Clinical Features of Tuberculous Serpiginouslike Choroiditis in Contrast to Classic Serpiginous Choroiditis

Daniel V. Vasconcelos-Santos, MD, PhD; P. Kumar Rao, MD; John B. Davies, MD; Elliott H. Sohn, MD; Narsing A. Rao, MD

Objective: To compare distinctive clinical features of presumed tuberculous serpiginouslike choroiditis (Tb-SLC) with classic serpiginous choroiditis (SC) in patients living in a region that is nonendemic for tuberculosis.

Methods: Retrospective comparative analysis of clinical features of 5 patients with recurrent Tb-SLC and 5 with SC.

Results: All patients with recurrent Tb-SLC primarily emigrated from areas highly endemic for tuberculosis and had been unsuccessfully treated with steroids/immunosuppressive agents. Results of uveitis investigations were negative except for positive tuberculin skin test results. These patients received oral tuberculostatic drugs, without recurrences (follow-up, 6-91 months). The ocular involvement in Tb-SLC was mostly unilateral, with multiple irregular serpiginoid lesions involving the posterior pole and periphery but usually sparing the juxtapapillary area. All 5 cases had inflammatory cells in the vitreous. Patients with SC were from areas nonendemic for tuberculosis, had negative uveitis workup findings (including tuberculin skin test results), and were successfully managed with steroids/immunosuppressive agents (follow-up, 6-72 months) with no recurrence. Ocular involvement in SC was usually bilateral, rarely multifocal, and primarily involved the posterior pole, especially around the optic disc and extending contiguously to the macula. No patient with SC presented with vitritis.

Conclusion: In areas nonendemic for tuberculosis, SC can be clinically differentiated from Tb-SLC. Patients with Tb-SLC come from highly endemic regions, show significant vitritis, and often present with multifocal lesions in the posterior pole and periphery. Cases of SC, in contrast, reveal minimal or no vitritis and frequently show bilateral involvement with larger solitary lesions extending primarily from the juxtapapillary area and sparing the periphery.

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Serpiginous Choroiditis (SC) is a rare, progressive, recurrent, idiopathic inflammatory disease involving the retinal pigment epithelium (RPE), choriocapillaris, and choroid. It is usually bilateral and typically affects middle-aged persons, with a slight predilection for males.1

A possible association between lesions resembling SC and tuberculosis was first considered in the middle of the 20th century.2 This issue was raised again in subsequent decades,3,4 but it was not until recently that tuberculous choroiditis simulating SC was recognized as a possibly distinct clinical entity and referred to as tuberculosis serpiginouslike choroiditis (Tb-SLC).5-7 Differentiating this tuberculous entity from classic SC is critical because treatment of the former with immunosuppressive drugs has several potential adverse effects8 and such treatment can have devastating consequences due to worsening of a concomitant tuberculous infection.9 Conversely, antituberculosis treatment may also be associated with significant adverse events,10-12 especially in older patients with classic SC.

Establishing a diagnosis of intraocular tuberculosis remains challenging.6,13 The current approach involves the exclusion of other etiologies, together with a suggestive clinical history and signs; supportive systemic investigations, such as positive tuberculin skin test (TST)/interferon γ release assay (IGRA) results; and chest radiography findings, as well as evidence of Mycobacterium tuberculosis or its DNA in ocular fluids/tissues.6,13-15 In the absence of supportive molecular evidence, active systemic tuberculosis, or positive culture results, a positive response to antituberculosis agents is considered significant for the
diagnosis, and such cases are labeled presumed intraocular tuberculosis. In the clinical setting, the vast majority of these patients are diagnosed as having presumed rather than definite intraocular tuberculosis.8 Distinctive clinical aspects could also be helpful for the diagnosis of Tb-SLC, but these have not been adequately elucidated, and some inconsistency still surrounds the terms serpiginous and serpiginous-like choroiditis.4,16-19

The aim of the present study was to compare the clinical features of patients with presumed Tb-SLC and patients with classic SC to detect aspects that could help distinguish these 2 entities in regions that are nonendemic for tuberculosis.

### METHODS

A retrospective medical record review was conducted to compare 5 cases of presumed Tb-SLC with 5 cases of classic SC consecutively seen at Doheny Eye Institute, University of Southern California, and Barnes Retina Institute, Washington University. The study protocol was approved by the institutional review boards and adhered to the tenets of the Declaration of Helsinki.

