CONCLUSION

Characteristics of serpiginous like tuberculous choroiditis

Patients with investigations supported serpiginous choroiditis due to tubercular aetiology are primarily from countries where tuberculosis is endemic, are suffering from the disease or have a history of contact with active pulmonary tuberculosis. In India, unlike in typical SC, the ocular involvement in tuberculosis related SC predominantly affects young-middle aged males, is mostly unilateral, with multiple lesions involving the mid periphery and periphery but usually sparing the juxtapapillary area. Lesions are adjacent to the retinal vasculature and the corresponding RPE defects are multiple and discrete. Those with tuberculosis related SC have vitritis and may sometimes have anterior chamber inflammation as well. Angiographic features do not help in confirming the aetiology but they do show a big difference in in the distribution of the lesions. SC of tubercular aetiology does not always have signs of active or healed pulmonary TB on chest X-ray. In our study many patients had a normal X-ray and tuberculin skin test. In such situations, high resolution CT or aqueous humour assay by PCR, RT-PCR or nested PCR proved to be more sensitive. The pathogenesis of SC due to TB may be due to reactivation of dormant foci from RPE cells. A study has found a similarity
between these cells and alveolar macrophages where TB bacilli remain dormant in latent pulmonary tuberculosis.

Loss of central vision is the main complication of concern. This occurs when the foveal or parafoveal lesions directly involve the area or when secondary features such as choroidal neovascular membranes and subretinal fibrosis develops. Choroidal neovascular membranes develop both during the active and healed stages and probably are due to ischemic injury to the choroid. Prompt treatment can lower the incidence of membranes if the active stage is treated effectively to hasten resolution. All patients with both active and healed stages irrespective of the aetiology should be instructed to perform Amsler grid monitoring daily and seek immediate opinion if a distortion is noted for early detection of CNV. Retinal vasculitis was not frequently noted in our study however cystoid macular oedema was seen in many patients. Tight anti-inflammatory measures may prevent exacerbations and recurrences and the lesions usually resolve when the choroiditis subsides.

Tuberculosis is currently a major public health problem. It is the second leading cause of death by a single infectious disease agent worldwide. Diagnosis is usually based upon clinical features and physician expertise. However, precise investigations are crucial for early eye-saving treatment and bringing down the
prevalence of ocular tuberculosis. The ophthalmologist has to choose between steroid treatment (for autoimmune disorders) and anti-tuberculous therapy, a decision that clearly has an impact on outcome. In several situations the differentiation between infective and non-infective aetiologies is not known due to inherent difficulties in clinical and microbiological diagnosis.

Tubercular choroiditis usually appears with two distinct patterns: multifocal, discrete choroiditis lesions that are initially non-contiguous and later progress to form diffuse lesions with an active edge resembling serpiginous choroiditis and less commonly a solitary, diffuse plaque-like lesion with an amoeboid extension. Addition of ATT to the conventional oral corticosteroids significantly prevents recurrences. Patients on ATT heal faster than those with non-tubercular aetiology. Those belonging to non-tubercular or autoimmune aetiology and treated with immunosuppressive drugs take a longer time to show visible clinical, angiographic or tomographic changes of healing.

Multifocal choroiditis that arises due to tubercular aetiology is entirely different and should not be thought to represent a subtype of serpiginous choroiditis. The fundus appearance may be sufficient for clinical diagnosis, but laboratory investigations are recommended to rule out infectious causes before initiating immunosuppressive treatment. Imaging studies are required to determine
activity, to monitor disease progression, to evaluate response to treatment and detect complications such as choroidal neovascularisation and macular oedema. However a difference can be observed in the pattern of presentation and following investigations. Systemic investigations in the majority of circumstances proves to be the clincher of diagnosis. However a combination of ocular and systemic investigations helps to clinch the diagnosis in the majority. The utility of RT-PCR to detect MTB in serpiginous choroiditis has never been reported and our results provide evidence that RT-PCR, on the aqueous humour can be applied to establish the diagnosis with certainty. It has the potential to significantly improve detection by virtue of its exquisite specificity and follow up for a longer period of time will help to evaluate progress and the recurrence pattern. In view of the ease of performing anterior chamber tap, the ability of RT-PCR to identify the presence of MTB DNA and the potential of this test to detect the response to treatment we recommend the use of this procedure to determine whether or not TB is the aetiology and to provide quantitative assessment of the bacterial load in the eye. The presence of confirmatory MTB DNA found by RT-PCR in only two of 28 eyes points out to the controversy of associating all serpiginous choroiditis with tuberculosis. Our study indicates that this association could be a chance association but when present, a very significant association (in an endemic country as India).
Analysis of vitreous aspirate by RT-PCR may provide more conclusive evidence by detecting MTB DNA in patients with serpiginous choroiditis.

