Reclassifying Idiopathic Uveitis: Lessons From a Tertiary Uveitis Center

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• PURPOSE: Idiopathic uveitis is frequently the most common diagnosis in series from uveitis clinics. This study sought to determine the percentage of patients initially diagnosed as idiopathic, noninfectious uveitis referred to a tertiary uveitis center who were subsequently found to have an identifiable cause of uveitis.

• DESIGN: Retrospective case series.

• METHODS: We performed a computerized database analysis of 179 consecutive patients who were referred to our practice with the diagnosis of idiopathic, noninfectious uveitis between 2008 and 2016. Patients were evaluated by a thorough history and ophthalmic examination with selected laboratory testing targeted by clues from the history and examination. Standardization of Uveitis Nomenclature (SUN) criteria were used to better assess different types of uveitis.

• RESULTS: Fifty-two out of 179 (29.0%) patients initially diagnosed with idiopathic uveitis were subsequently diagnosed with an underlying condition. Among patients referred with a diagnosis of idiopathic disease, female patients were most commonly affected (121/179; 67.6%). Among subsequent diagnoses, sarcoidosis was the most common (19/52 or 36.5%), followed by HLA-B27-associated uveitis (11/52, 21.1%), infectious uveitis (6/52, 11.5%), tubulointerstitial nephritis with uveitis (6/52, 11.5%), and juvenile idiopathic uveitis (4/52, 7.7%). Other diagnosable conditions included Behçet disease, multifocal choroiditis, panuveitis, Crohn disease, multiple sclerosis, and relapsing polychondritis. An underlying condition was not found in 127 of 179 (70.9%) patients.

• CONCLUSIONS: We report that 29% of patients referred to our tertiary uveitis center diagnosed as "idiopathic" had an associated identifiable cause. Identifying an underlying condition associated with uveitis could be potentially life-saving for some illnesses (eg, sarcoidosis with cardiac involvement) and is critical to management (eg, infection). Although we were able to use limited testing to classify many patients who had been previously incorrectly labeled with idiopathic uveitis, idiopathic uveitis remains the most common diagnosis in our uveitis clinic. (Am J Ophthalmol 2019;198:193–199. © 2018 Elsevier Inc. All rights reserved.)

UVEITIS MAY REQUIRE A POTENTIALLY COMPLICATED treatment regimen that may be unfamiliar to many ophthalmologists. Uveitis labeled as *idiopathic* adds further to this feeling of discomfort because it implies that the physician does not understand the disease process. Some experts in the field prefer the term *undifferentiated uveitis* with descriptors for the course, laterality, and anatomic location because most noninfectious forms of uveitis associated with a systemic disease such as sarcoidosis or ankylosing spondylitis are still thought to be *idiopathic*, that is, the pathogenesis of these systemic illnesses is incompletely understood.[1] Another proposal is to describe uveitis as *classified* if it is associated with an identifiable cause such as herpes simplex, sarcoidosis, or ankylosing spondylitis.[2] Using this nomenclature, idiopathic uveitis becomes known as *unclassified* uveitis.

Unfortunately, idiopathic is the most common diagnosis in most series at tertiary uveitis centers across the United States.[3–9] Three recent prominent randomized controlled trials confirmed the high prevalence of this diagnosis.[9–11] Other recent studies have identified causes of uveitis for inflammation that was previously deemed to be idiopathic. Tubulointerstitial nephritis and uveitis (TINU) syndrome and sarcoidosis are examples of diagnoses that are sometimes established in patients who were previously deemed to have idiopathic disease.[10,11] We examined records from a tertiary referral center, the Uveitis Clinic at Oregon Health & Science University. We sought to determine how frequently a more precise diagnosis can be ascertained for patients with a referral diagnosis of *idiopathic* uveitis. In addition, we wanted to know the relative frequency for the diagnoses that replaced idiopathic uveitis.

