ORIGINAL ARTICLE

Classification Criteria for Cytomegalovirus Anterior Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,*]

• PURPOSE: To determine classification criteria for cytomegalovirus (CMV) anterior uveitis.

• DESIGN: Machine learning of cases with CMV anterior uveitis 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 89 cases of CMV anterior uveitis, 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 CMV anterior uveitis included unilateral anterior uveitis with a positive aqueous humor polymerase chain reaction assay for CMV. No clinical features reliably diagnosed CMV anterior uveitis. The misclassification rates for CMV anterior uveitis were 1.3% in the training set and 0% in the validation set.

• CONCLUSIONS: The criteria for CMV anterior uveitis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 89–95. © 2021 Elsevier Inc. All rights reserved.)

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With the advent of clinically available polymerase chain reaction (PCR) methodology for detecting cytomegalovirus (CMV) DNA, it became evident that CMV could cause an anterior uveitis in immunocompetent individuals.[1,2] The pathogenesis appears to be due to replicating CMV in the eye, as evidenced by the detection of CMV DNA and RNA in the anterior chamber using PCR on aqueous specimens obtained by paracentesis.[1-3] The disease is distinct from CMV retinitis seen in immunocompromised patients. Although CMV anterior uveitis has been reported from multiple countries, most reports come from Asian countries.[3] In the United States, it is estimated to cause ~2% of cases of viral anterior uveitis.[3,4] Whether this regional variation represents environmental factors, genetic susceptibility, or a combination of factors is unknown at this time.

CMV anterior uveitis has several clinical appearances, including a recurrent acute hypertensive anterior uveitis consistent with Posner-Schlossman syndrome, a Fuchs

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uveitis syndrome (FUS)-like chronic anterior uveitis, and less frequently a recurrent or chronic anterior uveitis with iris atrophy.[2,3,5-7] Adding to the difficulty of diagnosis is that none of these phenotypes is consistently attributable to CMV. In regions with a high prevalence of CMV anterior uveitis, ~50% of Posner-Schlossman patients will have CMV anterior uveitis, and ~40% of FUS-like eyes will have CMV anterior uveitis.[5] No differences in phenotype can be detected between eyes with Posner-Schlossman syndrome with and without CMV, and although there are differences between eyes with FUS and with FUS-like CMV anterior uveitis, they do not seem to be consistent enough for reliable diagnosis.[5] Eyes with FUS-like CMV anterior uveitis are more likely to have endotheliitis, nodular or "coin-like" endothelial lesions, and iris atrophy without heterochromia.[2,5,6,7] The importance of correct diagnosis is emphasized by the clinical response of CMV anterior uveitis to topical ganciclovir therapy, including better intraocular pressure control, inflammation control, and diminishing endothelial cell loss.[8,9]

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.[10-16] Among the anterior uveitides studied was CMV anterior 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.[11,14,16]

• **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.[11]

• **CASE COLLECTION AND CASE SELECTION:** De-identified clinical information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.[14,16] 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.[14,16] Because the goal was to develop classification criteria, only cases with a supermajority agreement (>75%) that the case was the disease 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.[16] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For CMV anterior uveitis, the diseases against which it was evaluated were herpes simplex virus (HSV) anterior uveitis, varicella zoster virus (VZV) anterior uveitis, juvenile idiopathic arthritis–associated anterior uveitis, spondylitis/HLA-B27-associated anterior uveitis, tubulointerstitial nephritis with uveitis, FUS, sarcoidosis-associated anterior uveitis, and syphilitic anterior uveitis.

• **COMPARISON OF CASES FROM ASIAN PATIENTS AND NON-ASIAN PATIENTS:** For categorical variables, comparison of cases of CMV anterior uveitis in Asian and non-Asian patients was performed with the χ^2 test or the Fisher exact test if a cell was less than 5. For continuous variables, the Wilcoxon rank sum test was used. *P* values are nominal and 2-sided.

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 twelve cases of CMV anterior uveitis were collected, and 89 cases (79%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of CMV anterior uveitis were compared to 994 cases of other anterior uveitides, including 123 cases of VZV anterior uveitis, 101 cases of HSV anterior uveitis, 146 cases of FUS, 202 cases of juvenile idiopathic arthritis–associated anterior uveitis, 184 cases of spondylitis/HLA-B27-associated anterior uveitis, 94 cases of tubulointerstitial nephritis with uveitis, 112 cases of sarcoidosis-associated anterior uveitis, and 32 cases of syphilitic anterior uveitis. The characteristics of the cases with CMV anterior uveitis at presentation to a SUN Working Group investigator are listed in Table 1. The comparison of characteristics of Asian and non-Asian cases is shown in Table 2. Differences between Asian and non-Asian cases included (1) slightly older age in Asian cases; (2) greater proportion of cases with chronic uveitis in Asian cases; and (3) greater proportion of cases with mutton fat or nummular keratic precipitates (Figure 1) in Asian cases. The criteria developed after machine learning are listed in Table 3. No phenotypic features were selected,