RT-PCR allows fast detection and quantification of pathogen load in the tested specimen, with a minimized risk of carryover and cross-contamination. It may be helpful in confirming the diagnosis of clinically identified cases in laboratories having access to good research facilities. The prognostic or diagnostic significance of mycobacterial load in tubercular uveitis is as yet not known. However it is well known that tubercular uveitis may manifest clinically with variable clinical manifestation that may include chronic anterior uveitis, retinal vasculitis, and serpiginous-like choroiditis or even subretinal mass due to choroidal granuloma\(^{107}\). Recently, Rao et al. found \(1.7 \times 10^6\) copies of MTB genome from the micro dissected RPE cells of paraffin embedded sections of the globe from a patient with panuveitis\(^{108}\). The relatively lower number of copies of MTB in our cases compared to the previous report may be attributed to us choosing a different site of sampling (aqueous humour). Both these studies, however, justify a need to correlate the DNA load with clinical presentation in terms of morphology and severity of tubercular uveitis in a larger set of patients.

Our data showed that nested PCR was sufficiently accurate to corroborate initial clinical suspicion in cases and was also useful and safe to rule out this
diagnosis among controls. We acknowledge that DNA amplification tests are still under development, but the technique itself and its costs are becoming standard and less expensive daily with promising results in studies reported. In conclusion, the fact that this assay was so successful in depicting TB is highly valuable not only to confirm diagnosis, but also as a reliable and dependable diagnostic method. The main advantage of using the nested amplification is the minimal detection limits in the range of 10-100 bacilli \(^{109}\) per sample without the use of radioisotopes and in our set up nested PCR was standardized to detect even one single bacillus thus increasing the potential of this test.

At present, there is no adequate comparison to evaluate a PCR assay for diagnosis of tuberculosis other than culture results or clinical assessment in cases of extrapulmonary tuberculosis. Cultures often have been negative mainly because of the specimens being paucibacillary or presence of nonviable mycobacteria in them. Most often, clinical judgement, Mantoux test and radiological assessment are relied upon for the management of extrapulmonary tuberculosis. In this study, the low positivity (4\%) of the conventional culture technique could be either due to the presence of nonviable bacteria in the clinical specimens or due to the use of only the solid LJ medium on a few patients.
History of tuberculosis exposure, previous ATT, clinical examination, positive tuberculin test and x-ray chest had been used in the past for evaluating patients of posterior uveitis for systemic evidence of tuberculosis. Very few of our patients had history of tuberculosis exposure, none had ATT in the past, nor did symptoms and ESR help in diagnosis. Tuberculin skin testing provided supportive evidence only in some patients as it was not positive in all patients with TB.

Acute inflammatory lesions involving the RPE often cause a thickening at the level of RPE. It is believed that the lesions in SC arise deep in the retina, and the overlying retina appears oedematous. The oedema subsides as the lesions heal, and the RPE–choriocapillaries undergo atrophy. There is loss of photoreceptor–RPE complex with variable degrees of RPE hyperplasia. RPE may be the site of primary insult and hence, more severely damaged in serpiginous choroidopathy. Fundus autofluorescence (FAF) is a very sensitive imaging modality to evaluate inflammatory disorders affecting the chorioretinal interface. The FAF signals provide a strong clue to the status of RPE cells in various degenerative, inflammatory, and neoplastic disease processes. The fundus autofluorescence abnormalities were seen as hyperautofluorescence in active stage progressively becoming hypoautofluorescent in healed stage. The fundus
autofluorescence is increased (hyperautofluorescence) in the presence of increased metabolic activity of the RPE and decreased (hypoautofluorescence) when there is loss of the RPE.

Indocyanine green angiography is useful for identification and staging of new active SC lesions. Areas of choroidal nonperfusion during the acute stage is generally larger than the corresponding clinically observed retinal lesions. ICG shows larger area of cyanescence in active lesions than seen clinically or on FFA besides detecting lesions not picked up on FFA. Some authors report that the lesions which were not apparent on FFA can be detected with the help of ICG.

