Differentiation Between Presumed Ocular Histoplasmosis Syndrome and Multifocal Choroiditis With Panuveitis Based on Morphology of Photographed Fundus Lesions and Fluorescein Angiography

Jeffrey R. Parnell, MD; Lee M. Jampol, MD; Lawrence A. Yannuzzi, MD; J. Donald M. Gass, MD; Michael K. Tittel, MD

**Objective:** To evaluate whether inactive cases of presumed ocular histoplasmosis syndrome (POHS) and multifocal choroiditis with panuveitis (MFC) can be differentiated from each other by their appearance on fundus photography and fluorescein angiography.

**Methods:** Two masked observers classified 50 patients' photographs (27 with fluorescein angiograms) as POHS, MFC, or "indeterminate." Twenty-five patients had known POHS and 25 had known MFC. Statistical analysis was performed to assess agreement and interrater reliability.

**Results:** Observer A classified 33 patients and was indeterminate on 17. Of the 33, he was correct on 26 (79% crude accuracy; $\kappa = 0.560$; 95% confidence interval [CI], 0.286-0.834). Observer B classified 40 patients and was indeterminate on 10. Of the 40, he was correct on 33 (82% crude accuracy; $\kappa = 0.650$; 95% CI, 0.422-0.878). Both observers ventured a diagnosis on 28 common patients. Of these, they selected the same diagnosis on 26 (93% crude agreement). When the 2 observers' diagnoses were compared and indeterminate patients were factored in, the $\kappa$ value was 0.408 (95% CI, 0.215-0.601). When the indeterminate patients are excluded, the $\kappa$ agreement increased to 0.825 (95% CI, 0.592-1). When pictures only were available, observer A and observer B $\kappa$ values against the gold standard were 0.625 (95% CI, 0.270-0.980) and 0.588 (95% CI, 0.235-0.940), respectively. The pictures-only $\kappa$ values for observer A vs observer B were 0.382 (95% CI, 0.316-0.848) with indeterminate patients factored in and 1.0 (95% CI, 1.0-1.0) when indeterminate patients were excluded. Pictures and fluorescein angiogram $\kappa$ values were 0.493 (95% CI, 0.076-0.909) for observer A and 0.706 (95% CI, 0.413-0.999) for observer B against the gold standard. For observer A vs observer B, the $\kappa$ value was 0.261 (95% CI, −0.002 to 0.524) with indeterminate patients factored in and 0.567 (95% CI, 0.032-1) excluding indeterminate patients. Sensitivity for all cases for observer A was 60% (±13%) for POHS and 94% (±6%) for MFC. For observer B, the sensitivity for all cases was 70% (±10%) for POHS and 95% (±5%) for MFC.

**Conclusions:** Given adequate funduscopic information, the experienced observer can often accurately distinguish between POHS and MFC without the need for ancillary testing. Angiography in addition to fundus photography does not appear to increase diagnostic ability. There appears to be a higher sensitivity for MFC than for POHS.

MATERIALS AND METHODS

A set of 50 patients' photographs serving as a gold standard for the study was selected from a file archive of one of the authors (L.A.Y.). Informed consent was obtained. Twenty-five patients had known POHS and 25 had known MFC. To make these diagnoses, the patients previously had undergone detailed clinical ophthalmic and medical examination and histoplasmin skin testing, HLA-DR2 testing, and chest x-ray examination. All cases of MFC had demonstrated evidence of vitreous inflammation at some point. By definition, this excluded most cases of PIC, which do not show vitritis, even during the active phase. Conversely, the POHS cases could never have had any evidence of vitritis. For purposes of this study, the concept of a gold standard is imperfect since there is no definitive test that will correctly identify cases of POHS or MFC with 100% sensitivity and specificity. Some patients with POHS have negative skin test results, and some patients who live in endemic areas for Histoplasma can have a positive skin test result but true MFC. We acknowledge that some patients, especially those with few or nondescript fundus changes and those with resolved vitritis, could have their conditions misdiagnosed in the reference file. For this reason, a constellation of findings and tests was used to best determine the most likely diagnosis in creating the gold standard photograph. Attempts were made to exclude patients with other retinal diseases to avoid confounding information.

To be eligible for inclusion as 1 of the 50 cases, the photographs had to contain posterior pole and midperipheral images of the chorioretinal scarring. No photographs that had evidence of obvious media haze were allowed to avoid this sign as bias for MFC.

