Review Article

Enigma of serpiginous choroiditis

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Serpiginous choroiditis (SC) is an asymmetrically bilateral inflammation of the choroid that leads to loss of choriocapillaris atrophy or loss of overlying retinal pigment epithelium. Over the last few decades, SC has passed through a long evolution of nomenclature, etiologies and morphological variations. Initially diagnosed in patients with tuberculosis and syphilis, SC was predominantly considered as autoimmune process. With the advancement of molecular diagnosis, a new aspect of infectious subtypes of SC has emerged out. The terminologies such as serpiginous-like choroiditis (SLC) and multifocal serpiginoid choroiditis are now used to denote the subtypes of SC which are associated with infectious etiologies especially tuberculosis. In a country endemic for tuberculosis such as India, it is very important to differentiate between classic SC and SLC before initiating aggressive immunomodulatory therapy. Also, management of paradoxical worsening of the clinical condition with antitubercular treatment is another challenge in SLC and ophthalmologists should be aware of such situations. With advent of newer imaging modalities, monitoring the patient with choroiditis and identification of complications such as choroidal neovascular membrane have become much easier. This article aims to review the existing literature on SC with a special emphasis on management of SC and SLC.

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Serpiginous choroiditis (SC) is a recurrent, asymmetrically bilateral inflammation of the choroid that leads to loss of choriocapillaris, atrophy, or loss of overlying retinal pigment epithelium (RPE), degeneration, and loss of photoreceptor cells with adhesion of the degenerated retina with the choroid. A clinical description of SC was first available in 1900, when Jonathan Hutchinson described a condition with the appearance of borders in a map of a continent in his article "Serpiginous Choroiditis in Scrofulous Subjects: Choroidal Lupus."[1] SC has passed through a long evolution of nomenclature and association with various etiologies. The disease has been described by various other names in literature: peripapillary choroiditis, helicoid peripapillary choroidal sclerosis, helicoid peripapillary chorioretinal degeneration, geographic helicoid peripapillary choroidopathy, geographic helicoid choroidopathy, serpiginous choroidopathy, and recently serpiginous-like choroiditis (SLC). Initially described in patients with tuberculosis and syphilis by Hutchinson, the disease was subsequently considered as idiopathic choroiditis. With the advancement of molecular diagnosis and better understanding of the disease pathology, a new aspect of infectious cause associated with SC has emerged out. The term SLC and *multifocal serpiginoid choroiditis* (MSC) were used by Gupta and associates in 2003 and 2012, respectively, to differentiate SC due to tubercular etiology from classic SC (CSC).[2,3] Although the lesions in SC are not typically multifocal, they are often included in spectrum of white dot syndrome by many authors.[4] This review article provides a comprehensive overview of spectrum of SC, highlighting the morphological and etiological variation in presentation and management of the disease. SC was used as broad umbrella term in this review, as a large part of the existing literature on this clinical entity was published prior to recognizing the infectious subtypes. Throughout the manuscript, we have used the term CSC to denote the autoimmune, noninfectious variety of SC and the terminologies such as SLC and/or MSC were used to denote the infective etiology.

Epidemiology

SC is a relatively rare condition, prevalence ranging from 0.2% to 5% of all uveitis patients.[5-10] Majority of these institute-based studies were from tertiary eye care setup and did not differentiate between CSC and SLC. Prevalence rates in Southeast Asian countries were found to be higher than other parts of the world.[5,6,10-14] A possible role of infectious etiology can be implicated to explain the relative higher incidence of SC in these regions. However, there is uneven distribution of SC across the Southeast Asian countries and considerable regional difference exists even within the same geographical area.[9,12,7,15] The reported prevalence of SC in India varies widely

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from 1.2% to 5.4%.[9,12,16,17] However, relatively lower prevalence of SC have been reported from the other countries in Indian subcontinent.[10,18,19] In addition, relative higher prevalence of SC has been reported from countries like Germany and United states in literature.[7,15,20]

Etiology

Various conditions have been described in association with SC. However, majority of them are isolated case reports and may represent coincidental or anecdotal findings rather than true association with the inflammatory process.

