Sympathetic Uveitis/Ophthalmia

Sympathetic ophthalmia (SO) is a bilateral, chronic, diffuse, granulomatous panuveitis that can develop after ocular surgery or penetrating trauma. The disease is thought to be an autoimmune response to exposed uveal tissue, such that both the traumatized (exciting eye) and the fellow, so-called sympathizing, eye are affected, potentially leading to bilateral visual loss and disability.

Most cases are diagnosed based on history and presentation, and some are confirmed by the histologic analysis. SO represents approximately 1% to 2% of all uveitis cases. The true incidence and prevalence of SO has been hard to establish; however, a prospective study in England and Ireland by Kilmartin and associates estimated that SO affects 0.03 per 100,000 persons per year. In addition, its onset or diagnosis is often delayed for months or even years after the initial injury. SO is a relatively rare disease, and as a result of improvements in modern surgical and medical treatments, it has become even more uncommon, so that its incidence has greatly decreased during the last 30 years. Although earlier studies found traumatic SO to be more common, Kilmartin and associates demonstrated ocular surgery to be the most common cause. It may complicate numerous surgical procedures such as evisceration, glaucoma surgery, vitrectomy, cataract extraction, and retinal detachment surgery. Although advances in modern surgical techniques may help to reduce the incidence of SO, the more aggressive surgical management of severely traumatized eyes and the development of vitreous surgery might possibly be responsible for increasing the causative role of ocular surgery.

Presentation

Although the uveitis may start as early as 5 days or as late as 50 years after injury, well over 90% of cases occur after 2 weeks but within 1 year. Most of these (80%) occur within 3 weeks to 3 months postinjury. Males are found to have greater rates of post traumatic sympathetic ophthalmitis probably because of higher trauma rates.

Typically, the clinical onset of SO is preceded in an insidious or acute manner by the development of mild inflammation in the sympathizing eye and the worsening of inflammation in the exciting eye. (Figure 1 and 2).

Pain, photophobia, lacrimation, and blurring of vision are frequent prodromal symptoms.

Ciliary flush, ‘mutton fat’ keratic precipitates, cells and flare in the anterior chamber can be observed. Examination of the posterior segment typically reveals moderate to severe vitritis, optic nerve head edema, choroidal infiltration and midequatorial yellowish-white choroidal lesions that become confluent with time and correspond.

Figure 1: Sympathizing eye
histopathologically to the Dalen–Fuchs nodules. These are not pathognomonic for SO, as other granulomatous inflammatory eye diseases may also exhibit such lesions, but they might be suggestive of a more severe stage of the disease. Ocular complications, which occur in 25 to 30% of cases, include extensive anterior and posterior synechiae, iris thickening due to lymphocytic infiltration, pupillary membrane formation, rubeosis, glaucoma, cataract, optic atrophy, choroidal neovascularization, and possibly phtisis. Without adequate treatment, the disease usually runs a prolonged course, with recurrent episodes of painful inflammation and often eventual blindness. Extraocular manifestations occasionally include cerebral vasculitis, hearing loss, and skin or cerebrospinal fluid changes similar to those found in Vogt–Koyanagi–Harada disease.

Fluorescein Angiography and ICG Angiography are some of the investigations useful for diagnosis.

**Differential Diagnosis**
- Vogt–Koyanagi–Harada syndrome
- Sarcoidosis
- Phacoanaphylactic uveitis
- Chronic idiopathic uveitis
- Infectious granulomatous uveitis (bacterial and fungal) such as occurs in tuberculosis and syphilis

**Intraocular lymphoma**

Clinically, the diagnosis of SO is not always obvious. A history of ocular surgery and the absence of systemic involvement or ocular infection are some of the keys to its diagnosis. Although there are no specific laboratory studies which establish the diagnosis of SO, focused clinical tests can be used to rule out the presence of other diseases including PPD skin testing, chest radiograph, measurement of serum angiotensin converting enzyme, lysozyme, RPR and FTA-Abs, and possibly HLA typing and lumbar puncture.

**Pathology and Pathogenesis**

There is a diffuse, non necrotizing granulomatous inflammation involving the uvea, made up of lymphocyte infiltration intermixed with epithelioid cells. Dalen–Fuchs nodules are frequently reported and located in the midperiphery of the fundus, between Bruch’s membrane and the retinal pigment epithelium. In most cases, the inflammatory process does not involve the choriocapillaris or retina. Various histopathological features are possible, depending on the stage of the disease. Immunohistopathologic findings suggest that delayed hypersensitivity, mediated by the T-cells, is involved in the pathogenesis of SO.

The exact pathogenesis of SO is still unknown, however the most favored theory is an autoimmune process initiated by the breakdown of the blood–retinal barrier following a penetrating injury. The identity of the inciting antigen is uncertain but seems to be uveal rather than retinal. Association with HLA status suggests a genetic susceptibility to SO.