Demographic data were gathered from the medical records of all patients and compared between the 2 groups. Information collected included age, sex, and ethnicity, clinical information about medical and ocular history, results of laboratory tests (including TST and radiographs), previous treatments, and ophthalmologic examination (visual acuity, intraocular pressure, slitlamp examination, dilated fundus examination). Images from fundus photography and fluorescein angiograms were also collected and analyzed. Whenever available, optical coherence tomography and fundus autofluorescence images were also used.

The diagnosis of Tb-SLC was established by one of us (N.A.R.) based on fundus examination, positive TST results, and response to antituberculosis treatment, without recurrences. Tuberculous etiology in these cases was presumed in accordance with recently proposed criteria4 and reinforced by a history of previous exposure or infection by M tuberculosis and by lack of response to oral corticosteroid and/or immunosuppressive drug treatment alone. The diagnosis of classic SC was made based on typical fundus and angiographic findings and exclusion of other uveitis entities, as reviewed by Lim et al11 and supported by evidence of response to immunosuppressive therapy.

All 5 patients with presumed Tb-SLC originated from areas endemic for tuberculosis and had been unsuccessfully treated with steroids and/or immunosuppressive agents. Three of these patients were male and 2, female, with a mean (SD) age of 32 (6.1) years. Uveitis workup findings were negative in all cases except for a positive TST result, with the chest radiograph being invariably normal. In 2 patients, a history of BCG vaccination could be obtained, and this was not regarded as a confounding factor to the positive TST results, since the induration reaction of the TST exceeded 20 mm.20 All 5 patients were evaluated by a pulmonologist and tuberculosis expert who found no clinical evidence of tuberculosis elsewhere. The patients then received a course of oral tuberculostatic drugs in combination with prednisone, as previously recommended.5 Intracocular inflammation did not recur, with follow-up ranging from 6 to 91 months (median, 20 months) (Table 1).

### Table 1. Demographic and Clinical Features of Patients With Tb-SLC and Classic SC

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Ethnicity</th>
<th>Diagnosis</th>
<th>Tb Exposure</th>
<th>Visual Acuity</th>
<th>Prior Treatment</th>
<th>Anti-Tb Treatment</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/23</td>
<td>Asian/Indian</td>
<td>Tb-SLC</td>
<td>Endemic country</td>
<td>Initial: 20/400 Final: 20/60</td>
<td>Oral/subtenon corticosteroids, methotrexate</td>
<td>Izoniazid, rifampin 9 mo, prednisone 9 mo</td>
<td>15</td>
</tr>
<tr>
<td>M/40</td>
<td>Asian/Indian</td>
<td>Tb-SLC</td>
<td>Endemic country</td>
<td>Initial: 20/60 Final: 20/20</td>
<td>Oral prednisone, methotrexate</td>
<td>Izoniazid, rifampin, ethambutol 9 mo, prednisone 9 mo</td>
<td>6</td>
</tr>
<tr>
<td>F/34</td>
<td>Afghan</td>
<td>Tb-SLC</td>
<td>Endemic country</td>
<td>Initial: 20/50 Final: 20/40</td>
<td>Oral/subtenon corticosteroids, methotrexate, valacyclovir</td>
<td>Izoniazid, rifampin, ethambutol 9 mo</td>
<td>91</td>
</tr>
<tr>
<td>F/31</td>
<td>Hispanic</td>
<td>Tb-SLC</td>
<td>Treated for Tb 10 y before</td>
<td>Initial: 20/200 Final: 20/25</td>
<td>Oral prednisone</td>
<td>Izoniazid, rifampin, ethambutol 6 mo</td>
<td>6</td>
</tr>
<tr>
<td>M/32</td>
<td>Asian/Indian</td>
<td>Tb-SLC</td>
<td>Endemic country</td>
<td>Initial: 20/20 Final: 20/20</td>
<td>Oral prednisone</td>
<td>Izoniazid, rifampin, ethambutol 9 mo, prednisone 4 mo</td>
<td>20</td>
</tr>
<tr>
<td>M/38</td>
<td>White</td>
<td>Classic SC</td>
<td>No</td>
<td>20/20</td>
<td>Prednisone, cyclosporine, and MPM</td>
<td>Prednisone, ethambutol</td>
<td>9</td>
</tr>
<tr>
<td>M/26</td>
<td>White</td>
<td>Classic SC</td>
<td>No</td>
<td>20/400</td>
<td>Prednisone and cyclophosphamide, (cyclosporine, azathioprine, and valacyclovir before)</td>
<td>Prednisone and cyclophosphamide, (cyclosporine, azathioprine, and valacyclovir before)</td>
<td>40</td>
</tr>
<tr>
<td>F/32</td>
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<td>Classic SC</td>
<td>No</td>
<td>20/20</td>
<td>Prednisone, MPM (cyclosporine and azathioprine before)</td>
<td>Prednisone, MPM (cyclosporine and azathioprine before)</td>
<td>71</td>
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<tr>
<td>F/42</td>
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<td>Classic SC</td>
<td>No</td>
<td>20/25</td>
<td>Prednisone, cyclosporine, azathioprine</td>
<td>Prednisone, cyclosporine, azathioprine</td>
<td>6</td>
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<tr>
<td>F/81</td>
<td>White</td>
<td>Classic SC</td>
<td>No</td>
<td>CF 6 ft CF 3 ft</td>
<td>Oral/subtenon corticosteroids, methotrexate</td>
<td>Oral/subtenon corticosteroids, methotrexate</td>
<td>72</td>
</tr>
</tbody>
</table>

