Classification Criteria for Multifocal Choroiditis With Panuveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,*]

• PURPOSE: To determine classification criteria for multifocal choroiditis with panuveitis (MFCPU).
• DESIGN: Machine learning of cases with MFCPU and 8 other posterior uveitides.
• METHODS: Cases of posterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the posterior uveitides. The resulting criteria were evaluated on the validation set.
• RESULTS: One thousand sixty-eight cases of posterior uveitides, including 138 cases of MFCPU, were evaluated by machine learning. Key criteria for MFCPU included (1) multifocal choroiditis with the predominant lesions size >125 μm in diameter; (2) lesions outside the posterior pole (with or without posterior involvement); and either (3) punched-out atrophic chorioretinal scars or (4) more than minimal mild anterior chamber and/or vitreous inflammation. Overall accuracy for posterior uveitides was 93.9% in the training set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set. The misclassification rates for MFCPU were 15% in the training set and 0% in the validation set.
• CONCLUSIONS: The criteria for MFCPU had a reasonably low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research.

In 1984 Dreyer and Gass described a new posterior uveitic disease, multifocal choroiditis with panuveitis (MFCPU).[1] The disease had a retinal picture similar to that of the presumed ocular histoplasmosis syndrome in that there were "punched-out atrophic" chorioretinal scars of variable size, but differed in that there was a variable anterior chamber and vitreous inflammation and there was no evidence of prior histoplasmosis infection on serologic testing, skin testing, and chest radiography.[1] Most cases were bilateral. There often were lesions of variable character, including "active lesions" described as yellow to yellow-white, round or oval, sometimes irregular, and mildly elevated, with "punched-out atrophic" chorioretinal scars with variable hyperpigmentation at the edges. Lesions typically were >250 μm in size.[1,2]

Multifocal choroiditis with panuveitis is an uncommon uveitic disease. Most data on the disease come from case series.[2-5] In 1 6-year series of all patients with uveitis seen at a single, tertiary-case uveitis center in Australia, MFCPU accounted for 2.4% of all uveitic cases.[6] The incidence of MFCPU has been estimated at 0.03 cases per 100,000 population per year.[7] Multifocal choroiditis with panuveitis has been reported with a wide age range, but most cases occurred in young to middle-aged adults. Although MFPCU occurs in both men and women, the majority of reported cases have been in women. It has been reported in multiple ethnic groups, but the majority of cases seem to occur in white individuals.[2-5]

The etiology of MFCPU is unknown, and it is unassociated with a systemic disease. The differential diagnosis of MFCPU includes those diseases that can produce a multifocal choroidopathy, such as punctate inner choroiditis (PIC), syphilis, tuberculosis in endemic areas, and sarcoidosis. Rarely, late-stage, untreated birdshot chorioretinitis (BSCR) may have a similar appearance. Occasionally serpiginous choroiditis not adjacent to the disc may look

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like MFCPU, but the characteristic fluorescein angiogram of serpiginous choroiditis typically allows the correct diagnosis to be made.[2-5,8]

The active lesions of MFCPU have been described as yellow-orange, round or oval, sometimes elevated, and typically >250 μm in size. The "punched-out" atrophic scars involve loss of choroid and retinal pigment epithelium in a circular fashion, typically with pigment clumping at the edge. Fluorescein angiography of active MFCPU lesions has been reported as demonstrating multiple chorioretinal spots with progressive hyperfluorescence throughout the angiogram. By contrast, the atrophic scars demonstrate window defects on fluorescein angiography. Occasionally it can be difficult to differentiate choroidal neovascularization from an active MFCPU lesion of fluorescein angiography alone.[8] On indocyanine green angiography, active MFCPU lesions have been reported to present as hypofluorescent spots that fade by the late phases of the angiogram, suggesting that the lesions are at the level of the choriocapillaris and/or retinal pigment epithelium.[9] Fundus autofluorescence imaging has been reported as useful in assessing the activity of MFCPU lesions. Atrophic scars are hypoautofluorescent, whereas active lesions are mildly hyperautofluorescent.[10-13] More lesions may be visible on fundus autofluorescence imaging than are evident clinically.[13] Optical coherence tomography is useful in diagnosing macular edema and active choroidal neovascularization. It also has been reported to distinguish active choroidal lesions from atrophic scars. Optical coherence tomography angiography, although not routinely used, has been reported to differentiate choroidal neovascularization from active MFCPU lesions by detecting the abnormal subretinal vessels.[14]

