Multiple Evanescent White Dot Syndrome

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Objectives: To study the clinical and angiographic features of lesions in a case series of multiple evanescent white dot syndrome (MEWDS), to describe a newly recognized clinical variation of the disorder, and to gain insight into its pathophysiological nature.

Methods: Five patients with MEWDS (selected based on angiographic manifestations of the disorder) were examined using slitlamp biomicroscopy and studied using fluorescein angiography and indocyanine green angiography.

Results: All 5 patients exhibited the newly recognized angiographic features termed dots and spots, which varied in size and location in the fundus. Small dots were in the inner retina or at the level of the retinal pigment epithelium, and larger spots were more external in the subpigment epithelial area. All patients exhibited other characteristics typical of MEWDS, including field loss and foveal granularity.

Conclusions: In this case series of MEWDS, a clinical variant consisting of dual-layered lesions with specific features on clinical examination, fluorescein angiography, and indocyanine green angiography was identified. On late indocyanine green angiography, these lesions produced highly specific findings of small hypofluorescent lesions overlying larger hypofluorescent lesions. Based on the angiographic findings, it seems as if MEWDS is a chorioretinopathy with varying degrees of retinal and choroidal involvement.

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MULTIPLE EVANESCENT white dot syndrome (MEWDS) has been a known clinical entity in the fundus for nearly a quarter of a century. Although it is suspected to be the result of a viral-like infection, possibly with an immune-mediated mechanism in a genetically susceptible person, its precise pathogenesis remains unknown. Our knowledge of the clinical spectrum of MEWDS has increased in recent years. Clinical manifestations have been described in the retina, the choroid, and the optic nerve, including transient white fundus lesions, macular granularity, and mild inflammation of the optic nerve. However, there is controversy regarding important aspects of the disorder, such as the precise nature of the associated fundus lesions and their angiographic characteristics, as well as the relationship of the disorder with other rare chorioretinal inflammatory diseases such as multifocal choroiditis and acute zonal occult outer retinopathy. The ophthalmologic literature suggests that the evanescent lesions in MEWDS are located in the retinal pigment epithelium (RPE) and outer retina. This is based on their clinical and angiographic appearance and on electrophysiological evidence, which has demonstrated an electro-oculographic reduction in the light-dark ratio, as well as electroretinographic alteration of the a-wave and early receptor potential. The objectives of this study were to examine the clinical and fluorescein and indocyanine green (ICG) angiographic features of the lesions in a selected case series of MEWDS, to gain insight into their pathophysiological nature, and to describe a clinical variation of MEWDS not recognized previously.

METHODS

Five patients with MEWDS were examined using slitlamp biomicroscopy and were studied using fluorescein angiography (FA) and ICG angiography (ICGA). These patients were selected on the basis of a clinical diagnosis of MEWDS and a specific appearance of lesions on ICGA. Summaries of the findings are given in Table 1 and in Table 2. At initial examination, all of the patients had unilateral decreased visual acuity and enlargement of the blind spot, confirmed using Humphrey visual field testing, that improved after resolution of
the clinical manifestations in the fundus. Transient white lesions and foveal granularity were followed up clinically and were correlated with the findings on FA and ICGA. The size of the clinical lesions was measured using the Topcon digital program (Topcon America Corp, Paramus, NJ). The patients had characteristic early wreathlike hyperfluorescence on FA, and 2 patients had staining of the optic nerve. Late findings on ICGA of layered hypofluorescent lesions, termed dots and spots, were also present in all cases. This peculiar pattern on ICGA was the basis for the selection of these cases. The patients were followed up clinically until their fundus manifestations resolved. During this period, the clinical and angiographic features of these lesions were evaluated and studied prospectively. At the discretion of the managing retinal specialist (L.A.Y.), some lesions were angiographically examined after resolution of the acute manifestations.

RESULTS

CLINICAL FINDINGS

The MEWDS lesions of the fundus in these patients were variable in size, ranging from small lesions (approximately 100 µm) to larger lesions (≥200 µm). Small lesions (dots) were anterior to larger lesions (spots) on stereoscopic clinical biomicroscopy (Figure 1A and B). Dots appeared to be localized to the deep retina or RPE, while spots were localized to the RPE and inner choroid. Dots seemed to occur in larger numbers around the optic nerve and nasal retina. Some large lesions were found in the midperipheral fundus. During the acute phase of the disorder, new dots and spots appeared in a cluster as older lesions disappeared, with spots resolving before dots. Minimally evident foveal granularity persisted after the resolution of the acute clinical phase (Figure 1C).