Noninfective/Autoimmune etiology

Auto-reactivity of circulating lymphocytes to retinal S antigen has been observed in CSC, but not in acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[21] Though both the entities affect choriocapillaris as well as RPE, unlike APMPPE, CSC causes extensive structural and functional damage to the choriocapillaris, RPE, and surrounding structures. The role of retinal photoreceptor protein-mediated damage has been implicated in extensive damage to the retina by CSC.[21] Occlusion of choriocapillaris has been attributed to the etiopathogenesis of CSC.[22] Various mechanisms of choriocapillaris occlusion have been suggested in literature.[23] Role of a localized immune-mediated vasculitis leading to occlusion of the choroidal vessels has been suggested by Erkkilä *et al*.[24] King *et al*.[25] demonstrated elevated factor VIII/von Willebrand factor ratio in patients with CSC and also highlighted the role of endothelial injury caused by a vasculitis-induced vasoocclusion. There are also reports of CSC occurring in patients suffering from carcinoma.[26,27]

Infectious etiology

Various organisms have been implicated in the pathogenesis of SC, though treatment with specific antimicrobial agents did not show any significant positive clinical results in majority of the cases.

Mycobacterium tuberculosis is the most common infectious organism implicated in etiopathogenesis of SLC. Association between SC and presumed tuberculosis was first described by Hutchison.[1] Role of the *M. tuberculosis* in pathogenesis of SC was also described by Witmer in 1952, Schalegel in 1969, and Maumenee in 1970.[28] *M. tuberculosis*, which is believed to be sequestered in the RPE, has been implicated in eyes with panuveitis or related intraocular inflammation, including SLC by clinicopathologic study.[29] Though genomes of *M. tuberculosis* have been isolated from aqueous and vitreous samples of patients with SLC,[3,30] isolation of the bacilli in these patients remains a major challenge. In a study from North India, Bansal *et al*. isolated mycobacterial DNA in vitreous fluid samples obtained by diagnostic pars plana vitrectomy in patients with active MSC and latent tuberculosis by using various molecular techniques such as multitargeted polymerase chain reaction (PCR) analysis, Gene Xpert MTB/RIF assay, and the line probe assay (MTB DR plus assay). The role of autoimmunity in pathogenesis of ocular tuberculosis has been established by the isolation of autoreactive T cells in vitreous sample of patients with tubercular uveitis including MSC, which showed resistance to activation-induced cell death.[31]

Viral etiology in SC has been suggested by various authors. A case of SC following herpes zoster ophthalmicus was reported by Gass.[32] Using polymerase chain reaction, varicella zoster virus and herpes simplex virus have been isolated from aqueous humor of patients with SC.[33] All these patients had multifocal lesions involving macula and were associated with vitritis and anterior chamber reaction. However, antiviral therapy has not been reported to have any beneficial role in treatment of SC and there are reports of disease recurrence in spite of antiviral therapy.[34]

Toxoplasma gondii has also been implicated as possible etiological agent.[35] Evidence of disseminated fungal infection was suggested by Pisa *et al*.[36] They observed antibodies against *Candida* spp. in serum samples from four patients with SC and fungal genomes in peripheral blood were detected in four SC patients.[36] However, circulating fungal DNA in serum may not be conclusive evidence of ocular fungal infection and antigen analysis has low specificity. These reports need to be interpreted with caution; many of them may have anecdotal association and positive antibody tests may merely reflect previous exposure to these organisms.[37]

Pathology

Histopathological reports of eyes with SC remain sparse. An inflammatory reaction, localized primarily in choroid with extensive infiltration of choroid by lymphocytes, has been described by Wu *et al*.[38] This infiltration was relatively higher at the margins of the atrophic scars. The scarring was characterized by the loss of the RPE and photoreceptor layers with focal defects of the underlying Bruch membrane. Fibroglial tissue was observed over the inner surface of Bruch's membrane and some part of the fibroglial tissue was noted to invaginate into the choroid through the breaks in Bruch's membrane. Recently, Kawali *et al*.[39] have published a report on histopathological changes in SLC in a 28-year-old male. This patient, who initially received diagnoses of SC and APMMPE, developed deterioration of signs and symptoms with anti-tuberculosis therapy (ATT) and underwent vitreous and chorioretinal biopsies. Vitreous specimen was negative for herpes viruses, *T. gondii* and *M. tuberculosis* on smear, culture, and PCR.[39] Acid-fast staining was negative and histopathology of chorioretinal biopsy showed granulomatous inflammation with necrosis of the inner choroid and disruption of the RPE and photoreceptors. The patient subsequently developed rhegmatogenous retinal detachment and multiplex PCR from vitreous sample obtained during retinal detachment surgery was found positive for mycobacterial genome. The biopsy report in this patient was similar to that seen in tuberculosis and confirmed the exuberant nature of inflammation on histopathology which was consistent with paradoxical worsening of SLC. The negative result for acid-fast bacilli was attributed to ATT, paucibacillary of the infection, and low-sensitivity of acid-fast staining in extrapulmonary tuberculosis by the authors.[39]

Clinical Presentation

Patients with SC typically present with the complaints of diminution of central vision, metamorphopsia, or scotoma. Patient may remain asymptomatic until the macula is involved. CSC is a bilateral condition; ocular involvement is reported to be asymmetrically unilateral. Typically, anterior chamber and vitreous are usually quiet and remains clear in CSC.

