Chapter 16

SYMPATHETIC OPHTHALMIA

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INTRODUCTION

One of the most feared conditions in ophthalmology is sympathetic ophthalmia (SO), a condition in which, after one eye is injured, inflammation threatens blindness in both. Sir Stewart Duke-Elder probably gave the single most comprehensive description of this disease in 1966:

> Sympathetic ophthalmitis is a specific bilateral inflammation of the entire uveal tract of unknown etiology, characterized clinically by an insidious onset and a progressive course with exacerbations, and pathologically by a nodular or diffuse infiltration of the uveal tract with lymphocytes and epithelioid cells; it almost invariably follows a perforating wound involving uveal tissue.[1(pp558–559)]

SO, also known as sympathetic uveitis, is a rare, bilateral, granulomatous panuveitis that occurs after a penetrating injury to an eye. Following injury to an eye—a result of either surgery or accident—a variable period of time passes before a sight-threatening inflammation develops in *both* eyes. The injured eye is referred to as the *exciting* eye and the fellow eye as the *sympathizing* eye. The fact that injury to one eye can result in blindness of both has made SO of enormous concern to ophthalmologists. And because the highest recorded instances of this disease follow combat wounds, SO is of particular interest to military ophthalmic surgeons.

HISTORY

The concept of sympathetic inflammation is an ancient one; probably the first reference in the literature was in a note from Agathias in the anthology compiled from Constantius Cephalis (1000 CE [common era]): "the right eye when diseased often gives its suffering to the left."[1(p560)] The clinical disease was known to Hippocrates, and is also found in an old German textbook of ophthalmology.[1–3] Bartisch (1583) remarked that when one eye is injured "the other good eye is besides also in great danger."[1(p561)]

The modern history of the disease commences with the comprehensive clinical description of Mackenzie in 1840, who first termed the disease "sympathetic ophthalmia."[4] His report was supplemented 65 years later by the classic histopathological findings described by Fuchs.[5] In 1910, Elschnig was the first to propose the concept that SO was an autoimmune inflammatory disorder, possibly in response to uveal antigens.[6] Two well-known individuals were almost certainly victims of SO:

- Two years after an injury to one eye from a leather awl, Louis Braille, the French inventor of the Braille alphabet and teacher of the blind, experienced a gradual loss of vision in the other eye.[7]
- As a child, James Thurber, the American author and humorist, sustained a severe eye injury caused by an arrow during a game of William Tell, leaving him blind in one eye; eventually, "sympathetic ophthalmia overtook his other eye, leaving him totally blind amid his forties."[8]

Interestingly, SO was a condition well-known to veterinarians. Wardrop[9] drew attention to this fact in 1818:

> It is known among some farriers, that, if the eye first affected with this disease suppurates and sinks into the orbit, the disease does not attack the other eye, or subsides if it has commenced in it. Thus they have adopted a practice of destroying altogether the diseased eye, in order to save the other which is crudely done by putting lime between the eyelids, or thrusting a nail into the cavity of the eyeball, so as to excite violent inflammation and suppuration.[9(p139)]

The concept of inducing suppurative inflammation in an injured eye as a method of protecting the fellow eye became an accepted procedure in the treatment of human disease. Pre-Listerian surgeons intentionally produced a "beneficent" suppuration in a badly injured eye by passing a seton through it, believing that the purulent infection destroyed the factors responsible for the condition or prevented infection passing up the optic nerve by sealing the lymph spaces.[1] Prichard in 1851 was the first to practice enucleation as a therapeutic measure.[1] To this day, early removal of the injured eye remains the only sure way to prevent SO.

EPIDEMIOLOGY

Most cases of SO accompany perforating injuries of the globe in which uveal tissue, especially the ciliary body, is traumatized. Incarceration of uveal tissue has been a feature of nearly all cases (Figure 16-1).