Reported structural complications include macular edema, choroidal neovascularization, optic neuropathy, epiretinal membranes, and cataract.[2,9,10,15,16] Choroidal neovascularization has been reported as the most common cause of vision loss.[15] Incidences of visual impairment (20/50 or worse) and blindness (20/200 or worse) in involved eyes have been estimated at 0.19/eye-year (EY) and 0.12/EY, respectively, and in the better-seeing eye at 0.07/EY and 0.04/EY, respectively.[15] High-dose oral corticosteroids have been reported to control the inflammation and decrease the occurrence of retinal structural complications, but doses low enough for long-term use (<10 mg/day) appear to be largely ineffective.[15,17] Conversely, immunosuppression has been reported to reduce the occurrence of structural complications by more than 80%.[15,17] Hence, if treatment is needed, oral corticosteroids and immunosuppression appear to be the preferred approach.[15,18] Choroidal neovascularization typically is treated with adjunctive anti–vascular endothelial growth factor therapy.[10]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification. Among the diseases studied was MFCPU.[19-24]

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases, as previously described: (1) informatics, (2) case collection, (3) case selection, and (4) machine learning.[21-24]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[21]

• **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.[23,24] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying article.[23,24] Because the goal was to develop classification criteria,[25] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[23,24]

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[24] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For MFCPU, the diseases against which it was evaluated were acute posterior multifocal placoid pigment epitheliopathy, BSCR, multiple evanescent white dot syndrome, PIC, serpiginous choroiditis, sarcoidosis-associated posterior uveitis, syphilitic posterior uveitis, and tubercular uveitis.

The study adhered to the principles of the Declaration of Helsinki. Institutional review boards at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual institutional review boards.

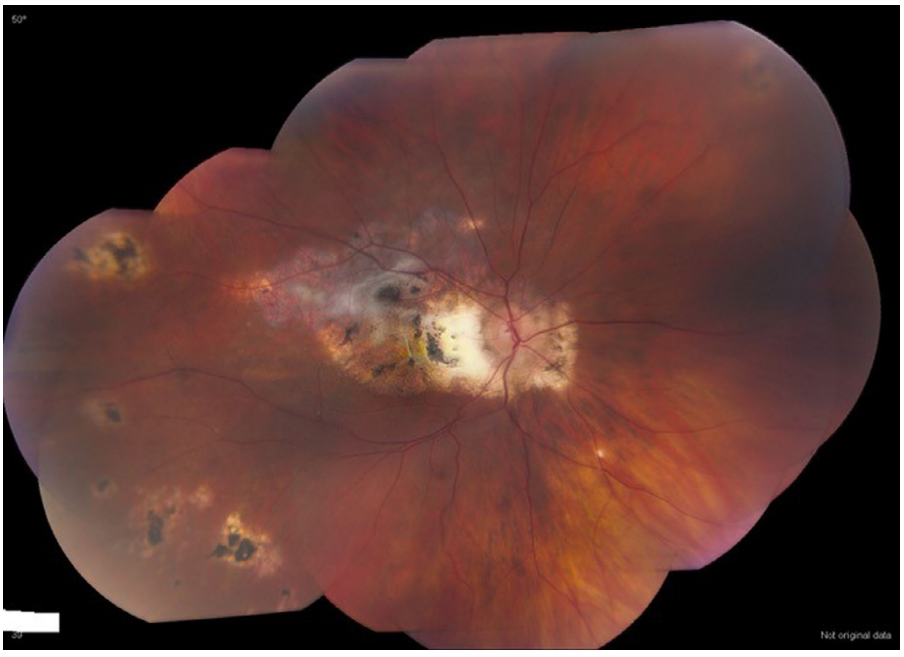

FIGURE 1. Fundus photograph of a case of multifocal choroiditis with panuveitis, demonstrating multiple punched-out atrophic chorioretinal lesions.