METHODS

A RETROSPECTIVE COHORT STUDY WAS CONDUCTED ON all patients with a referral diagnosis of idiopathic uveitis seen in the Uveitis Clinic of 1 of the authors (J.T.R.) at Oregon Health & Science University between the years

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January 1, 2008 to December 31, 2016. All patients were referred by ophthalmologists without specialized training in uveitis. The evaluation initiated by each referring physician was variable and limited. The only inclusion criterion for the study was a referral diagnosis of "idiopathic uveitis." Informed consent was not obtained because this was a retrospective review of medical charts. Approval for this chart review was obtained from the OHSU Institutional Review Board.

A complete history and comprehensive ophthalmic examination were performed at the first visit for each patient. Ophthalmic imaging tests such as fluorescein angiography, indocyanine green angiography, optical coherence tomography, and ultrasound were performed as clinically indicated for each case. Ordering of ancillary laboratory and imaging tests was guided by the history and examination findings.

For most patients, a diagnosis was determined primarily on the basis of history and clinical examination. Patients were anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) criteria.[12] Specifically, we would classify the uveitis as anterior, intermediate, posterior, or panuveitis. We would further classify it by the type of onset (sudden or insidious), laterality (unilateral, bilateral simultaneous, bilateral alternating), course (acute, recurrent, or chronic), and duration (limited or persistent). Categorizing the type of uveitis would help us form a proper differential diagnosis. Laboratory and imaging findings aided in making a determination in certain diagnoses including sarcoidosis, TINU, and human leukocyte antigen (HLA)-B27-related disease. The diagnosis of idiopathic uveitis was used to describe patients in whom an etiologic diagnosis was not able to be established. Patients were given a diagnosis of presumed sarcoidosis based on chest computed tomography (CT) or radiography findings, features of uveitis consistent with the diagnosis in accord with the recommendations of the International Workshop on Ocular Sarcoidosis (IWOS), and clues from the history and review of systems suggestive of the diagnosis.[13] HLA-B27-associated uveitis was established with the aid of positive testing for the HLA-B27 allele and a consistent phenotype of uveitis with most of the following characteristics: unilateral, anterior, recurrent, lasting less than 3 months per episode.[14] TINU syndrome was suspected in male or female patients in their adolescent years to 30 years of age with a bilateral anterior uveitis. An elevated urine beta-2 microglobulin, increased serum creatinine, elevated erythrocyte sedimentation rate (ESR), elevated liver enzymes, anemia, and urine microscopy abnormalities were used to aid in the diagnosis of TINU.[15] Additional details on patients diagnosed with TINU are provided in the results below. Infectious causes were established with the use of laboratory testing such as a positive rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption (FTA-ABS) for syphilis. For tuberculosis, we required a positive QuantiFERON TB-Gold test in association with a consistent pattern of uveitis such as granulomatous inflammation, a risk factor for acquiring tuberculosis such as birth outside the United States, or inflammation that had not responded to corticosteroids.