**Treatment**

The conventional and only truly known treatment of SO is the prevention of its occurrence by enucleation of the injured eye within 2 weeks of the traumatism, before its sensitization. This is not of course a recommendation to remove an eye with a reasonable prognosis for useful vision, and only applies to severely traumatized and sightless eyes. As a general guideline, careful wound toilet and prompt surgical closure of the injured eye should be performed, to prevent infection and the release of uveal antigens. Once SO develops, enucleation of the exciting eye is still subject to considerable controversy. A widely held principle is to try to save the injured eye if any potential for useful vision exists because it is a possibility that exciting eye eventually has a better visual acuity than the sympathizing eye. With respect to the surgical technique, enucleation seems to be better than evisceration, because the latter carries a risk, although it may only be slight, of SO developing from retained and potentially inciting antigenic tissue. In all cases, once the diagnosis of SO has been established, the most important factors associated with good visual outcomes are: time to initiation and adequacy of therapy. SO is a difficult disease to treat because the inflammation is often severe and chronic and results in significant vision loss. Vision loss is usually due to cystoid macular edema, chorioretinal atrophy, or hypotony.

Large doses of topical and systemic corticosteroids should be given, to improve visual outcome and prevent...
recurrences. Treatment is initiated with high doses of oral prednisone (1–2 mg/kg/day) combined with topical corticosteroids and cycloplegics, until the disease has been brought under control. In severe cases, intravenous pulse steroid therapy may be used (1 g/day methylprednisolone for 3 days), followed by oral prednisone. The gradual tapering of systemic and topical steroids may then be initiated depending on the clinical response of the uveitis. The minimum dose of prednisone necessary to control inflammation (generally between 5 and 10 mg/day) must usually be maintained for at least 1 year. In general, SO responds well to steroids, but in some patients the disease may be refractory to corticosteroids. Others may experience corticosteroid-related side effects. In all these cases, other immunosuppressive therapies may be considered. However, in view of the risk of serious side effects, it is highly recommended that these immunosuppressive treatments should only be used in cases of severe uveitis in which conventional treatment with prednisone is either not feasible or not effective. Antimetabolite agents, calcineurin inhibitors, alkylating agents, and more recently, biologic agents all have been used successfully. Cyclosporin, a potent inhibitor of T-cell function, may be used in combination with systemic administration of corticosteroids as a second-line treatment. Cyclosporin is also useful for inducing the resolution of secondary choroidal neovascularization. It is usually started at a dose of 5 mg/kg/day combined with 15–20 mg/day of oral prednisone, and increased until the inflammation is under control. Cyclosporin can then be slowly tapered (0.5 mg/kg/day every 1–2 months) depending on the level of activity of the disease.

However, patients need to be closely monitored, because the drug may be nephrotoxic, hepatotoxic, and neurotoxic, and may also cause hyperglycemia and hypertension. The recent success of infliximab, an anti-tumor necrosis factor α agent, may have promising results, but even this therapy has not controlled all cases of the disease, and prolonged drug-free remission has not been reported. Short-term, high-dose chlorambucil therapy has been reported to provide sustained periods of drug-free remission. It is administered orally; it is slower than other alkylators to show toxic effects (so it can be monitored with weekly complete blood count); and short-term side effects such as nausea, vomiting, anorexia, and alopecia are infrequent. However the reported increased risk of systemic malignancy when chlorambucil is used to treat systemic disease is the most frightening. The risk of malignancy has been correlated with duration of therapy and total chlorambucil dose. Apart from this, potential fertility issues, bone marrow suppression and risk of infection during or after the treatment exists. Therefore it should be considered only in recalcitrant and severe disease.

The administration of other agents, including azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil in combinations allowing the reduction of corticosteroid therapy to nontoxic levels, has been shown to suppress inflammation. However, their use requires a careful follow-up in cooperation with the house doctor, so that patients exhibiting intolerance or adverse reactions to one of these drugs can be switched to another drug.

Cell-mediated autoimmunity is restricted to the eye in SO, thus, local therapy such as periocular or intraocular corticosteroid injections has emerged as an important therapeutic adjuncts that can reduce the need for systemic therapy. These local methods are limited, however, by the need for frequent repeat injections because of the chronic nature of the disease. Local corticosteroid treatment is generally not effective long term. Triamcinolone acetonide can be given superior sub-Tenon’s, but usually is insufficient by itself for control of the inflammation. Triamcinolone acetonide can also be given intravitreally but the chronic nature of SO necessitates repeated injections. Vision is often permanently lost with each recurrence of inflammation in SO, so episodic treatment is not ideal. Another alternative in patients having recurrent inflammation or those who are not tolerating oral steroids/ immunosuppressives is flucinolone acetonide implant. The flucinolone acetonide implant delivers a continuous low dose of flucinolone over a 2.5-year period. However, either route of steroid dosing generally causes cataracts; approximately one third of patients develop steroid-induced glaucoma, which can be severe. Short-term therapy with corticosteroids or other immunosuppressive treatment has been recommended for ocular surgery performed on patients with a history of SO, even when it has been resolved. Long-term follow-up of these patients is essential.

References