The word *serpiginous* (Latin: *serpere* means "to creep") is used as an adjective which means "with a wavy or indented margin." Classically, CSC is characterized by similar wavy or amoeboid-like lesions in choroid. The choroiditis in CSC progresses in an irregular serpentine fashion centrifugally. These lesions start as ill-defined patches of grayish-white or creamy yellow color at the level of deep retina or RPE.[40] Overlying retina may be edematous due to the underlying inflammation and may develop serous retinal detachment in severe cases. Healing of these lesions is variable with or without treatment and most of the time lesions are observed in varying stages of resolution. The active lesions usually resolve by 6–8 weeks and are characterized by sharpening of border with irregular RPE hyperperturbations, diffuse RPE mottling with extensive atrophy of RPE, and choriocapillaris. Sometimes, the atrophy/destruction is so extensive that the larger underlying choroidal vessels are exposed and destruction of the entire choroid up to sclera can occur. Recurrences are common and usually occur at the edge of the previous healed lesions. The time interval between these recurrent attacks is variable and ranges from months to years.[40]

Serpiginous choroiditis

Based on the morphology and characteristics of lesions, CSC can be further subdivided into the following categories: *Peripapillary CSC is* the most common type of CSC described in literature. Approximately 80% of the cases of CSC reported are of peripapillary variety.[40,41] The lesion in peripapillary CSC is usually unifocal and occurs around the optic disc and progresses in a serpentine pattern centrifugally to involve macula [Fig. 1a]. *Macular CSC* [Fig. 1b] is relatively uncommon but dreaded cause of vision loss because of early involvement of macula and higher risk of developing choroidal neovascularization (CNV).[42] Few clinical entities have been described in literature which have clinical features similar to APMPPE and SC, reflecting different ends of a disease spectrum. Golchet *et al*.[43] described a condition in five patients, which they called *persistent placoid maculopathy (PPM)*, characterized by normal to mildly affected visual acuity in spite of long-standing geographic central whitish plaques involving fovea. However, other authors have reported variable disease course with poor visual outcome in patients with PPM.[44] Choroidal neovascular complications were much higher in these patients and occurred in 11 of 18 cases reported till date.[43,45] Choroidal vasculitis leading to ischemic choroidal infarcts has been implicated in PPM.[45] *Relentless placoid chorioretinitis (RPC)* is another term used by Jones *et al.* to describe an unusual clinical entity resembling APMPPE and SC both clinically and angiographically with an atypical clinical course.[46] Lesions in RPC are usually numerous (ranging from 50 to 100 in number) and involve posterior pole, mid-, and far-periphery predating or occurring simultaneously with macular involvement in contrast to the lesions seen in APMPPE, which are usually limited to posterior pole. Simultaneous presence of active and healed lesions scattered all over the fundus with prolonged and relapsing course was described as hallmark of RPC.[46] Pigmented chorioretinal atrophy usually develops as the lesions of RPC heal. Because of considerable overlap between the angiographic findings,[4,47,48] RPE hyperperturbations, recurrent nature of APMPPE and this subset of SC, a term "Ampiginous Choroiditis" has been used.[41,47] Foveal involvement is relatively less in ampiginous choroiditis when compared with other subtypes of SC. However, it is not clear whether ampiginous choroiditis or RPC represents isolated distinct variants of SC or a clinical variant of SLC/MSC. There are reports of ocular lesions resembling APMPPE which subsequently coalesced and healed with characteristic picture of SC.[4,49] In a retrospective analysis of 86 patients with SC, 20 patients who presented initially with clinical picture like APMPPE had progressed to SC over a period of several months to years.[4] In addition, role of an infectious etiology has been reported with these conditions. Bhuibhar and Biswas[50] isolated *mycobacterial* DNA from aqueous aspirate of a patient with ampiginous choroiditis, who was also tested positive for Mantoux test, interferon gamma release assay and had right hilar and paratracheal lymphadenopathy in high-resolution computerized tomography of chest. Khalifa *et al*.[51] reported ampiginous choroiditis in both eyes of a 17-year-old woman 3 weeks following the administration of the quadrivalent human papilloma virus vaccine.