TABLE 1. Characteristics of Cases of Cytomegalovirus Anterior Uveitis

Characteristic	Result
Number of cases	89
Demographics	
Age, median, years (25th, 75th percentile)	53 (39, 62)
Age category, years (%)	
≤16	2
17-50	39
51-59	29
≥60	29
Sex (%)	
Male	65
Female	35
Race/ethnicity (%)	
White, non-Hispanic	25
Black, non-Hispanic	8
Hispanic	2
Asian, Pacific Islander	43
Other	9
Missing/unknown	13
Uveitis history	
Uveitis course (%)	
Acute, monophasic	7
Acute, recurrent	37
Chronic	55
Indeterminate	1
Laterality (%)	
Unilateral	97
Unilateral, alternating	0
Bilateral	3
Ophthalmic examination	
Cornea (%)	
Normal	80
Corneal edema	19
Keratitis	1
Keratic precipitates (%)	
None	10
Fine	27
Round	33
Stellate	8
Mutton fat	17
Numular	6
Anterior chamber cells, grade (%)	
½+	28
1+	34
2+	22
3+	2
4+	0
Missing	14
Hypopyon (%)	0
Anterior chamber flare, grade (%)	
0	61
1+	29
2+	10
3+	0
4+	0
Iris (%)	
Normal	69
Posterior synechiae	9
Sectoral iris atrophy	2
Patchy iris atrophy	9
Diffuse iris atrophy	15
Heterochromia	2
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	18 (14, 30)
Proportion of patients with IOP > 24 mm Hg either eye (%)	54
Vitreous cells, grade (%)	
0	93
½+	3
1+	1
2+	2
3+	0
4+	0
Laboratory	
Aqueous PCR positive for CMV[a] (% cases)	99

(*continued on next column*)

TABLE 1. (*continued*)

CMV = cytomegalovirus; IOP = intraocular pressure; PCR = polymerase chain reaction.

[a]PCR positive for CMV in 88 of 89 cases tested.

and detection of CMV in the aqueous humor with PCR was selected by machine learning as necessary for diagnosis. The 1 case selected by the selection committee for inclusion in the final database without a positive PCR for CMV had an acute hypertensive anterior uveitis with corneal edema and elevated intraocular antibodies to CMV on Goldmann-Witmer analysis of an aqueous humor sample obtained by paracentesis. 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).[16] The misclassification rate for CMV anterior uveitis in the training set was 1.3% and in the validation set 0%.

DISCUSSION

The low misclassification rate for the criteria in Table 3 is due in part to the requirement for laboratory confirmation of the diagnosis of CMV anterior uveitis. This requirement occurs in part because no one phenotype can be reliably diagnosed as CMV anterior uveitis and because the CMV anterior uveitis–like phenotypes can occur in the absence of CMV disease.[3,5,17] For a Posner-Schlossman-like phenotype, no features reliably distinguish between cases attributable to CMV and those where CMV cannot be detected.[5] For FUS and FUS-like CMV anterior uveitis, endotheliitis, endothelial cell loss, and nodular

TABLE 2. Characteristics of Cases of Cytomegalovirus Anterior Uveitis in Asian and Non-Asian Patients

Characteristic	Asian Cases	Non-Asian Cases	*P* Value
Number of cases	38	51	
Demographics			
Age, median, years (25th, 75th percentile)	56 (40, 65)	51 (36, 56)	.03
Sex (%)			.92
Male	66	65	
Female	34	35	
Uveitis history			
Uveitis course (%)			.002
Acute, monophasic	4	9	
Acute, recurrent	20	50	
Chronic	76	39	
Indeterminate	0	2	
Laterality (%)			.79
Unilateral	97	98	
Bilateral	3	2	
Ophthalmic examination			
Cornea			.80
Normal	82	76	
Corneal edema	18	22	
Keratitis	0	2	
Keratic precipitates (%)			<.001
None	16	9	
Fine	8	41	
Round	24	39	
Stellate	8	8	
Mutton fat	32	0	
Numular	10	2	
Anterior chamber cells, grade (%)			.57
½+	21	33	
1+	32	35	
2+	29	18	
3+	3	2	
Anterior chamber flare, grade (%)			.32
0	58	63	
1+	26	31	
2+	16	6	
Iris (%)			
Normal	33	42	.27
Posterior synechiae	13	6	.21
Iris atrophy	16	36	.11
Heterochromia	3	2	.67
IOP, involved eyes			
Median, mm Hg (25th, 75th percentile)	18 (14, 30)	17 (15, 30)	.82
Percent of patients with IOP > 24 mm Hg either eye	42	37	.64
Vitreous cells, grade (%)			.88
0	92	94	
½+	5	2	
≥1+	3	4	

IOP = intraocular pressure.