Abbreviations: CF, counting fingers; ethambutol, ethambutol hydrochloride; Final, after anti-Tb treatment; MPM, mycophenolate mofetil; SC, serpiginous choroiditis; Tb, tuberculosis; Tb-SLC, presumed tuberculous serpiginous-like choroiditis; TST, tuberculin skin test; valacyclovir, valacyclovir hydrochloride.

a Prednisone was then kept at a low dose (2.5-10 mg) for several months.

b Patient had been treated irregularly for a period of 3 months.
The 5 patients with classic SC had a mean (SD) age of 43.8 (21.7) years. Two patients were male and 3, female. None had received BCG vaccination. All 5 had had negative uveitis workup findings (including TST results and chest radiographs) and had been managed with steroids and immunosuppressive agents, with follow-up ranging from 6 to 72 months (median, 37 months) (Table 1).

Ocular involvement in presumed Tb-SLC was unilateral in 3 of the 5 patients and typically consisted of multiple, irregular, variably pigmented chorioretinal lesions in a serpiginoid pattern. Lesions involved the posterior pole, were confluent in the macula, and usually spared the juxtapapillary area. These multifocal lesions also occurred in the periphery (Figure 1). Only 1 patient had a serpiginoid lesion confined to the posterior pole. Slitlamp examination of the anterior vitreous revealed significant inflammatory cell infiltration in all affected eyes, from 1+ to 2+ (Table 2).

Ocular involvement in the 5 patients with classic SC was present in only 1 patient. The serpiginoid/geographic lesions were primarily located in the posterior pole, especially around the optic disc and extending contiguously to the macula (Figure 2). Pigmentation was variable. On slitlamp examination, no eye revealed any inflammatory cell infiltration in the anterior vitreous (Table 2).

The angiographic pattern was similar in both classic SC and presumed Tb-SLC, with hypofluorescence of the center and hyperfluorescence of the margins of the lesions in the inactive stage (Figure 1B, D, and F and Figure 2B and D). Active lesions showed early blockage and late staining in both groups. Fundus autofluorescence images were available for 4 patients with presumed Tb-SLC and for 1 patient with classic SC, all at the inactive stage, invariably revealing decreased autofluorescence signal of the serpiginoid lesions; many are located in the retinal periphery.

Figure 1. Fundus aspects of patients with presumed tuberculous serpiginouslike choroiditis. A, Color fundus photograph of the left eye of patient 5, showing multiple grayish lesions in the posterior pole, as well as more peripherally. B, Intermediate-phase fluorescein angiogram photograph of the same eye, easily delineating the serpiginoid lesions, which are hypofluorescent and have hyperfluorescent margins. C, Image with montage of fundus autofluorescence of the same eye, after antituberculosis treatment. Note the hypautofluorescence of the choriotinal lesions; many of them are smaller and located in the retinal periphery. D and G, Color fundus photographs of the right (D) and left (G) eyes of patient 1, showing multiple confluent pigmented serpiginoid lesions in both eyes. E and H, Intermediate-phase fluorescein angiogram photographs of the same eyes (right [E] and left [H]), showing that the lesions are hypofluorescent, with hyperfluorescent margins. F and I, Image with montage of fundus autofluorescence of the same eyes (right [F] and left [I]), revealing unspecific decreased autofluorescence signal of the serpiginoid lesions; many are located in the retinal periphery.
variable thinning/thickening of the RPE-Bruch membrane layer, corresponding to the scars (Figure 3). Similar findings were observed in 1 patient with classic SC who underwent spectral domain optical coherence tomography.