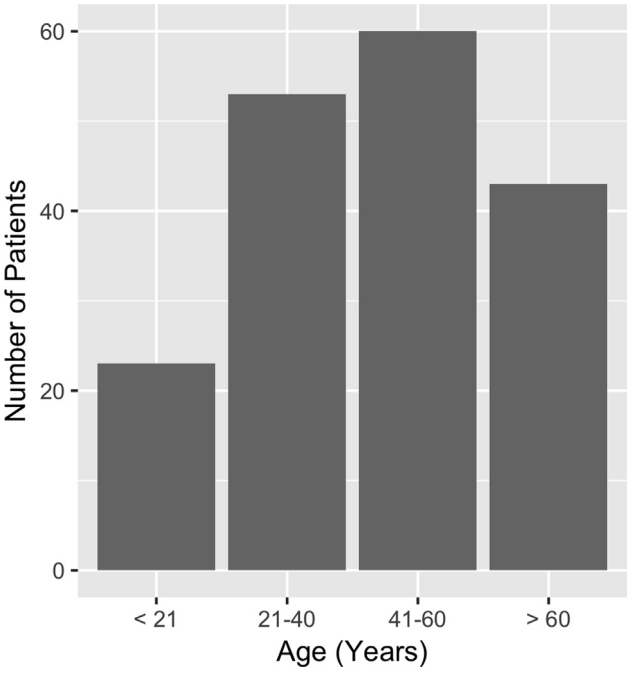

FIGURE. Number of patients in the study series who were less than 21 years of age, 21–40 years of age, 41–60 years of age, and more than 60 years of age.

Demographic information was recorded based on age at presentation to our Uveitis Service. χ^2 statistical analysis was performed using free software (R Foundation for Statistical Computing, version 3.5.0; R Core Team, Vienna, Austria). *P* values were computed by permutation owing to small frequencies in some categories. A *P* value less than .05 was considered statistically significant.

RESULTS

A TOTAL OF 249 PATIENTS WERE NEWLY REFERRED TO THE Uveitis Service of the Casey Eye Institute with a diagnosis of uveitis between 2008 and 2016. Of these, 179 (71.8%) of them were referred with a diagnosis of idiopathic uveitis. Of those 179 patients, 58 (32.4%) were male and 121 (67.6%) were female. The ethnicity of the majority of the patients was white (135/179, 75.4%), followed by Hispanic (15/179, 8.4%), Asian (7/179, 3.9%), African American (6/179, 3.4%), and other (6/179, 3.4%). Ten patients declined revealing their ethnicity. The median age of these patients was 43 years. The age distributions included 23 (12.8%) patients less than 21 years old, 53 (29.6%) patients

TABLE. Characteristics of the Most Common Uveitis Diagnoses Established

Characteristic	Sarcoidosis (N = 19)	HLA-B27 (N = 11)	TINU (N = 6)
Anatomic location			
Anterior	5 (26.3%)	11 (100.0%)	5 (83.3%)
Intermediate	10 (52.6%)	0	1 (16.7%)
Posterior	1 (5.3%)	0	0
Pan	3 (15.8%)	0	0
Age, years			
Mean	55	49	15
Range	35–82	12–72	10–30
Onset			
Insidious	12 (63.2%)	1 (9.0%)	1 (16.7%)
Sudden	7 (36.8%)	10 (91.0%)	5 (83.3%)
Laterality			
Unilateral	2 (10.5%)	6 (54.5%)	0
Bilateral[a]	17 (89.5%)	5 (45.5%)	6 (100.0%)
Sex			
Female	16 (84.2%)	6 (54.5%)	4 (66.7%)
Male	3 (15.8%)	5 (45.5%)	2 (33.3%)

TINU = tubulointerstitial nephritis and uveitis.

Results represent number (percentage) of patients, unless otherwise indicated.

[a]Includes patients who had involvement of both eyes but not necessarily simultaneously.

between 21 and 40 years of age, 60 (33.5%) patients between 41 and 60 years of age, and 43 (24.0%) patients above the age of 60 years (Figure). Unilateral disease was seen in 55 (30.7%) patients, 113 (63.1%) presented with bilateral simultaneous disease, and 11 (6.1%) presented with bilateral alternating disease. The most common anatomic diagnosis among this group was anterior uveitis (87/179, 48.6%), followed by intermediate uveitis (65/179, 36.3%), panuveitis (21/179, 11.7%), and posterior uveitis (6/179, 3.4%).

Out of the 179 patients with a referral diagnosis of idiopathic uveitis, we were able to establish a diagnosis in 52 (29.0%) patients. Of these 52, 26 (50%) had anterior uveitis, 17 (32.7%) had intermediate uveitis, 3 (5.8%) had posterior uveitis, and 6 (11.5%) had panuveitis. These percentages resemble the percentages of the idiopathic population as a whole and indicate that we were not more successful in reclassifying idiopathic uveitis on the basis of anatomic location of inflammation.

