

Classification Criteria for Syphilitic Uveitis



THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP^{1,2,3,*}

- **PURPOSE:** To determine classification criteria for syphilitic uveitis.
- **DESIGN:** Machine learning of cases with syphilitic uveitis and 24 other uveitides.
- **METHODS:** Cases of anterior, intermediate, posterior, and panuveitides 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 different uveitic classes. The resulting criteria were evaluated on the validation set.
- **RESULTS:** Two hundred twenty-two cases of syphilitic uveitis were evaluated by machine learning, with cases evaluated against other uveitides in the relevant uveitic class. Key criteria for syphilitic uveitis included a compatible uveitic presentation (anterior uveitis; intermediate uveitis; or posterior or panuveitis with retinal, retinal pigment epithelial, or retinal vascular inflammation) and evidence of syphilis infection with a positive treponemal test. The Centers for Disease Control and Prevention reverse screening algorithm for syphilis testing is recommended.

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The misclassification rates for syphilitic uveitis in the training sets were as follows: anterior uveitides 0%, intermediate uveitides 6.0%, posterior uveitides 0%, panuveitides 0%, and infectious posterior/panuveitides 8.6%. The overall accuracy of the diagnosis of syphilitic uveitis in the validation set was 100% (99% confidence interval 99.5, 100)—that is, the validation set's misclassification rates were 0% for each uveitic class.

• **CONCLUSIONS:** The criteria for syphilitic uveitis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 182–191. © 2021 Elsevier Inc. All rights reserved.)

SYPHILIS IS A SEXUALLY TRANSMITTED DISEASE CAUSED by the spirochete *Treponema pallidum*. If untreated, it results in a lifelong infection and typically progresses through identifiable stages. Primary syphilis is a genital ulcerative disease, though other tissues may be affected; secondary syphilis typically results in a disseminated rash, often with other systemic manifestations, such as fever, fatigue, myalgias, and adenopathy. Even if untreated, the symptoms and signs of primary and secondary syphilis spontaneously resolve, resulting in a state of latent infection, which may last indefinitely. Tertiary syphilis results in gumma formation and/or cardiac disease. Neurosyphilis may occur with any stage of syphilis. In 2000 and 2001, the rates of primary and secondary syphilis in the United States were at their lowest since reporting began in 1941, at a rate of 2.1 cases per 100,000 population.^{1,2} Since 2001, rates of primary and secondary syphilis have steadily risen in the United States, and by 2017 the rate was 9.5 cases per 100,000 population, an increase mirrored elsewhere in the world.^{1,2} This increase in the United States has occurred in all races and ethnicities and in both sexes, although the majority of cases occur in men, with approximately one-half of cases occurring in men who have sex with men. Human immunodeficiency virus (HIV) infection is a frequent co-infection among patients with syphilis, and a diagnosis of syphilis should lead to testing for HIV infection.^{1,2}

Serologic testing for syphilis relies on the use of nontreponemal tests, such as the rapid plasmin regain test and the Venereal Disease Research Laboratory test, and treponemal tests, which may be enzyme immunoassays (eg, the syphilis IgG test), chemiluminescence immunoassays (eg, fluorescent treponemal antibody test), or *Treponema pallidum* par-

ticle agglutination tests. The traditional screening algorithm involved screening with a nontreponemal test first and confirmation with a treponemal test.² More recently, a reverse sequence screening algorithm has been proposed and used in some laboratories, and it employs screening with a treponemal test followed by confirmation with a nontreponemal test or an alternate treponemal test.³ Although the rate of false-positive treponemal tests for syphilis is low (<1%), because false-positives occur, diagnosis requires 2 positive tests, with at least 1 treponemal test.¹⁻³ Nontreponemal test titers should fall with successful treatment and may convert to negative, whereas treponemal test results may remain positive despite successful treatment, indicating the utility of nontreponemal tests in disease management.²