Recent publications from regions endemic for tuberculosis highlight that intraocular tuberculosis may present with features simulating SC.5,6 Although intraocular tuberculosis is rare in nonendemic regions, cases of SLC in these areas have been also attributed to M tuberculosis infection.19,21 In the present study, we compared distinctive clinical aspects of presumed Tb-SLC with classic SC in patients living in a nonendemic region for tuberculosis. The differentiation between these 2 entities is very important because the heavy immunosuppressive treatment usually required for SC has several adverse effects8 and may lead to exacerbation of tuberculous infection or even death.9 On the other hand, the toxicity of antituberculosis treatment is significant, especially with regard to the liver.10-12 The incidence of serious adverse events in patients receiving these drugs approaches 10% in routine clinical practice and rises dramatically in older patients,11,12 who are more often affected by SC.

Tuberculous etiology has been suspected in cases of SC since 1952.2-4,16 In patients from areas endemic for tuberculosis, Gupta and colleagues5 described SLC of presumed tubercular etiology that mimicked SC. Except for direct or indirect evidence of tuberculous infection and response to antituberculosis therapy, no other distinctive feature of SLC compared with classic SC has been previously identified in the literature, to our knowledge. Inflammatory cell infiltration in the vitreous was a remarkable feature of our patients with presumed Tb-SLC living in a nonendemic region and was invariably absent in all cases of classic SC. Moreover, the distribution of the serpiginoid lesions differed between the 2 groups of patients. Patients with presumed Tb-SLC were more likely to have multifocal lesions involving the periphery, whereas individuals with classic SC were more likely to have bilateral, larger lesions extending from the juxtapapillary area. The angiographic pattern did not differ between the 2 entities; moreover, lesions tended to disrupt outer retina structure in both groups and be associated with loss of the RPE (Figure 3A), with subsequent decreased autofluorescence signals of the involved areas (Figure 1C, F, and I and Figure 2F), findings that are not specific but reveal the site of damage involving the outer retina and RPE, as noted in histopathologic examination of SC.1

Ustinova and colleagues16 previously compared the clinical features of SC (which they named peripapillary geographic choroiditis) with cases of established tuberculous chorioretinitis. They aimed to prove that the former was not associated with tuberculous etiology. The 32 cases in their first group were suspected to have tuberculous etiology, but this was later ruled out by further workup.
and empirical treatment. Interestingly, some patients with SC had evidence of pulmonary tuberculosis, similar to the patients with tuberculous chorioretinitis. Their cases of peripapillary geographic choroiditis had mostly bilateral involvement, extending from the peripapillary area, similar to the cases of classic SC in our series. This pattern differed from that observed in their cases of tuberculous chorioretinitis. However, their cases of tuberculous choroiditis encompassed solitary or multiple small lesions, which is seen in multifocal choroiditis and is less likely to be clinically confused with classic SC.

Tuberculous SLC is a rare entity, and many cases may occur without concomitant pulmonary/systemic involvement, as we observed. In a recent report of 70 cases diagnosed with SC in India, only 5 (7.1%) had immunologic evidence of M tuberculosis infection. None of these had signs of pulmonary involvement, and all 5 responded to a combination of steroid and immunosuppressive drug treatment, with the addition of antituberculosis agents in the presence of evidence of mycobacterial infection. Our 5 patients with SLC all had positive TST results as the sole marker of M tuberculosis infection and all came from areas endemic for tuberculosis. It may be that IGRA is a better test than TST for infection/exposure to M tuberculosis, but the former is also significantly more expensive and may thus be more useful as a complement to the TST in selected cases. The combined use of both tests simultaneously has also been suggested as an interesting approach in patients with tuberculous uveitis. However, the mere evidence of positive TST or IGRA findings is not indicative of active disease because these tests cannot distinguish active from latent infection. Either demonstration of the bacillus in ocular samples or a positive therapeutic response would be required to further consider tuberculous etiology. In a recent German series of patients with SC, 11 of 21 patients (32.4%) tested positive by IGRA for tuberculosis, a much higher rate than was found in controls (9% of 278 healthy health care workers and 13% of 45 patients with other uveitides), leading the researchers to conclude in favor of a tuberculous etiology for that uveitis subset. Only 4 individuals with SC (19.0%) presented evidence of cicatrical lung involvement, and 4 received antituberculosis treatment based on the results of IGRA/TST, with a favorable response and no recurrences. However, no clinical comparison was reported between patients with presumed tuberculous etiology and the remaining cases of SC in that study.