Presumed sarcoidosis was the most common diagnosis (19/52, 36.5%) established. The characteristics of this group are summarized in the Table. The frequency of sarcoidosis among patients with idiopathic uveitis in our clinic has been previously published by Han and associates.[16] In summary, 17 (17/19, 89.5%) of these patients had chest CT scans that revealed adenopathy strongly suggestive of sarcoidosis. One patient was presumed to have sarcoidosis based on hilar adenopathy seen on chest radiography and ocular findings consistent with sarcoidosis. Another patient was presumed to have sarcoidosis based on having the combination of an orbital mass, uveitis features consistent with sarcoidosis, and optic neuropathy. Most patients were female (16/19, 84.2%) vs male (3/19, 15.8%). The mean age was 55 years and the age range was between 35 and 82 years. Most patients were white (18/19, 94.7%), vs African American (1/19, 5.3%). The mean age of white patients was 56 years. The 1 African-American patient was 38 years of age. An insidious onset (12/19, 63.2%) was seen more often than a sudden presentation (7/19, 36.8%). Unilateral presentation was seen in 2 of 19 (10.5%) patients, whereas bilateral involvement was found in 17 of 19 (89.5%) patients. Intermediate uveitis was the most common anatomic diagnosis seen in this group (10/19, 52.6%), followed by anterior (5/19, 26.3%), pan (3/19, 15.8%), and posterior (1/19, 5.3%). Interestingly, 4 of 19 (21.0%) patients whom we diagnosed with sarcoidosis were also found to have cardiac involvement after a screening electrocardiogram (EKG) was ordered. All 4 patients showed ventricular tachycardia. Two of these patients (50%) had no cardiovascular symptoms, whereas the other 2 (50%) experienced palpitations that were found to be secondary to premature ventricular contractions.

The next most common diagnosis established was HLA-B27-associated anterior uveitis (11/52, 21.2%). The characteristics of this group are summarized in the Table. All patients had positive testing for HLA-B27. There was an approximately equal male-to-female ratio (5 [45.5%] male; 6 [54.5%] female). The mean age was 49 and age range was between 12 and 72 years. Ten out of the 11 (91.0%) patients had sudden-onset disease, whereas only 1 (9.0%) was insidious. Unilateral disease was seen in 6 of 11 (54.5%) patients, and bilateral disease was seen in 5 (45.5%) patients. Of the patients with bilateral disease, 2 were chronic and persistent, whereas the rest were acute recurrent alternating. All 11 patients (100%) had an anatomic diagnosis of anterior uveitis.

TINU was the third most common diagnosis to replace idiopathic uveitis in 6 of 52 (11.5%) patients. The characteristics of this group are summarized in the Table. The mean age was 15 and the age range was between 10 and 30 years. Four of the 6 were female (66.7%). The onset was sudden in 5 of the 6 cases (83.3%) and insidious in 1 case (16.7%). All 6 patients (6/6, 100%) had a bilateral presentation. Five of the 6 patients (83.3%) had anterior uveitis and 1 patient (16.7%) had intermediate uveitis. Four patients had an elevated beta-2 microglobulin level, which helped to establish the diagnosis. One patient had presumed TINU based on her bilateral presentation, young age of 10 years, female sex, elevated alanine transaminase and aspartate transaminase, elevated creatinine level, and elevated urine leukocyte count. Another patient was presumed to have TINU based on her bilateral presentation, young age of 10 years, female sex, mild anemia, elevated

ESR, elevated urinary leukocyte esterase, and prodrome of fatigue and abdominal pain. This patient was on oral corticosteroids for 4 months prior to her first appointment with our uveitis service, which could have masked any renal inflammation.

