Clinical and Imaging Factors Associated With the Outcomes of Tubercular Serpiginous-like Choroiditis

ANIRUDDHA AGARWAL, ALESSANDRO MARCHESE, ALESSANDRO RABIOLO, RUPESH AGRAWAL, REEMA BANSAL, AND VISHALI GUPTA

• PURPOSE: To analyze baseline clinical and imaging risk factors associated with poor outcome in patients with tubercular serpiginous-like choroiditis (TB SLC).
• DESIGN: Retrospective clinical study.
• METHODS: Charts and fundus photographs of consecutive patients with active TB SLC seen at a single tertiary referral center with 6 months follow-up after initiation of treatment were reviewed. Logistic mixed models were performed to determine the clinical and imaging factors associated with the response to therapy, including the opacity of choroiditis graded according to a 3-point scale.
• RESULTS: This study included 203 eyes of 183 patients with active TB SLC. Poor initial best-corrected visual acuity (BCVA) and foveal and optic disc involvement were associated with poor response to therapy at 6 months (odds ratio [OR] 4.489, 95% confidence interval [CI]: 1.92-10.47; $P = .001$; OR 2.892, 95% CI: 1.23-6.81; $P = .015$; OR 11.633, 95% CI: 3.17-42.71; $P < .001$, respectively). The high opacity grades (2 and 3) were also associated with poor outcomes OR 9.541; 95% CI: 2.94-30.91; $P = .001$). Poor baseline BCVA and high grade of opacity of the lesions were the composite risk factors for paradoxical worsening of TB SLC (OR 7.555, 95% CI: 1.78-32.02; $P = 0.006$; OR 7.434, 95% CI: 1.34-41.18; $P = 0.021$, respectively).
• CONCLUSIONS: TB SLC with higher grades of lesion opacity at baseline may be associated with greater risk of poor therapeutic response and paradoxical worsening. Grading of baseline lesion opacity may be used in future prospective studies to predict the biological behavior of the lesions and may serve as a guide to therapeutic interventions. (Am J Ophthalmol 2020;220: 160–169. © 2020 Elsevier Inc. All rights reserved.)

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From the Postgraduate Institute of Medical Education and Research, Chandigarh, India (A.A., A.M., R.B., V.G.); Department of Ophthalmology, Scientific Institute San Raffaele, University Vita-Salute San Raffaele, Milan, Italy (A.M., A.R.); Department of Ophthalmology, Gloucestershire Hospitals NHS, Cheltenham, United Kingdom (A.R.); National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore (R.A.); Singapore Eye Research Institute, Singapore (R.A.); and Moorfields Eye Hospital, London, United Kingdom (R.A.).

Inquiries to Vishali Gupta, Advanced Eye Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India; e-mails: vishalisara@gmail.com; vishalisara@yahoo.co.in

TUBERCULAR SERPIGINOUS-LIKE CHOROIDITIS (TB SLC) is a recurrent inflammation of the choriocapillaris, choroid, and retinal pigment epithelium seen in patients with evidence of systemic or latent tuberculosis.[1,2] TB SLC often affects young adults in the working-age group and is characterized by relentless progression with multiple recurrences if specific therapy is not initiated. The disease is believed to be an autoimmune response to *Mycobacterium tuberculosis* and is typically managed with systemic corticosteroids and immunosuppression to treat the inflammation along with antitubercular treatment (ATT) to reduce disease recurrences.[3–6] Development of complications such as choriocapillaris atrophy and choroidal neovascularization may occur over the follow-up, leading to severe visual loss.[7,8]

TB SLC is known to present as 2 phenotypes: multifocal and placoid.[4] In the former type, distinct lesions develop separately with an active edge that eventually progresses, and the lesions tend to coalesce over time. The latter variety presents as a single placoid lesion enlarging with a centrifugal pattern. Both variants are characterized by an active yellow edge and a central region showing healing. The character of active edge might vary from being prominent with elevated margins to ill-defined and flat. The placoid variety of TB SLC tends to be unilateral and takes a longer time to respond to therapy, with less favorable outcomes.[9] The exact mechanisms responsible for suboptimal healing in this phenotype are not clearly understood.

Similarly, paradoxical worsening of TB SLC lesions may be associated with significant visual morbidity. Paradoxical worsening following initiation of ATT is a major concern, and it requires higher doses of corticosteroids including adjunct intravitreal injections or immunosuppressive therapy to prevent permanent visual damage.[3,10,11]

There have been no studies to predict the response to therapy based on the baseline phenotype and morphology of the choroiditis lesions. Similarly, whether the morphology of the choroiditis lesions can help predict the development of paradoxical worsening and, thus,

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suboptimal vision has not been evaluated so far in the literature. The present study primarily aims to determine whether the anatomic characteristics of active lesions of TB SLC at the time of presentation can predict (1) the development of paradoxical worsening, and (2) progression of the lesions despite standard therapy.

METHODS

• **STUDY PARTICIPANTS:** This was a retrospective, clinical study of patients with active TB SLC seen at a single tertiary referral institution, the Advanced Eye Centre of the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, between May 2002 and August 2019, seen by either of 2 uveitis experts (V.G. and R.B.). The study was performed in agreement with the tenets of the Declaration of Helsinki for research on human patients and the rules laid down by Health Insurance Portability and Accountability Act of 1996. This retrospective study was approved by the Institutional Ethics Committee at PGIMER.