ANGIOGRAPHIC FINDINGS

Fluorescein Angiography

Fluorescein angiography revealed early hyperfluorescence corresponding to dots and to the margins of spots in the paramacular region and in the peripheral fundus. In all patients, there were more hyperfluorescent punctate dots noted on FA than on clinical examination (Figure 2). Dots often were first apparent in an incomplete wreath configuration. Most dots appeared during the choroidal-filling phase of FA and were localized to the RPE. Some dots, however, appeared to fluoresce during the retinal artery perfusion phase of FA, originating within the deep retina circulation. Dots varied in location but seemed to predominate at the level of the RPE or inner choroid.

Spots did not reveal complete, homogeneous abnormal fluorescence. Some of these lesions tended to stain slightly during the later phases of FA. Dots and spots seemed to be absent from the foveal area, despite the presence of foveal granularity that is typically seen on clinical examination in MEWDS. Mild focal segmental retinal vascular staining, or retinal phlebitis and optic disc staining, was also seen during the late phases of FA. As clinically evident dots and spots resolved over time, the findings normalized on FA. Mild staining of the optic nerve was evident in 2 patients after the lesions resolved.

Indocyanine Green Angiography

On ICGA, the early phase was generally unremarkable, with no evidence of abnormal choroidal perfusion. In 1
patient, dots and spots were visible during the mid-phase of the study. During the late phase (20 minutes after injection), all patients demonstrated small dots, apparently overlying larger, less densely hypofluorescent spots (Figure 3 and Figure 4). As on clinical examination, dots were superficial to spots in the fundus in a seemingly dual-layered pattern at the level of the RPE and inner choroid. Some dots corresponded to the hyperfluorescent lesions that were evident on FA, some of which localized to the deep retinal circulation stereoscopically. Confluence of clinically evident spots resulted in larger zonal areas of hypofluorescence on ICGA, particularly around the optic disc and at the site of any pre-existing chorioretinal scars (Figure 5). In addition, there was a lacy web of hypofluorescence at the margins of the peripapillary zonal abnormality. Spots and large zonal areas of hypofluorescence were noted to resolve before the more superficial dots in follow-up studies, as observed on clinical examination. As spots resolved clinically, the choroidal hypofluorescence disappeared, without evidence of proliferation or atrophy of the RPE. During the acute stages of the disease, focal segmental staining of choroidal vessels and discrete nodular hyperfluorescent areas in the inner choroid were noted during the mid-phases and late phases of ICGA in the midperipheral and peripheral fundus (Figure 3 and Figure 6). Some of these lesions initially or gradually became hypofluorescent (first at their centers) during ICGA, forming “doughnut” or “target” lesions; spots were eventually entirely hypofluorescent. Despite clinical resolution of the lesions during the follow-up period, some multifocal areas of nodular hyperfluorescence of the inner choroid and segmental staining of choroidal vessels remained evident on ICGA in some cases (Figure 3C). These hyperfluorescent lesions seen on ICGA were not seen on FA at the initial examination or during the follow-up period. Patient 1 in Tables 1 and 2 had persistent hyperfluorescent lesions on ICGA more than 2 years after her acute manifestations had resolved (Figure 7).

Despite symptoms, acute lesions were sometimes absent on clinical examination or FA but were seen on ICGA. A few discrete areas of hypofluorescence that corre-
sponded to clinically evident “punched-out” chorioretinal atrophic scars were also present in some patients. These lesions resembled the discrete chorioretinal atrophic and pigmentary scars that are characteristic of resolved multifocal choroiditis (Figure 8). Except for mild foveal granularity, these peripheral lesions were the only clinical signs of antecedent inflammation.

First reported in 1984, Jampol et al described MEWDS as an idiopathic intraocular inflammatory disorder characterized by the development of transient small gray-white lesions presumed to occur at the level of the retinal photoreceptors or RPE. The lesions are best char-

Figure 3. Indocyanine green angiograms. A, Composite angiogram reveals dots and spots. Many of the small hypofluorescent lesions seem to correspond to many of the small hyperfluorescent dots seen on fluorescein angiography in the same patient (Figure 2). Note the areas of hyperfluorescence surrounding choroidal vessels. B, Enlargement of a hyperfluorescent choroidal blood vessel. C, Enlargement of late angiographic findings in another patient demonstrating discrete nodular hyperfluorescent areas of the peripheral choroid. Some of the hyperfluorescent lesions have hypofluorescent centers, creating halo-shaped lesions.
acterized as wreathlike punctate areas of early hyperfluo-
rescence on FA. In contrast, ICGA in patients with MEWDS
reveals numerous hypofluorescent lesions that signifi-
cantly outnumber their counterparts seen on clinical ex-
amination and on FA. An irregular ring of hypofluores-
cence on ICGA surrounding the optic nerve that correlates
with visual field loss has been described as well.13

