Classification Criteria for Tubercular Uveitis

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

• PURPOSE: To determine classification criteria for tubercular uveitis.
• DESIGN: Machine learning of cases with tubercular uveitis and 14 other uveitides.
• METHODS: Cases of noninfectious posterior uveitis or panuveitis, and of infectious posterior uveitis or panuveitis, were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were analyzed by anatomic class, and each class was 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 intermediate uveitides. The resulting criteria were evaluated on the validation sets.
• RESULTS: Two hundred seventy-seven cases of tubercular uveitis were evaluated by machine learning against other uveitides. Key criteria for tubercular uveitis were a compatible uveitic syndrome, including (1) anterior uveitis with iris nodules, (2) serpiginous-like tubercular choroiditis, (3) choroidal nodule (tuberculoma), (4) occlusive retinal vasculitis, and (5) in hosts with evidence of active systemic tuberculosis, multifocal choroiditis; and evidence of tuberculosis, including histologically or microbiologically confirmed infection, positive interferon-γ release assay test, or positive tuberculin skin test. The overall accuracy of the diagnosis of tubercular uveitis vs other uveitides in the validation set was 98.2% (95% confidence interval 96.5, 99.1). The misclassification rates for tubercular uveitis were training set, 3.4%; and validation set, 3.6%.
• CONCLUSIONS: The criteria for tubercular uveitis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 142–151. © 2021 Elsevier Inc. All rights reserved.)

Globally, disease caused by *Mycobacterium tuberculosis* is one of the 10 leading causes of death. It is estimated that 10 million persons globally developed tuberculosis (TB) in 2017, and that 1.6 million persons died from TB. Although TB is worldwide in its distribution, in 2017 two-thirds of cases occurred in just 8 countries (India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa), and 87% of cases occurred in the World Health Organization's list of 30 high-TB-burden countries. Nine percent of cases of TB disease are co-infected with the human immunodeficiency virus (HIV), of which 72% occurred in Africa. Only 6% of cases occurred in the WHO European region and 3% in the WHO region of the Americas.[1] In the United States in 2017, there were 9,093 cases reported, 70% of which occurred in individuals born outside the United States.[2] Although 10 million persons developed tubercular disease (active TB) globally in 2017, latent TB is estimated to affect 1.7 billion people, about 23% of the world's population; these individuals are at risk for developing active TB.[1]

Several ocular uveitic presentations have been attributed to ocular TB. These include (1) anterior uveitis with iris nodules; (2) serpiginous-like tubercular choroiditis; (3) choroidal granuloma (ie, tuberculoma); (4) occlusive retinal vasculitis; and (5) in immunocompromised persons, multifocal choroiditis in the context of active systemic TB.[3-8] Complicating the diagnosis of ocular TB is the fact that a minority of persons with ocular TB have evident active systemic TB, and that approximately one-half or fewer have evidence of current or previous pulmonary infection on chest imaging.[3-7] As such, diagnosis of ocular TB usually

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employs evidence of TB infection with a tuberculin skin test (TST) or an interferon-γ release assay (IGRA), neither of which distinguishes between latent and active TB.[9,10] There are no randomized clinical trials demonstrating a response to antitubercular therapy, but there are several large case series.[3-7,11,12] However, evaluation of treatment studies often has been confounded by the concomitant use of corticosteroids and antitubercular therapy.[6,7,11] Nevertheless, most patients with the syndromes listed above seem to respond to antitubercular therapy,[4-7,11,12] and at least 1 study demonstrated a superior outcome among patients presumed to have ocular TB treated with antitubercular therapy compared to those not treated with antitubercular therapy.[12] Treatment regimens recommended for ocular TB typically presume underlying active TB and treat as such (eg, 4 drugs for 2 months, followed by 2 drugs for an additional 4-10 months).[4] Nevertheless, there is a lack of consensus on the diagnosis and treatment of tubercular uveitis.[13]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for the leading 25 uveitides using a formal approach to development and classification.[14-20] Among the uveitides studied was tubercular uveitis.

