BCVA for all 28 cases. Filled symbols indicate male patients. (B) The box-and-whisker plot shows changes in logMAR BCVA from the initial to the final visit for six male patients, 22 female patients, and all 28 patients. A statistically significant improvement in logMAR BCVA was observed in female patients and the in overall cohort but not in male patients (overall cohort: n = 28, $p < 0.001$; male: n = 6, $p = 0.07$; female: n = 22, $p < 0.001$).

Figure 1

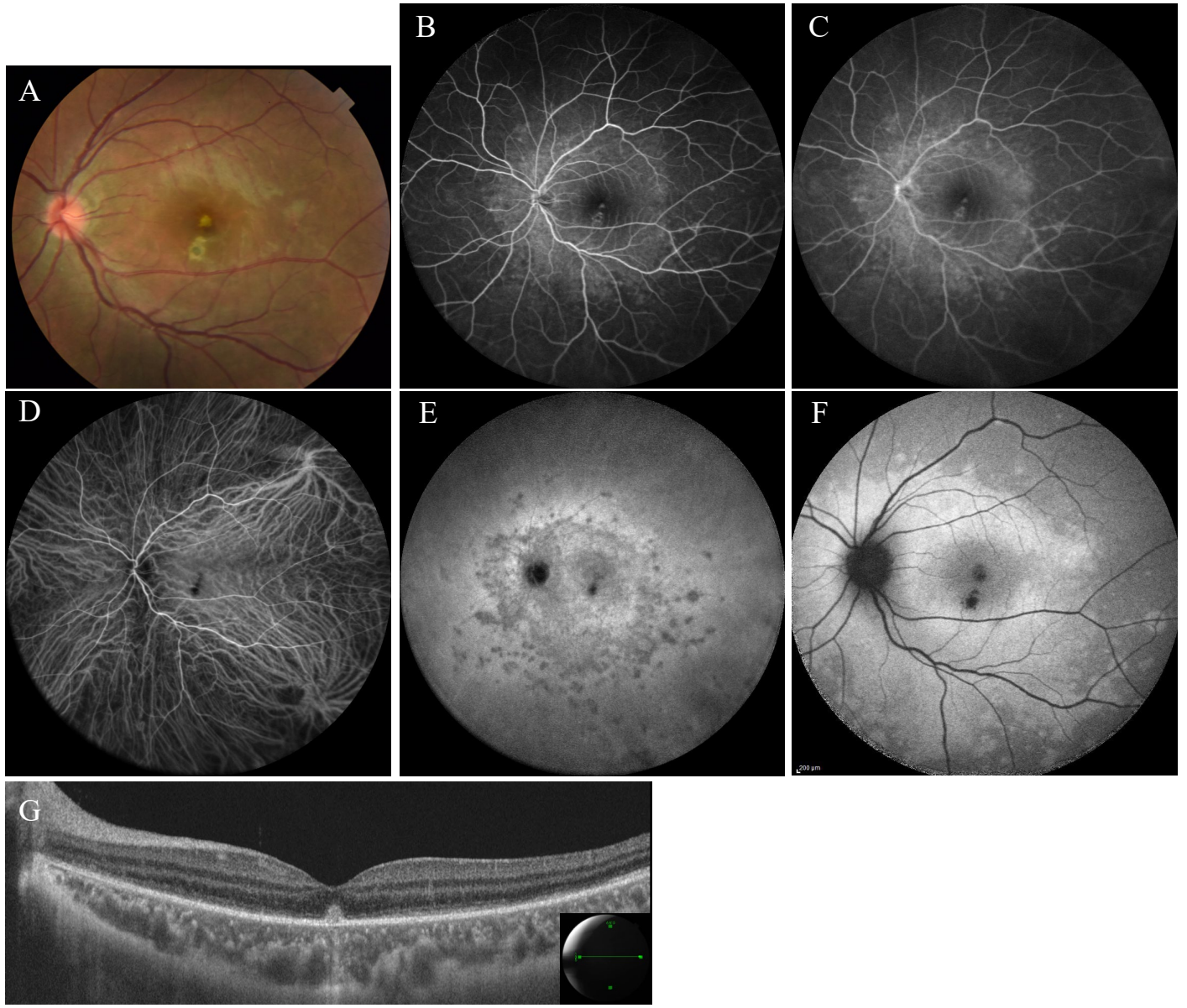
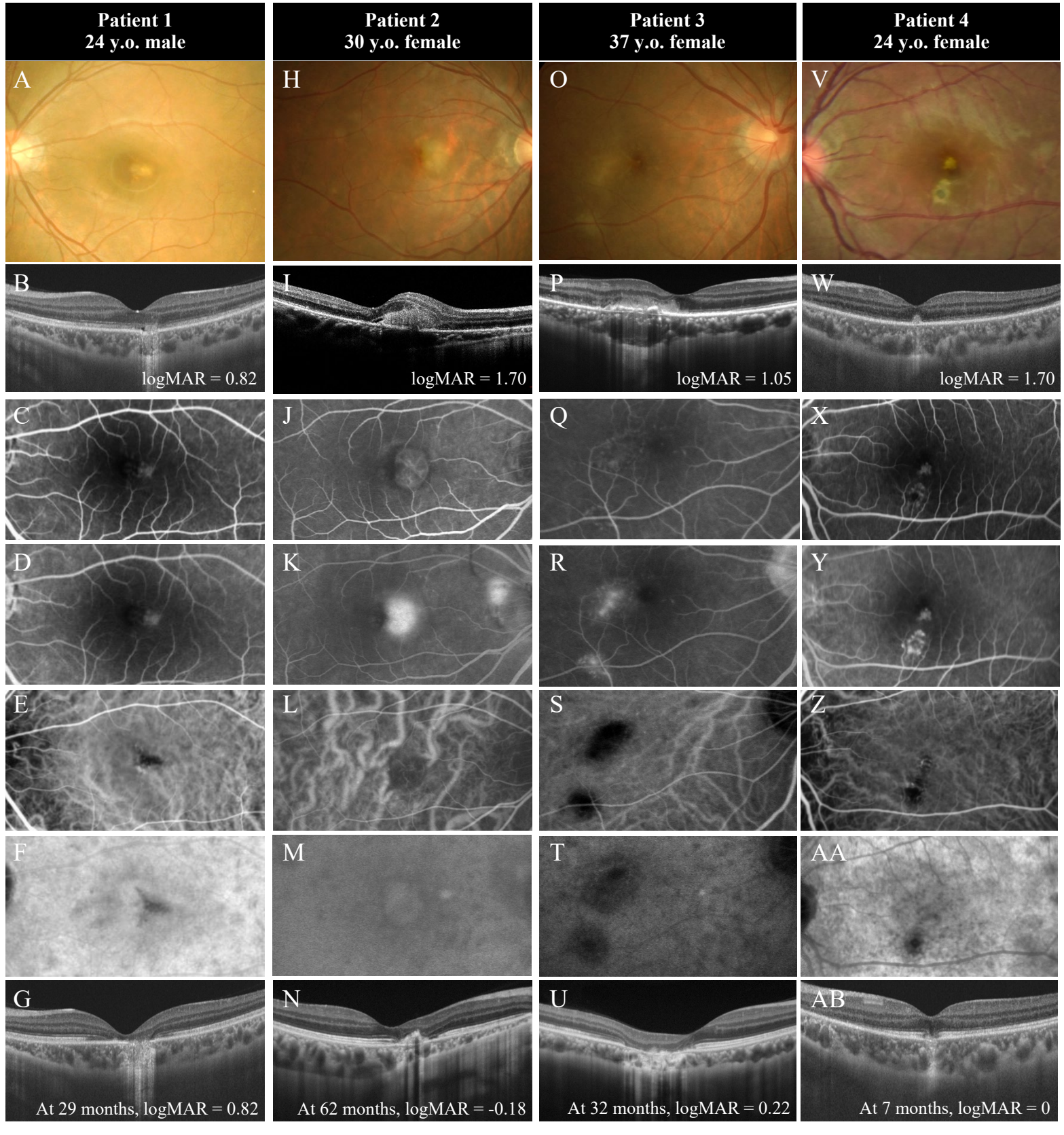
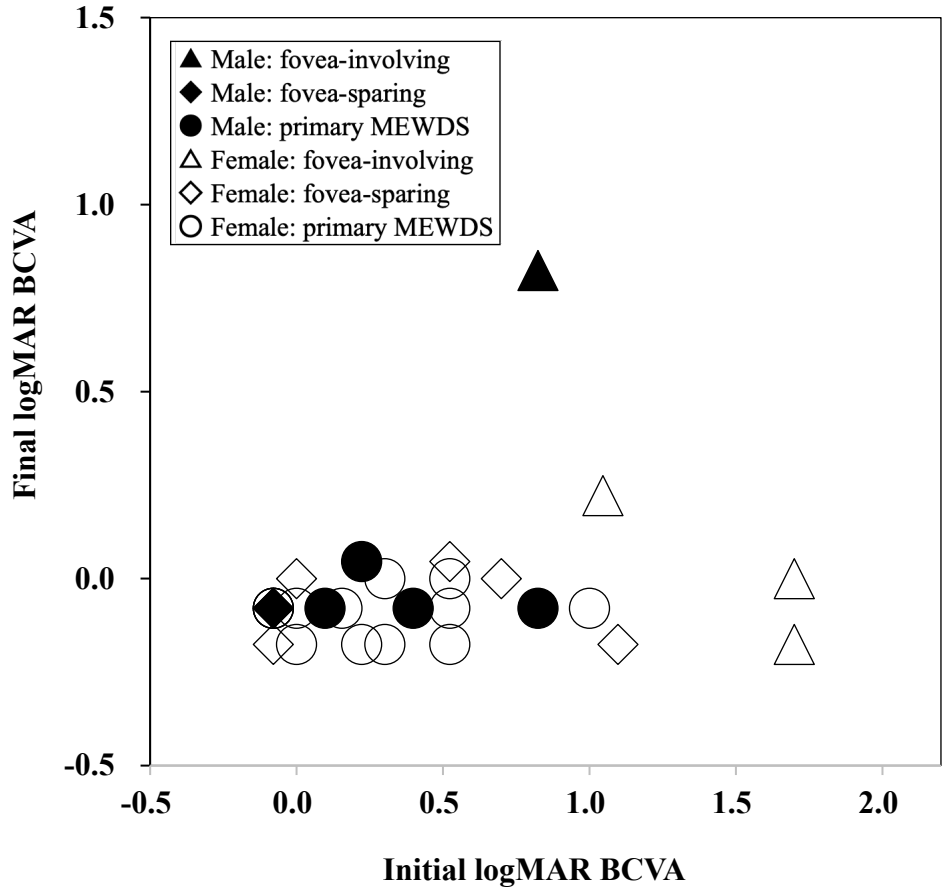


