Classification Criteria for Toxoplasmic Retinitis

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

• ABSTRACT:• PURPOSE: **To determine classification criteria for toxoplasmic retinitis.**

• DESIGN: **Machine learning of cases with toxoplasmic retinitis and 4 other infectious posterior uveitides / panuveitides.**

• METHODS: **Cases of infectious posterior uveitides / panuveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on 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 infectious posterior uveitides / panuveitides. The resulting criteria were evaluated on the validation set.**

• RESULTS: **Eight hundred three cases of infectious posterior uveitides / panuveitides, including 174 cases of toxoplasmic retinitis, were evaluated by machine learning. Key criteria for toxoplasmic retinitis included focal or paucifocal necrotizing retinitis and either positive polymerase chain reaction assay for *Toxoplasma gondii* from an intraocular specimen or the characteristic clinical picture of a round or oval retinitis lesion proximal to a hyperpigmented and/or atrophic chorioretinal scar. Overall accuracy for infectious posterior uveitides / panuveitides was 92.1% in the training set and 93.3% (95% confidence interval 88.2, 96.3) in the validation set. The misclassification rates for toxoplasmic retinitis were 8.2% in the training set and 10% in the validation set.**

• CONCLUSIONS: **The criteria for toxoplasmic retinitis had a low misclassification rate and seemed to perform sufficiently well for use in clinical and translational research. (Am J Ophthalmol 2021;228: 134–141. © 2021 Elsevier Inc. All rights reserved.)**

Toxoplasma gondii is a ubiquitous parasite worldwide and is the most common cause of retinal infection in most populations, resulting in a substantial burden of eye disease and vision loss.[1,2] *T. gondii* reproduces sexually only in the gut of felines, but can reproduce asexually in most other mammals and in birds. Infection occurs via 1 of several routes: through ingestion of materials contaminated with cat feces that contain öocysts; by eating raw or undercooked tissue of infected intermediate hosts; or vertically from mother to an unborn child during pregnancy. With rare exception, vertical transmission occurs only when the mother is first infected during the pregnancy.

In intermediate hosts, including food animals and human beings, öocysts become tachyzoites, the proliferative form of the parasite that can cause clinical disease, but parasites eventually encyst in various tissues, including the retina. These tissue cysts contain the bradyzoite form of parasite that does not induce clinical disease, but remains viable for prolonged periods of time. Tissue cysts reactivate from time to time, releasing bradyzoites, which again convert back to tachyzoites, but the factors that cause reactivation are poorly understood. Proliferation of tachyzoites is self-limited in people with normal immune function. People with postnatally acquired infections may develop a transient illness characterized by lymphadenopathy, fever, and sore throat, but the initial infection often is asymptomatic. Ocular involvement may occur at the time of initial systemic infection or months to years later.

In the United States the age-adjusted seroprevalence of anti–*T. gondii* antibodies during the period 2011-2014 was approximately 10%.[3] Seroprevalence increases with age and is higher among men, socioeconomically disadvantaged groups, and individuals born outside the United States.[3] It is estimated that, overall, 2% of *T. gondii*–infected in-

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dividuals in the United States have ocular involvement.[1] The risk of ocular involvement also is believed to be higher among Hispanic immigrants,[1] presumably because they are infected in their countries of origin by endemic parasites of greater virulence (see below). In 2010, it was estimated that nearly 5,000 people in the United States would develop symptomatic ocular toxoplasmosis each year.[4]

The rates of both infection and ocular involvement are higher in many other parts of the world; for example, in the area of Erechim, in southern Brazil, results of a population-based study showed that 21.3% of individuals over the age of 13 years had ocular toxoplasmosis,[5] and in a prior study from the same area, 98 of 100 children aged 10-15 were infected with *T. gondii*.[6]

The primary ocular site of *T. gondii* infection is the retina and eventually may result in full-thickness retinal necrosis. The subjacent choroid can also be destroyed, presumably by accompanying inflammation, which ultimately results in an atrophic scar with white center, owing to exposure of the sclera, and a variably pigmented border as the lesion becomes inactive. Tissue cysts are believed to persist at scar borders after resolution of an active episode. Recurrences arising from these tissue cysts account for the classic appearance of toxoplasmic retinitis: a focus of intense tissue inflammation adjacent to a pre-existing retinochoroidal scar. Not all lesions arise from scars, however. "Primary lesions" (those arising from normal-appearing retina) may occur at the time of an initial infection or may occur later; these late primary lesions are thought to arise from organisms that encyst in the retina at the time of initial infection, but do not immediately cause clinically apparent disease.[7,8]