RESULTS

Two hundred fifty-one cases of MFCPU were collected, and 138 (57%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of MFCPU were compared to cases of posterior uveitides, including 82 cases of acute posterior multifocal placoid pigment epitheliopathy, 207 cases of BSCR, 51 cases of multiple evanescent white dot syndrome, 122 cases of serpiginous choroiditis, 144 cases of PIC, 12 cases of sarcoid posterior uveitis, 35 cases of syphilitic posterior uveitis, and 277 cases of tubercular posterior uveitis or panuveitis uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[23] The characteristics of cases with MFCPU are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. Key features of the criteria include multifocal choroiditis with round or oval lesions >125 μm in size, involvement of the midperiphery and/or periphery, and punched-out atrophic scars (Figure 1) or active lesions with more than minimal vitritis. The overall accuracies for posterior uveitides were 93.9% in the training set and 98.0% (95% confidence interval 94.3, 99.3) in the validation set. The misclassification rate for MFCPU in the training set was 15%, and in the validation set 0%. The diseases with which MFCPU most often was confused in the training set were BSCR and PIC.

DISCUSSION

The classification criteria developed by the SUN Working Group for MFCPU have a reasonably low misclassification rate, indicating good discriminatory performance against other posterior uveitides.

Multifocal choroiditis is an ambiguous term that can refer to a clinical finding, a class of diseases, or a specific disease.[26] Some clinicians have used multifocal choroiditis to refer all posterior uveitides with choroidal involvement, others to MFPCU without anterior chamber or vitreous inflammation, and others as synonymous with MFCPU. Although not all cases of MFPCU have anterior chamber or vitreous inflammation, we prefer to use the term MFCPU as the diagnostic entity (regardless of the amount of anterior chamber and vitreous inflammation) and the term "multifocal choroiditis" as a clinical finding indicating multifocal choroidal inflammatory lesions or as a class of diseases characterized by multifocal choroidal inflammation (the multifocal choroiditides). Despite its name, which is used both for historical reasons and to avoid confusion with the use of multifocal choroiditis as a clinical finding or class of diseases, MFCPU is classified as a posterior uveitis, as its primary site of inflammation is in the choroid.[19,20]

In 1984 Watzke and associates[27] described the disease known as PIC, characterized by "punctate" choroidal lesions, typically <250 μm in size and often <125 μm in

TABLE 1. Characteristics of Cases of Multifocal Choroiditis With Panuveitis

Characteristic	Result
Number of cases	138
Demographics	
Age, median, years (25th, 75th percentile)	38 (28, 55)
Sex (%)	
Male	22
Female	78
Race/ethnicity (%)	
White, non-Hispanic	71
Black, non-Hispanic	9
Hispanic	2
Asian, Pacific Islander	3
Other	4
Missing	11
Uveitis history	
Uveitis course (%)	
Acute, monophasic	3
Acute, recurrent	1
Chronic	92
Indeterminate	4
Laterality (%)	
Unilateral	13
Unilateral, alternating	0
Bilateral	87
Ophthalmic examination	
Keratic precipitates (%)	
None	91
Fine	4
Round	3
Stellate	0
Mutton fat	1
Other	1
Anterior chamber cells, grade (%)	
0	54
½+	24
1+	12
2+	6
3+	3
4+	1
Anterior chamber flare, grade (%)	
0	78
1+	19
2+	3
3+	0
4+	0
Iris (%)	
Normal	96
Posterior synechiae	4
Iris nodules	
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	16 (13, 18)
Proportion of patients with IOP > 24 mm Hg either eye (%)	4
Vitreous cells, grade (%)	
0	29
½+	15
1+	36
2+	19
3+	1
4+	0
Vitreous haze, grade (%)	
0	58
½+	15
1+	16
2+	8
3+	3
4+	0
Chorioretinal lesion characteristics	
Lesion number (%)	
Unifocal (1 lesion)	0
Paucifocal (2-4 lesions)	5
Multifocal (≥5 lesions)	89
Missing	6
Lesion shape & character (%)	
Ameboid or serpentine	0
Oval or round	94
Placoid	0
Punched-out/atrophic scars	78
Punctate	0
Missing	6
Inflammatory lesion/scar location (%)[a]	
Posterior pole only involved	1.5
Posterior pole and periphery/midperiphery	56.5
Midperiphery and periphery only	42
Typical lesion size (%)	
<125 μm	0
125-250 μm	33
250-500 μm	37
>500 μm	23
Missing	7
Other features (%)	
Peripapillary atrophy	39
Retinal vascular sheathing	9
Retinal vascular leakage	13
Choroidal neovascularization	7

IOP = intraocular pressure.
[a]Based on 129 cases with photographs.