The clinical charts and imaging tests of consecutive patients with TB SLC were reviewed. The diagnostic criteria for tubercular choroiditis were based on the multicenter Collaborative Ocular Tuberculosis Study (COTS) Group highlighted below.[5,6] Patients who met the following inclusion criteria were enrolled for further analysis:

(1) Diagnosis of TB SLC based on the recognition of the typical clinical appearance of fundus lesions (multifocal or, rarely, unifocal yellow serpentine lesions with an active edge and well-defined gray area of central healing). Subjects with active chorioretinal lesions at baseline captured with central 50-degree fundus image were included.
(2) At baseline, the lesion activity was confirmed using fundus autofluorescence (FAF) imaging. Only eyes in which lesions were deemed active on FAF (belonging to stage 1 or stage 2 as per the grading on FAF)[12] were included in the study.
(3) Laboratory evidence of positive immunologic tests such as tuberculin skin test (induration more than 10 × 10 mm after 48-72 hours) and/or interferon gamma release assay such as QuantiFERON TB Gold.
(4) Evidence of healed or active tuberculosis on chest radiography or computerized chest tomography.
(5) Exclusion of other uveitic entities, where relevant, based on clinical manifestations of disease and regional epidemiology.
(6) Standard treatment and a minimum follow-up of 6 months.

Patients with poor image quality, absence of adequate follow-up, and presence of other chorioretinal disorders other than TB SLC were excluded from the study. Both eyes of the same patients were included if eligible.

• **STUDY VARIABLES:** Best-corrected visual acuity (BCVA; converted to logMAR units for analysis) was recorded for all the subjects at baseline and follow-up. TB SLC lesions (either placoid or multifocal) were evaluated on color fundus photographs (Carl Zeiss Visupac FF450; Carl Zeiss Meditec, Jena, Germany). In order to study the morphologic features of TB SLC lesions and perform grading of the active lesions at the time of initial presentation, we devised a strategy to select the most active (opaque/yellow) area of the lesions. Since TB SLC lesions are often present in various stages of evolution, the most opaque area of the active edge was taken for the analysis. This area of the active choroiditis edge was graded according to a self-designed 3-points scale (Figure 1), defined as follows: Grade 1: faint yellow-white lesion without retinal elevation, with ill-defined borders; Grade 2: moderate yellow-white opacification without retinal elevation, but with distinct borders; Grade 3: intense yellow opacification with retinal elevation and sharply demarcated borders.

Two independent, masked readers (A.A. and A.M.) performed the grading on 50-degree fundus photographs centered on the macula. Any disagreement was resolved by open adjudication. This grading based on the lesion opacity was performed using the photographs of the baseline visit only. Eyes with active lesions at baseline were evaluated for features potentially associated with (1) *high risk of suboptimal response*, and/or (2) *paradoxical worsening* during the course of follow-up. The high-risk factors were defined as optic disc involvement (defined as optic neuritis, disc elevation/edema, or active choroiditis extending to within 1 disc diameter of the optic nerve head; optic disc neovascularization was not included in this definition) or foveal/foveal-threatening lesion (defined as active lesions involving the fovea or within 300 μm from the foveal center).[3] Paradoxical worsening of TB SLC was defined as occurrence of new lesions or increase in the size of existing choroiditis lesions, typically within 3-8 weeks of initiating ATT.[13,14]

All the subjects were followed up for at least 6 months after initiation of therapy and their follow-up clinical data and fundus images were checked for development of paradoxical worsening. Those patients who did not have complete records including clinical data and fundus imaging were excluded from the analysis. At 3 and 6 months, the fundus images were once again analyzed by the 2 independent graders to determine if there were any new active lesions or persistence of inflammation or if the lesions had increased in size. Based on the healing response, the outcomes of patients were categorized as good or poor. Responses at 6 months was the primary study outcome. Results were categorized as good outcome if all the following occurred: no paradoxical worsening, no new lesions/progression, all the lesions have healed, and