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.[16,18,20]

• **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.[16]

• **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.[16,18,20] 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.[18,20] Because the goal was to develop classification criteria,[19] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[18,20]

• **MACHINE LEARNING:** The final database was analyzed by anatomic class, and each class was randomly separated into a learning set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[20] Machine learning was used on the learning sets to determine criteria that minimized misclassification. The criteria then were tested on the validation sets; for both the learning 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 tubercular uveitis the diseases against which it was evaluated in the machine learning phase included infectious posterior uveitis and panuveitides (acute retinal necrosis, cytomegalovirus retinitis, syphilitic uveitis, and toxoplasmic retinitis), noninfectious posterior uveitides (acute posterior multifocal placoid pigment epitheliopathy, birdshot chorioretinitis, multiple evanescent white dot syndrome, multifocal choroiditis with panuveitis, punctate inner choroiditis, serpiginous choroiditis), and noninfectious panuveitides (Behçet disease, sarcoidosis-associated uveitis, sympathetic ophthalmia, Vogt-Koyanagi-Harada disease), respectively. No cases of tubercular anterior uveitis were collected.

• **COMPARISON OF CASES WITH EVIDENCE OF SYSTEMIC TUBERCULOSIS VS THOSE WITHOUT AND COMPARISON OF CASES FROM HIGH-TUBERCULOSIS-BURDEN COUNTRIES VS THOSE NOT FROM SUCH COUNTRIES:** Cases with evidence of TB in an extraocular organ were compared to those with ocular disease alone and a positive TST or IGRA, and cases from high-TB-burden countries were compared to those not from high-TB-burden countries. For categorical variables, comparison was performed with the χ^2 test or the Fisher exact test when the count of a variable was less than 5. Continuous variables were summarized as medians and compared with the Wilcoxon rank sum test. For characteristics with multiple categorical grades, values above and below the median were compared. *P* values are nominal and 2-sided.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

RESULTS

Three hundred fifty-eight cases of tubercular uveitis were collected, and 277 (77%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. Cases of tubercular uveitis were evaluated in the machine learning for infectious posterior uveitides and panuveitides, noninfectious posterior uveitides, and noninfectious panuveitides. The details of the machine learning results for these diseases are outlined in the accompanying article.[20] The characteristics of cases with tubercular uveitis are listed in

TABLE 1. Characteristics of Cases of Tubercular Uveitis

Characteristic	Result
Number of cases	277
Demographics	
Age, median, years (25th, 75th percentile)	32 (25, 44)
Sex (%)	
Male	72
Female	28
Race/ethnicity (%)	
White, non-Hispanic	9
Black, non-Hispanic	4
Hispanic	1
Asian, Pacific Islander	80
Missing	6
Uveitis history	
Uveitis course (%)	
Acute, monophasic	25
Acute, recurrent	3
Chronic	66
Indeterminate	6
Laterality (%)	
Unilateral	44
Unilateral, alternating	0
Bilateral	56
Ophthalmic examination	
Keratic precipitates (%)	
None	88
Fine	5
Round	3
Stellate	0
Mutton fat	4
Anterior chamber cells, grade (%)	
0	70
½+	10
1+	6
2+	10
3+	3
4+	1
Anterior chamber flare, grade (%)	
0	86
1+	10
2+	3
3+	1
4+	0
Iris (%)	
Normal	93
Posterior synechiae	6
Iris nodules	1
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	15 (14, 18)
Proportion patients with IOP > 24 mm Hg either eye (%)	5
Vitreous cells, grade (%)	
0	34
½+	16
1+	27
2+	19
3+	4
4+	0
Vitreous haze, grade (%)	
0	65
½+	13
1+	12
2+	6
3+	4
4+	0
Vitreous snowballs (%)	11
Pars plana snowbanks (%)	1
Serpiginous-like tubercular choroiditis (%)	43
Choroidal nodule (ie, tuberculoma) (%)	4
Retinal vasculitis (%)[a]	53
Multifocal choroiditis (%)[a]	6
Systemic disease	
Bilateral hilar adenopathy	6
Immunocompromised patients (%)	2
Evidence of infection with Mycobacterium tuberculosis[b] (%)	100
Histologic or culture confirmation of infection in another organ	17
Positive IGRA	29
Positive tuberculin skin test (eg, PPD)	88

(*continued on next column*)

TABLE 1. (*continued*)

IGRA = interferon-γ release assay; IOP = intraocular pressure; PPD = purified protein derivative.

[a]Nine cases categorized as primarily retinal vasculitis also had a multifocal choroiditis, and 8 cases had a multifocal choroiditis accompanying systemic tuberculosis.