Ocular syphilis rates also have been increasing since 2000-2001.⁴⁻⁶ Syphilis may cause any anatomic class of uveitis, including anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis, although posterior uveitis and panuveitis have been reported as most common.⁷⁻¹² Syphilitic uveitis accounts for ~1% to 2.5% of uveitis cases at tertiary referral centers and an estimated 0.5% to 0.65% of syphilis cases.^{4,6,7,11,12} In Brazil, syphilis increased from 1.8% of uveitis cases in 1980 to 6.1% in 2012-2013.⁶ Ocular syphilis has been reported to occur in as many as 9% of HIV-infected persons with syphilis and has been reported to be the most frequent cause of uveitis in HIV-infected persons in the era of modern antiretroviral therapy.¹³⁻¹⁵ The British Ocular Syphilis Study estimated the annual incidence of ocular syphilis in the United Kingdom at 0.3 cases per 1 million adult population.⁵

Because as many as one-third of cases of ocular syphilis may be treponemal test–positive and nontreponemal test–negative,⁷ many uveitis experts recommend that patients with uveitis be screened for syphilis using the reverse sequence screening algorithm (ie, screening with a treponemal test, such as the fluorescent treponemal antibody or syphilis IgG test).¹⁶ Because of the frequent occurrence of neurosyphilis with ocular syphilis, estimated to be as high as 50%,^{7,10} the Centers for Disease Control and Prevention (CDC) recommend that patients with ocular syphilis undergo lumbar puncture, and that patients with ocular syphilis be treated with a neurosyphilis regimen, regardless of the results of cerebrospinal fluid examination.² A summary of the reverse sequence screening algorithm for syphilis is outlined in Table 1, and a summary of the CDC treatment recommendations for ocular syphilis management is outlined in Table 2.

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. Among the diseases studied was syphilitic uveitis.¹⁷⁻²³

TABLE 1. Reverse Sequence Syphilis Screening Algorithm

1. Screen with a treponemal test, either an enzyme immunoassay (eg, syphilis IgG) or a chemiluminescence assay (eg, FTA)
 - a. If treponemal test negative, syphilis is not present
 - b. If treponemal test positive, perform a nontreponemal test (eg, RPR or VDRL)
2. Confirmation with nontreponemal test result
 - a. If nontreponemal test positive, patient has syphilis
 - b. If nontreponemal test negative, perform a different specific test (eg, TP-PA)
3. Second (different) treponemal test result
 - a. If second treponemal test result positive, patient has syphilis
 - b. If second treponemal test result negative, patient does not have syphilis (may have false-positive test or treated syphilis)

FTA = fluorescent treponemal antibody; RPR = rapid plasma reagin; TP-PA = *Treponema pallidum* particle agglutination; VDRL = Venereal Disease Research Laboratory.
Adapted from references 2 and 3.

TABLE 2. United States Centers for Disease Control and Prevention Recommendations for the Treatment of Ocular Syphilis

- Test for HIV (frequent co-infection)
- Lumbar puncture even in the absence of clinical neurologic findings (neurosyphilis frequently present) for CSF examination
- If CSF examination abnormal, follow CSF with serial lumbar punctures as for neurosyphilis to assess treatment response
- Treat as neurosyphilis regardless of lumbar puncture results
- 3-4 million units aqueous crystalline penicillin G intravenously every 4 hours for 10-14 days (or 18 to 24 million units per day continuous infusion)
 - Consider adding following after completion of initial 10-14 days of treatment: benzathine penicillin, 2.4 million units once per week for up to 3 weeks
- If nontreponemal serologic test abnormal pre-treatment, follow titer at 6, 12, and 24 months to assess response to therapy
- Titers ≥1:32 should have a 4-fold decline in titer by 12-24 months

CSF = cerebrospinal fluid; HIV = human immunodeficiency virus.
Adapted from reference 2.