The clinical appearance of toxoplasmic retinal lesions may vary, based on the duration of parasite proliferation before encystment, and on the severity of associated inflammation[2,9-11] Infections that resolve early, with minimal inflammation, may result in only multiple small outer retinal opacities, a presentation of disease termed "punctate outer retinal toxoplasmosis."[12] Conversely, persistent infection, as may occur in immunocompromised individuals, may result in large areas of retinal necrosis, possibly mimicking other forms of necrotizing retinitis, such as cytomegalovirus (CMV) retinitis.[13] Occasionally, elderly individuals may develop extensive lesions.[2,14,15]

Variation in prevalence of infection and risk for ocular involvement among otherwise healthy individuals appears to reflect parasite strains of different virulence.[16,17] Genotypes of parasites endemic to different geographic areas vary considerably; the presence of more virulent strains in food animals of southern Brazil is thought to explain the fact that ocular toxoplasmosis is more prevalent and more severe in that region than in the United States.

Because of the relatively high seroprevalence of *T. gondii* antibodies in the general population and the relatively low risk of ocular involvement, the presence of IgG antibodies to *T. gondii* typically is not a useful feature for diagnosing toxoplasmic retinitis; however, a negative serologic test may help to exclude toxoplasmic retinochoroiditis in a patient with a nonspecific focus of retinal inflammation. Conversely, the presence of IgM antibodies may provide information about recently acquired systemic toxoplasmosis. Polymerase chain reaction (PCR) techniques can be used to identify *T. gondii* DNA in ocular fluids, and are particularly helpful in diagnosing ocular toxoplasmosis in patients with unusual presentations of disease.[18]

Although retinal lesions are self-limited in otherwise healthy individuals, it is believed that treatment with a combination of antimicrobial agents and corticosteroid will reduce tissue damage from associated inflammation. There is no consensus regarding the best antimicrobial agents; most common is use of both a dihydrofolate reductase inhibitor and a sulfonamide, such as pyrimethamine and sulfadiazine or combination trimethoprim-sulfamethoxazole.[19] Despite the absence of class I clinical trials demonstrating the efficacy of antimicrobial treatment of ocular toxoplasmosis, 1 comparative trial in which treatment was assigned by clinical center reported that treatment with pyrimethamine and sulfadiazine resulted in smaller scars than did no treatment, suggesting efficacy in limiting retinal damage. In this trial the recurrence rate was unaffected by the short-term course of treatment.[20] Subsequent small clinical trials suggested efficacy similar to pyrimethamine and sulfadiazine for trimethoprim-sulfamethoxazole, for pyrimethamine and azithromycin, and for intravitreal clindamycin and dexamethasone.[21-23] Retrospective cohort data suggest that treatment of ocular toxoplasmosis with corticosteroids alone is associated with increased risks of fulminant toxoplasmic retinitis,[24] ocular recurrences, and worse visual outcomes[10]; therefore, such management generally is discouraged. Severely immunocompromised patients can be treated with an antimicrobial agent alone and are likely to require continued antimicrobial therapy to maintain lesion inactivity.[25,26] Treatment with currently available drugs does not eliminate tissue cysts, but continued treatment with an antimicrobial agent, such as trimethoprim-sulfamethoxazole, reduces the risk of recurrences.[27,28]

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. Among the diseases studied was toxoplasmic retinitis.[29-35]

TABLE 1. Characteristics of Cases With Toxoplasmic Retinitis

Characteristic	Result
Number of cases	174
Demographics	
Age, median, years (25th, 75th percentile)	28 (21, 43)
Sex (%)	
Male	50
Female	50
Race/ethnicity (%)	
White, non-Hispanic	55
Black, non-Hispanic	8
Hispanic	9
Asian, Pacific Islander	11
Other	13
Missing	4
Uveitis history	
Uveitis course (%)	
Acute, monophasic	43
Acute, recurrent	24
Chronic	26
Indeterminate	7
Laterality (%)	
Unilateral	88
Unilateral, alternating	0
Bilateral	12
Ophthalmic examination	
Keratic precipitates (%)	
None	61
Fine	18
Round	10
Stellate	1
Mutton fat	9
Other	1
Anterior chamber cells, grade (%)	
0	45
½+	14
1+	16
2+	12
3+	10
4+	3
Anterior chamber flare, grade (%)	
0	63
1+	25
2+	9
3+	2
4+	1
Iris (%)	
Normal	97
Posterior synechiae	3
Iris nodules	0
Iris atrophy (sectoral, patchy, or diffuse)	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	16 (13, 18)
Proportion of patients with IOP > 24 mm Hg either eye (%)	7