[b]All cases had at least 1 positive test. A total of 242 of 259 (93%) cases tested with a tuberculin skin test were positive, and 79 of 79 (100%) cases tested with an IGRA were positive.

Table 1. Four patterns of cases emerged: (1) serpiginous-like tubercular choroiditis; (2) choroidal nodule (tuberculoma); (3) occlusive retinal vasculitis; and (4) in a small proportion of cases—all with systemic, extraocular TB—multifocal choroiditis. A small number of cases had both retinal vasculitis and multifocal choroiditis. A comparison of cases with evidence of systemic TB and those without (ie, with only a positive TST or IGRA for TB) is shown in Table 2. Patients in cases with evidence of systemic TB were less likely to be of Asian origin, more likely to have vitreous inflammation, and less likely to have serpiginous-like tubercular choroiditis. A comparison of cases from high-TB-burden countries and those not from high-TB-burden countries is shown in Table 3. Cases from high-TB-burden countries had a greater proportion of patients with serpiginous-like-choroiditis, whereas those from "low-TB-burden" countries had a greater proportion of patients with retinal vasculitis and with higher grades of anterior chamber and vit-

TABLE 2. Characteristics of Cases With Evidence of Systemic Tuberculosis vs Those Without

Characteristic	Evidence of Systemic TB[a]	Positive TST or IGRA[b] Only	*P* Value
Number of cases	48	229	
Demographics			
Age, median, years (25th, 75th percentile)	32 (23, 48)	32 (25, 44)	.69
Sex (%)			.60
Male	69	73	
Female	31	27	
Race/ethnicity (%)			.003
Asian	62	84	
Non-Asian	38	16	
Uveitis history			
Uveitis course (%)			.08
Acute, monophasic	23	24	
Acute, recurrent	0	3	
Chronic	62	67	
Indeterminate	14	4	
Laterality (%)			.57
Unilateral	38	46	
Bilateral	62	54	
Ophthalmic examination			
Keratic precipitates (%)			.07
None	80	90	
Fine	12	4	
Round	4	3	
Mutton fat	4	3	
Anterior chamber cells, grade (%)			.83
0	58	72	
≥½+	42	38	
Anterior chamber flare, grade (%)			.13
0	77	88	
≥1+	23	12	
Iris (%)			.89
Normal	92	88	
Posterior synechiae	8	9	
Iris nodules	0	3	
IOP, involved eyes			
Median, mm Hg (25th, 75th percentile)	14 (12, 17)	16 (14, 18)	.15
Percent cases with IOP > 24 mm Hg either eye	4	5	.84
Vitreous cells, grade (%)			.62
0 or ½+	50	50	
≥1+	50	50	
Vitreous haze, grade (%)			.02
0	50	68	
≥½+	50	32	
Serpiginous-like tubercular choroiditis (%)	17	49	<.001
Choroidal nodule (ie, tuberculoma) (%)	10	3	.03
Retinal vasculitis (%)	60	52	.29

IGRA = interferon-γ release assay for TB; IOP = intraocular pressure; TB = tuberculosis; TST = tuberculin skin test (eg, purified protein derivative).

[a] Systemic TB = evidence of infection in an extraocular organ.

[b] For example, QuantiFERON gold or T-spot.

TABLE 3. Characteristics of Cases by Case Source (High-Tuberculosis-Burden Country vs Low-tuberculosis-Burden Country)

Characteristic	Country Type for Case Source[a]		*P* Value
	High-TB-Burden	Low-TB-Burden	
Number of cases	188	89	
Demographics			
Age, median, years (25th, 75th percentile)	30 (23, 40)	41 (29, 57)	<.001
Sex (%)			.07
Male	76	65	
Female	24	35	
Uveitis history			
Uveitis course (%)			<.001
Acute, monophasic	34	8	
Acute, recurrent	2	2	
Chronic	64	73	
Indeterminate	0	17	
Laterality (%)			.01
Unilateral	49	33	
Bilateral	51	67	
Ophthalmic examination			
Keratic precipitates (%)			<.001
None	95	71	
Fine or round	3	19	
Mutton fat	2	10	
Anterior chamber cells, grade (%)			<.001
0	79	50	
≥½+	21	50	
Anterior chamber flare, grade (%)			.01
0	90	78	
≥1+	10	22	
Iris (%)			<.001
Normal	97	85	
Posterior synechiae	2	15	
Iris nodules	1	0	
IOP, involved eyes			
Median, mm Hg (25th, 75th percentile)	15 (14, 17)	16 (12, 18)	.91
Cases with IOP > 24 mm Hg either eye (%)	2	11	.002
Vitreous cells, grade (%)			.12
≤½+	52	46	
≥1+	48	54	
Vitreous haze, grade (%)			<.001
0	73	46	
≥½+	27	54	
Serpiginous-like tubercular choroiditis (%)	54	21	<.001
Choroidal nodule (ie, tuberculoma) (%)	4	3	.51
Retinal vasculitis (%)	46	68	.001