Serpiginous-like choroiditis

SLC is a distinct form of SC, characterized by multifocal choroidal lesions of varying shape and size which often coalesces to form diffuse choroiditis resembling SC in patients with presumed tuberculosis.[4] The term "serpigniod" and "multifocal serpigniod choroiditis" have also been used to refer these clinical entities.[3,40,52] In contrast to patients with CSC, patients with SLC are usually from tuberculosis endemic area and more likely to have unilateral presentation, relatively younger age of presentation, multifocal lesions [Fig. 1c], located in periphery of retina [Fig. 1d], frequent sparing of the juxtapapillary region, more inflammatory reaction in vitreous and continue to show progression with development of new lesions despite effective corticosteroid therapy.[4,2,52,53]

Ancillary Investigations

Fundus autofluorescence (FAF)

Being a non-invasive investigation, FAF has been emerged as a valuable tool for assessment and monitoring disease activity in patients with SC. Active inflammation in SC is usually manifested as a hypoautofluorescent halo that surrounds the edges of hyperautofluorescent lesions, which probably represents edema of the deep retina or RPE.[54,55] Subsequently, a sharp hypoautofluorescence border representing a transitional zone of inactivity surrounds the hyperautofluorescent lesions.[56] The healed lesions of SC are characterized by totally hypoautofluorescence area with very sharp border, indicating the complete loss of fluorophores [Fig. 2].[55,56] Autofluorescence in SLC has been described in 36 eyes of 29 patients by Gupta *et al*.[54] In a clinically inactive lesion with an inconclusive FFA, a stippled pattern of mixed autofluorescence on FAF reflects ongoing metabolic activity within a lesion.[54] Thus, FAF can be useful in picking up subclinical reactivation of a previously healed lesion. In contrast to diffuse, contagious pattern of hypoautofluorescence in SC, a complex, variegated pattern of hypoautofluorescence and hyperautofluorescence, has been described in patients with SLC.[54] This difference was attributed to the direct involvement of RPE in eyes with SLC causing a greater damage to RPE in patients with SLC. In SC, RPE is believed to be involved secondarily as a part of choroidal inflammatory process and may have variable degrees of hyperplastic RPE.[57] Using FAF, oral corticosteroid has been found to minimize the damage to the RPE in patients with CSC.[55]

Fundus fluorescein angiography

Because of hypoperfusion of choriocapillaris and blockage of fluorescence due to edematous inflamed RPE and retina, active lesions in SC demonstrate hypofluorescence with fuzzy, irregular borders in early phase of the angiogram. This is followed by leakage of the dye from the choriocapillaris at the border of the inflamed lesions, which is manifested by gradual hyperfluorescence at the border of the lesions in mid-phase of the angiogram. Gradually, there is profuse leakage of the dye from larger choroidal vessels which is observed as hyperfluorescence of the lesions [Fig. 3].

FFA in healed lesions of SC is characterized by mottled hyperfluorescence. Healed lesions of SC are characterized by hypofluorescent areas with sharp margins in early phases of angiogram which can be attributed to the extensive destruction of choriocapillaris. As the fluorescein diffuses into the scarred area from the surrounding normal choriocapillaris, the margins of the healed lesions show increased hyperfluorescence followed by diffuse staining of these lesions. Ultra-wide-field FFA, which enables nearly 200° of retina in a single frame, has been described to be an excellent tool for treatment and monitoring of peripheral involvement in cases with SC or SLC, and paradoxical worsening with antitubercular therapy.[58,59]

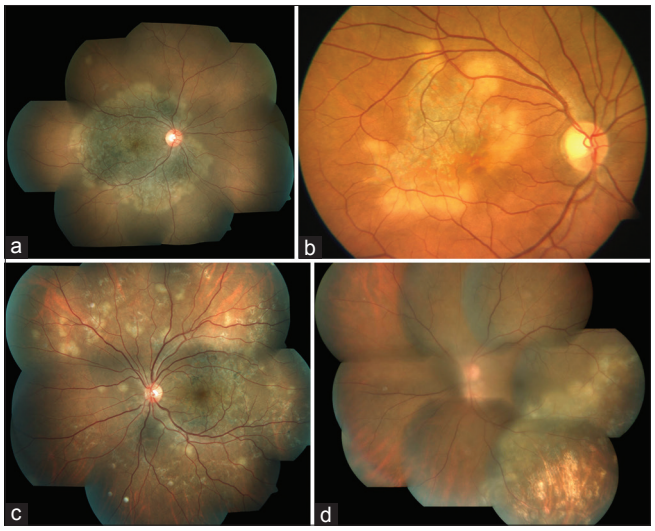

Figure 1: Various morphological variant of serpiginous choroiditis: (a) peripapillary classic serpiginous choroiditis, (b) macular classic serpiginous choroiditis, (c) multifocal serpiginoid choroiditis, and (d) serpiginous-like choroiditis involving peripheral retina in a patient with presumed ocular tuberculosis