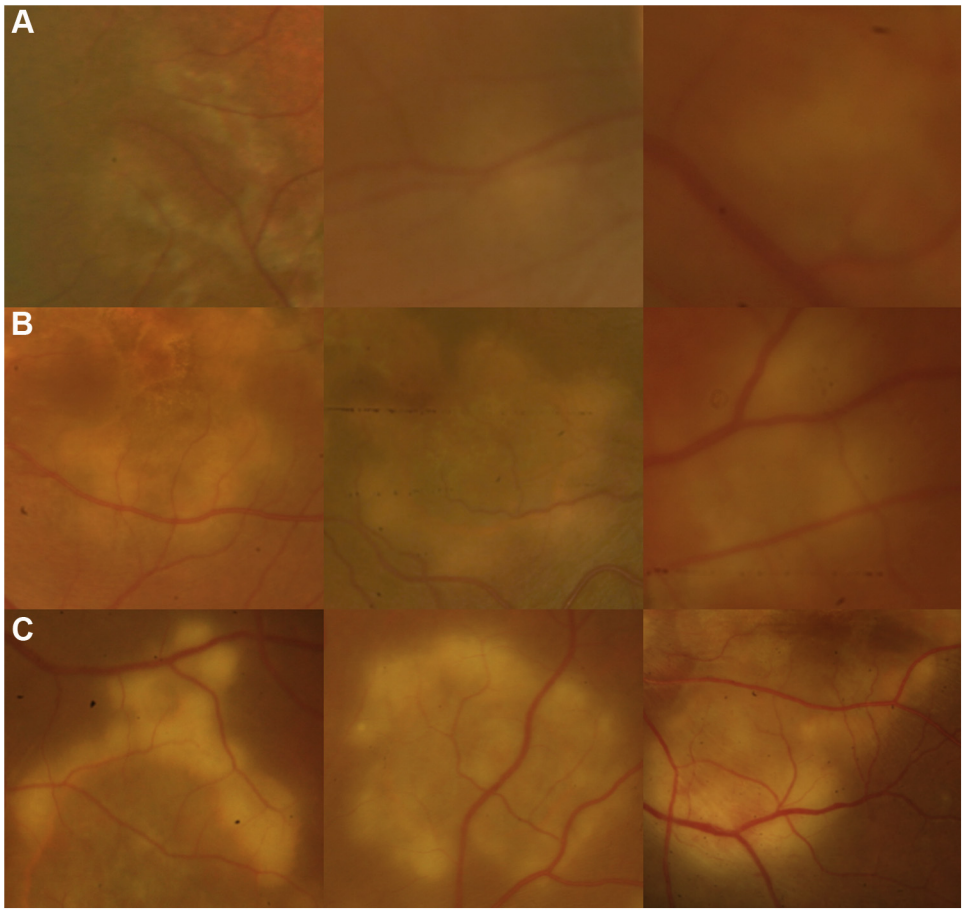

FIGURE 1. Three-points scale grading of the most opaque edge of tubercular serpiginous-like choroiditis. (A) Grade 1 eyes show faint yellow-white lesions without retinal elevation, with ill-defined borders. (B) Grade 2 eyes show moderate yellow-white opacification without retinal elevation, but with distinct borders. (C) Grade 3 eyes show intense yellow opacification with retinal elevation and distinct borders.

stabilization/reduction in the final size of the SLC lesions. Results were categorized as poor outcome if any of the following developed: paradoxical worsening, new active lesions, persistence of activity, or increase in the final size of the lesion from baseline.

Standard treatment of all the patients consisted of systemic corticosteroids (prednisolone 1 mg/kg/day with gradual tapering off over 1-2 months based on the healing of the lesions) and ATT. ATT consisted of 4-drug chemotherapy, including 2 months with isoniazid, rifampicin, ethambutol, and pyrazinamide.[15] Thereafter, patients continued rifampicin and isoniazid for additional 7 months. Immunosuppression was introduced at clinician discretion if the patients required steroid-sparing therapy. None of the subjects included in the study received intravitreal therapeutic agents. Paradoxical worsening was treated with an increase in oral corticosteroids (prednisolone) and/or addition of immunosuppressive therapy whenever felt necessary by the treating physician.

• **STATISTICAL ANALYSIS:** All statistical analyses were performed with R software (version 3.3.2; The Foundation for Statistical Computing, Vienna, Austria). Continuous variables were checked for normality through the visual inspection of frequency histograms and Q-Q plot. Descriptive statistics of normal and non-normal variables were reported as mean ± standard deviation (SD) and median (interquartile range [IQR]), respectively; frequencies and proportions were reported for categorical variables. All tests were 2-sided and P value $<.05$ was set as significant.

Agreement between outcome at 3 and 6 months was estimated with Cohen's kappa, while agreement between the 2 clinicians in grading the opacity of TB SLC was evaluated with weighted kappa statistic for ordinal data. The level of agreement was defined as poor for κ values ranging between 0.00 and 0.20, slight between 0.21 and 0.40, moderate between 0.41 and 0.60, substantial between 0.61 and 0.80, and excellent for κ equal to 0.80 or above.[16]

TABLE 1. Baseline Demographic and Clinical Features of Patients With Tubercular Serpiginous-like Choroiditis Included in the Study

Total eyes (subjects) included	203 (183)
Age (years) ± standard deviation)	34.6 ± 11.0
Sex, n (%)	
Male	133 (72.7)
Female	50 (27.3)
Phenotype of choroiditis, n (%)	
Multifocal	171 (84.2)
Placoid	32 (15.8)
Laboratory assessments	
Positive tuberculin skin test,[a] n (%)	175 (95.6)
Positive interferon gamma release assay, n (%)	148 (80.9)
Positive radiologic features,[b] n (%)	104 (56.8)
Baseline visual acuity (logMAR units), median (IQR)	0.70 (0.44-1.00)
Grade of opacity, n (%) eyes	
Grade 1	63 (31.0)
Grade 2	84 (41.4)
Grade 3	56 (27.6)
Number (%) of eyes with foveal involvement	72 (35.5)
Number (%) of eyes with optic disc involvement	46 (22.7)

IQR = interquartile range.
[a]Indicates induration ≥10 mm × 10 mm by Mantoux test after 48-72 hours.
[b]Indicates evidence of healed or active tuberculosis on chest radiography.