IOP = intraocular pressure; TB = tuberculosis.
[a]High-burden defined by World Health Organization.

reous inflammation. The criteria developed after machine learning are listed in Table 4. The key features of the criteria are a compatible ocular uveitic syndrome and evidence of infection with TB. Compatible uveitic syndromes included anterior uveitis with iris nodules, serpiginous-like tubercular choroiditis (Figure 1), a choroidal nodule ("tuberculoma"; Figure 2), and occlusive retinal vasculitis (Figure 3). The overall accuracies by anatomic class were infectious posterior uveitides and panuveitides, learning set 92.1% and validation set 93.3% (95% confidence interval [CI] 88.1, 96.3); noninfectious posterior uveitides, learning set 93.9% and validation set 98.0% (95% CI 94.3, 99.3); and noninfectious panuveitides, learning set 96.3% and validation set 94.0% (95% CI 89.0, 96.8).[16] The over-

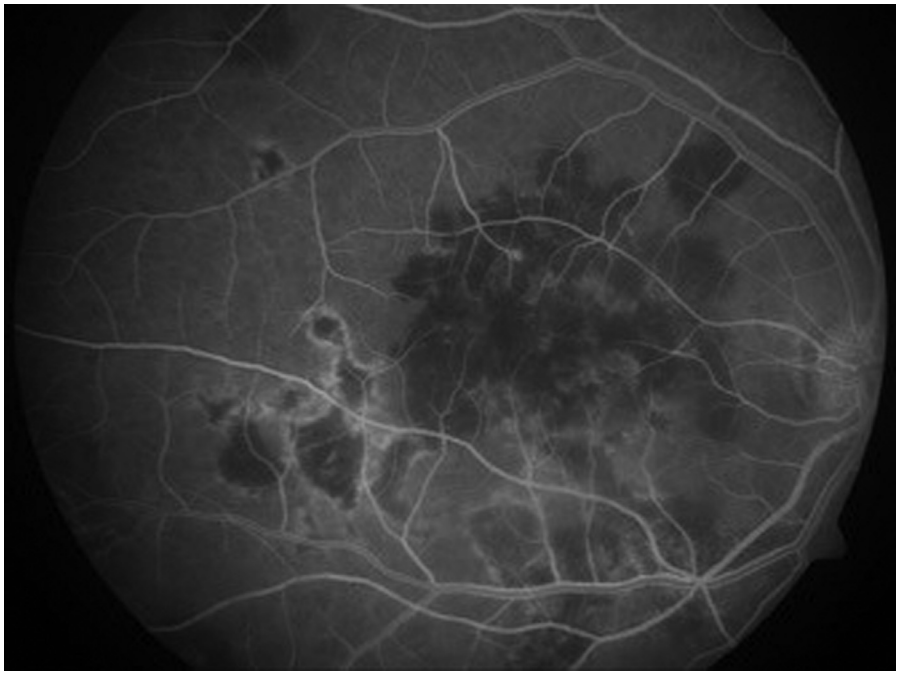

FIGURE 1. Fluorescein angiogram of serpiginous-like tubercular choroiditis, demonstrating the late staining of the borders of several of the multifocal choroidal lesions.