Previous studies have attempted to localize and in-
terpret the lesions of MEWDS on a clinical and angio-
graphic basis. Jampol et al1 originally presumed that the
wreathlike early hyperfluorescence seen on FA was caused
by choroidal transmission defects in the RPE, or so-
called window defects. The results of our study support
this assumption but not completely. Ikeda et al14 sug-
gest that certain patients with MEWDS and periphlebi-
tis could have an intraretinal microangiopathy that dem-
onstrates early hyperfluorescence lesions on FA. Again, our
findings agree with this interpretation but not com-
pletely. Both of these explanations by Jampol et al and
Ikeda et al are consistent with standard interpretations
(i.e., window defects or retinal vascularity) of early hy-
perfluorescence on FA.

Nevertheless, previous findings using ICGA are more
difficult to interpret. Ie and associates15 speculate that the
hypofluorescent lesions on ICGA correspond to choroi-
dal inflammatory cellular deposits that divert choroidal
blood flow and simultaneously compromise the outer RPE
blood-retina barrier. Obana and colleagues16 suggest that
the hypofluorescent lesions seen in patients with MEWDS
on ICGA are the result of a choroidal circulatory inter-
ference or a permeability abnormality. They hypothe-
sized that there is poor choriocapillaris flow by virtue
of inflammatory-mediated shunting, low perfusion pres-
sure, or occlusion. Although these explanations could ac-
count for the hypofluorescent lesions seen on ICGA, they
are inconsistent with the early hyperfluorescence seen
on FA. No choroidal perfusion abnormalities are seen in
patients with MEWDS on FA. Furthermore, acute in-
flammatory lesions of the choroid with exudation or
perfusion inhibition are generally associated with early
hypofluorescence and late staining on FA. Examples of
diseases with this typical pattern on FA include acute posterior multifocal placoid pigment epitheliopathy and serpiginous choroidopathy. This early blockage and late staining sequence on FA is not seen in MEWDS. There was also no mention in previous reports on MEWDS of the dual-layered lesions seen on ICGA that we describe herein as dots and spots. Observations by other authors were based on cases of MEWDS involving uniplanar lesions, perhaps representing a more common subset of patients within the overall clinical spectrum of the disorder and noted in our experience, as well.

Our observations about MEWDS lesions in this case series expand the clinical and angiographic spectra of the disorder. By any interpretation, the early hyperfluorescent lesions seen on FA must represent window defects, retinal vascular abnormalities, or a combination of both.
Based on our stereoscopic observations on clinical examination and on FA, we believe that most dots are window defects generated by perfusion of the choriocapillaris through inflammatory lesions, disrupting the RPE. Some dots, however, are of retinal vascular origin. A possible explanation of the pathophysiology of the window defects is an accumulation of inflammatory cells within or beneath the RPE, which stretches the RPE layer. Such cellular exudation must be transparent on FA because it does not obscure the choriocapillaris perfusion, which is essential to the production of window defects. We believe that the inflammatory exudates create focal areas of RPE thinning, or temporary window defects, because perfusion of the choriocapillaris remains intact; these findings on FA disappear when the inflammation resolves. Another possible explanation of the mechanism for the development of these temporary defects may be that the RPE cells become enlarged because of the inflammatory inoculum. This creates a stretching effect beneath the RPE and within the individual cells. In the fovea, where the RPE cells are more columnar in shape and have increased amounts of pigment (melanin and xanthophyll), these small window defects do not exist. However, outside the fovea, the RPE cells are smaller and have less pigmentation, so that an increase in their size (or swelling) as a result of the normal response to inflammation at their basal border creates a temporary window defect. The late hypofluorescence of dots on ICGA could represent the contrast between normal staining of the extravascular space and reduced staining of the inflammatory exudates, which do not have an affinity for ICG molecules. Because spots resolve before dots, one may presume that the exudates resolve before they cause an inflammatory cell effect on the RPE.

The retinal contribution to the early hyperfluorescence on FA may result in dots of vascular origin. A retinal capillary microangiopathy producing early hyperfluorescence would not likely be clearly seen with the large ICG molecules and the prevalent, even larger ICG-protein bioconjugates circulating in the bloodstream during FA. Relative to ICGA, this concept is similar to the weak discrimination of classic choroidal neovascularization, which involves small-caliber choriocapillaris proliferation. Fluorescein angiography demonstrates these abnormal vessels better than ICGA. Any leakage from these retinal vascular abnormalities would produce late staining on FA and an expanded area of hypofluorescence on ICGA. The absence of retinal vascular abnormalities in the foveal area is because of the perifoveal capillary-free (avascular) zone. Therefore, dots are of choriocapillaris and retinal origin, resulting in window defects and early retinal vascular hyperfluorescence on FA and in late hypofluorescence on ICGA.