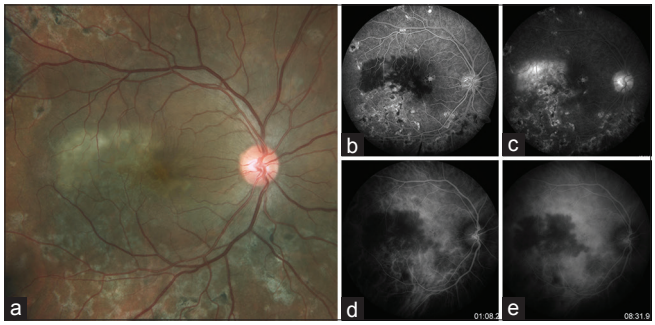

Figure 3: Color fundus photograph (a) and early (b and d) and late-phase (c and e) fundus fluorescein angiography and indocyanine green angiography pictures of a 32-year-old male with serpiginous-like choroiditis, who presented with reactivation of choroiditis in fovea. Active choroiditis appears as hypofluorescence with fuzzy, irregular borders in early phase (b), followed by profuse leakage of the dye leading to hyperfluorescence in late phase of fundus fluorescein angiography (c). Active lesions in indocyanine green angiography show blockage of the dye beginning from the early phase (d) to the late phase (e)

Indocyanine green angiography

Active lesions of SC show blockage of the dye beginning from the early to the late phase in ICG, a feature which is thought to be contributed by a combination of both abnormalities in choroidal perfusion and blockage of fluorescence by the inflamed RPE and outer retina [Fig. 3].[60] The extent of involvement of choroidal inflammation observed in ICG is beyond the limits delineated by corresponding fluorescein studies or by clinical examination.[61,62] Similar observations were reported in subacute and healed lesions of SC, where ICG can show better and earlier delineation of resolution of choroiditis than corresponding fluorescein changes.[61] ICG is very helpful in differentiating CNV in presence of active choroiditis as both CNV and choroiditis leak fluorescein. Choroiditis usually show early hypofluorescence on ICG, whereas hyperfluorescence is observed in CNV.

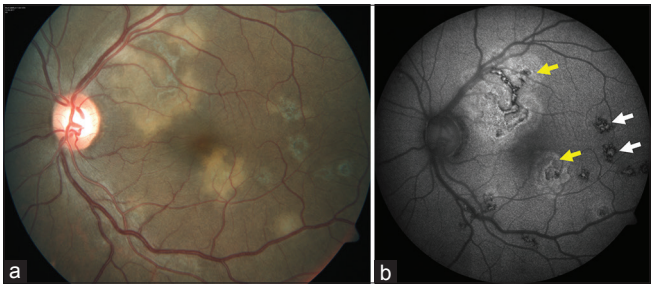

Figure 2: (a) Fundus photograph of the left eye showing multifocal choroidal lesions of varying shape and size and at various stages of resolution in a patient with serpiginous-like choroiditis and (b) autofluorescence of the left eye showing variegated pattern of hypoautofluorescence and hyperautofluorescence (yellow arrow). Note the healed choroiditis lesions (white arrows) characterized by total hypoautofluorescence area with sharp borders

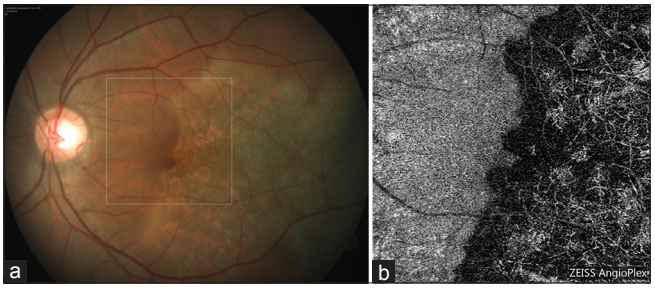

Figure 4: (a) Color fundus photo of right eye showing active edge of serpiginous choroiditis encroaching fovea with temporal healed lesion and (b) optical coherence tomography angiography at choriocapillaris segmentation of the area in the dotted square in (a) showing flow void area corresponding to the active edge and loss of choriocapillaris at the healed areas with high reflectivity from underlying medium-sized choroidal vessels