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.¹⁹⁻²²

- **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a stan-

standardized, menu-driven hierarchical case collection instrument.¹⁹

• **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.^{20,22} Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database.^{20,22} Because the goal was to develop classification criteria,²³ only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were “selected”), using formal consensus techniques described in the accompanying article.^{21,22}

• **MACHINE LEARNING:** The final database then was analyzed by anatomic class, and cases in each class were 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.²² Machine learning was used on the learning set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; 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. Because syphilis can present as any class of uveitis, relevant cases were analyzed within each class of uveitides. Cases of syphilitic anterior, intermediate, and posterior uveitis and syphilitic panuveitis were evaluated in the machine learning phase against anterior uveitides (cytomegalovirus anterior uveitis, herpes simplex virus anterior uveitis, juvenile idiopathic arthritis-associated anterior uveitis, sarcoidosis-associated anterior uveitis, spondyloarthritis/HLA-B7-associated anterior uveitis, tubulointerstitial nephritis with uveitis, varicella zoster virus anterior uveitis), intermediate uveitides (multiple sclerosis-associated intermediate uveitis; pars planitis; intermediate uveitis, non-pars planitis type; sarcoidosis-associated intermediate uveitis), noninfectious posterior uveitides (acute posterior multifocal placoid pigment epitheliopathy, birdshot chorioretinitis, multifocal choroiditis with panuveitis, punctate inner choroiditis, sarcoidosis-associated posterior uveitis, serpiginous choroiditis), noninfectious panuveitides (Behçet disease, sarcoidosis-associated panuveitis, sympathetic ophthalmia, Vogt-Koyanagi-Harada disease), and infectious posterior uveitides and panuveitides (acute retinal necrosis, cytomegalovirus retinitis, tubercular uveitis, and toxoplasmic retinitis).

RESULTS

Two hundred fifty cases of syphilitic uveitis were collected; 222 of these cases (89%) achieved supermajority agreement on the diagnosis during the “selection” phase and were used in the machine learning phase. The details of the machine learning results for these diseases are outlined in the accompanying article.²² The characteristics of cases of syphilitic uveitis are listed in Table 3. The characteristics of the cases of syphilitic uveitis by anatomic class are listed in Table 4. Review of images for posterior segment involvement by syphilitic uveitis suggested that posterior uveitis and posterior segment involvement in panuveitis typically presents as either (1) placoid inflammation of the retinal pigment epithelium (sometimes previously termed “placoid chorioretinitis,” even though it is the retinal pigment epithelium and not the choroid that is involved; Figures 1 and 2); (2) necrotizing retinitis akin to that seen with cytomegalovirus retinitis or acute retinal necrosis (Figure 3); (3) a multifocal inflammation of the retina and/or retinal pigment epithelium (Figures 4 and 5); and (4) retinal vascular disease with either an occlusive retinal vasculitis or retinal vascular sheathing and/or leakage. The multifocal lesions were typically 250-500 μ m in size, with some variability. In the SUN database necrotizing retinitis was seen only in cases with HIV infection. The criteria developed after machine learning are listed in Table 5. Because any anatomic class of uveitis can be caused by syphilis, and because of its protean manifestations, a positive treponemal test for syphilis was selected as the key diagnostic feature. For anterior and intermediate uveitis, the clinical features were not distinct from other anterior or intermediate uveitides. However, for posterior uveitides, the posterior segment involvement is inflammation of the retina or retinal pigment epithelium with a limited number of presentations. The overall accuracies by anatomic class were as follows: anterior uveitides, learning set 97.5% and validation set 96.7% (95% confidence interval [CI] 92.4, 98.6); intermediate uveitides, learning set 99.8% and validation set 99.3% (95% CI 96.1, 99.9); noninfectious posterior uveitides, learning set 93.9% and validation set 98.0% (95% CI 94.3, 99.3); noninfectious panuveitides, learning set 96.3% and validation set 94.0% (95% CI 89.0, 96.8); and infectious posterior uveitides / panuveitides, learning set 92.1% and validation set 93.3% (95% CI 88.1, 96.3).²² The misclassification rates for syphilitic uveitis in the learning set were as follows: against anterior uveitides 0%, intermediate uveitides 6%, noninfectious posterior uveitides 0%, noninfectious panuveitides 3.4%, and against infectious posterior uveitides and panuveitides 8.6%. In the validation set the misclassification rates were as follows: against anterior uveitides 0%, intermediate uveitides 0%, noninfectious posterior uveitides 0%, noninfectious panuveitides 0%, and infectious posterior uveitides and panuveitides 0%.

