REVIEW

Sympathetic Ophthalmia: Where Do We Currently Stand on Treatment Strategies?

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Abstract: Sympathetic ophthalmia is a rare bilateral diffuse granulomatous panuveitis that usually results from surgical or penetrating trauma to one eye. The symptoms range from impaired near vision to pain, photophobia, and loss of visual acuity. Anterior segment manifestations include bilateral acute uveitis with mutton-fat keratic precipitates and posterior segment findings include vitritis, multifocal neurosensory retinal detachment, choroiditis, optic nerve edema, and Dalen–Fuchs nodules. The diagnosis is clinical. Ancillary investigations include fundus fluorescein angiography, indocyanine green angiography, optical coherence tomography (OCT), ultrasound B scan, and autofluorescence imaging. The management options include corticosteroids (topical and systemic) as the first line along with immunomodulatory therapy started at the presentation of the disease. Recent advances include imaging with OCT-angiography, enhanced depth imaging-OCT (EDI-OCT, choroidal vascular index/CVI), targeting IL-23/IL-17 pathway, and use of biologics for the management of this rare entity. Recent advances in early diagnosis and prompt treatment has led to improved final visual outcomes in both the sympathizing and exciting eye. This review is aimed at giving a comprehensive overview of sympathetic ophthalmia along with a special emphasis on current treatment strategies and recent advances.

Keywords: ocular trauma, inciting eye, exciting eye, corticosteroids, open globe injury, infliximab, adalimumab

Introduction

Sympathetic ophthalmia (SO) also known as "sympathetic ophthalmitis" or "sympathetic uveitis" is a rare inflammatory condition caused by a delayed hypersensitivity reaction. It results in bilateral diffuse granulomatous panuveitis, which usually occurs following surgical or penetrating trauma to one eye with uveal tissue incarceration. The traumatized or operated eye is called the exciting or inciting eye, whereas the non-injured contralateral eye is called the sympathizing eye.[1] The time interval between ocular trauma to the development of symptoms is unpredictable and may vary from 5 days[2] to even several (up to 66) years[3] following injury; however, 80% of the cases of SO develop within 3 months and 90% of the cases present within 1 year of trauma to the exciting eye.[4] Most cases were seen in childhood and young adults owing to the higher incidence of accidental injuries in previously published reports.[5] The increased incidence in the age group of 60–70 years may be due to a higher incidence of surgical procedures.[4] Though a rare condition, SO is one of the most dreadful ophthalmic conditions, which can cause bilateral blindness.[6]

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History

The concept of SO dates back to the writings of Hippocrates.[5] The clinical description was first given by William Mackenzie in 1840[7] who also coined the term SO. He hypothesized that SO was an inflammatory process that spreads from the exciting to the sympathizing eye via the optic nerve and optic chiasma. The histopathologic description of the disease was given by Ernst Fuchs[8] who described it as a mixed-cell inflammatory infiltration of the uveal tract, particularly affecting the choroid, and then along with Dalen, he described the inflammatory nodular aggregates as Dalen–Fuchs (DF) nodules.[9]

Epidemiology

It has been proposed that SO is a hypersensitivity reaction triggered by melanin.[10] Correlation of uveal injury to SO was further confirmed by the presence of anti-uveal antibodies in many patients, suggesting the pathogenic role of uvea-retina.[11] However, the most convincing theory is the cell-mediated immune response to antigens (type 4 hypersensitivity reaction) from the retinal photoreceptor layer.[12] The exact target antigen in SO is still being investigated, but skin immunization in experimental animals with various antigens including retinal antigens (retinal S-antigen, now identified as arrestin; interphotoreceptor retinoid-binding protein, rhodopsin), melanocyte-associated tyrosinase, and retinal pigment epithelium (RPE)-associated antigens result in autoimmune uveitis very similar or indistinguishable from SO.[11,13–16]

The commonest causes of SO include penetrating injury to the eye from trauma or surgery (Table 1). Vitreoretinal surgery (pars plana vitrectomy/PPV),[17] in particular, is becoming one of the most prominent causes of SO in current practice and some authors suggest that risk of SO should be discussed before considering such interventions as the estimated risk of SO after PPV may be as high as 1 in 799.[18] However, in a large series of SO from India, SO was noted to occur in 0.038% of all cases undergoing PPV.[19]

Penetrating surgical interventions causing SO include cataract surgery,[20] intravitreal injection,[21] iridencleisis,[22] and iris/uveal inclusion in the wound.

Corneal infections by various organisms including acanthamoeba,[23] and fungus (*Aspergillus fumigatus*, leading to corneal perforation and evisceration)[24] can predispose to SO.

Table 1 Triggering Events in SO Patients

Mechanism	Triggering Events
Trauma	Penetrating eye injuries[83]
	Closed globe injuries/Blunt trauma[25,26]
	Chemical ocular injuries[29]
	Intraocular foreign body[28]
	Thermal burn[30]
Procedures	Pars plana vitrectomy[17]
	Transscleral cyclophotocoagulation[31]
	Cataract surgery[20]
	Intravitreal injection[21]
	Scleral buckling[32]
	Helium ion therapy for choroidal melanoma[34]
	Ruthenium plaque for iris melanoma[35]
	Proton beam radiation for choroidal melanoma[33]
	Enucleation[36]
	Penetrating keratoplasty[37]
	Repair of cyclodialysis cleft[43]
	Phakic intraocular lens implantation[39]
	Evisceration[40]
	Iridectomy[41]
	Paracentesis[44]
	Iris inclusions in wound
	Intravitreal injection[21]
	Trabeculectomy[42]
	Iridencleisis[22]
	Conjunctival flap procedure for perforated corneal ulcer[38]
Other diseases	Acanthamoeba keratitis[23]
	Fungal keratitis[24]

Few cases of SO have also been reported following closed globe injuries or blunt trauma,[25–27] intraocular foreign body,[28] chemical injuries,[29] and even thermal eye injuries.[30] Various surgical procedures can cause SO, including transscleral cyclophotocoagulation,[31] scleral buckling,[32] proton beam radiation,[33] helium ion therapy for choroidal melanoma,[34] ruthenium plaque for iris melanoma,[35] enucleation,[36] penetrating keratoplasty,[37] conjunctival flap procedure for perforated corneal ulcer,[38] phakic intraocular lens implantation,[39] evisceration,[40] iridectomy,[41] trabeculectomy,[42] repair of cyclodialysis cleft,[43] and paracentesis.[44]