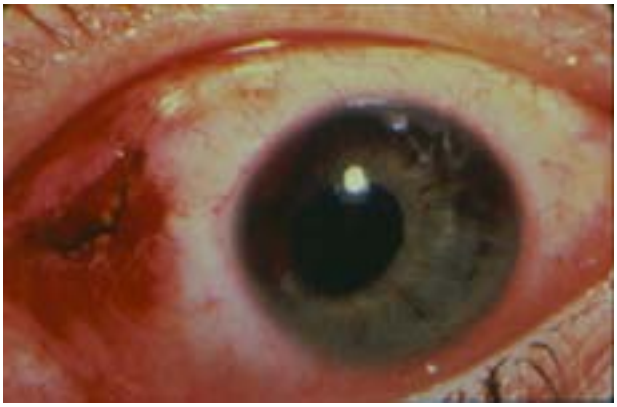

Fig. 16-1. An example of a penetrating eye injury from the Vietnam War. Note the dark uveal tissue emanating from the scleral laceration temporally. It is the exposure of uveal tissue to the conjunctival lymphatic system that is believed to be a major factor in the development of sympathetic ophthalmia. Photograph: Courtesy of Francis G. La Piana, MD, Colonel, Medical Corps, US Army (Ret), Ashton, Maryland.

Accidental wounds now account for about 65% of cases, and another 25% follow surgical wounds.[10] In 1972, Liddy and Stuart[11] reported an incidence of 0.19% following penetrating injury and 0.007% following intraocular surgery. SO occurs more often in children because of the high risk of accidental trauma. Elderly patients also appear to be at an increased risk of the disease because of the greater frequency of intraocular surgery in the aged. The disease does not appear to have a predilection for any race or for either gender, except that its incidence mirrors the increased incidence of ocular trauma in males.

The most common surgical procedures leading to SO include cataract extraction (particularly when complicated), iris surgery (including iridectomy), retinal detachment repair, and vitreoretinal surgery.[7,12–14] Surgical procedures complicated by the incarceration of the iris or the lens capsule in the wound are particularly prone to develop the condition. Other penetrating surgical procedures reported to have resulted in SO include paracentesis, cyclodialysis, and keratectomy, and the risk of SO increases when these surgical procedures are accompanied or followed by additional operations, particularly in the posterior segment of the eye.[15] The incidence of postvitrectomy SO has been estimated at 0.01%.[16] SO may occur after evisceration, probably as a result of remaining uveal tissue in the scleral emissary channels.[17]

Only very rarely has SO been diagnosed in cases where there was no perforating wound of the eye, and in many of these cases, the possibility of an occult globe rupture cannot be completely excluded. However, SO has been reported[18] following laser cyclocoagulation without apparent globe rupture. Occasionally, the disorder follows perforating corneal ulcers, ocular contusion without rupture of the globe, and intraocular malignancies.[19–21] SO has been diagnosed months after helium ion irradiation of a choroidal melanoma; however, a clinically inapparent scleral scar was detected on histopathological examination, possibly indicating an occult scleral rupture.[22]

The highest recorded incidences of SO have occurred during military conflict. In the American Civil War (1861–1865), 16% of all ocular injuries reportedly led to the development of SO. In the Franco–Prussian War (1870–1871), the reported prevalence of SO after ocular injuries was 55.5% among the Germans and 50% among the French. The disease was still relatively common in the Russo–Japanese War (1904–1905), during which it complicated 5% of eye injuries. In contrast, only rare cases of SO were reported in World Wars I and II, and none were reported in the Korean, Vietnam, and Persian Gulf wars.[1,3] Some of the earlier figures must be viewed with some skepticism: in the older literature in particular, SO probably was often confused with other forms of uveitis, and there were few, if any, specialized ophthalmologists among physicians in most wars before this century. Nevertheless, it is interesting and says much for the advances in eye care in the theater of operations that there has been such a dramatic decrease in the incidence of SO in the past century.