TABLE 3. Characteristics of Cases of Syphilitic Uveitis

Characteristic	Result
Number of cases	222
<i>Demographics</i>	
Age, median, years (25th, 75th percentile)	49 (37, 56)
Sex (%)	
Male	80
Female	20
Race/ethnicity (%)	
White, non-Hispanic	50
Black, non-Hispanic	14
Hispanic	12
Asian, Pacific Islander	5
Other	8
Missing	11
<i>Uveitis history</i>	
Uveitis course (%)	
Acute, monophasic	62
Acute, recurrent	2
Chronic	24
Indeterminate	12
Laterality (%)	
Unilateral	44
Unilateral, alternating	0
Bilateral	56
<i>Ophthalmic examination</i>	
Keratic precipitates (%)	
None	45
Fine	33
Round	11
Stellate	2
Mutton fat	9
Anterior chamber cells, grade (%)	
0	26
½+	9
1+	21
2+	24
3+	17
4+	3
Hypopyon (%)	0
Anterior chamber flare, grade (%)	
0	50
1+	25
2+	17
3+	8
4+	1
Iris (%)	
Normal	86
Posterior synechiae	10
Iris nodules	4
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	15 (13, 18)

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TABLE 3. (continued)

Characteristic	Result
Proportion patients with IOP > 24 mm Hg either eye (%)	12
Vitreous cells, grade (%)	
0	18
½+	11
1+	24
2+	25
3+	17
4+	5
Vitreous haze, grade (%)	
0	33
½+	10
1+	20
2+	18
3+	11
4+	7
Vitreous snowballs (%)	6
Pars plana snowbanks (%)	0
Optic disc edema (%)	19
Placoid inflammation of the retinal pigment epithelium (%)	16
Multifocal inflammation of the retina/retinal pigment epithelium (%)	21
Necrotizing retinitis	7
Occlusive retinal vasculitis (%)	5
Retinal vascular sheathing/leakage (%)	34
<i>Systemic disease</i>	
Immunocompromised patient (%) ^a	40
<i>Anatomic uveitic class (%)</i>	
Anterior uveitis	13
Intermediate uveitis	39
Posterior uveitis	15
Panuveitis	33

IOP = intraocular pressure.

^aAll immunocompromised patients were human immunodeficiency virus infected.

The overall accuracy of the diagnosis of syphilitic uveitis in the test set was 100% (95% CI 99.5, 100).

Results of treponemal tests for syphilis were available on 2,608 cases in the database, of which 222 had syphilitic uveitis. All cases of syphilitic uveitis had a positive treponemal test for syphilis. Nine cases of other diseases had a positive treponemal test for syphilis, typically with a history of treated syphilis and a well-characterized alternative disease. There were 2,377 cases of other uveitides with a negative treponemal test. Using this population, the sensitivity, specificity, and positive and negative predictive values for syphilitic uveitis would be calculated as 100%, 99.6%, 96.1%, and 100%, respectively.

TABLE 4. Characteristics of Cases of Syphilitic Uveitis by Anatomic Class

Characteristic	Uveitic Anatomic Class			
	Anterior Uveitis	Intermediate Uveitis	Posterior Uveitis	Panuveitis
Number of cases	32	85	35	70
<i>Demographics</i>				
Age, median, years (25th, 75th percentile)	50 (34, 61)	48 (38, 55)	52 (39, 55)	46 (35, 56)
Sex (%)				
Male	84	79	83	82
Female	16	21	17	18
Race/ethnicity (%)				
White, non-Hispanic	50	45	57	57
Black, non-Hispanic	28	12	3	15
Hispanic	6	18	6	7
Asian, Pacific Islander	9	5	3	3
Other	6	5	19	7
Missing	1	15	12	11
<i>Uveitis history</i>				
Uveitis course (%)				
Acute, monophasic	31	62	62	69
Acute, recurrent	0	4	3	0
Chronic	41	21	26	23
Indeterminate	28	12	9	8
Laterality (%)				
Unilateral	56	35	46	53
Bilateral	44	65	54	47
<i>Ophthalmic examination</i>				
Keratic precipitates (%)				
None	41	40	94	23
Fine	28	36	6	49
Round	13	12	0	17
Stellate	0	4	0	3
Mutton fat	19	8	0	9
Anterior chamber cells, grade (%)				
0	0	26	94	3
½+	6	9	3	14
1+	38	24	0	20
2+	44	14	3	40
3+	13	22	0	20
4+	0	5	0	3
Anterior chamber flare, grade (%)				
0	53	47	97	31
1+	25	27	3	33
2+	19	13	0	24
3+	3	11	0	10
4+	0	2	0	1
Iris (%)				
Normal	90	90	100	86
Posterior synechiae	6	8	0	14
Iris nodules	9	2	0	0
IOP, involved eyes				
Median, mm Hg (25th, 75th percentile)	15 (14, 17)	15 (13, 18)	15 (12, 20)	15 (12, 17)
Percent patients with IOP > 24 mm Hg either eye	6	9	28	4