The pathophysiology of presumed Tb-SLC is unknown. There is speculation that it might be associated with a hypersensitivity to M tuberculosis, clinically manifesting as an inflammatory involvement of the RPE, choriocapillaris, and choroid that mimics SC. However, a relevant infectious component in these cases cannot be ruled out. The finding of tuberculous bacilli at the level of the RPE and the similarity of some of these cells to alveolar macrophages may indicate this site as a possible sanctuary for dormant bacilli. Either reactivation of dormant bacilli or, less commonly, choroidal seeding due to reactivation elsewhere in the body may lead to local inflammation. This hypothesis of an infectious component is reinforced by the favorable response only after initiation of tuberculostatic drug treatment as observed in all 5 of our patients, for whom treatment consisting solely of steroids/immunosuppressive drugs failed before. One of our patients had a short and irregular treatment for tuberculosis in the past and this patient also responded to a repeated course of antituberculosis treatment without recurrences (Table 1).

Some of our cases of presumed Tb-SLC with more extensive involvement resembled relentless placoid chorioretinitis, an idiopathic entity characterized by numerous multifocal lesions located in the posterior pole, but especially involving the retinal periphery (Figure 1D-I). Diagnosis of relentless placoid chorioretinitis may also be confined with SC and acute posterior multifocal placoid epitheliopathy, and even with persistent placoid maculopathy. The latter is characterized primarily by long-standing geographic macular plaques sparing the peripapillary area, but also the periphery, with virtually all affected eyes developing choroidal neovascularization. In acute posterior multifocal placoid epitheliopathy, in turn, there are multiple postequatorial placoid lesions, which spontaneously fade after a couple of weeks, with a relatively good
prognosis. However, evidence of tuberculous infection in our patients and the favorable clinical response only after tuberculous treatment makes the diagnoses of relentless placoid chorioretinitis, acute posterior multifocal placoid epitheliopathy, or persistent placoid maculopathy unlikely. Entities such as toxoplasmosis, herpes zoster infection, syphilis, and sarcoidosis have also been reported to mimic SC, and it may be that other conditions with extensive involvement of the RPE and choriocapillaris could produce a similar picture. Such diverse etiologies presenting with features of SC/serpiginoid choroiditis suggest that the site of tissue damage for various infectious agents can lead to such clinical features. Nevertheless, the exclusion of these etiologies, in addition to evidence of tuberculosis infection, may support the association with M tuberculosis.

Though the present study was retrospective in nature and was too small to pursue statistical analysis, this comparative series raises the important issue of clinically distinguishing Tb-SLC from classic SC, both for diagnostic purposes and for subsequent relevant therapeutic and prognostic reasons. Immunologic evidence of tuberculosis infection, as well as therapeutic response and follow-up, support the correct diagnosis.

In conclusion, those patients in our series with presumed Tb-SLC emigrated from areas that were highly endemic for tuberculosis and presented more often with multifocal lesions in the posterior pole/periiphery, usually sparing the juxtapapillary choroid, but in all cases having significant inflammatory cells in the vitreous. Those patients with classic SC, in contrast, more frequently had bilateral involvement with larger solitary geographic or serpiginoid lesions, extending primarily from the juxtapapillary area, with no concomitant vitritis. Distinguishing between the 2 conditions is important because those patients with Tb-SLC require antituberculosis treatment, while those with SC may be managed with immuno-suppressive agents. Both treatments are associated with significant adverse effects. Further prospective studies in larger cohorts from the nonendemic regions are required to address the validity of the proposed differences between these 2 entities.

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Correspondence: Narsing A. Rao, MD, Doheny Eye Institute, 1355 San Pablo St, DVRC 211, Los Angeles, CA 90033 (nrao@usc.edu).

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REFERENCES