Gomi et al[45] suggested the incidence of SO to be approximately 0.3% of all uveitis cases. The overall incidence of SO may be up to 0.2% to 1%[46] after penetrating ocular trauma and 0.01% after intraocular surgery.[46] Liddy and Stuart reported the occurrence of SO in 0.2% of non-surgical wounds[47] of which 0.19% were following

penetrating injuries and 0.007% were following intraocular surgery, whereas Holland reported SO in 0.5% of the eyes with trauma.[48] Gass et al, reported the prevalence of SO following routine pars plana vitrectomy to be 0.01% but prevalence increased to 0.06% when vitrectomy was performed for penetrating ocular trauma.[49] The prevalence of post-traumatic SO is higher in males, with men being affected 1.8 times more than women.[50] This is due to a higher incidence of accidental trauma and penetrating ocular injuries in men attributable to occupational hazards and more outdoor activities. However, the ratio for post-surgical SO is equal for males as well as females, and the incidence of post-surgical SO is increasing recently.[51] Castiblanco et al[52] found that 44% of the cases were contributed by post-surgical trauma of which 21% occurred after pars plana vitrectomy. A common link is the presence of a penetrating injury in which wound healing is complicated by incarceration of the iris, ciliary body, or choroid.[4]

Pathophysiology

The exact cause of SO is unknown. The predominant predisposing factors such as accidental penetrating trauma and penetrating surgical trauma contribute to 60–70% and 30% of the cases, respectively.[53] Although it has been believed in the past that the SO was aided by infectious etiology, it has been proven that most cases of SO develop in the absence of intraocular infection.[1]

Marak[46,54] and Wong et al[11] demonstrated that patients with SO have lymphocytes that are sensitized to some components of uveal-retinal antigen. Genetic factors play an important role in the development of SO. Proposed Human Leukocyte Antigen (HLA) associations include HLA-A11, HLA-B40, HLA-DR4/DRw53, and HLA-DR4/DQw3 haplotypes.[55,56] A significant correlation exists between HLA-DRB1*4 and HLA-DQB1*04 and the development of SO.[57–59]

It is thought that the penetrating trauma or surgery activates the afferent phase of an autoimmune reaction. This may be due to the exposure of sequestered ocular antigens to the immune system after trauma or an alteration of the immune tolerance to ocular antigens (Figure 1).[60] The eye does not have a lymphatic system. The antigen-presenting cells (APCs, usually macrophage or dendritic cells) process the antigen and present the antigen peptide to abnormal (autoreactive) CD4+ T cells at lymph nodes or spleen via HLA II molecules. The antigen peptide is recognized by the T cell receptor (TCR) and this leads to the activation of CD4+ cells
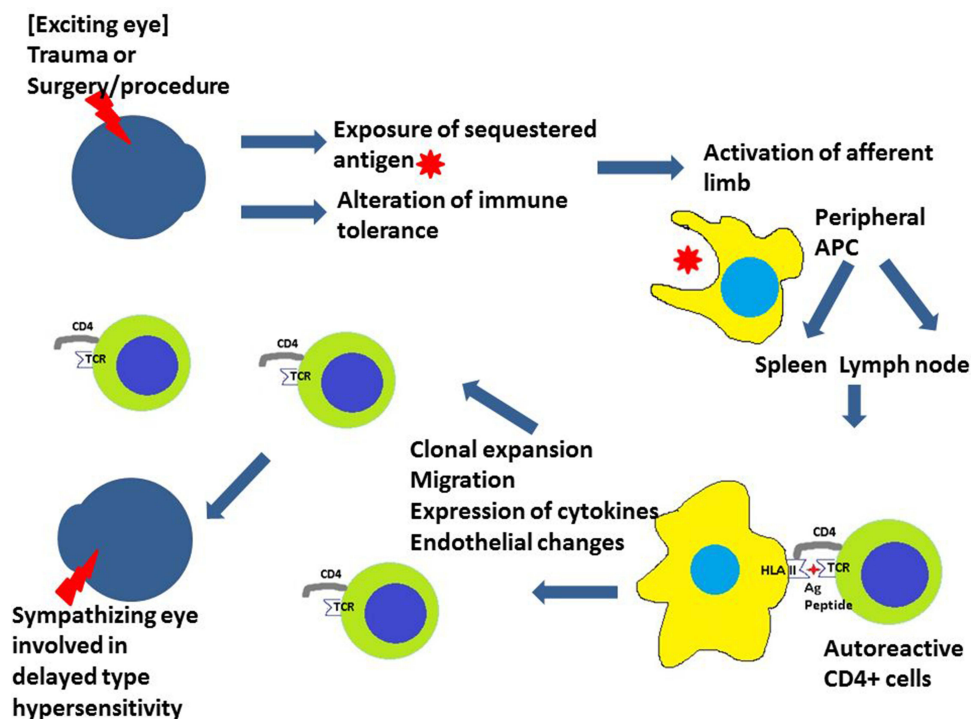
Figure 1 After the inciting event, the antigen-presenting cells (APC) present the antigen peptide to autoreactive CD4+ cells. This activates the CD4+ cells and brings about the autoimmune reaction damaging the other (sympathizing) eye.
Abbreviations: TCR, T-cell receptor; HLA, human leucocyte antigen; Ag, antigen.

(mainly Th1 cells). Clonal expansion of Th1 cell happens and these cells migrate. There are endothelial changes, change in cytokine milieu, and activation of multiple effector pathways causing damage to the sympathizing eye.[61]

Immunopathology

The immunopathological alterations consist of a diffuse granulomatous inflammation of the uveal tract, made up of lymphocytes, plasma cells, and nests of epithelioid histiocytes.[1,11] Pigment is often present within these epithelioid cells and also within the giant cells.[62] The inflammatory process does not involve the choriocapillaris or the retina in histopathology.[63,64] Rao showed that although SO and Vogt–Koyanagi–Harada (VKH) syndrome are different entities, these conditions share similar clinical features, immunohistochemistry, histology, HLA associations, and T cell response to different antigens in - vitro.[64] The sparing of choriocapillaris in both these diseases was hypothesized to be due to anti-inflammatory factors (including transforming growth factor-beta) released from the RPE.[64] However, in chronic recurrent VKH syndrome, granulomatous inflammation is noted and the choriocapillaris is involved.[65]