Optical coherence tomography

OCT in active phase of SC supports evidence of a choriocapillary disease, where atrophy of the photoreceptor layer and varying damage to the choriocapillaris and choroid can occur. Typical lesion of CSC in OCT is characterized by hyper-reflectivity in the outer retina with loss of inner segment and outer segment junction and loss of RPE in subsequent phases of inflammation.[63] Extensive mononuclear cell infiltrate in the choriocapillaris and choroid, as reported in histopathology, can be observed as early choroidal hyperreflectivity which is often described as "waterfall" effect.[64] Using enhanced depth imaging, Rifkin *et al*.[65] reported a focal elevation of the neurosensory retina and RPE-Bruch's membrane complex in a patient of SLC, which was thought to represent an underlying elevated choroidal nodule. Using enhanced depth imaging, Agarwal *et al*.[66] compared the choroidal vascular changes between patients with MSC and normal healthy controls. Patients with active MSC demonstrated significant increase in choroidal thickness, total choroid area, volume of both vascular as well as stromal/interstitial component of choroid, and a significant decrease in these parameters in healed stage of the disease.

Optical coherence tomographic angiography

OCT-A is relatively a new modality of noninvasive investigation which can produce depth-resolved, high-resolution images of retinal and choroidal vasculature by detecting intravascular blood flow based on split-spectrum amplitude-decorrelation angiography without injecting the dye. OCTA in CSC demonstrated decreased vascularity on choriocapillaris but intact retinal vascularity [Fig. 4].[67] El Amin and Herbert[68] compared the OCT-A and ICG images in SC and observed that the hypofluorescent, hypoperfused areas on ICG correspond to the dark areas seen in the choriocapillaris layer of OCT-A. The authors found ICG more preferable because of its ability to delineate choriocapillary lesions more clearly than OCT-A.[68] In a study of OCT-A in 18 eyes of 16 patients of SLC, OCT-A was found to provide higher resolution images of choriocapillaris within the lesion and better distinction between choriocapillaris atrophy and hypoperfusion.[69]

Visual fields

Examination of visual fields in active SC demonstrates dense absolute and/or relative scotoma, which corresponds to the size, shape, and location of the lesions, and with resolution of the lesions, the scotoma may become less dense. A dese scotoma corresponding to the main lesion surrounded by a relative scotoma was reported by Weiss *et al*.[49] In a retrospective study on visual field changes in patients with SC from India by Balarabe and Biswas,[70] multiple foci of defects – usually central or paracentral scotoma – coexisting with isolated field defects in the nasal or temporal field were the commonest form of field defect.

Complications

CNV is the most dreaded and commonest complication associated with SC. The reported incidence of CNV in patients with SC ranges from 10% to 25%.[71] CNV typically arises close to the edge of choroidal lesions and can occur in both active or healed choroiditis. Choriocapillaritis-induced ischemia to choroid, Bruch's membrane, and outer retina have been implicated in etiopathogenesis of CNV in SC. CNV in patients with choroiditis can be easily missed or overlooked and diagnosis of CNV especially occult CNV requires high index of suspicion.[72] Classic CNV, which is usually characterized by early hyperfluorescence, can easily be distinguished from SC lesions which shows early hypofluorescence in FFA. Because of its subtle or less pronounced hyperfluorescence, the diagnosis of occult CNV in SC poses significant challenge and may need imaging techniques such as OCT, ICG, etc.[72,73] Subretinal fibrosis is another long-term, sight-threatening complication reported in patients with SC.[4,74] Other less common complications include retinal vasculitis, vascular occlusions, secondary neovascularization and vitreous hemorrhage, serous retinal detachment, and cystoid macular edema.[75]

Treatment

Treatment of classic serpiginous choroiditis

Corticosteroids

In patients with CSC, reduction in visual acuity usually depends on macular involvement, and thus, it is very crucial to initiate rapid and effective treatment to preserve retinal function in this sensitive part of the eye. High-dose intravenous pulse steroids is useful in macula-threatening conditions. Recurrence of inflammation is very common and another major concern in management of patients with SC. Higher doses of corticosteroids have been proved to cause prompt resolution of inflammation but usually fail to prevent recurrence.[34] Relapse of inflammation during tapering or after discontinuation of corticosteroids is common.

