Commentary: Serpiginous choroiditis—so near yet so far

Pattern recognition remains the key to etiological diagnosis of most uveitis entities, despite rapid advances in laboratory diagnostic techniques. Typical examples would include infections such as ocular toxoplasmosis, acute retinal necrosis, and cytomegalovirus retinitis, as well as noninfectious entities such as Vogt–Koyanagi–Harada disease, HLA-B27 associated uveitis, and various "white dot syndromes." Serpiginous choroiditis occupies a unique place among all these pattern recognition entities for several reasons. First, the clinical pattern, albeit with some differences, is seen in both infectious and noninfectious conditions. Second, unlike most other conditions listed earlier, a wide range of imaging modalities have been applied to identify the degree, extent, and progression of inflammation. Third, even when associated with an infection (in this case, tuberculosis [TB]), the disease carries a significant risk of worsening (paradoxical worsening), following initiation of antimicrobial therapy, which challenges the validity of the etiological diagnosis used

for testing. In this issue of the journal, Dutta Majumder *et al.* have provided a comprehensive overview of the disease that will assist treating clinicians in developing a holistic approach to this clinical presentation.[1]

Our understanding of serpiginous choroiditis has evolved significantly since the time it was first reported more than a century ago. As the authors mention, the term serpiginous choroiditis was first used in 1900 in the context of scrofulous lymphadenopathy that is typically associated with TB or syphilis.[2] Since then, the serpiginous pattern has been linked to various etiological factors, including autoimmune response, vascular occlusion in the choriocapillaris, as well as other infectious agents such as herpes viruses, toxoplasma, and fungi. None of these etiologies, however, completely explain the *serpiginous pattern of inflammation*—be it peri-papillary (as seen in the classic variety), or at the macula or in the periphery (as seen in the tubercular variety). Nor does it explain the *progression at the edges* of the lesions, with healing in the center, despite the differences in etiologies. Also not explained is the relative sparing of the fovea (and therefore good visual acuity) till the last stage of the disease. It is possible that multiple etiologies converge at a final common pathway that leads to the development of a serpiginous pattern of inflammation.

Alternatively, it is possible that some of the associations are incidental. This is particularly relevant in case of infections, where the etiological association was made either on the basis of diagnostic polymerase chain reaction or indirect serological tests—both of which are prone to false-positive results. For example, it is difficult to conceive how herpes viruses or *Toxoplasma gondii* that are typically associated with retinitis lesions would lead to predominant inflammation in the choroid or retinal pigment epithelium. The association with TB, the most widely reported of all infectious associations of serpiginous choroiditis, too is prone to the above shortcomings. However, this association has stood the test of time, gaining acceptance across the world, and probably represents one of the most notable contributions from the Indian uveitis community. The game-changing report of TB-associated serpiginous choroiditis was published in 2003 by Gupta *et al.*,[3] more than a century after Jonathan Hutchison's long forgotten paper, but only a year after the same group had reported a large series of serpiginous choroiditis (of unknown etiology then) from India.[4] Since then, the terminology of this condition has evolved from serpiginous-like choroiditis (SLC) to multifocal serpigenoid choroiditis, to distinguish it from the classical variety. SLC has been reported from other TB-endemic countries as well as nonendemic countries.[5] All these reports have found associations of TB-SLC with TB-endemic/immigrant populations, presence of systemic TB, and/or mycobacterial DNA in ocular fluids, and favorable response to anti-TB therapy in the long-term. Thus, a broad consensus has developed between ophthalmologists from across the world, about the association between TB and SLC, at least in TB-endemic populations.

Despite these advances, some questions about TB-SLC remain unanswered. It is not clear why TB-SLC should behave differently from other clinical presentations of TB-associated uveitis (TBU). For example, paradoxical worsening, although reported, is rare in other forms of TBU, such as focal choroiditis or retinal vasculitis. TB-SLC also requires more intensive and prolonged antiinflammatory therapy as compared with other TBU. Indeed, attempts have been made to treat SLC with only anti-inflammatory therapy. In a study from India, rapid resolution of "macular serpiginous choroidopathy" lesions was noted following the pulse cyclophosphamide therapy, without any anti-TB therapy.[6] The study is of interest because three of nine treated eyes had recurrent inflammation 6–8 months after the initiation of treatment. Although the median follow-up was 13 months in this study, it is likely that the number of recurrences would have been higher if the patients had been followed up longer. Here lies the dilemma of the TB-associated SLC. On the one hand, we have a disease that is linked to TB based on indirect evidence, but can develop initial worsening after anti-TB therapy. On the other hand, the same disease can show rapid resolution only with antiinflammatory therapy, giving an impression of cure, only to recur months later. Hopefully, the comprehensive review by Dutta Majumdar *et al*. will provide sufficient insight to treating ophthalmologists, to apply their judgement in approaching this enigma of the serpiginous pattern.

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Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1686_18

Cite this article as: Basu S. Commentary: Serpiginous choroiditis—so near yet so far. Indian J Ophthalmol 2019;67:333-4.