Twenty-seven patients had fluorescein angiograms included with the color photographs to evaluate the value of fluorescein angiography in distinguishing between the 2 disorders. Fourteen of the 27 had known POHS and 13 had MFC.

The photograph sets were duplicated, coded, masked, and randomized for distribution to the observers, designated A (L.M.J.) and B (J.D.M.G.). The observers were instructed to independently evaluate each case as MFC, POHS, or “indeterminate.” The indeterminate category was added for cases in which the observer deemed there was inadequate representation of lesions, poor photographic coverage, or confounding abnormalities. All patients' photographs were nonstereoscopic. The diagnostic sheets of each observer were then sent back to the originating center for comparison against the master list of the gold standard.

Both observers formulated their own criteria in selecting their diagnosis (Table 1). For observer A, a diagnosis of MFC was facilitated by clusters of lesions, growth of lesions, bridging subretinal scars, myopic disc changes, hyperplastic retinal pigment epithelium (RPE), RPE changes between scars, sheathing of vessels, and subretinal fibrous hyperplasia around the disc.

Observer B used the following characteristics for MFC: multiple small white or yellow chorioretinal lesions, often clustered in the macula, some appearing atrophic (punched out), and others appearing more solid; multiple loci of tightly clustered atrophic and/or solid small chorioretinal lesions in the peripheral fundus; RPE changes between focal scars; subretinal fibrous metaplasia of the RPE; intraretinal migration of RPE; and narrowing of retinal vessels in the zones of RPE changes.

The sizes of the lesions and the presence of disciform scars, choroidal neovascular membranes, and Schlüe lines were deemed not helpful.

Activity was not relevant to the patients in this study because active cases were excluded. For both observers, MFC could be diagnosed in the face of obvious inflammation: active white lesions, vitritis, and disc blurring with leakage and cystoid macular edema.

Statistical analysis that incorporated chance-expected agreement into the assessment of interrater reliability was performed to measure agreement. When comparing the observer vs the gold standard, values were generated excluding indeterminate patients. However, the values were calculated with and without the indeterminate patients factored in when the observers’ responses were compared with each other. Additional analysis was performed to evaluate the agreement when a fluorescein angiogram was included with the photographs vs cases that had color photographs only. A value greater than 0.75 denotes excellent agreement, a χ of 0.4 to 0.75 denotes good agreement, a χ of 0.4 to 0.0 denotes marginal agreement, and χ less than 0 indicates that observed agreement is less than chance agreement.

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The 3 patients for whom they selected the incorrect diagnosis were the same for both observers. The \( \kappa \) values for observer A vs observer B (color photograph only patients), therefore, were 0.582 (95% CI, 0.316-0.848) with indeterminate patients factored in and 1.0 (95% CI, 1.0-1.0) when indeterminate patients were excluded. Thirteen of 28 had an angiogram in addition to color photographs. Observer A was correct on 9 (69%) of 13 and observer B was correct on 11 (85%) of 13. The \( \kappa \) values for observer A vs observer B (color photographs and angiogram) were 0.261 (95% CI, -0.002 to 0.524) with indeterminate patients factored in and 0.567 (95% CI, 0.032-1) excluding indeterminate patients. Observer A was correct on 24 (86%) and observer B was correct on 26 (93%) of the 28 common patients whose conditions they attempted to diagnosis.

Observer A classified 17 as indeterminate and made a diagnosis for 33. Seven (41%) of the indeterminate cases had MFC and 10 (59%) had histoplasmosis. Observer B classified 10 as indeterminate and attempted a diagnosis on 40. Five (50%) of his indeterminate cases had MFC and 5 (50%) had histoplasmosis.

Twenty-three (70%) of 33 of observer A’s diagnosed cases had MFC and 10 (30%) of the 33 had histoplasmosis. Observer A was correct on 17 (74%) of 23 cases with MFC and 9 (90%) of 10 cases with histoplasmosis. Twenty-five (62%) of 40 of observer B’s diagnosed cases had MFC and 15 (38%) of 40 had histoplasmosis. He was correct for 19 (76%) of 25 patients with MFC and 14 (93%) of 15 patients with histoplasmosis.