Immunosuppressive agents

There is no consensus as to the utility of corticosteroids used alone or in combination with immunosuppressive agents. Immunosuppressive agents such as methotrexate, azathioprine, cyclosporine, chlorambucil, or cyclophosphamide can help to attain longer period of disease inactivity and reduce the risk of potential side effects associated with high-dose systemic steroids. However, immunosuppressive agents usually take longer time to attain the desired level of therapeutic concentration of the drug and thus cannot be used to treat acute exacerbations. Immunosuppressive treatment with alkylating agents (chlorambucil and cyclophosphamide) has been found to be associated with long-term drug-free remission of CSC.[76,77] However, alkylating agents should be used judiciously and cautiously in these patients because of their potential life-threatening complications such as leucopenia, risk of malignancy, etc. Cyclosporine has been used in patients with CSC with mixed results – there are reports of treatment failure and recurrence with the drug.[76,78,79] A triple-agent immunosuppressive regimen consisting of cyclosporine (5 mg/kg/day initially), azathioprine (1.5 mg/kg/day), and prednisolone (1 mg/kg/day) was found to be effective in the management of SC.[80-83]

Intravitreal agents

Intravitreal corticosteroid injection has been found to be a promising alternative therapeutic option as a rescue therapy in CSC by inducing rapid remission without the systemic side effects seen with systemic immunosuppression.[84-86] Intravitreal corticosteroid injections have been reported to be useful in the management of active serpiginous lesions, in the presence of systemic corticosteroids contraindication, and in secondary CNV. Long-term control of inflammation with intravitreal

fluocinolone implant in a patient of CSC was reported by Seth and Gaudio,[86] but the treated eye required trabeculectomy because of persistent high intraocular pressure, refractory to medical therapy. In a retrospective case series, Miserocchi *et al*.[87] evaluated the safety and efficacy of intravitreal dexamethasone implant in eight eyes of seven patients with active CSC already receiving maximal tolerated systemic immunosuppressive therapy. Intravitreal corticosteroid implant was planned in these patients because of the presence of systemic disease like uncontrolled hypertension and diabetes mellitus, gastric ulcer, cardiac disease, or osteoporosis, the severity of which contraindicated the further increase in the dose of corticosteroids in these patients despite progressing inflammation. Saatci *et al*.[88] reported a case of 46-year-old woman with unilateral extrafoveal CNV associated with an active SC, who was treated with a simultaneous intravitreal dexamethasone implant and intravitreal injection of ranibizumab. However, these reports must be interpreted and applied cautiously into the clinical practice in a tuberculosis-endemic country like India. Care should be taken to rule out SLC before planning any intravitreal injection for the management of SC. However, intravitreal immunosuppressive like methotrexate has been administered in patients with SLC.[89]

Biologicals

Biologicals have been found to be very useful in the management of uveitic conditions refractory to other modalities of treatment. Recently, biologicals have been tried in the management of CSC.[90-92] Seve *et al*.[90] reported successful management of a 43-year-old patient with SC with infliximab who developed relapse even after treatment of multiple recurrences with intravenous methylprednisolone, intravenous cyclophosphamide, mycophenolate mofetil, cyclosporine, and oral corticosteroid. The patient was on antitubercular treatment and authors emphasized the need of prior antituberculous chemotherapy before administration of biologicals. Another case report from Spain reported the paradoxical worsening of symptoms and signs of SLC with antitubercular medications, oral corticosteroid in a 23-year-old woman who was subsequently successfully treated with adalimumab.[91] Many authors have recommended the use of biological therapy in recalcitrant cases of CSC, where other modalities of treatment have failed and advised the need of antitubercular therapy in these patients.[90,92] However, most of them are isolated case reports and no large scale data are available on safety of biological agents in these patients. Cordero-Coma *et al*.[93] reported a case of presumed SLC in a 48-year-old lady who died of disseminated tuberculosis after treatment with infliximab. The patient developed multiple relapses even after therapy with various immunosuppressive agents and her investigations, including tuberculin skin test and interferon gamma release assay, were negative.[93] Extreme caution should be taken while planning anti-TNF alpha or other modalities of biological therapy in patients with CSC, and in a tuberculosis-endemic country, the authors would suggest biological therapy as a last resource for the management of CSC.