(*continued on next column*)

TABLE 1. (*continued*)

Characteristic	Result
Vitreous cells, grade (%)	
0	21
½+	13
1+	30
2+	27
3+	7
4+	2
Vitreous haze, grade (%)	
0	30
½+	19
1+	27
2+	14
3+	9
4+	1
Retinitis characteristics	
Number of lesions per eye, including active lesions & scars (%)[a]	
Unifocal (1)	5
Paucifocal (2-4)	82
Multifocal (≥5)	8
Indeterminate (lesion not photographed or dense vitritis)	5
Number of active lesions per eye (%)[a]	
Unifocal (1)	78
Paucifocal (2-4)	2
Multifocal (≥5)	0
Indeterminate (lesion not photographed or dense vitritis)	20
Proximate/adjacent hyperpigmented/atrophic scars (%)[a]	
Present	82
Absent (active lesion only)	16
Indeterminate (dense vitritis)	2
Lesion shape (%)	
Round or ovoid	59
Placoid	16
Ameboid	9
Wedge-shaped	3
Punctate	2
Missing	11
Lesion character (%)	
Circumferential	1
Confluent	7
Granular	1
Lesion location (%)	
Posterior pole involved	52
Midperiphery and/or periphery only	48
Lesion size (%)	
<250 μm	6
250-500 μm	10
>500 μm	84
Other features (%)	
Retinal vascular sheathing or leakage or occlusion	17
Retinal hemorrhage	6

(*continued on next page*)

TABLE 1. (*continued*)

Characteristic	Result
Systemic disease	
Immunocompromised patients (%)	6
Human immunodeficiency virus infection	5
Organ transplant	0
Chemotherapy or other immunosuppression	1
Laboratory data (%)	
Aqueous or vitreous specimen PCR[b] positive for *Toxoplasma gondii*	10
Positive serology for antibodies to *Toxoplasma gondii*[c]	75
Positive IgM antibodies to *Toxoplasma gondii*	21
Positive IgG antibodies to *Toxoplasma gondii*	74

IOP = intraocular pressure; PCR = polymerase chain reaction.
[a]Based on evaluation of photographs of 158 cases.
[b]Seventeen of 20 cases tested (85%) were positive.
[c]Either IgG or IgM antibodies to *Toxoplasma gondii* were present in 131 of 131 cases tested (100%). IgM antibodies were present in 36 of 131 cases tested (21%) and IgG antibodies were present in 128 of 131 cases tested (98%).

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.[31-34]

• **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.[31]

• **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.[32,34] 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.[33,34] Because the goal was to develop classification criteria,[35] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (ie, were "selected").[33,34]

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of the cases) and a validation set (~15% of the cases) for each disease, as described in the accompanying article.[34] 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 infectious posterior uveitides and panuveitides, the diseases against which toxoplasmic retinitis was evaluated were acute retinal necrosis (ARN), CMV retinitis, syphilitic uveitis, and tubercular uveitis.

RESULTS

Two hundred thirteen cases of toxoplasmic retinitis were collected and 174 (82%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of toxoplasmic retinitis were compared to cases of infectious posterior uveitides / panuveitides, including 186 cases of ARN, 211 cases of CMV retinitis, 35 cases of syphilitic posterior uveitis, and 197 cases of tubercular uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[34] The characteristics of cases with ocular toxoplasmosis are listed in Table 1, and the classification criteria developed after machine learning are listed in Table 2. Key features of the criteria include a unifocal or paucifocal (<5 lesions) active retinitis and either (1) evidence of infection with *T. gondii*, either from PCR of an intraocular fluid specimen or serum IgM antibodies to *T. gondii* (evidence of acute infection); or (2) classic clinical picture (Figure 1) with hyperpigmented and/or atrophic scar accompanied by either a round or oval area of active retinitis or a recurrent area of active retinitis. The overall accuracy for infectious posterior uveitides / panuveitides was 92.1% in the training set and 93.3% (95% confidence interval 88.2, 96.3%) in the validation set. The misclassification rate for toxoplasmic retinitis in the training set was 8.2% and in the validation set 10%. In the training set the disease with which it was most often confused was CMV retinitis, whereas in the validation set no one disease predominated.