Analysis of the incorrect selections revealed that observers A and B were incorrect for 7 (21%) of 33 and 7 (18%) of 40, respectively. Five (71%) of 7 incorrect selections were common patients for observers A and B. Three had pictures only and 2 had pictures and an angiogram. All 5 of the common patients whose conditions were incorrectly diagnosed had known POHS but were thought to have MFC by the observers. For each observer, 6 (86%) of the 7 incorrect selections had known POHS but were called MFC. Thus, only 1 of 7 for each observer had known MFC but was misdiagnosed as POHS. The observers were much more likely to misdiagnose cases with POHS as MFC than the reverse scenario.

Each observer’s sensitivity for a particular diagnosis was as follows. The sensitivity of observer A for all cases was 60% (±13%) for POHS and 94% (±6%) for MFC. When he had pictures only, sensitivity was 63% (±17%) for POHS and 100% for MFC. With pictures and fluorescein angiography, sensitivity for POHS was 57% (±19%) and 90% (±9%) for MFC. The sensitivity of observer B

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Table 1. Observer Criteria for Multifocal Choroiditis With Panuveitis

<table>
<thead>
<tr>
<th>Observer A</th>
<th>Observer B</th>
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<tbody>
<tr>
<td>Progressive growth of lesions</td>
<td>Multiple small white lesions often clustered in macula</td>
</tr>
<tr>
<td>Bridging scars, retinal pigment epithelium (RPE) changes between scars</td>
<td>Mixture of acute and inactive lesions</td>
</tr>
<tr>
<td>Progressive pigment proliferation</td>
<td>Clusters at equator</td>
</tr>
<tr>
<td>Hyperplastic or “metaplastic” RPE, napkin ring around disc</td>
<td>RPE changes between scars</td>
</tr>
<tr>
<td>Myopic disc changes</td>
<td>Subretinal fibrous metaplasia</td>
</tr>
<tr>
<td>Sheathing of vessels</td>
<td>Intraretinal pigment migration</td>
</tr>
<tr>
<td>Clustering of lesions (macula and periphery)</td>
<td>Narrowed vessels</td>
</tr>
<tr>
<td>Inflammation: disc swelling, acute lesions, cystoid macular edema (CME)</td>
<td>Inflammation: CME, vitritis, disc edema</td>
</tr>
</tbody>
</table>

Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Age, mean ± SD, y</th>
<th>Multifocal Choroiditis With Panuveitis</th>
<th>Presumed Ocular Histoplasmosis Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>Multifocal Choroiditis With Panuveitis</td>
<td>Presumed Ocular Histoplasmosis Syndrome</td>
</tr>
<tr>
<td>Refraction, diopters</td>
<td>30 ± 10</td>
<td>20 ± 10</td>
</tr>
<tr>
<td>Positive histoplasmin, No. (%)</td>
<td>0/22</td>
<td>0/22</td>
</tr>
<tr>
<td>Hilar adenopathy, No. (%)</td>
<td>0/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>
for all cases was 70% (±10%) for POHS and 95% (±5%) for MFC, 67% (±6%) for POHS and 91% (±9%) for MFC with pictures only, and 73% (±13%) for POHS and 100% for MFC with pictures and fluorescein angiography.

**COMMENT**

This study shows that experienced observers can usually distinguish correctly between inactive cases of POHS and MFC by noting differences in fundus appearance between these 2 disorders.

These entities do resemble each other. Differentiating features between these 2 conditions are the presence or absence of inflammation and progressive vision loss due to the waxing and waning nature of MFC. Patients with MFC are usually female. At the time of presentation with acute lesions or thereafter when inactive, they may have an enlarged blind spot or, less frequently, other visual field defects not explained by fundus changes. The same is true for photopsia. In contrast, patients with POHS by definition do not have evidence of anterior or posterior segment inflammation. They tend to be asymptomatic unless they develop macular or peripapillary choroidal neovascularization. Current theory states that patients with POHS have previously been infected with the fungus *H capsulatum*. Although this fungus has never been cultured from peripheral chorioretinal scars or disciform macular scars, it has been reported histopathologically in these same scars. Furthermore, this disorder is seen much more commonly in endemic areas in the Ohio and Mississippi River valleys; 95% of patients with the characteristic eye findings in these endemic areas will have a positive histoplasmin skin test result. There may be a genetic susceptibility to POHS in that affected patients who develop choroidal neovascularization exhibit a higher prevalence of the HLA-B7 antigen than MFC patients and the general population at large. Furthermore, a high prevalence of HLA-DR2 antigen has been reported in POHS patients, with a total absence in MFC patients. When both POHS and MFC conditions are quiescent and there is no previous examination or documentation of the patient’s fundus appearance, differentiation can be difficult. Inactive lesions can look identical. Furthermore, patients in both categories can be asymptomatic, and there may be no evidence of current or previous anterior or posterior inflammation. Nevertheless, it is very important to attempt to differentiate the disorders because the course, prognosis, and treatment can be very different. Because of the chronic relapsing nature of MFC, patients may need to be followed up more closely. There is also a possible beneficial role for periocular or systemic corticosteroids in the treatment of the choroiditis and perhaps choroidal neovascularization for MFC. On the other hand, there are well-established studies that describe a known benefit of laser treatment for extrafoveal and juxtafoveal choroidal neovascular membranes in POHS. For POHS cases where the choroidal neovascular membrane is too close to the fovea to apply laser treatment, there may be a benefit from corticosteroids or even submacular surgical excision, but this remains unproved.