The relationship between the clinical response of the active lesions of TB SLC (poor vs good), paradoxical worsening, increased lesion size at 6 months, and the baseline variables were investigated with a logistic mixed model. For all the models, the following baseline factors were tested as fixed factors: age, sex, eye laterality, BCVA, TB SLC opacity grade, placoid subtype, fovea involvement, and optic disc involvement. In all our models, the patient identification number was included as a random factor to compensate for within-subject correlations owing to the inclusion of both eyes of the same patient. Factors with a *P* value <.05 at the univariable analysis were included in the multivariable model in addition to age and sex, which were kept in the model irrespective of their *P* value at the univariable analysis.

The BCVA variable was dichotomized using as a cut-off the median value in our cohort of patients (0.7 logMAR). Activity grade was binarized into categories: grade 1 and grade 2 or 3. Dichotomization of these variables was done because maximum likelihood estimation suffered from small-sample bias leading to disproportionate odds ratio (OR) and 95% confidence interval (CI).

RESULTS

WE SCREENED CLINICAL AND IMAGING DATA OF 355 PATIENTS diagnosed with TB SLC from our database. Of those, 172 patients did not meet the study criteria for various reasons, such as incomplete follow-up, lack of active lesions in the central 50°, ungradable images, and irretrievable fundus images (from records more than 10 years ago). A total of 203 eyes of 183 patients with TB SLC (all Asian Indian subjects, 133 male) were eventually included. The baseline characteristics, including demographic details, laboratory assessments, and clinical phenotypes, are summarized in Table 1.

Overall, 63 (31%), 84 (41.4%), and 56 (27.6%) eyes were categorized as grades 1, 2, and 3, respectively, based on the grading provided by the image readers. A discrepancy between the 2 raters for grading the opacity of TB SLC was observed in 12 eyes (6%). However, a difference of more than 1 grade point was not observed. The level of agreement between the 2 readers was excellent (weighted κ [95% CI] = 0.93 [0.89-0.97]).

Based on the definition used in the methodology, good outcome (Figure 2) at 6 months was observed in 104 eyes (51.2%). Ninety-nine eyes (48.8%) had poor outcome (Figure 3), of which paradoxical worsening (Figure 4) was observed in 68 eyes (33.5%) (6/63 eyes with grade 1 opacity – 9.5%; 33/84 eyes with grade 2 opacity – 39.3%; and 29/56 eyes with grade 3 opacity – 51.8%). These patients were treated with intravenous methylprednisolone and increase in oral corticosteroids. Oral immunosuppression was used in 3 patients (azathioprine in 2 subjects and mycophenolate mofetil in 1 subject). Thirty-one eyes (15.3%) had poor outcomes owing to presence of new active lesions

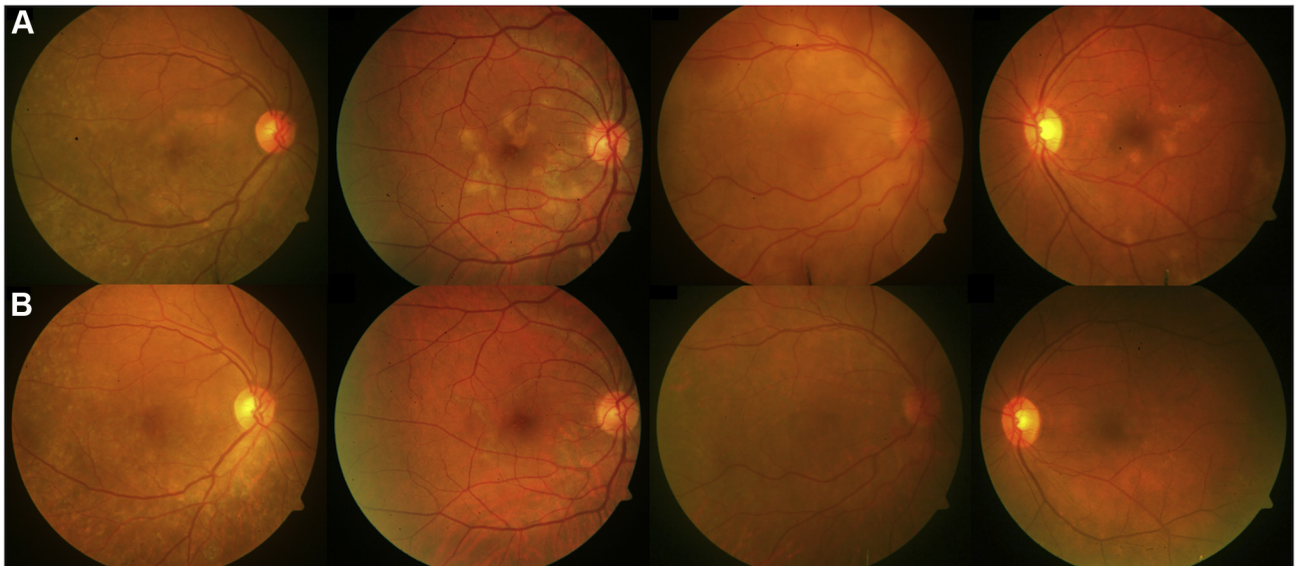

FIGURE 2. Eyes showing good response to therapy of tubercular serpiginous-like choroiditis. (A) Baseline fundus photographs illustrate yellow-white lesions of active choroiditis. (B) After 6 months of follow-up, fundus photographs show a good response to therapy with almost complete resolution of choroiditis.