DISCUSSION

Necrotizing retinitides are characterized by full-thickness retinal necrosis with or without inflammation, which, upon resolution, leave an atrophic and gliotic scar in the involved areas. Clinically, the initial presentation is white-to-yellow retinal edema and opacity with or without hemorrhage. Necrotizing retinitides may have relatively well demarcated borders, as in the case of ARN, or have satellites extending into adjacent retina, as is seen in CMV retinitis. The classification criteria developed by the SUN Working Group

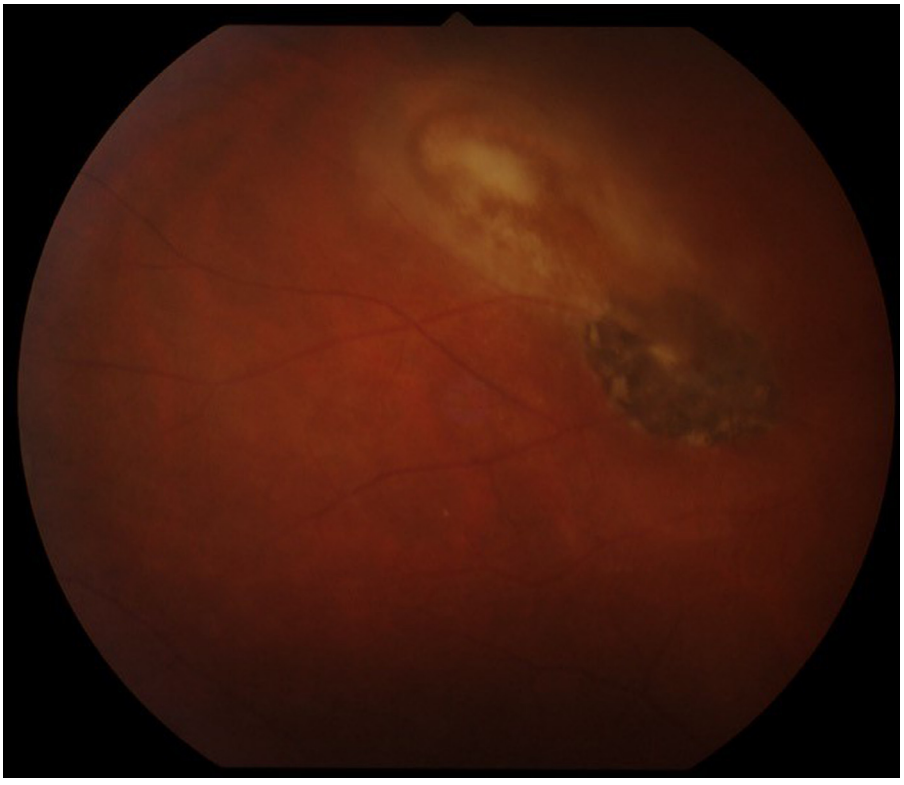

FIGURE 1. Fundus photograph of a case of toxoplasmic retinitis with an area of focal retinitis characterized by retinal necrosis and edema, adjacent to a hyperpigmented chorioretinal scar.

for toxoplasmic retinitis have a relatively low misclassification rate, indicating reasonably good discriminatory performance against other infectious posterior uveitides and panuveitides.

The criteria were developed to diagnose active toxoplasmic retinitis but do not address the diagnosis of chorioretinal scars in the absence of active retinitis. Although these scars may have an appearance similar to those described in the criteria and a reasonable inference made, the scars also may be nonspecific. This limitation is applicable to congenital toxoplasmosis, where the eye examination may demonstrate chorioretinal scars without active retinitis.

In ocular toxoplasmosis, the retinitis seems to be attributable to the proliferation of tachyzoites, whereas the anterior uveitis, vitritis, and vascular sheathing seem to be attributable to the immunologic response to *T. gondii*.[2,36] As such, the clinical appearance will vary depending on the immunologic status of the host.[13,25,26] Nevertheless, in immunocompetent adults, a characteristic picture is present permitting diagnosis based on the clinical morphologic appearance: a single round or oval area of active retinitis is adjacent to an atrophic and hyperpigmented scar or scars and is associated with vitritis. The presumed reason for this appearance is that the immune response typically causes *T. gondii* to encyst again without ongoing cell lysis, resulting in well-demarcated scars. In contrast, viral retinitides spread in a brushfire manner owing to persistent viral replications with expanding areas of retinal necrosis.