An infectious cause was identified in 6 of 52 (11.5%) cases. This included herpesvirus-associated anterior uveitis (1/6, 16.7%), acute retinal necrosis (1/6, 16.7%), tuberculosis-associated panuveitis (3/6, 50%), and syphilis-associated anterior and intermediate uveitis (1/6, 16.7%). Juvenile idiopathic uveitis (JIA)-associated anterior uveitis was established in 4 of 52 (7.7%) cases. The remainder of patients with an identifiable cause of uveitis included patients with Behçet disease, multifocal choroiditis and panuveitis, punctate inner choroidopathy, Crohn disease, multiple sclerosis, and relapsing polychondritis.

Though we were able to establish a diagnosis in many of the cases with a referral diagnosis of idiopathic uveitis, the majority of these patients (127/179, 71.0%) were still deemed to have a diagnosis of idiopathic uveitis despite further evaluation by our team. A χ^2 analysis was performed to determine whether male and female sex was represented across all diagnoses (sarcoidosis, HLA-B27, TINU, JIA, infectious, other, idiopathic) after evaluation proportionally to their numbers in the sample. The analysis produced a nonsignificant χ^2 value ($\chi^2 = 8.41$, $P = .30$), indicating that neither male nor female subjects were overrepresented in any of the groups. There was a significant association between type of onset (sudden vs insidious) and the diagnosis ($\chi^2 = 27.14$, $P = .0005$), as well as between the anatomic location (anterior, intermediate, posterior, and pan) and the diagnosis ($\chi^2 = 55.64$, $P = .002$).

DISCUSSION

IDIOPATHIC UVEITIS IS THE PREDOMINANT DIAGNOSIS IN most series from tertiary clinics. Past studies have shown that the percentage of patients with this diagnosis ranges from 24.2% to 52.5%.[3–8] Even the more recent VISUAL I and VISUAL II studies revealed that idiopathic uveitis is the most common diagnosis across uveitis centers, reporting it to be 37.3% and 36%, respectively.[9,10] The term *idiopathic* is unsatisfying to patients because it implies that the treating physician has a limited understanding of the disease process. The label "idiopathic" is not confined to uveitis. For example, many patients with nonspecific orbital inflammation or pseudotumor are labeled as having idiopathic orbital inflammation. The term *idiopathic* often becomes embedded into how a disease is known. For example, DISH is diffuse idiopathic skeletal hyperostosis and IPF is idiopathic pulmonary fibrosis. In this study, we sought to determine the percentage of patients initially referred to our uveitis clinic with a diagnosis of idiopathic uveitis who were subsequently found to have an identifiable cause of uveitis. We report that 71.8% (179/249) of all referred patients had an initial diagnosis of idiopathic uveitis. Of these cases, a diagnosis was established in 29.0% (52/179). The 3 leading diagnoses established were sarcoidosis, HLA-B27-associated, and TINU.

Sarcoidosis is an autoimmune disorder primarily characterized by noncaseating granulomatous inflammation of multiple organ systems. Approximately 25%–60% of patients with systemic sarcoidosis have ocular manifestations. As we reported previously, 36.5% (19/52) of patients with a referral diagnosis of idiopathic uveitis were found to have sarcoidosis.[16] Of these, 21.0% (4/19) were found to have cardiac involvement with EKG testing, all of whom eventually required intracardiac defibrillator implantation. A diagnosis of sarcoidosis was found in all 4 of these patients with the use of chest CT imaging. These results substantiate the importance of using CT chest imaging as a screening modality in patients for whom sarcoidosis is a likely diagnosis based on review of systems and features of uveitis, as has been noted in a previous study from the Cole Eye Institute.[17] Furthermore, we recommend that all patients with a diagnosis of sarcoidosis obtain an EKG to screen for any potentially life-threatening arrhythmia. Despite the superiority of chest CT imaging compared to routine radiographs, we are reluctant to order a chest CT scan in a patient under 40 years of age owing to the radiation exposure from the procedure.