(*continued on next page*)

size, no to minimal anterior chamber and vitreous inflammation, and a high rate of choroidal neovascularization.[2] Because of the rare occurrence of PIC-like lesions in 1 eye and MFCPU in the other, and because of a similar appearance on multimodal imaging (other than lesion size), some

TABLE 2. Classification Criteria for Multifocal Choroiditis With Panuveitis

Criteria
1. Multifocal choroiditis with
a. Oval or round lesions AND
b. Predominant lesion size >125 μm
AND
2. Characteristic appearance
a. "Punched-out atrophic" chorioretinal scars OR
b. Active lesions with more than minimal vitreous inflammation
AND
3. Inflammatory lesions and/or characteristic scars involving the midperiphery or periphery with or without posterior pole involvement
Exclusions
1. Positive serologic test for syphilis using a treponemal test
2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)
3. In tuberculosis-endemic regions or tuberculosis-exposed individuals,[a] evidence of infection with *Mycobacterium tuberculosis*
a. Histologically or microbiologically confirmed infection with *M. tuberculosis*[b] OR
b. Positive interferon-γ release assay[c] OR
c. Positive tuberculin skin test[d]

[a] Testing not needed in tuberculosis nonendemic regions.
[b] For example, biopsy, fluorochrome stain, culture, or polymerase chain reaction–based assay.
[c] For example, QuantiFERON gold or T-spot.
[d] For example, purified protein derivative; a positive result should be >10 mm induration

investigators have considered PIC and MFCPU to be variants of the same disease.[26,28] Conversely, other investigators, classifying the 2 diseases based solely on chorioretinal morphology, have found clear-cut differences, namely the absence of anterior chamber and vitreous inflammation and the absence of uveitis-related structural complications other than choroidal neovascularization in PIC,[2] and differences in the course with prognostic import.[20] There also are differences in the location of the inflammatory lesions/scars; cases of MFCPU typically have midperipheral or peripheral involvement, whereas the lesions in PIC typically are concentrated in the posterior pole.[29,30] A study of cases of MFCPU and PIC using cluster analysis determined that 2 distinct clusters existed, conforming to the diagnoses of PIC and MFCPU, and that the 2 distinguishing features were anterior chamber and vitreous inflammation (largely absent in PIC) and lesion location (posterior in PIC and peripheral in MFCPU).[29]

In the series by Shimada and associates,[31] histologic evaluation of surgically removed choroidal neovascular membranes removed surgically demonstrated inflammatory infiltrates in some cases of MFCPU but not in PIC, suggesting that they might be distinct diseases. Conversely, in the case series by Olsen and associates[32] histologic evaluation of surgically removed choroidal neovascular membranes from patients with PIC demonstrated the occasional lymphocyte, suggesting that the pathology may not be completely dissimilar from that of MFCPU. A genetic risk factor association study suggested similar haplotype associations in the *IL-10* and *TNF* loci for MFCPU and PIC, suggesting possible similarities in pathogenesis, but allowing for different inciting events or epigenetic factors to influence phenotype.[33] Finally, if they were a single disease, one might expect the clinical presentation to be a Gaussian distribution, with the overlap syndrome to be the most common presentation, which is not the case. The paradigms are the most common presentations, and overlap is uncommon. Hence, the SUN Working Group has elected to define the diseases separately, recognizing that there will be cases with an overlap appearance. Most such cases behave more like MFCPU than PIC and might be classified as MFCPU, but probably should be classified as an overlap syndrome at this time.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of MFCPU should not be made in their presence. In prospective studies, many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. In these studies the presence of an exclusionary criterion excludes MFCPU, but the absence of such testing does not always exclude the diagnosis of MFCPU if the criteria for the diagnosis are met.

Classification criteria are employed to diagnose individual diseases for research purposes.[25] Classification criteria differ from clinical diagnostic criteria in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[25] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients

without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead, it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis is moderate at best,[21] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. As such, some cases that clinicians would diagnose as MFCPU may not be so classified by classification criteria.

In conclusion, the criteria for MFCPU outlined in Table 2 seem to perform sufficiently well for use as classification criteria in clinical research.[24]

CREDIT ROLES

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