The cases in the SUN database have characteristics similar to those from other case series, suggesting good generalizability, including presence of retinochoroidal scars, anterior segment inflammation, vitritis, disease course, and lesion location.[3,9-11,37,38] Although the macula represents only 5% of the retinal area, the posterior pole is disproportionally affected by ocular toxoplasmosis: 52% of cases in the SUN database had posterior pole involvement, a result seen in case series of congenitally acquired ocular toxoplasmosis[37] and to a slightly lesser extent in international case series of ocular toxoplasmosis.[38] The reasons for this disproportionate involvement of the posterior pole are unknown, but theoretically could relate to the density of the retinal vasculature and the presence of parasitemia during the initial systemic infection.[38-40]

There can be variation in the clinical presentation, including lesion size, shape, pigmentation, and presence of scars.[2,9-14] Although multiple factors likely contribute to this variability, the host's immune status and age are 2 of the more important ones. Persons with immunocompromise (eg, acquired immunodeficiency syndrome, organ transplant, etc) may have large, persistently active

TABLE 2. Classification Criteria for Toxoplasmic Retinitis

Criteria
1. Focal or paucifocal necrotizing retinitis[a]
AND (#2 or #3)
2. Evidence of infection with *Toxoplasma gondii*
a. Positive PCR for *Toxoplasma gondii* from either the aqueous or vitreous specimen OR
b. Positive serum IgM antibodies against *Toxoplasma gondii*
OR
3. Characteristic clinical ocular features
a. Hyperpigmented and/or atrophic chorioretinal scar ("toxoplasmic scar") AND (b. or c.)
b. Round or oval retinitis lesions OR
c. Recurrent acute (episodic) course
Exclusions
1. Both negative IgG AND IgM antibodies against *Toxoplasma gondii* (unless there is a positive PCR for *Toxoplasma gondii* from an aqueous or vitreous specimen)
2. Positive serology for syphilis using a treponemal test
3. Intraocular specimen PCR-positive for herpes simplex virus, varicella zoster virus or cytomegalovirus (unless there is immune compromise, morphologic evidence for >1 infection, the characteristic picture of toxoplasmic retinitis, and the intraocular fluid specimen also has a positive PCR for *T. gondii*)

PCR = polymerase chain reaction.

[a] "Active" retinitis lesions in immunocompetent patients. Immunocompromised patients may have a multifocal retinitis or a diffuse necrotizing retinitis. Number of scars may be ≥5.

lesions, attributable to the failure of the immune response, continued tachyzoite proliferation, and the resultant ongoing tissue destruction.[13,24,25] Ocular lesions also may be more severe in newborns, who have immature immune defenses, and have been reported to be more severe in the elderly.[14,15] Similarly, patients with newly acquired ocular toxoplasmosis may have focal necrotizing retinitis without an adjacent scar,[2,8] as may some patients with remote infection without active retinal disease, resulting in tissue cysts but no scars.[10,37,38] In atypical presentations, confirmation of intraocular infection with *T. gondii*, by assaying an intraocular fluid specimen (eg, by PCR), may be required[18]; and in cases without an adjacent toxoplasmosis scar owing to recently acquired systemic toxoplasmosis, confirmation of acute systemic infection by detection of IgM antibodies to *T. gondii* in the serum may be helpful. Because of the high prevalence of IgG antibodies to *T. gondii* in the general population, the presence of IgG antibodies to *T. gondii* generally is not helpful in establishing the diagnosis.

Aqueous humor can be sampled to detect presumed intraocular antibody production using the Goldmann-Witmer coefficient (GWC) analysis. An elevated GWC for pathogens has been taken as evidence of intraocular infection, although it actually suggests an immunologic antibody response to the pathogen and does not detect the pathogen itself. Several studies have suggested that analysis of intraocular fluid using GWC analysis may be beneficial in the evaluation of patients with intraocular infections.[41-43] However, these retrospective studies suffer from a lack of a "gold standard" and a presumption of superior accuracy of the GWC analysis. Nevertheless, there seems to be value in its use, and GWC analysis may be complementary to PCR analysis in that PCR detection of pathogen DNA may decline with treatment. Although used extensively in some clinics, unlike PCR analysis of intraocular fluid, GWC coefficient analysis is not widely used throughout the world. In the SUN machine learning, the GWC analysis did not emerge as a useful factor, perhaps because of its limited use by SUN investigators. Prospective studies against standardized diagnosis may demonstrate its utility and lead to its inclusion in the criteria in the future.

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of toxoplasmic retinitis 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 toxoplasmic retinitis, but the absence of such testing does not always exclude the diagnosis of toxoplasmic retinitis if the criteria for the diagnosis are met.

Classification criteria are employed to diagnose individual diseases for research purposes.[35] 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,[35] 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,[32] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. As such, some cases that clinicians would diagnose with toxoplasmic retinitis may not be so classified by classification criteria.

In conclusion, the criteria for toxoplasmic retinitis outlined in Table 2 seem to perform sufficiently well for use as classification criteria in clinical research.[34]

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