HLA-B27-associated is the most common diagnosis in noninfectious anterior uveitis. HLA-B27 is a protein expressed on the cell surfaces seen in roughly 8% of the white population and up to 5% in African and Asian populations.[18–21] Most patients who are HLA-B27 positive do not manifest any inflammatory manifestations; however, as many as 20% can develop seronegative spondyloarthropathies, which include ankylosing spondylitis and reactive arthritis. Since many individuals are HLA-B27 positive without evidence for disease, merely identifying someone as HLA-B27 positive does not establish a diagnosis. We considered a patient to have HLA-B27-associated disease if we also identified spondyloarthropathy or if the eye inflammation fit with the recognized pattern of HLA-B27-associated uveitis as described in the methods section. In our series, 6.1% (11/179) of patients with a referral diagnosis of idiopathic uveitis were found to have HLA-B27-associated uveitis. Two patients were eventually found to have ankylosing spondylitis after further evaluation by a rheumatologist. Another patient had a history of reactive arthritis without any ocular manifestations. Prior studies have shown that a large portion of HLA-B27-positive patients with anterior uveitis were subsequently found to have spondyloarthritis and were unaware that their chronic back pain was related to their eye inflammation. The SENTINEL study found that 69.8% and 21.9% of HLA-B27-positive patients with anterior uveitis had undiagnosed axial and peripheral spondyloarthropathy,

respectively, according to Assessment of Ankylosing Spondylitis (ASAS) criteria.[22] The Dublin Uveitis Evaluation Tool (DUET) study determined that roughly 40% of patients presenting to an emergency department in Ireland with idiopathic anterior uveitis have undiagnosed spondyloarthritis.[23] A proper review of systems and HLA-B27 testing are important in patients with unilateral, acute anterior uveitis to screen for any undiagnosed spondyloarthropathy, since early diagnosis and treatment of spondyloarthropathies is known to improve quality of life and outcomes.[24,25]

TINU is an immune-mediated disorder characterized by acute interstitial nephritis and bilateral anterior uveitis.[15,26] It is classically seen in young female patients up to the age of 30 years. Systemic symptoms may include fevers, chills, arthralgias, myalgias, and fatigue prior to ocular inflammation. Urine studies can reveal an elevated urine beta-2 microglobulin, white cell casts, eosinophils, and red blood cells. Laboratory investigations may also show a high sedimentation rate (ESR), serum creatinine, and liver enzymes. In our series, a diagnosis of TINU was established in 11.5% (6/52) of patients with an initial diagnosis of idiopathic uveitis. The diagnosis was supported by an elevated urinary beta-2 microglobulin in 4 of the 6 patients. The other 2 were presumed to have TINU based on their clinical history and presentation, as well as blood and urinalysis results consistent with the diagnosis. It is possible that the associated interstitial nephritis resolved in these 2 cases at the time of presentation, which would account for their normal urine beta-2 microglobulin levels. Nonetheless, a urinary beta-2 microglobulin and serum creatinine should be obtained in all patients suspected of having TINU, as 1 prospective study determined that the positive predictive value of having elevations in both these measurements was 100% for detecting definitive and/or probable TINU.[27] However, one should keep in mind that the renal disease is transient. Therefore, beta-2 microglobulin levels in the urine and serum creatinine may no longer be elevated by the time a suspected patient is seen by an ophthalmologist. In addition, TINU is usually a disease in children whose normal serum creatinine is lower than that of adults. A study from Japan found that only 25% of children with TINU had an elevated serum creatinine.[28]