The absence of necrosis is another characteristic feature.[4] The choroid is the main seat of activity, while the retina is mostly spared.[4] Dalen–Fuchs (DF) nodules are clinically seen as yellow-white lesions in the peripheral retina, which may extend towards the optic disc or even involve the posterior pole. Sometimes, these lesions can be confluent.[66]

DF nodules have been reported in around 25%−35% of the cases with SO.[1] As DF nodules may occur early in the peripheral retina, incidence increases to 41.5% if evidence of at least one peripheral DF nodule is taken into account.[1] Involvement of the RPE in SO may be of three different morphologies.[67] The first type showed focal RPE hyperplasia and aggregation. The second type or typical DF nodule is characterized by intact RPE overlying lymphocytes and epithelioid cells. The third type showed degeneration of RPE and disorganized DF nodule with a possible subretinal release of the contents of the DF nodule.[67]

Initially, DF nodules have "substance" in them which gives an elevated appearance of the overlying retina, and with time atrophy ensues. DF nodules are nodular clusters of epithelioid cells containing pigment lying between the RPE and Bruch's membrane.[68] Font et al[69] found that the

nodules were visible as minute (130–160 μm), round, greyish-white mounds elevating the RPE. Under electron microscopy, the "epithelioid" cells had round to oval nuclei with abundant, relatively lucent cytoplasm containing parallel profiles of rough-surfaced endoplasmic reticulum, prominent Golgi lamellae, clusters of polyribosomes, and scattered mitochondria.[69] Under ultraviolet light, they appeared as myriad autofluorescent yellowish-orange dots consistent with lipofuscin.[69] This provided support to the concept that the "epithelioid" cells in DF nodules represent transformed retinal pigment epithelial cells forming a cage-like framework within the nodule.[70]

Although the retina is spared, few enucleated eyes of SO show collections of mononuclear cells around the blood vessels and in the areas overlying the DF nodules.[1]

The sclera is involved along the emissary veins and inflammatory exudates involve the optic nerve along with the meninges.[70] Along with breaks in the lens capsule, features of phacoanaphylaxis, with zonal granulomatous inflammation around the lens material may be seen as an atypical histopathological feature.[70]

Immunohistochemical studies have revealed infiltration of predominantly T lymphocytes in the uveal tract.[68,71] B lymphocytes are seen in long-standing cases and patients receiving corticosteroids.[72,73] Helper (CD4+) T cells predominate early in the disease driving a T helper 1(Th1) response with the secretion of proinflammatory cytokines such as interferon-γ, interleukin 2 (IL-2), and interleukin 17 (IL-17).[74–76] Suppressor/cytotoxic (CD8+) T cells are observed in chronic cases.[72,73] M1 macrophages have been reported to predominate in the granulomas, with significant expression of interleukin 23 (IL-23), chemokine ligand 19 (CCL19), and C-X-C motif chemokine 11 (CXCL11).[74,64]

Tumour necrosis factor-alpha (TNF-α)-mediated mitochondrial oxidative stress in the outer retina of enucleated human globes leading to the apoptosis of photoreceptors, could be an early mechanism leading to vision loss in SO.[77,78] However, higher levels of protective molecules like α-A-crystallin have also been detected in the outer retinal layers.[79] The expression of Fas and Fas ligand (FasL) is increased in eyes with SO and it has been suggested that apoptosis may play a role in limiting ocular inflammation.[76,80]

Zhong et al[81] described the role of the interleukin-23/interleukin-17 signalling pathway in autoinflammatory and autoimmune uveitis pathologies like SO. They showed that IL-17 targets RPE cells and disturbs their retinal barrier function, thereby promoting intraocular inflammation.

They proposed that future studies focusing on drugs targeting the IL-23/IL-17 pathway may help in the improvement of diagnosis and treatment of this autoimmune uveitis entity.[81]

Downregulation of microRNAs (hsa-miR-1, hsa-let-7e, hsa-miR-9, and hsa-miR182) has been associated with the expression of proinflammatory cytokines, particularly TNF-α and nuclear factor-kappa B1 (NF-κB), that are crucial to the pathogenesis of the disease.[82]

Clinical Features

SO is described as a rare, bilateral, granulomatous uveitis that follows ocular trauma or surgical procedures to one eye (inciting eye) threatening sight in the fellow eye (sympathizing eye).

The most common event that can trigger the development of SO is penetrating eye injuries (Figure 2).[83] The usual period between inciting event and SO is 2 weeks and

3 months, but cases have been described as early as 5 days and as late as 66 years after the initial incident.[84,85]

Patients may present with symptoms like diminution of vision, ranging from mild visual disturbance to significant visual loss, pain, redness, photophobia, photopsia, and floaters.[86] Due to changes in accommodation, near vision may be compromised in the early course of the disease.[85]

Anterior segment examination often reveals bilateral acute anterior uveitis with mutton-fat keratic precipitates on the corneal endothelium.[66,87] However, non-granulomatous reaction involving the anterior segment may also be noted in some cases of SO.[88] Lymphocytic infiltration of the iris may result in thickening and synechiae while variation in the intraocular pressure may be attributed to ciliary body shutdown or blockage of the trabecular meshwork.[66]