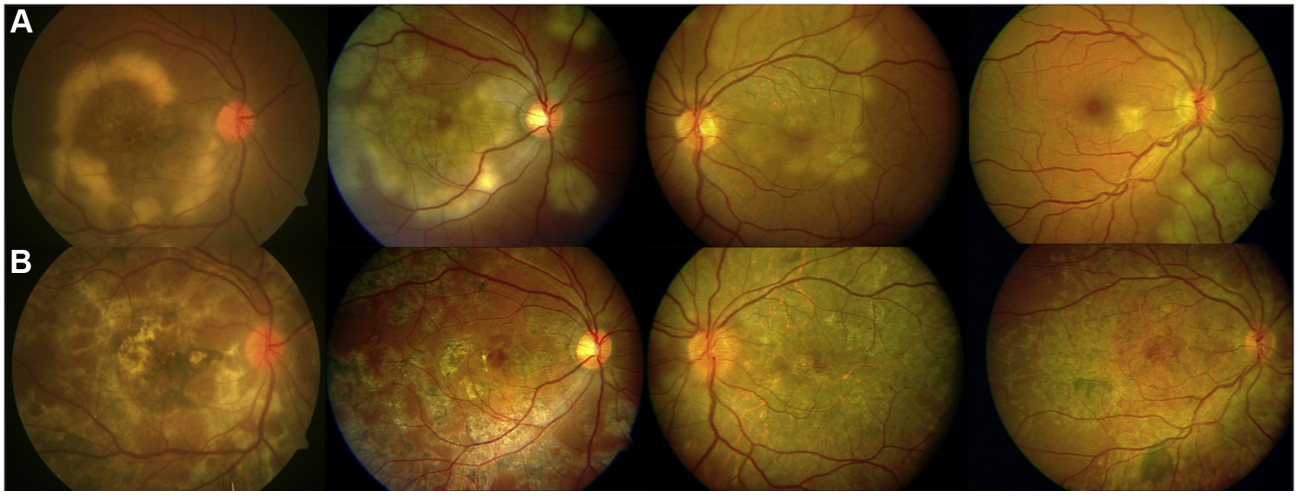

FIGURE 3. Eyes showing poor response to therapy of tubercular serpiginous-like choroiditis. (A) Baseline fundus photographs illustrate intense yellow-white lesions of active choroiditis. (B) After 6 months of follow-up, fundus photographs show a significant increase in the final size of the lesions from baseline.

(13 eyes) and persistence of activity (18 eyes). Information about the outcome at 3 months were available in 188 eyes (92.6%); of those, 91 (48.4%) and 97 (51.6%) eyes had good and poor outcome, respectively. The agreement between outcome at 3 and 6 months was excellent (Cohen's κ [95% CI] = 0.97 [0.93-1.00]).

In order to analyze the baseline factors associated with poor outcome, both univariable and multivariable risk factor analysis was performed. Table 2 illustrates the results of univariable risk factor analysis for poor outcome. This analysis revealed that increasing age was slightly associated with a better outcome, while poor baseline BCVA (>0.7 logMAR), placoid subtype, and high-risk features (foveal and/or optic disc involvement) were all factors associated with poor outcomes. The opacity grades 2 and 3 were also associated with poor outcomes and showed the highest OR among the studied variables in our patients. At the univariable analysis, grade 3 lesions were associated with higher odds of poor outcomes than grade 2 lesions (OR [95% CI]: 28.31 [6.48-123.75], $P <$ .001). All the significant factors observed at the univariable analysis also remained significant in the