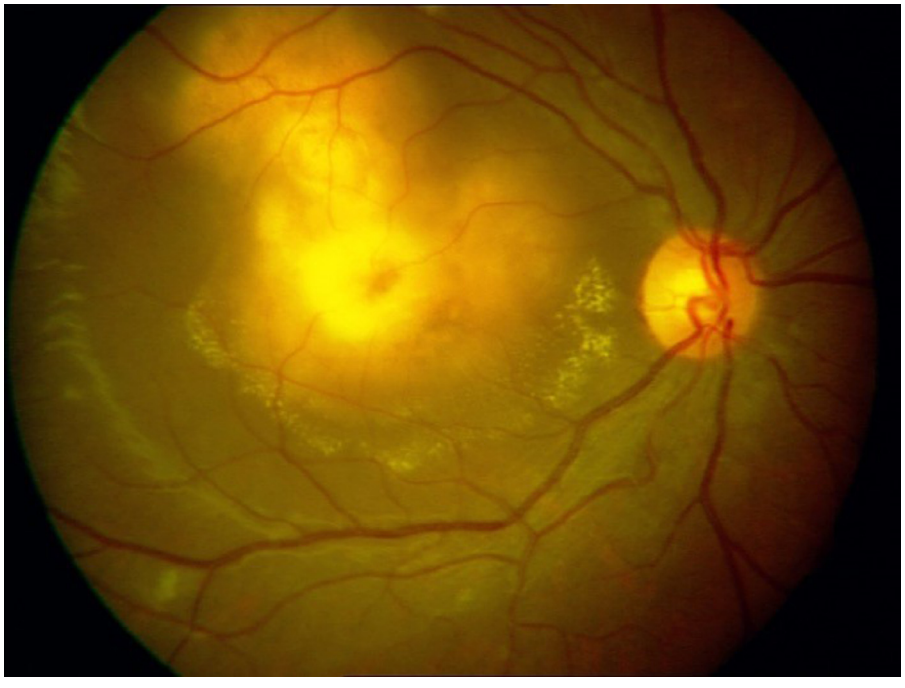

FIGURE 2. Fundus photograph of a choroidal tuberculoma with overlying serous fluid.

all accuracy of the diagnosis of tubercular uveitis vs other uveitides in the validation set was 98.2% (95% CI 96.5, 99.1). The misclassification rates for tubercular uveitis in the learning set were as follows: against noninfectious posterior uveitides 7.5%, against noninfectious panuveitides 5.3%, and against infectious posterior uveitides and panuveitides 1.3%. Overall the misclassification rate for tubercular uveitis in the learning set was 3.4%. In the validation set the misclassification rates were as follows: against noninfectious posterior uveitides 0%, against noninfectious panu-

FIGURE 3. Fundus photograph of retinal vasculitis owing to tuberculosis, demonstrating intraretinal hemorrhage and vascular sheathing.

veitides 6.7%, and against infectious posterior uveitides and panuveitides 5.0%. Overall, the misclassification rate for tubercular uveitis in the validation set was 3.6%.

Data on testing for TB were available on 1,397 cases in the SUN database, of which 277 patients had tubercular uveitis and 1120 did not. A TST was positive in 111 of 917 (12%) cases without tubercular uveitis and a documented TST result, and an IGRA was positive in 23 of 252 (9%) cases without tubercular uveitis and a documented IGRA result. None of these TB test–positive not-tubercular-uveitis cases had a TB-compatible uveitic syndrome, and all had well-defined alternative uveitic diagnoses.

DISCUSSION

The classification criteria developed by the SUN Working Group for tubercular uveitis have a low misclassification rate, indicating good discriminatory performance against other uveitides. Because of the high prevalence of latent TB and the fact that less than 1% of individuals with latent TB will have active TB, not all cases of uveitis with a positive tuberculin skin test or a positive IGRA assay will have uveitis owing to TB. In fact, it has been estimated that the positive predictive values for a positive tuberculin skin test and a positive IGRA for ocular TB in the United States are 1% and 11%, respectively.[9,10] As such, a compatible uveitic syndrome (one typically associated with TB) is required for diagnosis in the classification criteria. Owing to the selective nature of the SUN case collection, great care should be taken in extrapolating the SUN TB test data, as the database was enriched for TB compared to what is seen in clinical care in the United States and other low-TB-burden countries. Nevertheless, if the calculated sensitivity and specificity of the SUN data were to be applied to a United States (or other low-TB-burden country) population, the positive predictive value of a positive purified protein derivative test would be <1% and of a positive IGRA would be 30%, results qualitatively similar to the published data, and again emphasizing the need for a TB-compatible uveitic syndrome in the criteria.