An infectious cause was identified in 6 of 52 (11.5%) cases for which a diagnosis was established. This included herpesvirus-associated anterior uveitis, acute retinal necrosis, tuberculosis-associated panuveitis, and syphilis-associated anterior and intermediate uveitis. These diagnoses were made by taking a thorough history, performing a meticulous clinical examination, and using serology testing selectively. The case of syphilitic uveitis revealed a positive RPR and FTA-ABS test. The 2 cases were presumed to be tuberculosis-associated uveitis based on ocular findings consistent with tubercular uveitis, prior residence in an endemic area for tuberculosis, and testing positive on the QuantiFERON TB-Gold assay. A presumed diagnosis of herpesvirus-associated anterior uveitis was made based on clinical features consistent with this diagnosis, such as elevated intraocular pressure, iris atrophy, and a history of oral ulcers. Furthermore, this patient had marked improvement of their inflammation after initiating oral acyclovir. The diagnosis of acute retinal necrosis was made by clinical history and examination findings consistent with the diagnosis. It is crucial to determine whether the cause of uveitis is infectious, as the treatment regimen requires antimicrobial agents as opposed to immunosuppressants as in the cases of noninfectious etiologies. Though DNA- or RNA-based molecular diagnostic testing was not used to identify infectious etiologies in our case series, the literature shows the advantages of this technology.[29] Polymerase chain reaction (PCR) is a powerful technique that amplifies DNA or RNA, such as that derived from pathogens, which makes them easier to detect than classic culturing techniques. This is particularly advantageous in ophthalmology, where limited tissue quantity can be obtained from the aqueous humor or the vitreous fluid. PCR analysis of aqueous and vitreous specimens in a retrospective study was shown to have a positive predictive value of 98.7% in patients with posterior segment infectious uveitis.[30] Infectious agents in this study included cytomegalovirus, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, and toxoplasmosis. Another retrospective study determined that there was a relatively low diagnostic advantage to using anterior chamber paracentesis with PCR in patients with suspected viral causes of anterior uveitis.[31] More sophisticated techniques, such as pan-bacterial and pan-fungal primers for ribosomal DNA sequences as well as metagenomic deep sequencing, can be used to reveal infectious causes that were once thought to be idiopathic.[29,32]

A limitation of our study is that the time of onset of symptoms and the presumptive diagnosis of "idiopathic uveitis" was not always documented in the referring physician's note, which presents the possibility that elapsed time resulted in evolution of the clinical presentation, allowing for the underlying cause to be more easily identified upon arrival to our facility. However, the most common diagnoses established in our study, sarcoidosis, TINU, and HLA-B27, can be silent diseases, as often their systemic signs and symptoms are not overbearingly obvious.

In conclusion, we were able to establish a diagnosis in a significant proportion of patients with a referral diagnosis of idiopathic uveitis. However, consistent with reports from other tertiary uveitis centers, idiopathic uveitis was the most common diagnosis in our case series. This is a very unsatisfying diagnosis for patients and doctors alike because it highlights the lack of understanding of the mechanism governing the disease. Judicious use of ancillary laboratory testing and sophisticated molecular techniques can help shrink this imperfect diagnosis.

