Classification Criteria for Tubulointerstitial Nephritis With Uveitis Syndrome

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

• PURPOSE: To determine classification criteria for tubulointerstitial nephritis with uveitis (TINU).
• DESIGN: Machine learning of cases with TINU and 8 other anterior uveitides.
• METHODS: Cases of anterior uveitides 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 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 anterior uveitides. The resulting criteria were evaluated on the validation set.
• RESULTS: One thousand eighty-three cases of anterior uveitides, including 94 cases of TINU, were evaluated by machine learning. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval 92.4, 98.6). Key criteria for TINU included anterior chamber inflammation and evidence of tubulointerstitial nephritis with either (1) a positive renal biopsy or (2) evidence of nephritis (elevated serum creatinine and/or abnormal urine analysis) and an elevated urine β-2 microglobulin. The misclassification rates for TINU were 1.2% in the training set and 0% in the validation set.
• CONCLUSIONS: The criteria for TINU had a low misclassification rate and seemed to perform well enough for use in clinical and translational research. (Am J Ophthalmol 2021;228: 255–261. © 2021 Elsevier Inc. All rights reserved.)

The syndrome of tubulointerstitial nephritis with uveitis (TINU) was first described as a distinct entity in 1975.[1] It is considered a rare condition, with approximately 200 cases described in the literature through 2018.[2-10] Tubulointerstitial nephritis with uveitis accounts for 0.2% to 2% of case series of uveitis, but it accounts for ~10% to 20% of cases presenting with bilateral simultaneous acute anterior uveitis.[2,3,5] Over 80% of cases present as an anterior uveitis, and 77% are bilateral at presentation.[2] Retinal (eg, macular edema) and optic nerve (eg, disc edema) structural complications of the uveitis in TINU may occur, but in addition an anterior/intermediate uveitis and a panuveitis with either small choroidal lesions or retinal vascular findings (eg, cotton-wool spots, vascular sheathing, intraretinal hemorrhages) have been described.[2,3,8] Although the review by Mandeville and associates[2] described posterior findings in 17% of cases, 100% of cases had evidence of an anterior segment inflammation (anterior chamber cells and flare). Although typically presenting as an acute-onset anterior uveitis, chronic disease requiring long-term therapy, including immunosuppression, may occur.[2,5,9]

The syndrome of TINU is one of many diseases with tubulointerstitial nephritis (TIN) as the renal disease manifestation. The most commonly reported etiology for TIN is drug reaction, with antibiotics, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors most often implicated. Other rheumatic diseases, such as systemic lupus erythematosus, Sjögren syndrome, systemic vasculitis, and IgG4 disease, also may have TIN as their renal manifestation.[7] Despite the implication of drug reaction with TIN in general, none of the cases of TINU reported by Mackensen and associates[3] seemed to be drug-related, suggesting that TINU may be distinct from drug-induced TIN.

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Definitive diagnosis of TIN is made on renal biopsy.[2,4,6,7] However, renal biopsy is not always performed, especially when the renal disease is mild. Other renal laboratory findings reported in TINU include elevated serum creatinine in ~90%,[2] abnormal urine analysis, and elevated urine $\beta 2$-microglobulin. Urinary abnormalities include proteinuria in ~78% to 86%, microscopic hematuria in ~42%, and aseptic leukocyturia in ~55 to 70%.[2,4] Elevated urine $\beta 2$-microglobulin has been reported to be present in nearly all patients tested at presentation and may correlate with the activity of the disease.[2,4,10] Signs and symptoms of a systemic illness are reported in slightly over one-half of cases, including fever, fatigue and malaise, and weight loss, but are nonspecific.[2,4]

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.[11-17] Among the anterior uveitides studied was TINU.

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.[12,14,15]

• **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.[12]

• **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.[5,7] 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.[15,17] Because the goal was to develop classification criteria, only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of cases) and a validation set (~15% of cases) for each disease, as described in the accompanying article.[17] 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

TABLE 1. Characteristics of Cases of Tubulointerstitial Nephritis With Uveitis

Characteristic	Result
Number of cases	94
Demographics	
Age, median, years (25th, 75th percentile)	17 (13, 42)
Age category, years (%)	
≤16	46
17-50	33
51-59	7
≥60	12
Missing	2
Sex (%)	
Male	36
Female	64
Race/ethnicity (%)	
White, non-Hispanic	70
Black, non-Hispanic	5
Hispanic	7
Asian, Pacific Islander	4
Other	4
Missing/unknown	8
Uveitis history	
Uveitis course (%)	
Acute, monophasic	14
Acute, recurrent	6
Chronic	60
Indeterminate	20
Laterality (%)	
Unilateral	14
Unilateral, alternating	0
Bilateral	86
Ophthalmic examination	
Cornea	
Normal	100
Keratitis	0
Keratic precipitates (%)	
None	49
Fine	40
Round	4
Stellate	2
Mutton fat	4
Other	0
Anterior chamber cells, grade (%)	
½+	16
1+	30
2+	31
3+	16
4+	7
Hypopyon (%)	0
Anterior chamber flare, grade (%)	
0	55
1+	28
2+	14
3+	2
4+	1