The potential for a false-positive TST among patients with a history of bacille Calmette-Guérin (BCG) vaccination for TB has been an item of concern among ophthalmologists. However, it seems that for individuals receiving BCG vaccination as an infant, by 10 years after vaccination the TST will be negative in ~99% of persons (ie, estimated false-positive rate ~1%),[21] and the TST (positive result >10 mm) can be used reliably to diagnose TB in adults even with a history of BCG vaccination as an infant. Although the false-positive rate may be higher if vaccination is given after infancy, the absolute prevalence of false-positive tuberculin skin tests ow-

TABLE 4. Classification Criteria for Tubercular Uveitis

Criteria
1. Evidence of a tubercular uveitis compatible uveitic syndrome
a. anterior uveitis with iris nodules
b. serpiginous-like tubercular choroiditis
c. choroidal nodule (ie, tuberculoma)
d. in individuals with active systemic tuberculosis, multifocal choroiditis
e. occlusive retinal vasculitis
AND
2. Evidence of infection with *Mycobacterium tuberculosis*, either
a. histologically or microbiologically confirmed infection with *M. tuberculosis*[a] OR
b. positive IGRA[b] OR
c. positive tuberculin skin test[c]
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Positive biopsy for sarcoidosis (and therefore an absence of histologic or microbiologic confirmation of infection with *M. tuberculosis*)
3. Uveitic syndrome compatible with either sarcoidosis-associated uveitis or tubercular uveitis and bilateral hilar adenopathy on chest imaging without histologic or microbiologic confirmation of the diagnosis of infection with *M. tuberculosis*[d]

IGRA = interferon-γ release assay.

[a]For example, biopsy, fluorochrome stain, culture, or polymerase chain reaction–based assay.

[b]For example, QuantiFERON gold or T-spot.

[c]For example, purified protein derivative skin test; a positive result should be >10 mm induration. However, a positive skin test and a negative IGRA should be taken as evidence of atypical mycobacterial infection and not tuberculosis.

[d]In patients with a uveitic syndrome compatible either with sarcoidosis-associated uveitis or with tubercular uveitis, bilateral hilar adenopathy, and evidence of latent tuberculosis (eg, positive tuberculin skin test or IGRA), the classification requires histologic or microbiologic confirmation of the diagnosis (ie, classification cannot be made without such confirmation).

ing to BCG vaccination has been estimated at <1% to 2.3%.[21]

Polymerase chain reaction (PCR) is a sensitive technique for identifying pathogens in small volume samples, such as from the eye, and is used routinely to diagnose viral intraocular infections (eg, cytomegalovirus, herpes simplex virus, varicella zoster virus) and ocular toxoplasmosis.[20] Small case series have suggested promise for mycobacterial PCR analysis of aqueous specimens obtained by paracentesis.[22-24] Reported sensitivity has ranged from ~55% to 75%, and specificity as high as 100% has been reported.[22-24] However, negative results in patients with active systemic TB and uveitis[24] and discordant results between assays (using different primers and amplification conditions) as high as 30% have limited its widespread adoption.[23] In its analysis of PCR for ocular TB, the Collaborative Ocular Tuberculosis Study concluded that "PCR is not commonly done for diagnosing intraocular TB and … may not influence management."[24] Furthermore, no studies have compared the performance of PCR for different presentations of tubercular uveitis (eg, serpiginous-like tubercular choroiditis vs choroidal tuberculoma vs panuveitis with occlusive retinal vasculitis), where mycobacterial load in the aqueous and/or vitreous fluid might be expected to vary. We had few data on the use of PCR for ocular TB and could not evaluate its performance. Given the utility of PCR for other pathogens,[20] it might be reasonable to diagnose ocular TB with a positive PCR assay from intraocular fluids, but the relatively low sensitivity suggests that it cannot be used to exclude ocular TB at this time. Moreover, the limited amount of data, the discordance between assays, and the lack of widespread use resulted in its not being included in the criteria at this time. As assays are developed further, are standardized, performance is improved, and appropriate clinical studies are performed, one might expect a positive PCR for TB from an intraocular fluid specimen to be added to the SUN Classification Criteria in the future.