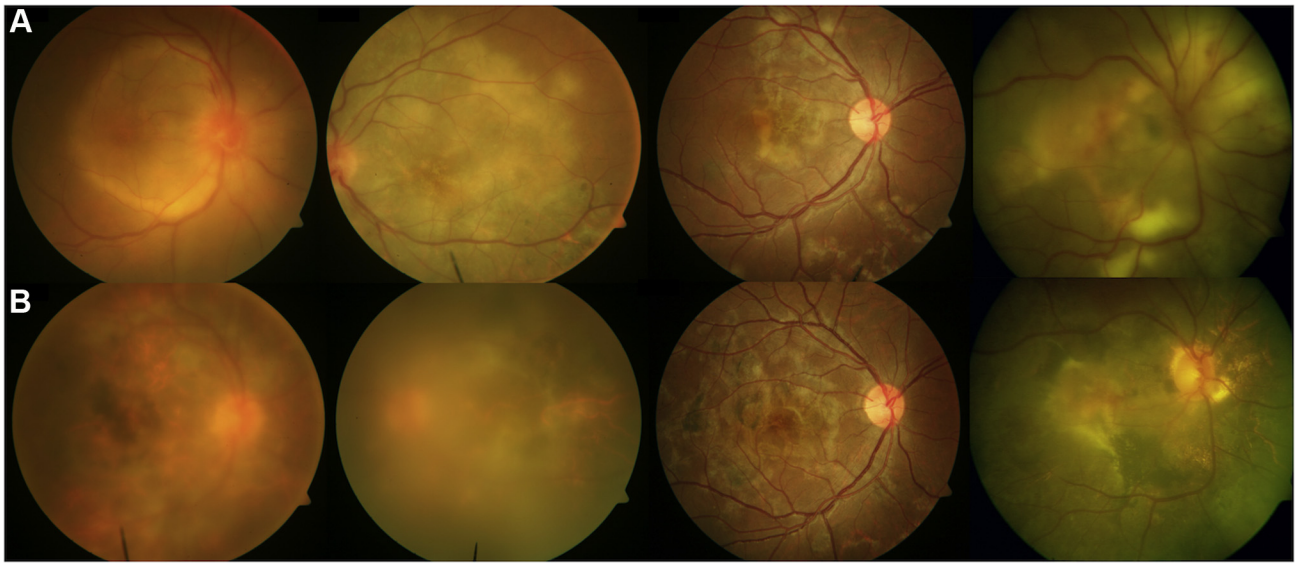

FIGURE 4. Eyes showing paradoxical worsening of tubercular serpiginous-like choroiditis. (A) Baseline fundus photographs illustrate intense yellow-white lesions of active choroiditis. (B) Following initiation of antitubercular treatment, fundus photographs show the paradoxical worsening of tubercular serpiginous-like choroiditis.

TABLE 2. Results of Univariable and Multivariable Risk Factor Analysis for Poor Outcome at 6 Months Follow-up

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, per 1-year increase	0.947 (0.914-0.980)	.002*	0.947 (0.907-0.989)	.014*
Male sex	1.139 (0.581-2.235)	.70	0.897 (0.379-2.120)	.80
Right eye	0.562 (0.301-1.048)	.07		
Baseline BCVA >0.7 logMAR	4.862 (1.919-12.322)	.014*	4.489 (1.924-10.473)	.001*
Opacity grade 2+3 (ref: grade 1)	56.507 (7.136-447.440)	<.001*	9.541 (2.945-30.907)	<.001*
Placoid subtype (ref: multifocal)	4.681 (1.920-11.412)	.001*	2.526 (0.819-7.787)	.11
Fovea involved	5.824 (2.665-12.727)	<.001*	2.892 (1.229-6.808)	.015*
Optic disc involved	24.890 (6.055-102.311)	<.001*	11.633 (3.169-42.708)	<.001*

BCVA = best-corrected visual acuity.
Only age, sex, and variables with a $P \leq .05$ at univariable analysis were included in the multivariable model.
*indicates statistically significant values at $P<.05$

multivariable model, with the exception of the placoid variety of TB SLC.

The results of risk factor analysis for paradoxical worsening (Figure 4) are illustrated in Table 3. This analysis showed that baseline BCVA >0.7 logMAR, opacity grades 2 and 3, and disc involvement were both significant risk factors for paradoxical worsening of TB SLC both at the univariable and multivariable models. At univariable analysis, grade 3 lesions were associated with higher odds of paradoxical worsening than grade 2 (OR [95% CI]: 3.25 [1.82-8.93], $P = .022$).

Overall, at 6 months, the final sizes of choroiditis lesions increased in 79 eyes (38.9%), including 68 eyes with paradoxical worsening. The results of univariable risk factor analysis for increased TB SLC lesion size at 6 months are illustrated in Table 4. At both univariable and multivariable analyses, variables significantly associated with increased lesion size were younger age, baseline BCVA >0.7 logMAR, opacity grades 2 and 3, fovea involvement, and optic disc involvement. At the univariable analysis, grade 3 was associated with higher odds of increased lesion size than grade 2 (OR [95% CI]: 12.00 [5.00-28.79], $P < .001$).

DISCUSSION

TB SLC IS CHARACTERIZED BY BILATERAL, CHRONIC, RECURrent inflammation of choriocapillaris, choroid, and the

TABLE 3. Results of Univariable and Multivariable Risk Factor Analysis for Paradoxical Worsening At 6 Months Follow-up

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, per 1-year increase	0.962 (0.929-0.997)	.03*	0.967 (0.920-1.016)	.18
Male sex	1.089 (0.523-2.272)	.82	0.882 (0.333-2.339)	.804
Right eye	0.740 (0.381-1.438)	.37		
Baseline VA >0.7 LogMAR	12.645 (4.276-37.390)	<.001*	7.555 (1.783-32.023)	.006*
Opacity grade 2+3 (ref: grade 1)	22.538 (5.460-93.027)	<.001*	7.434 (1.342-41.179)	.021*
Placoid subtype (ref: multifocal)	4.945 (1.578-15.503)	.006*	3.260 (0.800-13.291)	.107
Fovea involvement	3.079 (1.350-7.022)	.007*	1.323 (0.506-3.462)	.57
Disc involvement	8.848 (4.206-18.615)	<.001*	7.180 (1.315-39.204)	.023*

VA = visual acuity.
Only age, sex, and variables with a $P \leq .05$ at univariable analysis were included in the multivariable model.
*indicates statistically significant values at $P<.05$

TABLE 4. Results of Univariable and Multivariable Risk Factor Analysis for Increased Lesion Size at 6 Months Follow-up

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, per 1-year increase	0.957 (0.927-0.988)	.006*	0.959 (0.923-0.997)	.034*
Male sex	1.473 (0.777-2.794)	.24	1.116 (0.511-2.434)	.78
Right eye	0.673 (0.374-1.211)	.19		
Baseline BCVA >0.7 logMAR	4.069 (1.976-8.376)	<.001*	2.212 (1.008-4.852)	.048*
Opacity grade 2+3 (ref: grade 1)	24.605 (6.685-90.556)	<.001*	7.236 (2.003-26.146)	.003*
Placoid subtype (ref: multifocal)	1.497 (0.671-3.341)	.32		
Fovea involved	5.254 (2.821-9.786)	<.001*	3.681 (1.71-7.922)	.001*
Optic disc involved	9.544 (4.36-20.894)	<.001*	5.836 (2.306-14.772)	<.001*