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REFERENCES

1. Jabs DA, Busingye J. Approach to the diagnosis of the uveitides. *Am J Ophthalmol* 2013;156(2):228–236.
2. Jakob E, Reuland MS, Mackensen F, et al. Uveitis subtypes in a German interdisciplinary uveitis center–analysis of 1916 patients. *J Rheumatol* 2009;36(1):127–136.
3. Merrill PT, Kim J, Cox TA, Betor CC, McCallum RM, Jaffe GJ. Uveitis in the southeastern United States. *Curr Eye Res* 1997;16(9):865–874.
4. Rosenbaum JT. Uveitis. An internist's view. *Arch Intern Med* 1989;149(5):1173–1176.
5. Oruc S, Kaplan AD, Galen M, Kaplan HJ. Uveitis referral pattern in a Midwest University Eye Center. *Ocul Immunol Inflamm* 2003;11(4):287–298.
6. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol* 1996;114(5):593–599.
7. Henderly DE, Genstler AJ, Smith RE, Rao NA. Changing patterns of uveitis. *Am J Ophthalmol* 1987;103(2):131–136.
8. Perkins ES, Folk J. Uveitis in London and Iowa. *Ophthalmologica* 1984;189(1-2):36–40.
9. Jaffe GJ, Dick AD, Brezin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016;375(10):932–943.
10. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive noninfectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet* 2016;388(10050):1183–1192.
11. Nguyen QD, Merrill PT, Clark WL, et al. Intravitreal sirolimus for noninfectious uveitis: a phase III Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA). *Ophthalmology* 2016;123(11):2413–2423.
12. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140(3):509–516.
13. Herbort CP, Rao NA, Mochizuki M, members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm* 2009;17(3):160–169.
14. Rosenbaum JT. Uveitis in spondyloarthritis including psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. *Clin Rheumatol* 2015;34(6):999–1002.
15. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol* 2001;46(3):195–208.
16. Han YS, Rivera-Grana E, Salek S, Rosenbaum JT. Distinguishing uveitis secondary to sarcoidosis from idiopathic disease: cardiac implications. *JAMA Ophthalmol* 2018;136(2):109–115.
17. Kaiser PK, Lowder CY, Sullivan P, et al. Chest computerized tomography in the evaluation of uveitis in elderly women. *Am J Ophthalmol* 2002;133(4):499–505.
18. Rosenbaum JT. New developments in uveitis associated with HLA B27. *Curr Opin Rheumatol* 2017;29(4):298–303.
19. Kitamei H, Kitaichi N, Namba K, et al. Clinical features of intraocular inflammation in Hokkaido, Japan. *Acta Ophthalmol* 2009;87(4):424–428.
20. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol* 2005;50(4):364–388.
21. Bawazeer AM, Joharjy HI. The association of human leukocyte antigen B27 with anterior uveitis in patients from the western region of Saudi Arabia: a retrospective study. *Clin Ophthalmol* 2013;7:2107–2111.
22. Juanola X, Loza Santamaria E, Cordero-Coma M, Group SW. Description and prevalence of spondyloarthritis in patients with anterior uveitis: the SENTINEL Interdisciplinary Collaborative Project. *Ophthalmology* 2016;123(8):1632–1636.
23. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). *Ann Rheum Dis* 2015;74(11):1990–1995.
24. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009;60(4):946–954.
25. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum* 2003;48(8):2224–2233.
26. Mackensen F, Smith JR, Rosenbaum JT. Enhanced recognition, treatment, and prognosis of tubulointerstitial nephritis and uveitis syndrome. *Ophthalmology* 2007;114(5):995–999.
27. Hettinga YM, Scheerlinck LM, Lilien MR, Rothova A, de Boer JH. The value of measuring urinary beta2-microglobulin and serum creatinine for detecting tubulointerstitial nephritis and uveitis syndrome in young patients with uveitis. *JAMA Ophthalmol* 2015;133(2):140–145.

28. Goda C, Kotake S, Ichiishi A, Namba K, Kitaichi N, Ohno S. Clinical features in tubulointerstitial nephritis and uveitis (TINU) syndrome. *Am J Ophthalmol* 2005;140(4):637–641.
29. Taravati P, Lam D, Van Gelder RN. Role of molecular diagnostics in ocular microbiology. *Curr Ophthalmol Rep* 2013;1(4).
30. Harper TW, Miller D, Schiffman JC, Davis JL. Polymerase chain reaction analysis of aqueous and vitreous specimens in the diagnosis of posterior segment infectious uveitis. *Am J Ophthalmol* 2009;147(1):140–147.e2.
31. Anwar Z, Galor A, Albini TA, Miller D, Perez V, Davis JL. The diagnostic utility of anterior chamber paracentesis with polymerase chain reaction in anterior uveitis. *Am J Ophthalmol* 2013;155(5):781–786.
32. Doan T, Wilson MR, Crawford ED, et al. Illuminating uveitis: metagenomic deep sequencing identifies common and rare pathogens. *Genome Med* 2016;8(1):90.