(*continued on next column*)

TABLE 1. (*continued*)

Characteristic	Result
Iris (%)	
Normal	68
Posterior synechiae	32
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (12, 17)
Proportion of patients with IOP > 24 mm	1
Hg either eye (%)	
Vitreous cells, grade (%)	
0	30
½+	27
1+	32
2+	5
3+	6
4+	0
Vitreous haze, grade (%)	
0	81
½+	7
1+	4
2+	6
3+	1
4+	1
Vitreous snowballs	0
Choroidal lesions	2
Laboratory (%)	
Elevated serum creatinine	58
Elevated serum creatinine among cases with results reported	89
Elevated urine β-2 microglobulin	23
Elevated urine β-2 microglobulin among cases with results reported	88
Abnormal urine analysis	58
Abnormal urine analysis among cases with results reported	89
Positive renal biopsy	31
Positive renal biopsy[a] among cases with biopsy results reported	100

IOP = intraocular pressure.
[a] Abnormal renal biopsy present in 29 of 29 cases with biopsy results reported.

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 TINU, the diseases against which it was evaluated were cytomegalovirus anterior uveitis, herpes simplex virus anterior uveitis, varicella zoster virus anterior uveitis, juvenile idiopathic arthritis–associated

TABLE 2. Characteristics of Cases of Tubulointerstitial Nephritis With Uveitis With and Without Renal Biopsy Confirmation

Characteristic	Positive Renal Biopsy	No Renal Biopsy	*P* Value
Number of cases	29	65	
Demographics			
Age, median, years (25th, 75th percentile)	41 (16, 55)	16 (13, 30)	.004
Age category, years (%)			.003
≤16	28	54	
17-50	31	34	
51-59	21	1	
≥60	21	11	
Sex (%)			.49
Male	31	38	
Female	69	62	
Race/ethnicity (%)			.76
White, non-Hispanic	79	69	
Black, non-Hispanic	7	5	
Hispanic	7	8	
Asian, Pacific Islander	0	6	
Other	0	7	
Missing/unknown	7	5	
Uveitis history			
Uveitis course (%)			.51
Acute, monophasic	7	15	
Acute, recurrent	7	8	
Chronic	72	54	
Indeterminate	14	23	
Laterality (%)			.98
Unilateral	14	14	
Bilateral	86	86	
Ophthalmic examination			
Keratic precipitates (%)			.55
None	55	46	
Fine	31	45	
Other	14	9	
Anterior chamber cells, grade (%)			.10
½+	17	14	
1+	48	22	
2+	24	34	
3+	7	20	
4+	3	9	
Anterior chamber flare, grade (%)			.59
0	48	58	
1+	38	23	
2+	14	14	
3+	0	3	
4+	0	2	
Iris (%)			
Normal	76	57	.08
Posterior synechiae	21	37	.12

(*continued on next column*)

TABLE 2. (*continued*)

Characteristic	Positive Renal Biopsy	No Renal Biopsy	*P* Value
IOP, involved eyes			
Median, mm Hg (25th, 75th percentile)	15 (13, 17)	14 (12, 16)	.07
Percent patients with IOP > 24 mm Hg either eye	3	0	.43
Vitreous cells, grade (%)			.44
0	35	28	
½+	35	23	
1+	27	34	
2+	0	8	
3+	3	8	
Vitreous haze, grade (%)			.63
0	86	79	
½+	10	6	
1+	0	6	
2+	3	8	
3+	1	0	
Laboratory (%)[a]			
Elevated serum creatinine	76	51	.06
Abnormal urine analysis	62	57	.59

IOP = intraocular pressure.
[a]Data on urine β-2-microglobulin either not performed or not reported in all cases with positive renal biopsy.

anterior uveitis, spondylitis/HLA-B27-associated anterior uveitis, Fuchs uveitis syndrome, sarcoidosis-associated anterior uveitis, and syphilitic anterior uveitis.

• **COMPARISON OF CASES WITH AND WITHOUT A RENAL BIOPSY RESULT REPORTED:** Comparison of the characteristics of cases with and without renal biopsy results reported was performed with the χ^2 test for categorical variables 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.