BCVA = best-corrected visual acuity.
Only age, sex, and variables with a $P \leq .05$ at univariable analysis were included in the multivariable model.
*indicates statistically significant values at $P<.05$

retinal pigment epithelium (RPE).[17] TB SLC is a distinctive phenotype of the disease most strongly associated with latent or active tuberculosis and affects young to middle-aged adults especially from TB-endemic areas.[1] The active lesions of TB SLC are yellowish white in color and the borders are elevated, whereas the center of the lesion is relatively flat, with pigmentary changes at the level of the RPE suggestive of a healing process in the center. The edges of these lesions are noncontiguous initially and show a wave-like progression over a period of 1-4 weeks and gradually become confluent.[4]

Thus far, there is a paucity of histologic studies that elucidate the exact nature of the microanatomic alterations that occur at the active edge of the lesions in TB SLC.[17,18] Limited histopathologic data (including reports related to autoimmune variety of serpiginous choroiditis) suggest that there is extensive infiltration of the choroid by mononuclear lymphocytes, especially at the margins of the atrophic scars. Kawali and associates have recently described a case of an Asian Indian patient who developed macular TB SLC lesions and was subjected to vitreous and chorioretinal biopsies (during the active disease) through a pars plana approach.[19] The biopsy revealed granulomatous inflammation with necrosis involving the inner choroid with disruption of the RPE and photoreceptors. In the area of healed lesions/scarring, histopathology showed loss of the RPE and photoreceptor layers with focal defects of the underlying Bruch membrane, along with fibroglial tissue.

It is not clear whether higher mycobacterial (or antigenic) load correlates with increased lesion opacity at the active edge of the lesions. Whether baseline lesion characteristics can predict the clinical response and serve as biomarkers of disease activity in TB SLC remains to be studied. Since there are no previous "grading scales"

available that define the morphology or "activity" of the active lesions in TB SLC, we devised a 3-score image-based scale that showed an excellent level of agreement among the graders. TB SLC with higher grades of lesion opacity at baseline may be associated with greater risk of poor therapeutic response and paradoxical worsening. All of these contributed to explain poor outcomes in our series (Table 2). These observations are extremely relevant, because clinicians can follow an easy-to-interpret 3-step grading scale and predict which patients may require a close follow-up and possibly aggressive treatment. In addition, high-risk factors such as foveal involvement/fovea-threatening lesions and close proximity of lesions to the optic nerve head were also high-risk factors in these patients.

Higher grades of opacity in TB SLC lesions might simply reflect higher activity and immunologic response in the lesions. Higher immunologic load in these active edges may be responsible for progression of these lesions or their tendency to have persistent inflammation despite therapy. The increased inflammatory cellular infiltrate may result in higher grades of opacity owing to loss of the normal retinochoroidal architecture in these lesions. In this context, it is relevant to discuss cytomegalovirus (CMV) retinitis, in which opacity of the lesion is considered to be a reliable sign of disease activity.[20] In contrast to TB SLC, the descriptions of intraocular viral load, systemic viremia, and level of immune function/dysfunction in CMV retinitis are far more satisfactory. The Studies of the Ocular Complications of AIDS (SOCA) have greatly impacted our understanding of CMV retinitis.[21–23] Holland and associates recently used the SOCA research database and graded the CMV lesion opacity using a Reading Center–based approach into 6 grades.[24] The authors evaluated the grade of the opacity with various factors such as systemic HIV viremia, CD4+ T-cell count, age, lesion size, and other high-risk features such as bilaterality, and concluded that higher lesion opacity grades are positively associated with worse disease. While the pathogenesis of TB SLC is completely different in comparison with CMV retinitis, the positive association of higher opacity grade with worse fate of the lesions suggests that clinical grading of the lesions at baseline may be a useful predictor to determine the response. Patients with more yellow, highly opaque, elevated, and voluminous lesions may require stronger immunosuppressive therapies for adequate control of inflammation. In addition, the association of higher grade of opacity with paradoxical worsening suggests that higher mycobacterial antigenic load may result in highly yellow and opaque chorioretinal lesions at baseline. When therapy with ATT is initiated, the release of this high antigenic load may be responsible for higher risk of paradoxical worsening in these patients.

Other clinical features associated with poor response to therapy included foveal and optic nerve involvement at baseline (defined as an active lesion at the disc/fovea, or 1 disc diameter from the disc/300 μm from the fovea). Macular and peripapillary lesions are vision-threatening and require urgent anti-inflammatory therapy, often with pulse intravenous corticosteroids. Again, these may be associated with higher immunologic response to mycobacteria and can be used as a predictive factor that is easily assessable at baseline. These findings can be extrapolated to macular toxoplasmosis, which requires urgent antibiotic and anti-inflammatory therapy, as well as to CMV retinitis, where zone 1 disease (involving the posterior pole) is severe with more opaque lesions, and is possibly associated with increased virus activity.[24] Similarly, other autoimmune macular choroiditis lesions such as multifocal choroiditis and acute multifocal placoid pigment epitheliopathy may also require urgent therapy in order to preserve vision.