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TABLE 4. (continued)

Characteristic	Uveitic Anatomic Class			
	Anterior Uveitis	Intermediate Uveitis	Posterior Uveitis	Panuveitis
Vitreous cells, grade (%)				
0	59	1	43	7
½+	25	8	6	10
1+	13	26	17	36
2+	3	35	20	23
3+	0	21	11	20
4+	0	8	3	4
Vitreous haze, grade (%)				
0	0	18	51	23
½+	0	13	11	10
1+	0	27	9	23
2+	0	15	17	26
3+	0	12	6	17
4+	0	15	6	1
Vitreous snowballs (%)	0	9	14	0
Optic disc edema (%)	1	21	14	26
Placoid inflammation of the retinal pigment epithelium (%)	0	0	34	36
Multifocal inflammation of the retina/retinal pigment epithelium (%)	0	0	49	43
Necrotizing retinitis (%)	0	0	12	16
Occlusive retinal vasculitis (%)	0	2	0	9
Retinal vascular sheathing or leakage (%)	0	34	48	41
Systemic disease				
HIV-infected (%)	47	35	40	36

HIV = human immunodeficiency virus; IOP = intraocular pressure.



FIGURE 1. Red-free fundus imaging of a case of ocular placoid syphilis, demonstrating the placoid-appearing area of abnormality.

DISCUSSION

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

Syphilitic uveitis can present as any anatomic class of uveitis. Previous case series have suggested that anterior uveitis occurs in 18% to 29%, intermediate uveitis in 6% to 25%, isolated posterior uveitis in 9% to 19%, and panuveitis in 47% to 49%.^{7,8} In this series nearly half the cases had posterior segment involvement. Because of its protean manifestations, syphilis typically is in the differential for most uveitides, and its exclusion typically is needed. No ocular findings routinely identified syphilitic uveitis, so serologic testing is needed, particularly for anterior and intermediate uveitic presentations. For posterior uveitic and panuveitic presentations, imaging suggested that syphilis typically involves the retina, retinal pigment epithelium, or retinal blood vessels. Ocular “placoid” syphilis is a form of posterior segment syphilis that has a characteristic appearance, hyperautofluorescence on fundus autofluorescence (Figure 1), a characteristic fluorescein angiogram (late diffuse hyperfluorescence with a well-demarcated circular border), and

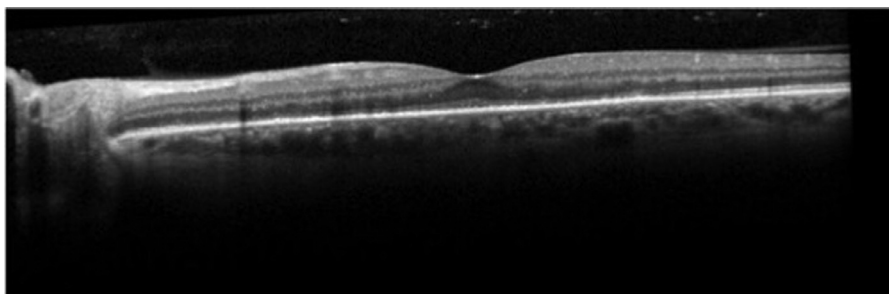


FIGURE 2. Optical coherence tomogram of a case of ocular placoid syphilis, demonstrating the irregular appearance of the retinal pigment epithelium.