Posterior segment examination often reveals multifocal serous retinal detachment, exudative retinal detachment, moderate-to-severe vitritis, choroiditis, thickening of the
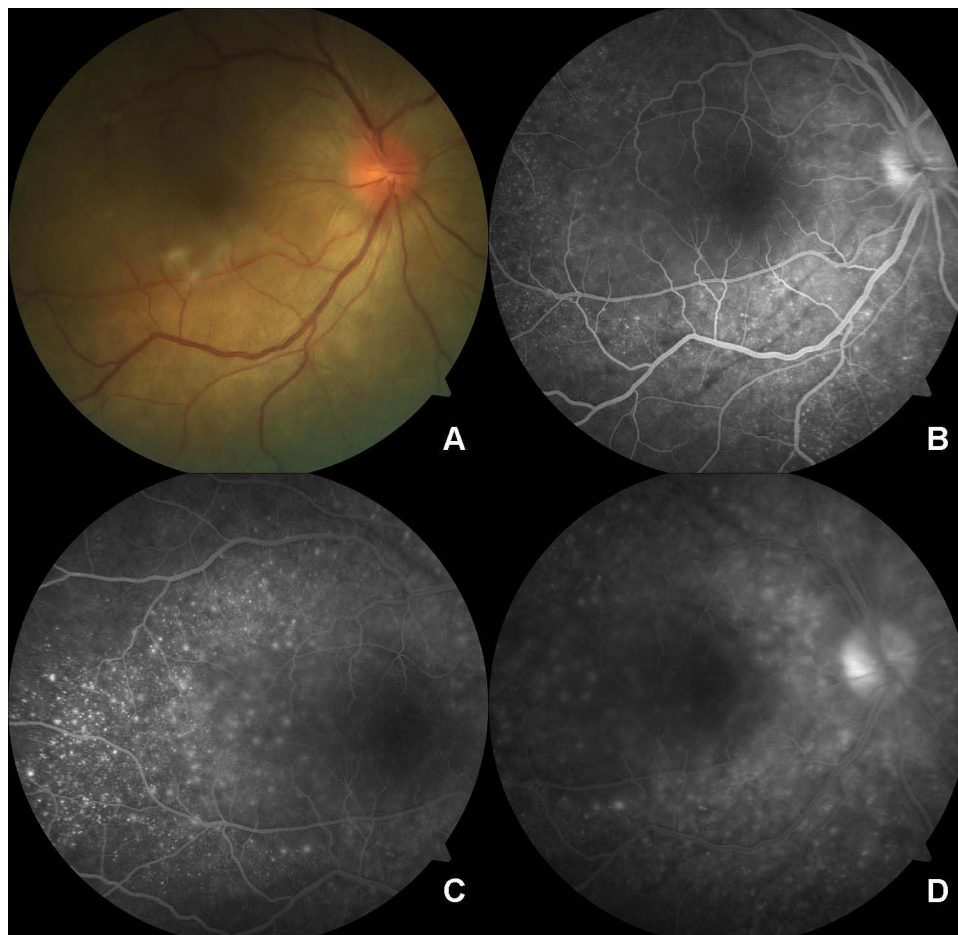
Figure 2 (A) Fundus photo of the posterior pole of the sympathizing eye shows a blurred margin of the optic disc, radial retinal folds around the optic disc, and subretinal fluid at the posterior pole. (B) FFA image at early venous phase shows disc leak, choroidal folds, and pinpoint leaks. (C) FFA image at mid-venous phase shows the typical multiple pinpoint leaks more clearly. (D) FFA image at late venous phase shows disc leak and blurred margins of pinpoint leaks.
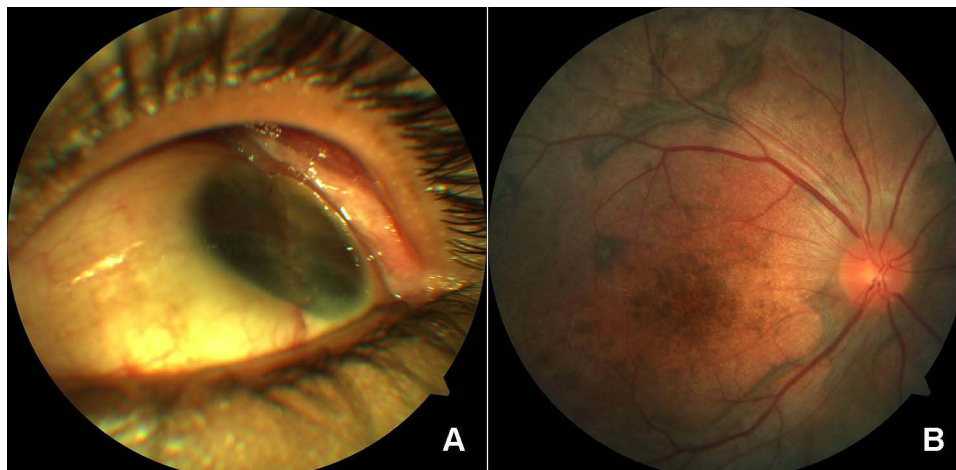
Figure 3 (**A**) Anterior segment photo shows a phthisical eye with evidence of repair of globe rupture. (**B**) Posterior segment photo of the other eye shows depigmented fundus (sunset glow) with areas of fibrotic pigmentary changes.

peripapillary choroid, and edema or hyperemia of the optic nerve in the acute phase (Figure 2).[66,87] Yellow-white lesions beneath the level of RPE signify DF nodules that are not specific to SO and they may not be present in 30–50% of the cases.[89]

The degree of intraocular inflammation is found to be similar in the exciting eye and the sympathizing eye. In the chronic phase of the SO, the most common presentation is panuveitis or anterior uveitis with extensive chorioretinal damage. Subretinal fibrosis (Figure 3) and choroidal neovascularization[90] may be noted in chronic cases. Depigmentation of the choroid in pigmented individuals and the appearance of multiple nummular chorioretinal scars located mostly in the periphery of the fundus are seen.[91,92]

The co-existing extra-ocular findings documented in some cases of SO include headache, meningismus, deafness, poliosis, vitiligo, and cerebrospinal fluid (CSF) pleocytosis.[89] The association of SO and hearing loss is rare but is possible as both uvea and auditory labyrinth share antigens owing to their common origin from the neural crest cells.[89] The spectrum of varying clinical presentations in cases of SO is summarized in Table 2.[52,1,6,19,20,127]

Complications that may follow the chronic phase of SO are cataract, glaucoma, choroidal atrophy, subretinal fibrosis, choroidal neovascularization (CNV), hypotony, and phthisis.[93]

Investigations

Key criteria to consider the diagnosis of SO in the case of bilateral uveitis include

1. Antecedent history of unilateral ocular trauma or surgery, and
2. An intraocular inflammation (anterior chamber and vitreous) or a panuveitis with choroidal involvement.[94]

The ancillary investigations work as an adjunct to support the diagnosis, to determine the severity of the disease, to assess the response to treatment during follow-up, and to detect possible secondary complications like CNV.[91]

Table 2 Clinical Features of Patients with Sympathetic Ophthalmia (SO)

Symptoms	Signs
• Redness	• Keratic precipitates (granulomatous or nongranulomatous)
• Sensitivity to light	• Anterior chamber cells/Flare
• Vision loss (near vision loss may be early)	• Synechiae
• Pain	• Vitritis
• Watering of eye	• Optic disc hyperemia
• Floaters	• Serous retinal detachment (may be multifocal)
• Flashes (photopsia)	• Choroiditis
• Metamorphopsia	• Dalen–Fuchs nodule
• Hearing complaints (tinnitus, hearing loss, dysacusis)	• Macular edema
• Headache	• Vasculitis (rare)
• Meningismus	• Cataract
	• Choroidal neovascularization
	• Sub-retinal hemorrhage
	• Subretinal fibrosis
	• Pigmentary atrophy

In patients who present only with posterior segment manifestations, the most commonly used imaging modality is fundus fluorescein angiography (FFA).[95] Other tests that can offer useful information include indocyanine green angiography (ICGA), optical coherence tomography (OCT), ultrasound B scan, and autofluorescence imaging.