Figure2


Patient 1
24 y.o. male
Patient 2
30 y.o. female
Patient 3
37 y.o. female
Patient 4
24 y.o. female
A
H
O
V
B
logMAR = 0.82
I
logMAR = 1.70
P
logMAR = 1.05
W
logMAR = 1.70
C
J
Q
X
D
K
R
Y
E
L
S
Z
F
M
T
AA
G
At 29 months, logMAR = 0.82
N
At 62 months, logMAR = -0.18
U
At 32 months, logMAR = 0.22
AB
At 7 months, logMAR = 0


Male: fovea-involving
Male: fovea-sparing
Male: primary MEWDS
Female: fovea-involving
Female: fovea-sparing
Female: primary MEWDS
Final logMAR BCVA
Initial logMAR BCVA
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0

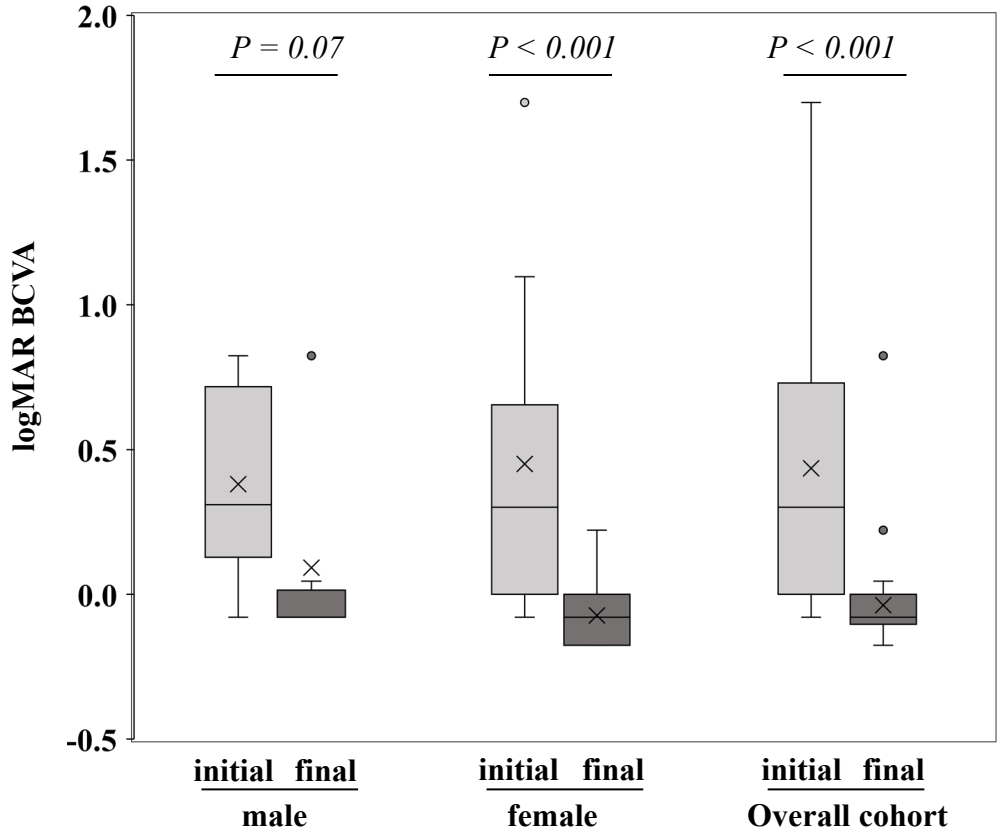

P = 0.07
P < 0.001
P < 0.001
logMAR BCVA
2.0
1.5
1.0
0.5
0.0
-0.5
initial final
male
initial final
female
initial final
Overall cohort

Table 1. Demographic and clinical characteristics of the patients in this study. LogMAR: logarithm of the minimum angle of resolution; FA: fluorescein angiography; BAF: blue-light fundus autofluorescence.

Age (years), mean±SD (range; median)		33.6±13.0 (14 to 70; 32.5)
Sex (Male:Female)		10:26 (Female 72.2%)
Photopsia		19/27 (70.4%)
Prodromal flu-like symptoms		3/17 (17.6%)
History of systemic autoimmune disease		0/36 (0.0%)
Spherical equivalent (D), mean±SD (range; median)		-6.69±3.03 (-12.0 to 0.88; -7.00)
Initial logMAR BCVA mean±SD (range; median)		0.40±0.48 (-0.08 to 1.70; 0.22)
Anterior vitreous cell		26/32 (81.3%)
Foveal granularity		24/35 (68.6%)
Late staining of the optic disc		36/36 (100%)
Systemic corticosteroid treatment (intravenous or oral)		4/36 (11.1%)
Hyperautofluorescence of MEWDS lesions on BAF		22/22 (100%)
Presence of active chorioretinal lesion at the onset	Fovea	4/36 (11.1%)
	Extra-fovea	10/36 (27.8%)
Presence of chorioretinal atrophy	Fovea	0/36 (0.0%)
	Extra-fovea	3/36 (8.3%)

Table 2. Simple and multiple stepwise linear regression analysis of initial clinical variables on final best-corrected visual acuity. LogMAR: logarithm of the minimum angle of resolution. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

		Simple linear regression analysis		Multiple stepwise linear regression analysis	
		r	***p value***	***β***	***p value***
Age (years)		0.05	0.80	-	-
Sex (male)		0.36	0.06	0.15	0.03 *
Initial logMAR BCVA		0.20	0.31	-0.14	0.09
Photopsia		0.05	0.81	-	-
Spherical equivalent (diopters)		0.03	0.87	-	-
Anterior vitreous cell		0.32	0.10	-	-
Foveal granularity		0.10	0.63	-	-
Presence of active chorioretinal lesions at the onset	Fovea	0.55	0.002 **	0.45	<0.001 ***
	Extra-fovea	0.03	0.86	-	-
Presence of chorioretinal atrophy	Fovea	-	-	-	-
	Extra-fovea	0.03	0.89	-0.12	0.19