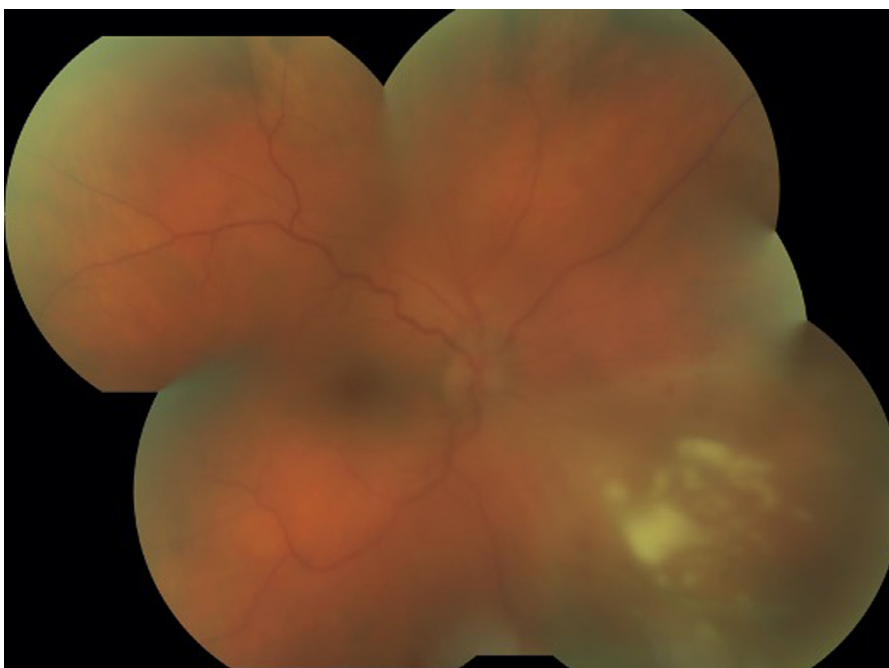


FIGURE 3. Fundus photograph of necrotizing retinitis in a patient with ocular syphilis.

a characteristic optical coherence tomographic appearance (“ratty” irregular retinal pigment epithelium, Figure 2),²⁴ but it accounts for a minority of cases and still requires serologic testing for diagnosis. Other posterior segment involvement included necrotizing retinitis (Figure 3) and a multifocal inflammation of the retina and/or retinal pigment epithelium (Figures 4 and 5), both of which also require serologic testing for diagnosis. Necrotizing retinitis was seen only in cases with HIV infection and may be a variant associated with immunocompromise. The SUN database did not contain sufficient information on immune status, such as CD4+ T cells, which might have enabled us to establish a relationship between necrotizing retinitis and immunocompromise.

Serologic diagnosis of syphilis requires 2 positive tests, at least 1 of which must be a treponemal test.¹⁻³ Because of the possibility (albeit rare) of a false-positive trepone-

mal test, CDC guidelines require a second test also be positive. With the reverse sequence screening algorithm, this can be either a nontreponemal test or a treponemal test.¹⁻³ Although all cases in the database had a positive treponemal test, the data were not granular enough to confirm that all cases had 2 positive tests. Nevertheless, we recommend that CDC guidelines should be followed and that the reverse sequence screening algorithm should be used.³ Although our data suggest good performance for the use of a treponemal test for syphilis in the classification of syphilitic uveitis, some caution should be exercised. The cases collected do not represent a prospectively collected cohort but rather a retrospectively collected cohort with an attempt to obtain similar numbers of individual diseases. As such, positive and negative predictive values, which are population dependent, might vary from our calculated numbers in other situations. Nevertheless, the sensitivity and



FIGURE 4. Fluorescein angiogram of multifocal retinal/retinal pigment epithelium inflammation in a patient with ocular syphilis.

specificity of the SUN data are in line with reported values for treponemal tests for diagnosing secondary, latent, and tertiary syphilis,²⁵ providing some reassurance of their performance in diagnosing syphilitic uveitis.