We observed that in the very initial stages of disease occurrence, when there was feeble hyperautofluorescence in the areas of new lesions, the OCT showed hyperreflectivity in the outer retinal layers that was fuzzy and ill defined. The choroid did not show any reflectance. This is an important OCT finding during the acute stage of SC that may reflect the site of primary insult in serpiginous choroiditis. However, SD-OCT technology is not yet able to image the choroid similarly to the retina, and hence, the absence of choroid changes on SD-OCT is not enough to definitely exclude its primary involvement in SC. Hyperreflectivity in the outer retinal layers in an active SC lesion is believed to be suggestive of
acute inflammation involving deeper retinal and choroidal structures. OCT findings seem to suggest that in an acute lesion of SC, there is an increased metabolic activity caused by primary inflammation of the RPE cells. Release of inflammatory mediators into the retinal layers adjacent to the RPE causes a fuzzy, hyperreflective appearance on SD-OCT. Following an acute inflammatory episode, the RPE cells undergo hyperplasia and hypertrophy which is evident as hyperautofluorescence on FAF due to increased collection of lipofuscin. Once these damaged RPE cells undergo atrophy, there is an irreversible loss of photoreceptors giving rise to the loss of the outer retinal layers on OCT. The simultaneous increased hypoautofluorescence depicts the atrophied RPE cells. The late pigmentation of the retinal scar associated with RPE hypertrophy or hyperplasia also leads to a decreased fundus autofluorescence signal (especially when photoreceptors are disrupted). The baring of choroidal vessels in healed lesions of SC in contrast to their masking by hyperpigmentary changes of the RPE in SC due to TB may also be due to entirely different entities affecting the inner choroid and the RPE cells, respectively.

The limitations of our study include a small number of cases and lack of clinicopathologic correlation. The outer retinal bands on SD-OCT, particularly
IS/OS junction, have not been correlated to the histological structures, and such correlation was not possible by us. However, the sequential ultrastructural changes in the outer retinal morphology on SD-OCT scans as seen in our patients provide important information that may add a new dimension in understanding the primary site of pathology in inflammatory conditions affecting the choroid and the RPE–photoreceptor complex.

OCT, by providing unprecedented details of the outer retina, has enhanced our understanding of the ultrastructure of the retina. The SD-OCT changes in healed scars of SC have shown disruption of the outer retina at the site of scars with loss of junction between the inner and outer segments of photoreceptors and thinning of RPE/Bruch membrane complex and a correspondent increase in light reflectivity from the choroid. Areas of thickening of RPE/Bruch membrane complex have also been shown in the regions of scars. However, there is no difference of SD-OCT changes in any active and healing stages of SC lesions. While reviewing patients with complications the role of OCT is complementary to the conventional fundus photography and fundus fluorescein angiography (FFA). The combined FAF and OCT signals can be effectively used in the evaluation of uveitic macular oedema in terms of visual outcome.
Even though the gold standard for diagnosis of ocular tuberculosis should be isolation of microorganisms in ocular tissues or fluids\textsuperscript{111,112}, this is time consuming and often not observed until enucleation of the eye. Therefore, one needs to rely on other diagnostic criteria, clinical symptoms, physical findings, and physician expertise, as usually done in routine practice at referral centres\textsuperscript{113,114}. In this setting some of the tests performed could be of marginal significance. However, under other circumstances such as in general hospitals, it could conceivably have more significant impact because it can corroborate diagnosis and exclude other potential causes of uveitis. We acknowledge that DNA amplification tests\textsuperscript{115} are still under development\textsuperscript{116}, but the technique itself and its costs are becoming standard and less expensive daily with promising results in studies recently reported from India and other countries\textsuperscript{117,118}. The fact that this assay was so successful in depicting TB is highly valuable not only to confirm diagnosis, but also as a reliable and dependable diagnostic method\textsuperscript{119}.

Neither the anatomical location nor the functional incapacitation of the initial choroiditis has any bearing on the rate of recurrence\textsuperscript{120}. The presentation of serpiginous choroiditis is noted to vary across different study populations, and there is a need for increased reporting of cases for better understanding of this
disease. We have not encountered serpiginous choroiditis due to other foci of tuberculosis apart from military tuberculosis, pulmonary and central nervous system forms although it can occur following other forms of systemic tuberculosis. The overall objective of the study was to explore serpiginous choroiditis and its association with tuberculosis. The limitation of the study is that details in patients with non-tubercular aetiology will not be analysed and thus a conclusion on other causative microbials (viral, protozoal or bacterial) will not be possible.

We recommend that every patient with serpiginous choroiditis should undergo testing for previous exposure to tuberculosis, and undergo complete antituberculous treatment if lesions are progressive and sight-threatening. In conclusion, with reference to the Indian population, this study showed that serpiginous choroiditis due to TB is a more frequent than serpiginous choroiditis due to autoimmune diseases and latent tuberculosis is the cause in the majority.