The present study demonstrates a good diagnostic ability when the individual observers believed they had enough information to venture a selection. Moreover, there was a high degree of agreement between the 2 observers. Although the observers were allowed to decline making a diagnosis on cases with too little information to classify, the predictive value was high with or without the indeterminate patients factored into the statistical analysis. It should be noted that a subset of MFC patients had PIC. This variant of MFC does not typically have inflammatory signs or cells, and there tends to be a clustering of lesions in the macula without the peripheral scarring seen in MFC. By excluding potential cases of MFC because of the absence of a history of vitreous cells (eg, PIC), some of the more difficult cases to distinguish from POHS may not be included in this study. Furthermore, because there is no true gold standard test to distinguish these 2 disorders, it is possible that the reference photofile could contain some incorrect diagnoses.

There was no specific bias toward POHS or MFC in the indeterminates for observer A or B. Most indeterminate patients’ photographs either had too few lesions and not enough information to classify or had inadequate photographic quality. Interestingly, almost 75% of the incorrect selections were common for observers A and B. All of these patients were misdiagnosed as having MFC when they actually had POHS. In fact, both observers had a tendency to misclassify cases that had POHS as having MFC. For each observer, only 1 patient with MFC was diagnosed as having POHS. This concordance may be due to the similarity of clinical clues and criteria that the observers applied to arrive at their diagnoses. Thus, because there are enough distinct clinical characteristics in patients with MFC, these patients were very rarely misdiagnosed as having POHS. The converse does not seem to be true.

There was little or no benefit in improving the accuracy of diagnosis when fluorescein angiography was available. This was true in regard to the observers’ ability to arrive at the correct diagnosis and their tendency to be more likely to attempt a diagnosis. Almost half of all the indeterminate patients had a fluorescein angiogram and color photographs. Curiously, observer A was slightly less accurate when he had both color pictures and an angiogram.

**CONCLUSIONS**

This series demonstrates that experienced observers can often accurately differentiate MFC from POHS by fundus appearance alone, without the need of clinical history, histoplasmin skin testing, chest x-ray examination, or HLA testing. Each observer formulated diagnostic criteria, which were similar. The concordance between the observers is not surprising given their similar criteria. Because these cases were derived from a nonstandardized photofile, there were a large number of patients who the observers believed did not have enough or adequate fundusscopic information to venture a diagnosis. Nevertheless, because only inactive cases without inflammatory signs were included in this study, the observers were forced to make their decisions based on the appearance and characteristics of the fundus lesions alone. Perhaps it is not surprising that the additional informa-
tion provided by the fluorescein angiography was not helpful because these cases were inactive and therefore would be less likely to demonstrate vascular staining, disc leakage, or leakage from active lesions. The observers’ criteria seem to have a higher sensitivity for MFC cases, because almost all the incorrect selections had POHS but were misdiagnosed as having MFC.

This study has emphasized the fundus photographic clues to differentiate POHS from MFC. In the examining room, the clinician has available other clues that will increase his or her accuracy in diagnosis. Clues that suggest MFC include a history of photopsias, floaters (particularly during the early stage of the disease), and a temporal blind spot. On physical examination, visual field defects (particularly an enlarged blind spot) not explained by fundus findings, postinflammatory changes in the vitreous, including cells, vitreous strands, and a Weiss ring also point to MFC.

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Corresponding author and reprints: Lee M. Jampol, MD, 645 N Michigan Ave, Suite 440, Chicago, IL 60611.

REFERENCES