FFA (Fundus Fluorescein Angiography)

Abnormal angiographic features seen in SO are of two distinct types: initial pinpoint hyperfluorescent leaks and multiple hypofluorescent spots with pooling of the dye in the later phases. These pinpoint leaks slowly increase in size and coalesce under focal retinal detachments. This results in multilobular pooling of the dye with staining of the subretinal fluid.[95] Early angiographic features of the acute phase of Vogt–Koyanagi–Harada (VKH) disease are also similar to this. The second type of angiographic feature is less common and comprises hypofluorescent foci during the early phase of angiography. These become hyperfluorescent subsequently. This pattern is identical to that seen in patients with acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[96] In the chronic phase of SO, the nummular scars show window defects from chorioretinal adhesions, and focal RPE and inner choroidal damage. The subretinal fibrotic changes give rise to a gradual increase in hyper fluorescence and staining.[97] The presence of choroidal neovascularization shows leakage of the dye at the macula.

ICGA (Indocyanine Green Angiography)

ICGA is the modality of choice specifically to assess the choroid and to search for the presence of choroidal infiltrates.[98,99] Multiple hypocyanescent spots are the common findings on ICGA in patients with SO. These spots occur due to the presence of cellular infiltration of the choroid, DF nodules, or overlying edema. Casella et al[100] showed that these hypocyanescent spots persist throughout the phases of ICGA. These hypocyanescent spots are noted to lessen or vanish once the treatment with corticosteroid is started and are consistent with clinical improvement.[99,101]

Autofluorescence Imaging (AF)

Autofluorescence imaging (AF) is a simple and non-invasive procedure. It is based on the detection of fluorophores denoted mainly by lipofuscin in the RPE.[102] The amount of lipofuscin is thought to be an indicator of the activity and viability of the RPE. AF can not only aid in the early detection of disease activity but also permits for the evaluation of the extent of damage and identification of sequelae such as choroidal neovascularization secondary to inflammation.[103,104] Fleischman et al[104] described a petaloid area of hyperautofluorescence centered on the optic nerve corresponding to areas of exudative retinal detachment before initiation of treatment. Following treatment, speckled areas of hyper- and hypoautofluorescence similar to leopard spots were seen in the previous areas of exudative detachment.[104] However, owing to limited studies reporting the use of AF in SO, further studies are necessary to establish the pattern of AF in posterior uveitis, especially that of SO.[104,105]

Ultrasound B-Scan

B-scan ultrasonography in SO characteristically demonstrates diffuse choroidal thickening (60% of the cases) and the presence of serous retinal detachment at the posterior pole.[106] In the presence of posterior synechiae or dense cataracts where the retinal examination is not possible, B-scan ultrasonography can provide vital information towards the diagnosis.[107]

Optical Coherence Tomography

In time-domain optical coherence tomography (TD-OCT), DF nodules appear as "discrete nodules at the RPE level with shallow serous detachments of the neurosensory retina overlying some of these areas".[108] A hyperreflectivity of the overlying photoreceptor layer may denote inflammation of the overlying retina as has been demonstrated in histological studies.[108]

Spectral-domain optical coherence tomography (SD-OCT) with or without enhanced depth imaging (EDI-OCT) and swept-source optical coherence tomography (SS-OCT) are non-invasive imaging modalities. These are widely used in the diagnosis and the management of several retinal diseases and uveitides. Multiple serous detachments of the neurosensory retina can be documented using OCT. The distinctive feature in SO and VKH is the presence of hyper-reflective septa crossing dividing the fluid into pockets, also called bacillary layer detachment.[109]

Bacillary layer detachment is a newly described SD-OCT feature that denotes an intraretinal split at the photoreceptor inner segment myoid. Polyak SL described the bacillary layer in 1941 as the combination of inner

segment and outer segment of photoreceptors.[109] Mehta et al proposed the term presumed bacillary layer detachment in SD-OCT to describe an intraretinal split at the level of myoid of photoreceptor inner segment, which separates the cell body from the outer segment and ellipsoid zone.[109]

Other SD-OCT features of SO include RPE folds and fluctuations of the internal limiting membrane.

EDI-OCT helps in demonstrating the presence of choroidal thickening, subretinal choroidal folds, and the loss of the physiologic choroidal vascular pattern. Photoreceptors' outer segments seem elongated as a result of the photoreceptors' disconnection from the RPE and the resultant interruption in the shedding of the outer segments.[107]

SD-OCT shows "multiple hyperreflective lesions at the level of the RPE with associated disruption of the photoreceptor inner segment/outer segment (IS/OS) junction" at the location of DF nodules at the active stage.[110] On the resolution of the inflammation, disruptions of the IS/OS junction are noted with disruption or disturbance of the RPE.[110]

Rogaczewska et al[111] noted a minimal disintegration of the RPE, the interdigitation zone (IZ), and the ellipsoid zone (EZ) before the appearance of any obvious signs of uveitis in SO. Agrawal et al[112] described choroidal structural changes in SO on swept-source optical coherence tomography (SS-OCT). They showed that choroidal thickness (CT) and choroidal vascularity index (CVI) were significantly increased in SO, representing a novel non-invasive biomarker of disease activity that can be potentially explored in the diagnosis and follow-up of patients with SO.

Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is used to non-invasively study the retinochoroidal vasculature without the need for intravenous dye. It is used to detect multiple small foci of choriocapillaris flow-void that correlate with ICGA findings.[113] These areas of flow void in choriocapillaris can be used to monitor the treatment response to therapy as these resolve following successful therapy.[114]

OCTA has also been stated to be more sensitive than conventional imaging techniques like fluorescein angiography and OCT in denoting choroidal neovascularization.[115]. Brar et al[114] reported the treatment response in SO as assessed by widefield OCT angiography. They highlighted that OCTA can detect possible ischemic changes within the choriocapillaris in SO and demonstrated that these can be used as an anatomic marker to monitor treatment response.[114]

Differential Diagnosis
Vogt–Koyanagi–Harada Syndrome

Vogt–Koyanagi–Harada syndrome is a bilateral granulomatous panuveitis. It is most commonly seen in between the second and fifth decade[116] with a racial predisposition towards Asians.[116] It is often associated with a prodrome of meningeal and auditory symptoms.[4] In acute as well as chronic phases, the clinical and histopathologic features of the disease are identical to SO, except the absence of a history of trauma. However, some findings such as vitiligo and alopecia,[116] and cerebrospinal fluid (CSF) pleocytosis[117] are more closely associated with Vogt–Koyanagi–Harada syndrome than with SO. History of penetrating trauma is helpful in differentiating between SO and VKH syndrome.[4,65]

Ocular Sarcoidosis, Tuberculosis (TB), Syphilis, Multifocal Choroiditis, and Panuveitis

Sympathetic ophthalmia must be differentiated from several infectious and non-infectious uveitides, including syphilis, tuberculosis, sarcoidosis, multifocal choroiditis, and panuveitis. Other bacterial and fungal infections can also produce granulomatous anterior and/or posterior uveitis. They are usually differentiated from each other by history and associated clinical findings.[4] Tuberculosis associated with uveitis is commonly observed in Southeast Asian, Western Pacific, and Eastern Mediterranean regions.[118–120] Idiopathic multifocal choroiditis is mostly seen in Caucasians,[121] during the second and sixth decades of life.[122,123]

Phacoanaphylactic Uveitis

It is the immunological response to lens proteins due to a rupture (surgical or traumatic) of the lens capsule as severe granulomatous uveitis. It can simulate the clinical picture of sympathetic ophthalmia, and these two entities may even coexist in the same eye. Although phacoanaphylactic endophthalmitis is mostly unilateral, there have also been rare reports of bilateral cases.[124] In contrast to SO, in bilateral phacoanaphylaxis, the timing of inflammation in each eye is

different and choroidal thickening is minimal even in very severe forms of phacoanaphylactic endophthalmitis.[125] Evidence of rupture of lens capsule helps in clinching the diagnosis and should be carefully looked for. Lens extraction is the mainstay of management in phacoanaphylactic uveitis.[125]

Treatment
Medical Treatment

A retrospective study conducted by the National Eye institute in 1995 showed good visual outcomes following SO when early treatment with high doses of steroids and immunosuppressive agents was instituted.[126]

Corticosteroids

Although corticosteroids are the mainstay of treatment of SO, they may not prevent the occurrence of SO when given prophylactically.[52] It is recommended to start additional immunomodulator therapy at the initial presentation itself.[52] An initial high dose of oral prednisone is used with a dose ranging from 1 mg/kg/day to 2 mg/kg/day.[127] Intravenous (IV) pulse steroid therapy with methylprednisolone at 1g/day for 3 days has been used for severe cases.[6] Pulse dexamethasone therapy[127] (100 mg dexamethasone in 250 mL of 5% dextrose per day for 3 days) is a cheaper and safer alternative to pulse intravenous methylprednisolone.[128] In severe cases, intravenous pulse steroid is used daily for 3 days, followed by the use of high-dose oral steroids from the fourth day. Oral proton pump inhibitors (including omeprazole or pantoprazole or rabeprazole) and calcium supplements should also be started from the first day.

The anterior chamber reaction needs to be treated with topical steroids and cycloplegics according to the severity. Response to therapy is clinically monitored by visual acuity, anterior chamber cells, media haze/vitritis, optic disc hyperemia, choroiditis, and subretinal fluid. Optical coherence tomography helps in monitoring by objectively documenting subretinal fluid, bacillary layer detachment, the convex appearance of the RPE, and choroidal thickness. Once the inflammation is adequately controlled, very gradual tapering of steroids over 3–6 months is started, with a close watch on clinical features and OCT.[127] SO is a chronic disease with a very high chance of recurrence on reducing steroids/immunomodulators. Thus, the aim is to maintain remission either on a low daily dose of steroids (maintenance dose of oral prednisolone of ≤10mg daily),

or by using a low daily dose of steroids in combination with immunomodulators, or only immunomodulator/s. If the disease recurs, the acute phase needs to be managed by increasing the oral dose of prednisolone (depending on the severity of recurrence, the dose may be generally adjusted to 0.5–1mg/kg).

Foster et al have proposed that for most cases of uveitis if a patient has been in remission for at least 2 years on immunomodulator/s without steroids, weaning the patient of immunomodulatory therapy should be tried in a very gradual process.[129] Such patients may then go into long-term remission. However, some cases of SO may be an exception to this and would require lifelong therapy with immunomodulators to prevent relapses.

Complications of systemic steroid therapy include worsening of diabetes mellitus, adrenal insufficiency, obesity, susceptibility to infections, aseptic necrosis of the hip, and osteoporosis.[130]

The intravitreal route helps in reducing the systemic doses of steroids and other immunosuppressive agents necessary to maintain remission.[131] The intravitreal approach lessens some of the steroid-induced systemic side effects and enables the delivery of high concentrations of drug directly at the site of illness.[132] Reduction of intraocular inflammation, improvement in the visual field, visual acuity, and lessening the doses of systemic therapy have been reported with the use of IVTA (intravitreal triamcinolone acetonide).[133] Mahajan et al[134] described eight patients treated with an implantable fluocinolone acetonide implant device (Retisert, Bausch & Lomb, Rochester, NY). Potential risks associated with the use of intravitreal steroid injections include cataract formation, secondary glaucoma, retinal detachment, retinal tears, and endophthalmitis.[66]

Meira et al[135] showed that 0.19 mg fluocinolone acetonide intravitreal implant was effective in controlling recurrent non-infectious uveitic macular edema in a patient with 'presumptive diagnosis of idiopathic panuveitis and sympathethic ophthalmia'. They also suggested that sustained control of inflammation enables better control of macular edema, and benefits of intraocular implant may persist even after cessation of the direct anti-inflammatory effect.

Wocker et al[136] demonstrated the effective use of intravitreal dexamethasone implant in cystoid macular edema cases secondary to SO.