Treatment of serpiginous-like choroiditis/multifocal serpiginoid choroiditis

In presence of characteristic clinical lesions and suggestive history (such as contact with TB-patients, origin from TB-endemic region), treatment of SLC is usually decided either by presumptive diagnosis such as positive tuberculin skin test and radiological evidence pulmonary involvement or definitive diagnosis such as isolation of *M. tuberculosis* genome in aqueous or vitreous sample of the patient. Although there is no clear-cut recommendations or guidelines, ATT in patients with SLC has been proven to control active inflammation as well as prevent future recurrences.[94,95] Usually, four-drug ATT, including isoniazid (5 mg/kg), rifampicin (450–600 mg), ethambutol (15 mg/kg), and pyrazinamide (25–30 mg/kg) first 3–4 months followed by rifampicin and isoniazid for another 9 months, are recommended. Bansal *et al*.[96] detected rifampicin resistance with the help of line probe assay (MTB DR plus) from vitreous samples of three patients in a series of patients with active MSC and latent tuberculosis who initially responded poorly to ATT. Multidrug resistance tuberculosis, in patients with MSC or SLC, requires high index of suspicion, especially in presence of atypical findings or poor response to therapy. Continued progression of choroiditis lesion was reported in 14% of the patients with SLC following ATT from a study from India.[97] Paradoxical worsening of ocular lesions with ATT is a serious concern and has reported in literature by various authors.[98-100] It is characterized by continued progression of preexisting tuberculous lesions or the development of new lesions in a patient who initially improves with ATT and oral steroid. In absence concomitant oral steroid therapy, Jarisch–Herxheimer reaction characterized by a strong inflammatory immunologic reaction in anterior chamber or vitreous can occur.[74,98] Exact mechanism of paradoxical worsening with ATT remains largely unknown. Presence of lipoarabinomannan in mycobacterial cell wall and subsequent activation of inflammatory cascade has been attributed.[97,101] In a recently published study of 44 eyes of 29 patients with MSC,[59] 36.4% eyes showed paradoxical worsening of ocular lesions, and in 18.7% eyes, paradoxical worsening was observed in peripheral fundus. Thus, clinicians must be aware of this entity; and regular follow-up and meticulous fundus examination should be carried out in patients with SLC while on ATT.

Treatment with ATT alone is not sufficient for the management of SLC. Tissue damage following strong inflammatory reaction in SLC and the risk of paradoxical worsening with ATT warrant high-dose corticosteroid therapy, which can be achieved through local or systemic mode of administration. Usually, oral corticosteroids (1–1.5 mg/kg/day) in tapering doses are used. There is paucity of literature on local immunosuppression in SLC or MSC.[102-104] In addition to bypassing potential systemic side effects, intravitreal injection of corticosteroid can prevent the risk of activation of latent tuberculosis. In addition, in conditions where the presence of an active extrapulmonary or pulmonary tuberculosis needs use of systemic immunosuppression with extreme caution, intravitreal corticosteroid can be a useful adjunct with ATT. Jain *et al*.[103] administered intravitreal sustained release dexamethasone implant (Ozurdex; Allergan, Irvine, CA) in nine eyes of six patients with MSC in addition to ATT. Only one patient required additional systemic immunosuppression as appearance of newer lesions was observed following ozurdex injection. The patient also received second-line ATT. None of the patients developed recurrence of inflammation and one eye required implant removal because of raised IOP. In a larger series of 19 eyes of 17 patients with tubercular uveitis, Agarwal *et al*.[104] reported successful management of choroiditis lesions with dexamethasone implant in six patients

with MSC. Two eyes with paradoxical worsening showed improvement with dexamethasone implant as adjunct to oral corticosteroid. Various authors have reported the role of local immunosuppression in the management of paradoxical worsening. Julian *et al.*[89] have reported the efficacy of a single intravitreal injection of methotrexate (400 mg/0.1 mL) in three eyes of two patients of presumed tuberculous SLC, where the lesions were progressing and threatening macula despite the use of antitubercular therapy. Resolution of lesions without any significant side effects was reported in these patients. The authors attributed the local immunosuppressive action of intravitreal methotrexate in controlling progressive lesions of SLC which they thought may be because of active disease or paradoxical immune reaction to bacterial lysis.[89]

Conclusion

SC is primarily a recurrent, vision-threatening inflammation which affects the outer retina and inner choroid and has plethora of presentations. Infective etiologies especially tuberculosis in endemic regions have been implicated as possible etiology in the disease process. Newer imaging techniques and newer treatment options have been rapidly emerging over the last decade, but the enigma of this uncommon condition continues. As our understanding of the disease evolves, various therapeutic armamentarium have been tried in the management of SC; however, one must exercise sufficient caution prior administering local immunomodulatory therapy, especially in tuberculosis-endemic regions like India.

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Conflicts of interest

There are no conflicts of interest.

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