We believe that spots are the result of inflammation without significant ischemia of the RPE and inner choroid. Ischemia would likely demonstrate perfusion abnormalities on FA, which in our experience shows an intact choriocapillaris. A better explanation of these imaging characteristics would be the shallow infiltration of inflammatory cells beneath the RPE, within the inner choroid, or outside the choriocapillaris. This inflammatory exudate is transparent on FA and does not inhibit the normal fluorescence of the choriocapillaris. Some of the early choroidal lesions that were undetectable on clinical examination or FA revealed staining on ICGA that progressed from hyperfluorescent round lesions to targetlike configurations during the course of MEWDS. The lesions eventually lost their staining characteristics and formed hypofluorescent spots, presumably as the inflammatory debris in the inner choroid lost its affinity for the ICG molecules (first centrally and then centripetally) (Figures 3C and 6). The lesions are hypofluorescent in contrast to the surrounding choroid, which assumes an isofluorescent appearance from the normal leakage of ICG into the extravascular space. These hyperfluorescent lesions seen on ICGA may be due to a protein-laden exudate that binds strongly to ICG during the acute phase; such lesions are transparent on FA. As the acute inflammation resolves, a transudate may persist that does not have high affinity for ICG molecules. Therefore, the previously hyperfluorescent lesions are hypofluorescent in contrast to the surrounding choroid, which assumes an isofluorescent appearance of normal staining in contrast to the staining pattern of the extrachoroidal vasculature; these later inner choroidal lesions remain transparent on FA.

Another way of understanding the staining characteristics on ICGA is to consider the molecule fibrin, which is present in patients with central serous chorioretinopathy. This exudate is transparent on FA but stains on ICGA. In MEWDS, the exudates responsible for spots are transparent on FA and are hypofluorescent on ICGA. Although ICG molecules have an affinity for fibrin and combine with it readily, they do not share this affinity with the exudate that is responsible for hypofluorescent spots in MEWDS. Similar angiographic characteristics are seen in acute cases of multifocal choroiditis, in which inner choroidal lesions are hypofluorescent on ICGA and are undetectable on FA.

Unlike acute posterior multifocal placoid pigment epitheliopathy and other choroidal inflammations, there is not enough inhibition of choroidal flow in MEWDS to affect the RPE clinically as a white infiltrate, which on FA gives the classic pattern of early hypofluorescence followed by late staining. Spots in MEWDS, however, affect the physiology of the RPE and outer segments and cause electroretinographic changes and visual field loss, particularly around the optic nerve (blind spot enlargement). Some of these lesions may affect the RPE to a greater degree, inducing an alteration in the outer blood-retina barrier that manifests as late staining on FA, or producing sufficient cellular damage to create a permanent chorioretinal scar resembling the discrete lesions seen in multifocal choroiditis. We have observed these peculiar choroidal lesions in other cases of MEWDS without dots and spots (Figure 8). To our knowledge, this choroidal lesion has not been previously reported in MEWDS.

Based on our observations described herein, we suggest that MEWDS may manifest as marked variability in the associated lesions in the fundus, affecting the RPE, the inner choroid, the retina, or some combination thereof. From combined retinal and choroidal imaging, it is clear that MEWDS is a chorioretinopathy. Like many posterior segment inflammatory conditions, the degree of retinal and choroidal involvement may vary among pa...
tients. In all of the variants, there seems to be a particular predilection for the peripapillary circulation, where there is a plentiful source of ciliary arteries that communicate axonally with the retinal circulation, which accounts for the characteristic enlargement of the blind spot in this disorder. However, the choroidal component cannot be appreciated unless patients are examined using ICGA. In patients with MEWDS with predominantly larger clinical lesions, ICGA reveals more numerous spots in the inner choroid, again with conspicuous involvement of the peripapillary area circulation. These patients may predominantly have choroiditis. The fact that many more lesions are seen on ICGA than on clinical examination or on FA suggests that the overall choroidal inflammatory nature of MEWDS may be greater than previously recognized. The combination of dots and spots, to our knowledge not previously reported, produces a pattern on ICGA that appears to be pathognomonic of MEWDS. Overall, our case series emphasizes the clinical variability of MEWDS in terms of its characteristics observed on clinical examination, FA, and ICGA.

Despite these expanded clinical and angiographic observations, the pathophysiology of MEWDS remains unclear. It seems evident that there are multiple forms of MEWDS and that the choroid has a major role, at least in some patients. More studies are required to determine the precise etiology of MEWDS. Further research is also needed to investigate host susceptibility, immune-mediated mechanisms, and genetic predispositions, all of which are likely implicated in the nature of this perplexing disorder.

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REFERENCES