The results of serologic testing for syphilis should be interpreted in the context of the history of treatment for syphilis. Adequate (a neurosyphilis treatment regimen) treatment for syphilis suggests that the uveitis may not be due to syphilis, as a positive treponemal test typically persists despite adequate treatment.²⁶ However, remote treat-

TABLE 5. Classification Criteria for Syphilitic Uveitis	
Criteria	
1. Uveitis with a compatible uveitic presentation, including	
a. Anterior uveitis OR	
b. Intermediate uveitis or anterior/intermediate uveitis OR	
c. Posterior uveitis or panuveitis with 1 of the following presentations:	
i. Placoid inflammation of the retinal pigment epithelium or	
ii. Multifocal inflammation of the retina/retinal pigment epithelium or	
iii. Necrotizing retinitis or	
iv. Retinal vasculitis	
AND	
2. Evidence of infection with <i>Treponema pallidum</i> , either	
a. Positive treponemal test and nontreponemal test	
b. Positive treponemal test with 2 different treponemal tests	
Exclusions	
1. History of adequate treatment for syphilitic uveitis ^a	
^a Adequate treatment outlined in Table 2.	

ment may be associated with reinfection and may require careful interpretation of nontreponemal test (eg, the Venereal Disease Research Laboratory or rapid plasmin regain) titer data. Treatment for earlier stages of syphilis with inadequate treatment regimen for the syphilitic uveitis may not exclude a diagnosis of syphilitic uveitis, and syphilitic uveitis may still be present. Nevertheless, a history of adequate treatment for syphilis should exclude classification as syphilitic uveitis, despite the presence of a positive treponemal test, especially if there is evidence of an adequate

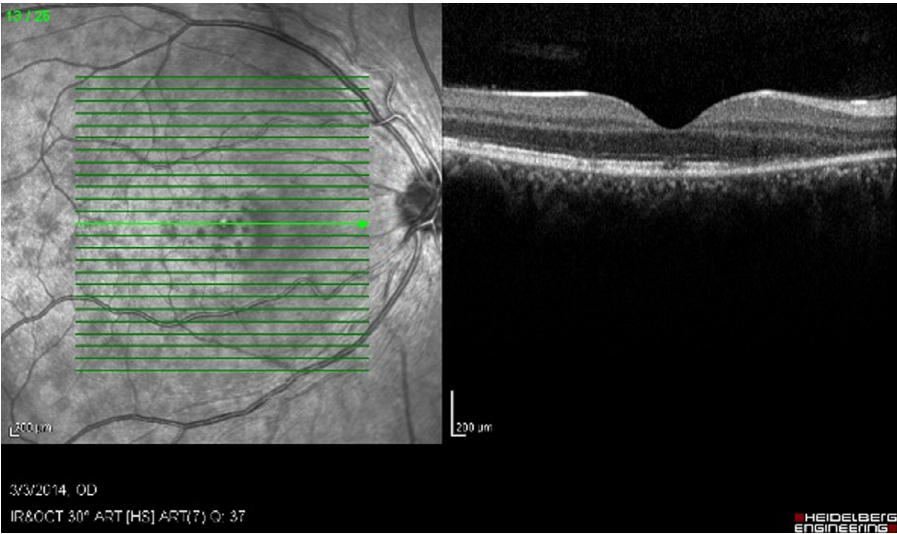


FIGURE 5. Optical coherence tomogram of a case of multifocal retinitis in a patient with ocular syphilis, demonstrating multiple, variably sized areas of ellipsoid zone and outer retinal damage.

treatment response (eg, a ≥ 4 -fold decline in nontreponemal test titer).

In retrospective studies response to treatment of the uveitis has been and could be used as a criterion for diagnosis of syphilitic uveitis. However, the SUN criteria were developed for prospective use, including possible treatment trials. As such, treatment response is not part of the SUN criteria. Nevertheless, some investigators may choose to add that the uveitis responds to adequate treatment as a criterion when conducting retrospective studies.

Classification criteria are employed to diagnose individual diseases for research purposes.²³ 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,²³ 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,²⁰ 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 might diagnose with syphilitic uveitis may not be so classified by classification criteria.

In conclusion, the criteria for syphilitic uveitis outlined in Table 5 seem to perform sufficiently well for use as classification criteria in clinical research.²²

CREDIT ROLES

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