Mansour[137] reported the use of multiple dexamethasone implants (Ozurdex, Allergan Inc, Irvine, CA) as sole

therapy in a 46-year-old woman who denied systemic immunosuppression. The intraocular pressure was controlled medically. This is an exclusive report of SO treated merely with slow-release dexamethasone implants without systemic therapies. However, this is not the accepted standard therapy till now.[137]

Immunomodulators

Earlier indications of immunomodulators in SO included the cases where there is a contraindication for steroid use, the occurrence of significant steroid-induced side effects, flare-ups on tapering or stopping of steroid therapy, or cases who do not respond adequately to steroid therapy.[104] A large multicenter retrospective case series noted that 70.7% of 130 SO patients needed immunosuppressive therapy.[138]

However, many authors recommend that SO is one of the few indications in which early initiation of immunomodulators should be considered.[19,129,139,140] This would enable achieving an adequate effect of immunomodulators before the steroids are tapered to low levels. Owing to the significant toxicities of these agents, close monitoring is necessary preferably in consultation with a rheumatologist or internist.[66]

Azathioprine

Azathioprine is a prodrug of 6-mercaptopurine. It inhibits purine synthesis and affects the maturation of the B-lymphocytes and T-lymphocytes. Thiopurine methyltransferase (TPMT) metabolizes tche drug, and azathioprine should be avoided in patients with low or absent TPMT activity to avoid toxicity.

Azathioprine has been used at 50–150 mg per day (1–3 mg/kg/day)[129] dose with regular monitoring of complete blood count. Azathioprine is very effective in the management of SO[141] and also has a steroid-sparing effect; hence, it can be given in case of intolerance to steroids or with decompensated diabetes.[142] Tan et al noted that azathioprine was used in around 80% of 130 patients with SO.[138]

Methotrexate

Methotrexate is a folic acid analogue and prevents thymidylate production by inhibiting dihydrofolate reductase and also affects the rapidly dividing leucocytes. Anti-inflammatory effects may be related to adenosine release. The usual dose of methotrexate is 7.5–25 mg/week.[143] Methotrexate or azathioprine is usually used as the initial choice of immunomodulatory therapy in our

practice for such cases. Methotrexate is a preferred choice for pediatric disease. The advantages of methotrexate include low cost, once-weekly dosage, efficacy, relative safety, and long experience with the drug. Side effects include gastric upset, weakness, hepatic compromise, and pneumonitis. However, it is teratogenic and must be avoided if pregnancy/conception is being planned. In our series of 14 patients with SO, 5 patients were initially started on methotrexate, and 3 patients were started with azathioprine along with systemic steroids. At the final follow-up, five patients were on methotrexate, and azathioprine was being used in one patient.[127] Eight percent of patients were treated with methotrexate in a large case series.[138]

Mycophenolate Mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid and inhibits inosine monophosphate dehydrogenase resulting in inhibition of purine synthesis. It has to be taken in an empty stomach.

Mycophenolate is given 1–3 g once daily.[129] It can be used to treat refractory panuveitis or posterior uveitis unresponsive to high-dose maintenance steroids[144] with fewer/manageable side effects[145] even when other immunosuppressive drugs fail or are not well tolerated.[146]

Cyclosporine

Cyclosporine is a T-cell inhibitor (calcineurin inhibitor). The recommended dose for cyclosporine is 2.5–5 mg/kg/day,[147] tapering to a maintenance dose of 1mg/kg/day slowly over a 1–2 month period.[148] The drug is wboth ofell tolerated by children and adolescents[149] and can give a complete response in even progressive and severe inflammation caused by sympathetic ophthalmia.[150] Additionally, cyclosporine may help in controlling inflammation in cases resistant to systemic steroids and cytotoxic agents.[151]

Regular monitoring of blood pressure and renal function is important, while the patient is on cyclosporine therapy. Combination of cyclosporine and azathioprine along with steroids controls the intraocular inflammation at a lower dose of corticosteroids, thereby reducing the steroid-related side effects.[152] An analysis of 130 cases with SO showed that cyclosporine was used in 13% of the patients and mycophenolate was used in 12% of the cases.[138]

Alkylating Agents

Alkylating agent like cyclophosphamide is used in the dose of 1–3 mg/kg/day.[153] The usual dose of chlorambucil is 2–12 mg/kg/day orally. Patel et al noted that high-dose short-term chlorambucil was effective in controlling inflammation in 16 patients with SO.[86,154] Hence, chlorambucil is an alternative to steroids in the case of steroid-resistant sympathetic ophthalmia but has serious side effects demanding a long-term follow-up.[155]

Biologic Therapy

The term biologic agents or biologic response modifiers includes the class of drugs that inhibit various cytokines. They were first utilized in the treatment of uveitis in the year 1990.[156] They are considered to play an important role in the treatment of uveitis because of their ability to provide targeted immunosuppression. Unlike the evidence of the use of biologic agents in various systemic disorders, the mainstream literature of these therapies in uveitis treatment is either in the form of uncontrolled trials or case series.[157]

Elevated levels of TNF-α, a key pro-inflammatory cytokine, are found in serum and ocular fluids in patients with SO.[158] This shows credible evidence that the therapy with TNF-α antagonists may be useful for the treatment of SO.[159]

Of the available anti-TNF-α agents, the currently recognized ones for the treatment of SO are infliximab and adalimumab. Infliximab is a mouse-human chimeric monoclonal IgG1 antibody against TNF-α, whereas adalimumab is a fully humanized monoclonal IgG1 antibody against TNF-α. Both of them bind efficiently to the soluble and transmembrane forms of TNF-α.[160] The usual administered dose of infliximab is 5–20 mg/kg/day and adalimumab is 40 mg once every 2 weeks.[161] Adalimumab has been approved by the US Food and Drug Administration in 2016 for non-infectious intermediate, posterior, and pan-uveitis.[162] Gupta et al[163] reported the successful treatment of refractory SO in a child using infliximab. The child had not responded to therapy with high-dose oral prednisone, methotrexate, cyclosporine, mycophenolate, and daclizumab. Infliximab was administered at a dosage of 10mg/kg every 4 weeks. The inflammation was controlled within 2 weeks of starting therapy. The quiescence was maintained for more than 2 years, permitting for discontinuation of all systemic treatment. Infliximab can also be used earlier in sympathetic ophthalmia when treatment with corticosteroids is to be shortened.[164] Soheilian et al[39] documented the use of adalimumab in treating a patient with refractory SO after phakic intraocular lens implantation. Kim et al[165] successfully used adalimumab therapy in the treatment-refractory pediatric SO after trauma. Vallet et al[166] demonstrated that adalimumab and infliximab are equally efficacious for the treatment of non-infectious uveitis.

Hiyama et al[42] demonstrated the efficacy of adalimumab in steroid or immunosuppressant refractory SO, particularly for glaucoma subjects, in whom long-term steroid therapy should be avoided. They achieved control of intraocular inflammation with the use of adalimumab and also showed that intraocular pressure (IOP) stayed within the target range for 7 months.