CLINICAL FEATURES

SO begins after a latent period following an injury to the eye. In general, 65% of SO cases occur 2 weeks to 2 months after injury, and 90% occur within the first year.[3,7] However, SO has been reported as early as 5 days after injury and as late as 66 years.[1,7] These figures become clinically important in the prevention of SO. Because the only known prevention is enucleation of the injured eye prior to the onset of the disorder, obviously such enucleation must be performed early. It is generally agreed that enucleation of an irreparably damaged eye should occur within 2 weeks of injury. Furthermore, although it may be assumed that the risk of SO is extremely small after 3 months, it may never reach zero. Any patient who has sustained a penetrating ocular injury should be considered to

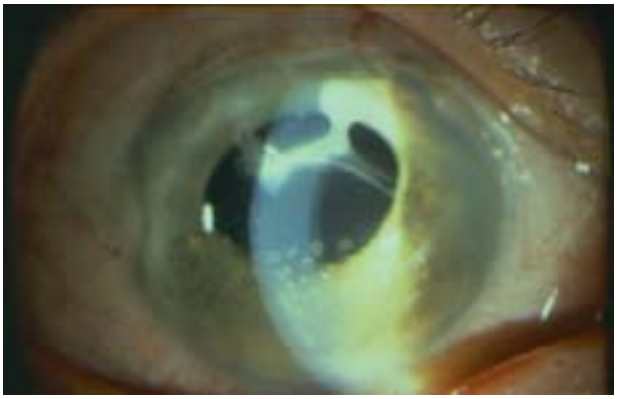

Fig. 16-2. An eye with sympathetic ophthalmia demonstrating the "mutton-fat" keratic precipitates characteristic of granulomatous intraocular inflammation. Scarring from the original injury is present in the superior cornea. Photograph: Courtesy of G. Foulks, MD, Chairman, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, Pa.

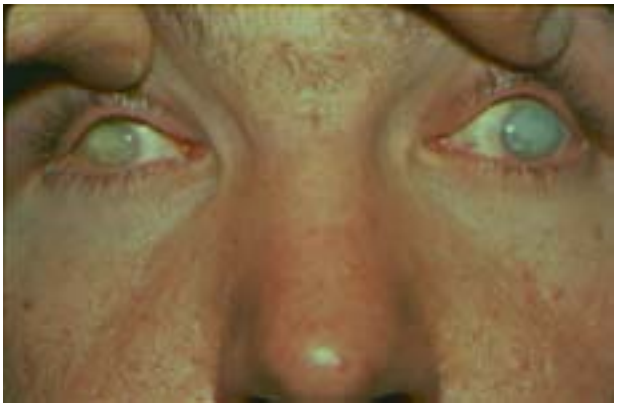

Fig. 16-3. Severe, bilateral granulomatous inflammation leading to loss of vision in both eyes. Note the shrunken appearance of the right eye indicating early phthisical changes. Photograph: Courtesy of G. Foulks, MD, Chairman, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, Pa.

be at lifelong risk, albeit very small, for the development of this disease.

The diagnosis, especially the early diagnosis, of SO is one of the most important in ophthalmology because prompt and aggressive therapy is required to save vision. The presenting symptoms of the disease include changes in accommodative amplitude, photophobia, and epiphora. Early signs on clinical examination include a low-grade, persistent uveitis associated with granulomatous ("mutton-fat") or small, white keratic precipitates (Figure 16-2). A diffuse thickening of the iris or iris nodules similar to that seen in sarcoidosis sometimes occurs. Posteriorly, small, yellow-white chorioretinal lesions (Dalen-Fuchs nodules), vitreous cells and haze, choroidal infiltration and thickening, retinal vascular sheathing, and disk edema may be seen. A similar clinical picture develops in the exciting eye and both eyes may proceed to blindness (Figure 16-3).