Placoid phenotype of TB SLC was also associated with poor response to therapy in our series, and this is comparable to the results shown by Kawali and associates in their study.[9] In their manuscript, the authors classified the lesions based on the shape on autofluorescence imaging into dendritic pattern (n = 14), advanced dendritic pattern (n = 13), and placoid form (n = 6). The visual prognosis was poorer in the placoid form of the disease, but the authors did not observe any recurrence/new lesions, possibly because of smaller sample size and relatively short follow-up. Typically, placoid TB SLC is characterized by large, diffuse, plaque-like lesions, often involving the posterior pole and peripapillary retina, and are associated with significant central choriocapillaris and RPE atrophy.[4] On the other hand, multifocal phenotype of TB SLC presents with discrete multiple lesions that later on tend to coalesce. Thus, placoid TB SLC may require institution of early and aggressive anti-inflammatory therapies in order to prevent visual morbidity and risks of persistent activity/development of new lesions, especially in the macular area.

The results of univariable analysis revealed that young age may be a risk factor for poor response to therapy and higher/persistent inflammatory response. Younger age groups may be at a higher risk of immune-mediated chorioretinal damage owing to heightened immune response compared to older populations. Studies evaluating the risk of infection with *Mycobacterium tuberculosis* in pediatric populations also provide a similar age-based analysis.[25] Such an analysis has not been provided in TB SLC prior to this report, and strengthens the immunologic basis of choroidal involvement owing to mycobacteria in this condition. Although the association between higher opacity grade and immune function observed in this study is indirect, this has important implications for patient care and design of future studies.

Overall, 99 eyes in our study (48.8%) were defined to have poor outcome, of which 68 eyes (representing 33.5% of total eyes studied) developed paradoxical worsening. The definition of poor outcome included paradoxical worsening, persistence of inflammation, and development of new lesions. Therefore, this definition did not indicate poor therapeutic response to ATT. The

prevalence of paradoxical worsening in our series is in line with our previous report, which suggests that over one-third of patients may develop paradoxical worsening within 3-8 weeks of initiating ATT.[11] Since 31 eyes (15.3%) had persistence of inflammation/new lesions, these eyes represented "treatment failure" of ATT as per the definition used by the COTS. The COTS group has previously reported a treatment failure of 12.7% with ATT, which is consistent with the results of the index study.[5] The higher percentage of paradoxical worsening in our series may also be attributable to selection bias, owing to which patients with worse disease may have more stringent follow-up and higher chances of fundus imaging.

Our study has several limitations that need to be addressed. Unlike Holland and associates,[24] we did not use a Reading Center-based grading approach. We used a smaller 3-step grading scale for analyzing the active lesion edges. However, this scale may be more useful and practical in the clinical setting. Retrospective clinical chart review is a potential source of bias because of possible inaccuracies in the documentation and collection of information from the medical records.[26] Because data collection was performed from 2002 onward, it is likely that improvements in the technology and image capture may be a limitation of the study. Although the image acquisition was performed in a large period between 2002 and 2019, the images were taken using the same type of camera (Carl Zeiss Visupac FF450) by the same photographer. Though there may be some variations in the images obtained, adequate quality was ensured prior to inclusion in the study. In certain patients, the "most active/opaque" lesion could have been in the periphery and therefore not analyzed on the 50-degree fundus photographs. Presence of additional lesions outside fundus photographs centered on the macula may be responsible for an overestimation of the placoid variety of TB SLC. Selection bias is a well-known limitation of retrospective clinical study. As we excluded a significant number of patients who did not fulfill the study criteria, the reader should be aware of the possibility of a selection bias in our study. For instance, patients with more severe or poorer response to treatment might have had a more stringent follow-up and, thus, greater changes to undergo a complete imaging panel. On the other hand, patients with severe disease and poor fixation could have been excluded, as imaging acquisition might not feasible. Overall, we have included 203 eyes with heterogenous demographic and clinical characteristics, which we believe are representative of our clinical pool of patients. Limitations such as subjective image assessment, lack of "multimodal" approach (no correlation with optical coherence tomography, autofluorescence, and fluorescein/indocyanine green angiographies), and differences in the therapeutic (especially corticosteroid) dosages/durations may affect the results. Some of our analyses may be underpowered, and certain significant predictors have wide confidence intervals, suggesting uncertainty in the exact estimates. In other words, the results of this study through multiple analyses clearly indicate that baseline lesion opacity and characteristics such as lesion location and phenotype can serve as useful biomarkers of the disease associated with the response to therapy, but the exact magnitude of these factors is still uncertain. Variable selection for multivariable models was performed through univariable mixed models, and this may lead to increased alpha error owing to multiple comparison and potential for false-positives. Because of the exploratory nature of this study, we refrained from performing any statistical adjustment for multiple comparisons. The investigators of this study are leading the worldwide initiative of the COTS group, which plans a prospective analysis of retinal images to overcome the limitations of the current analysis at least in part.

In conclusion, our study shows that TB SLC lesions that have a higher grade of opacity at baseline may be associated with overall poor response to treatment, greater risk of lesion progression, and paradoxical worsening during the follow-up. Other factors such as young age, peripapillary and macular involvement of TB SLC are also risk factors for poor outcomes. In future prospective studies, grading of baseline lesion opacity may be used to predict the biological behavior of the lesions and validate the results of this study, and may serve as a guide to therapeutic interventions.

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