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.

RESULTS

One hundred twenty-five cases of TINU were collected, and 94 (75%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of TINU uveitis were compared to 989 cases of other anterior uveitides, including 89 cases of cytomegalovirus anterior uveitis, 101 cases of herpes simplex virus anterior uveitis, 146 cases of Fuchs uveitis syndrome, 202 cases of juvenile idiopathic arthritis–associated anterior uveitis, 184 cases of spondylitis/HLA-B27-associated anterior uveitis, 123 cases of varicella zoster virus anterior uveitis, 112 cases of sarcoidosis-associated anterior uveitis, and 32 cases of syphilitic anterior uveitis. The characteristics of cases with TINU at presentation to a SUN Working Group investigator are listed in Table 1. A comparison of cases with and without renal biopsy data reported is provided in Table 2. There were no significant differences between the 2 groups in the clinical characteristics of the uveitis. However, patients without a biopsy were younger, particularly <16 years of age. Patients without a biopsy were significantly more likely to have an elevated urine β-2-microglobulin reported, suggesting that it may be substituting for a renal biopsy in some patients or that when a positive biopsy is obtained, the test was deemed unnecessary or not reported.

The criteria developed after machine learning are listed in Table 3. The key features are the presence of an anterior uveitis and evidence of TIN. Although an anterior/intermediate uveitis or panuveitis may be present, anterior chamber inflammation should be present. Tubulointerstitial nephritis is best diagnosed by renal biopsy, but TIN can be inferred with appropriate other renal/urinary findings. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval 92.4, 98.6).[17] The misclassification rate for TINU in the training set was 1.2% and in the validation set 0%.

DISCUSSION

The classification criteria outlined in Table 3 seem to perform well, with acceptably low misclassification rates.

The criteria selected herein are similar to those proposed by Mandeville and associates,[2] but do have differences: the SUN criteria are simpler, eliminate the concepts of probable and possible TINU, and do not include the nonspecific characteristics of fever, weight loss, fatigue and malaise, etc. Nevertheless, the SUN Criteria for TINU seem to perform acceptably well, with a low misclassification rate.

Although histologic evidence of TIN on renal biopsy is the definitive method of diagnosing TIN, a renal biopsy may not always be performed. Therefore, other laboratory evidence of TIN used to make the diagnosis was included in the criteria. The comparison of cases with and without renal biopsy confirmation revealed no substantial differences other than the younger age of patients in cases without a biopsy and the apparent use of urinary β-2-microglobulin for diagnosis in cases without a biopsy. The retrospective nature of the SUN data collection did not permit the

TABLE 3. Classification Criteria for Tubulointerstitial Nephritis With Uveitis Syndrome

Criteria
1. Evidence of anterior uveitis
a. Anterior chamber cells
b. If vitritis or choroiditis or retinal vascular changes are present, anterior chamber inflammation also should be present
AND
2. Evidence of tubulointerstitial nephritis, either
a. Positive renal biopsy OR
b. Elevated urine β-microglobulin and either abnormal urine analysis or elevated serum creatinine
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata)

evaluation of the rate of urine β-2-microglobulin elevation among patients with a positive renal biopsy. Nevertheless, in a small case series by Goda and associates,[18] 92% of cases of renal biopsy–confirmed TINU had an elevated urine β-2-microglobulin, suggesting good overlap of these findings.

In small case series, TINU has been reported to have HLA-DQ and HLA-DR risk factor associations, particularly with HLA-DQA1*01, HLA-DQB1*05, and HLA-DRB1*01, with reported relative risks of ~16 to 26.[19] HLA-DRB1*0102 has been reported to be associated with TINU and bilateral simultaneous acute anterior uveitis but not with TIN without uveitis, suggesting a possible genetic risk factor for the uveitis component.[20] Our database did not have HLA data for TINU, so we could not evaluate its usefulness. Nevertheless, given the relatively low frequency of TINU in uveitis series and even in the subset of bilateral simultaneous acute anterior uveitis, the positive predictive value of these alleles can be estimated[21] to be in the 0.04 to 0.4 range (data not shown), and therefore may not contribute substantially to the diagnostic criteria at this time.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the diagnosis of TINU 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 TINU, but the absence of such testing does not exclude the diagnosis of TINU if the criteria for the diagnosis are met.

Classification criteria are employed to diagnose individual diseases for research purposes.[16] 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,[16] 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,[15] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. Therefore, it is possible that there may be some cases of patients in clinical care that the clinician believes have TINU that will not meet classification criteria.

In conclusion, the criteria for TINU outlined in Table 3 appear to perform sufficiently well for use as classification criteria in clinical research.

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