A combination of adalimumab and methotrexate was needed in around 70% of the patients with VKH/SO compared to around 20% of the patients with Behçet disease to control inflammation in a study by Hiyama et al.[167]

However, as for infliximab, a nonsignificant trend towards a higher rate of serious side effects was noted, including infections, hypersensitivity reactions, autoimmune disease, and neoplasia.[166] Also, patients need to be tested for tuberculosis exposure before starting infliximab therapy. The study conducted by Simonini et al[168] showed a higher rate of long-term quiescence with the use of adalimumab compared with infliximab. They also depicted that adalimumab is less expensive, can be administered subcutaneously, and can provide more comfort for patients. This alleviates the need for hospitalization required in case of intravenous administration of infliximab.[168]

Thus, in non-infectious uveitis entities such as SO, where TNF-α is considered to play a role in the pathogenesis, TNF-α antagonists, particularly adalimumab may be a strong contender as a first-line corticosteroid-sparing agent. Dosage and route of administration of various immunomodulatory agents including biologics used to treat sympathetic ophthalmia are mentioned in Table 3.[147,161]

Mesquida et al[169] reported the 24-month efficacy and safety of the interleukin-6 receptor antagonist tocilizumab (TCZ) for refractory uveitis-related macular edema (ME) in various non-infectious uveitides including SO. This study showed that TCZ was effective and had a comparable safety profile when used for the treatment of refractory uveitis-related ME.

Other Medical Therapy

Saatci et al[90] successfully used intravitreal aflibercept as an adjunct to systemic therapy in the case of choroidal neovascular membrane associated with SO.

Table 3 The Spectrum of Various Immunomodulatory Agents Used in the Treatment of Sympathetic Ophthalmia (SO)

Class	Drug	Route of Administration	Dosage
Inhibitors of T-cell signaling	Cyclosporine	Oral	2.5–5 mg/kg/day
Antimetabolites	Azathioprine Methotrexate Mycophenolate mofetil	Oral Oral/Subcutaneous/ Intramuscular/Intravenous Oral	1–3mg/kg/day 7.5–25mg/week 1–3 mg once a day
Alkylating agents	Cyclophosphamide Chlorambucil	Oral/Intravenous Oral	1–3 mg/kg/day orally or1 g/m^2(BSA) infusions 2–12 mg/kg/day
Biologics	Infliximab Adalimumab	Intravenous Subcutaneous	5–20 mg/kg/day[129] 40 mg once every 2 weeks[161]

Graham et al[170] studied apheresis therapy in the treatment of ophthalmologic diseases including SO. Apheresis affects the disease by modifying blood plasma and modulating disease-causing agents.

Surgical Treatment

In situations where the exciting eye is blind or severely traumatized, the indicated surgical options are evisceration or enucleation of the exciting eye. However, there is debate about which procedure is the most suitable and when the procedure should be carried out if at all needed. The classic dictum regarding the prevention of sympathetic ophthalmia is by enucleation of the injured eye within 2 weeks of its injury.[171] Lubin et al[1] showed that if enucleation took place within 2 weeks of SO onset then 74% of their patients had retained a visual acuity of 20/70 or better. Controversy remains regarding the benefit of enucleating the exciting eye once the disease process has started. Some studies stated that early enucleation of the exciting eye aid in improving the visual potential of the sympathizing eye.[1] Another review showed no benefit to the sympathizing eye from enucleation of the exciting eye at any time during the disease course.[63] Since in the course of the disease, the exciting eye may have better vision[127]; therefore, enucleation should be considered only in cases where there is little or no prognosis for useful visual function.

Dogra et al[172] stated that surgical intervention in the inciting eye including keratoplasty, glaucoma surgery, and pars plana vitrectomy is a viable option for improving anatomic and functional outcomes in these eyes. However, the essential prerequisite for this is adequate control of inflammation with the use of oral steroids and immunosuppressive agents.

Prognosis

Galor et al[173] analyzed the findings of 85 patients with SO and stated in this series that about 60% of sympathizing eyes sustained a visual acuity of at least 20/50 while 75% retained a visual acuity better than 20/100. Payal and Foster[174] showed that with a minimum follow-up of 2.5 years about 57.9% achieved at least 20/50 visual acuity in the sympathizing eye.

Chawla et al[127] demonstrated that with the initiation of treatment within 15 days of onset of symptoms of SO, they were able to achieve a visual acuity of 20/40 or better in 85.7% sympathizing eyes, and 21.4% exciting eyes maintained visual acuity of at least 20/80.

Dutta Majumdar et al found that a final visual acuity of at least 20/40 could be maintained in 70% of sympathizing eyes of 20 cases with pediatric SO.[175] Three exciting eyes also had a good visual outcome. Seventeen of 20 patients received immunomodulatory therapy in addition to systemic steroids.[175]

Steroid and immunosuppressives were used in all cases in a series with SO after PPV, and significant improvement in vision was noted in 15 of 16 patients.[19]

Yang et al noted that the final visual outcome was worse in patients with SO compared to patients with VKH.[88]

Method of Literature Search

Search engines used included Google Scholar, PubMed, and Google books. The search phrases included sympathetic ophthalmia and sympathetic ophthalmitis. We reviewed English articles and articles in other languages were also reviewed using their English abstract or English translation.

Conclusion

All the past and recent literature on SO reinforce the importance of prompt diagnosis and treatment in achieving better visual outcomes in these patients. Immunomodulatory therapy has revolutionized the treatment of SO patients by helping them achieve remission without or on low-dose steroids.[127] Hence, the key to success in the management of this blinding disease is early recognition of SO, a rapid institution of therapy, and further titration of the dosage of immunomodulatory agents to minimize their side effects. Biologics may further improve upon the outcomes in selected cases of SO. Advances in imaging modalities including OCT, OCTA, and ICGA help in detecting subclinical inflammation and may guide immunosuppression leading to better visual outcomes.

Most physicians now prefer to avoid enucleation or evisceration of the exciting eye as useful vision can be maintained in some of these eyes with early treatment. SO after vitreoretinal surgery should be kept in mind as more and more such procedures are being performed. SO is increasingly being seen in the older population likely related to ocular surgical exposure. Also, both genders are now equally involved in developed countries, which should be an impetus for the development of injury prevention programs.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas: took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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