Fewer than one-half of individuals with ocular TB have evidence of systemic disease,[4,5] a result also seen with our data. We compared those with evidence of extraocular TB to those without. Those without evidence of extraocular TB were more likely to be Asian and have serpiginous-like tubercular choroiditis, although serpiginous-like tubercular choroiditis was seen among those with evidence of systemic TB. Whether this difference represents ascertainment bias, regional diagnostic bias, regional variation in the presentation of ocular TB, chance variation, and/or other, unidentified factors is unknown. However, the successful treatment of serpiginous-like tubercular choroiditis with antitubercular therapy has been reported several times, suggesting that it is owing to *M. tuberculosis* infection.[4,6,11,12] Although there were differences in the distributions of the disease presentations between cases with systemic, extraocular TB and those without, a similar set of presentations of disease were present, suggesting that these patterns of disease are related to TB. Similarly, cases from high-TB-burden countries and those from low-TB-burden countries had different distributions of disease presentations, but the same set of disease presentations, suggesting generalizability of these criteria.

The presence of any of the exclusions in Table 4 suggests an alternate diagnosis, and the diagnosis of tubercular uveitis 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. Hence the presence of an exclusionary criterion excludes tubercular uveitis, but the absence of such testing does not always exclude the diagnosis of tubercular uveitis if the criteria for the diagnosis are met. However, there are several tubercular uveitis compatible ocular syndromes that also are compatible with sarcoidosis-associated uveitis, including chronic anterior uveitis with

iris nodules, a choroidal nodule, and panuveitis with retinal vascular sheathing/occlusion. In TB-nonendemic areas these ocular findings and bilateral hilar adenopathy on chest imaging nearly always are sarcoidosis.[25] However, in TB-endemic areas, bilateral hilar adenopathy may be attributable to TB, and patients with evidence of latent TB (eg, positive TST or IGRA), bilateral hilar adenopathy, and uveitis could have either disease.[25] In these situations, the only way to confirm the diagnosis is biopsy. In the SUN database, patients in 6.1% of cases of TB uveitis had bilateral hilar adenopathy on chest imaging, of whom 76% were Asian (and therefore presumably from a TB-endemic country). A study of patients with uveitis and a positive IGRA in a nonendemic country suggested that when a biopsy (or bronchoalveolar lavage) is performed ~75% of these patients will have sarcoidosis and not TB.[5] Nevertheless, 36% of the patients with uveitis and bilateral hilar adenopathy in this study did not undergo additional testing and were presumed to have ocular TB. As such, patients with a uveitis compatible either with sarcoidosis or with tubercular uveitis, bilateral hilar adenopathy, and a positive tuberculin skin test or IGRA cannot be reliably diagnosed as sarcoidosis or TB without biopsy or microbiologic confirmation of the diagnosis.

Classification criteria are employed to diagnose individual diseases for research purposes.[19] 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,[19] 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,[18] 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 with tubercular uveitis may not be so classified by classification criteria.

One excluded disease was intermediate uveitis with evidence of latent TB. There was no consensus as to whether this represents an "ocular TB–compatible syndrome." Studies of antitubercular therapy for presumed ocular TB have reported disappointing results for intermediate uveitis, with substantially greater failure rates than for other syndromes,[11] suggesting that many if not most such cases represent uveitis with unrelated latent TB rather than ocular TB. Demonstration of a distinct morphologic syndrome or development of a widely used reliable PCR assay for intraocular TB that could diagnose tubercular intermediate uveitis could lead to the inclusion of intermediate uveitis in the criteria. We had no cases of chronic anterior uveitis with iris nodules in the SUN database, and could not evaluate it. However, anterior uveitis with iris nodules is a well-described manifestation of tubercular uveitis,[5] and it was included as a tubercular uveitis–compatible presentation in the criteria.

The Collaborative Ocular Tuberculosis Study (COTS) has used a Delphi approach to derive consensus guidelines for the management of ocular TB.[7,11,24] These guidelines differ from the SUN classification criteria, which are targeted for clinical research and may be, of necessity, more restrictive than COTS guidelines for clinical care. Nevertheless, they seem to contain overlapping elements, including recognition of several of the major TB uveitis presentations.

In conclusion, the criteria for tubercular uveitis outlined in Table 4 seem to perform sufficiently well for use as classification criteria in clinical research.[20]

CREDIT ROLES

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