endothelial lesions, often "coin-shaped" and with a surrounding halo, all suggest CMV disease.[3,5,17] Furthermore, FUS iris atrophy is diffuse, may transilluminate, and typically results in heterochromia, whereas the iris atrophy with CMV anterior uveitis is typically "patchy," does not transilluminate, and rarely produces heterochromia.[3,17] FUS has been thought to have a postinfectious pathogenesis, with rubella most often implicated in white patients,[18,19] and as

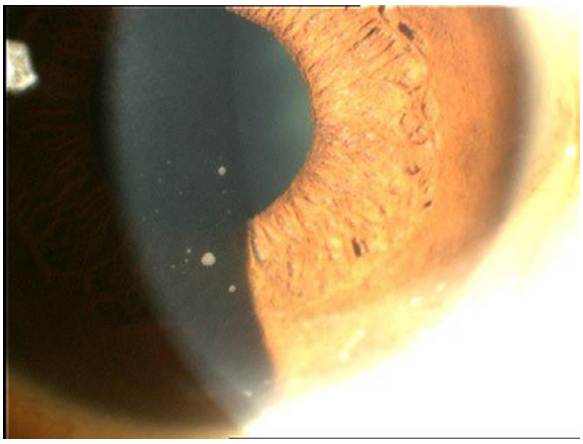

FIGURE 1. Nummular corneal endothelial lesion in a case of cytomegalovirus anterior uveitis.

TABLE 3. Classification Criteria for Cytomegalovirus Anterior Uveitis

Criteria
1. Evidence of anterior uveitis
a. anterior chamber cells
b. if anterior vitreous cells are present, anterior chamber inflammation should be present
c. no evidence of retinitis
AND
2. Evidence of cytomegalovirus infection in the eye
a. Positive PCR for cytomegalovirus on aqueous specimen
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)
3. Aqueous specimen PCR positive for herpes simplex virus or varicella zoster virus

PCR = polymerase chain reaction.

such should be distinguished from the "FUS-like" anterior uveitis due to CMV, seen most often in Asian patients. Using a Goldmann-Witmer analysis of aqueous humor from eyes with FUS, elevated levels of antibodies to rubella have been detected, suggesting an immunologic response to rubella. Conversely, real-time PCR for rubella nearly always is negative (and positive only in younger patients) in the aqueous humor from eyes of patients with Fuchs, suggesting that Fuchs may not be due to active viral infection,[18,19] but rather may be attributable to an immunologic response to prior infection. However, an uncontrolled case series using metagenomic deep sequencing, a more sensitive method for detecting viral RNA, detected rubella RNA in the eyes of 3 patients with FUS, suggesting that low-level viral replication may have a role in the pathogenesis of Fuchs.[20] Nevertheless, it currently remains uncertain as to whether Fuchs is due to viral replication, an immunologic response to the virus, or a more complex combination of the two. CMV anterior uveitis tends to have milder inflammation and lower endothelial cell counts than HSV and VZV anterior uveitis, providing clinical clues, but these features are suggestive and do not reliably distinguish between CMV anterior uveitis and either HSV or VZV anterior uveitis.[21] Because CMV anterior uveitis is uncommon in the West, and other viral infectious anterior uveitides often can be diagnosed reliably on morphologic grounds, paracentesis for aqueous PCR for viruses may not be performed routinely.[4,16] Nevertheless, the diagnosis of CMV anterior uveitis requires aqueous paracentesis for PCR for CMV, and CMV should be sought in those cases with a compatible syndrome and especially those cases with suggestive features.

A case series from France of patients with CMV anterior uveitis suggested that white patients may have a different presentation than Asian patients, as no cases of "FUS-like" anterior uveitis were seen among their cases.[22] Sixty-nine percent of the cases in this series presented as a Posner-Schlossman syndrome and 31% as a chronic anterior uveitis.[22] In the cases in the SUN database, the comparison of cases of CMV anterior uveitis in Asian and non-Asian patients demonstrated a greater proportion of chronic uveitis in Asian cases and a greater proportion of recurrent uveitis in non-Asian cases. These results might be compatible with the differing morphologic variants reported previously, but the SUN data set did not have sufficient syndromic data to confirm this reported difference.

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

Classification criteria are employed to diagnose individual diseases for research purposes.[15] 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,[15] 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,[14] the selection of cases for the final database ("case

selection") included only cases that achieved supermajority agreement on the diagnosis. As such, there may be cases that the clinician believes are CMV anterior uveitis, but that do not satisfy classification criteria.

In conclusion, the criteria outlined in Table 3 seem to perform well enough for use as classification criteria for CMV anterior uveitis.

CREDIT ROLES

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TOC

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus technique–based case selection, and machine learning, classification criteria for cytomegalovirus (CMV) anterior uveitis were developed. Key criteria included unilateral anterior uveitis with positive aqueous humor polymerase chain reaction assay for CMV. The resulting criteria had a low misclassification rate.

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