The presence of Dalen-Fuchs nodules is among the most classic findings in SO, so classic that they were once considered pathognomonic for the disorder. These nodules may occur anywhere in the fundus but are more common in the mid periphery.[3,23] They are yellowish white lesions, typically 60 to 700 μm (microns) in diameter, found in the subretinal space in at least one third of cases (Figure 16-4).[24] Dalen-Fuchs nodules are no longer considered pathognomonic for SO, as they have also been reported in other cases of granulomatous uveitis, such as sarcoidosis, tuberculosis, and the Vogt-Koyanagi-Harada syndrome (VKH).[24] Often, microscopic breaks occur in Bruch's membrane underneath the nodules.[25,26] These defects in Bruch's membrane may lead to the rare development of subretinal neovascularization.[27,28]

Systemic findings in SO are uncommon but possible. Vitiligo, poliosis, alopecia, dysacusis, and meningeal irritation—findings more commonly reported in the VKH syndrome—may be noted.[3,29] An

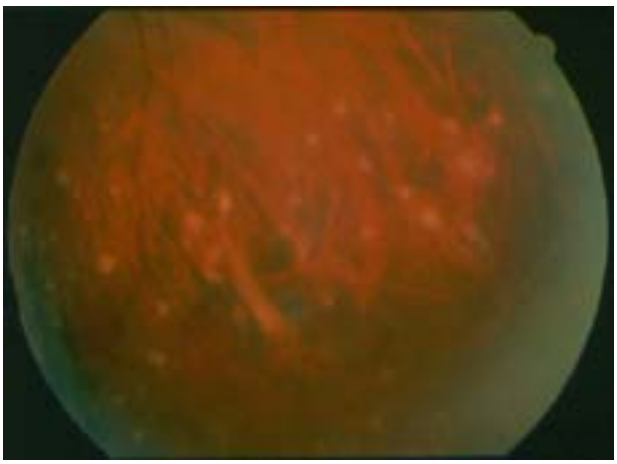

Fig. 16-4. The fundus of the eye of a patient with sympathetic ophthalmia. Note the characteristic yellowish white Dalen-Fuchs nodules in the mid periphery. These granulomatous lesions are found in at least one third of cases. Photograph: Courtesy of G. Foulks, MD, Chairman, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, Pa.

increased number of cells (mostly lymphocytes) in the cerebrospinal fluid can also be infrequently observed.[15] These similarities with the VKH syndrome suggest a possible relationship between the two diseases.

Fluorescein angiography seldom is necessary to establish the diagnosis of SO. There appear to be two types of abnormal fluorescence. The most frequently reported type is similar to that usually seen in VKH and consists of multiple sites of choroidal leakage with late coalescence of dye under serous retinal detachments. The sites of choroidal leakage correspond to the Dalen-Fuchs nodules observed clinically. The second, less-common angiographic appearance is similar to that seen in a number of other causes of posterior uveitis, such as acute posterior multifocal placoid pigment epitheliopathy. This form demonstrates lesions that (1) block the background choroidal fluorescence during the early phases and (2) stain late.[3,15,26,30]

SO runs a chronic course, with a marked tendency toward relapses, and the disease may culminate in a phthisical eye (or eyes) and blindness. Before the advent of corticosteroid therapy, the visual prognosis was extremely poor, with approximately 70% of affected eyes becoming permanently blind.[31] The more severe the inflammation, the poorer the prognosis; the earlier the diagnosis and more intensive the therapy, the better the outlook. Complications, including cataract, secondary glaucoma, exudative retinal detachment, choroidal scarring, and optic atrophy, are common in long-standing cases.

HISTOPATHOLOGY

The histopathological findings in SO, first described by Fuchs in 1905, consist of a diffuse, granulomatous uveitis with a massive lymphocytic infiltration and nests of macrophages, epithelioid cells, and multinucleated giant cells in both the exciting and the sympathizing eyes (Figures 16-5 and 16-6).[5] The inflammation is nonnecrotizing, and the epithelioid cells are often seen engulfing melanin pigment. The exciting eye differs from the sympathizing eye only by the evidence of and complications stemming from the preceding injury or surgical procedure. Nodules containing macrophages, epithelioid cells, and retinal pigment epithelial cells frequently occur between Bruch's membrane and the retinal pigment epithelium (ie, Dalen-Fuchs nodules; these are discussed in greater detail below). Eosinophils may be present in the uvea, especially in early cases.[7,32] The inflammatory process

Fig. 16-5. This low-power photomicrograph demonstrates the diffuse uveal thickening secondary to inflammatory cells in a case of sympathetic ophthalmia (hematoxylin-eosin stain, original magnification x 1).

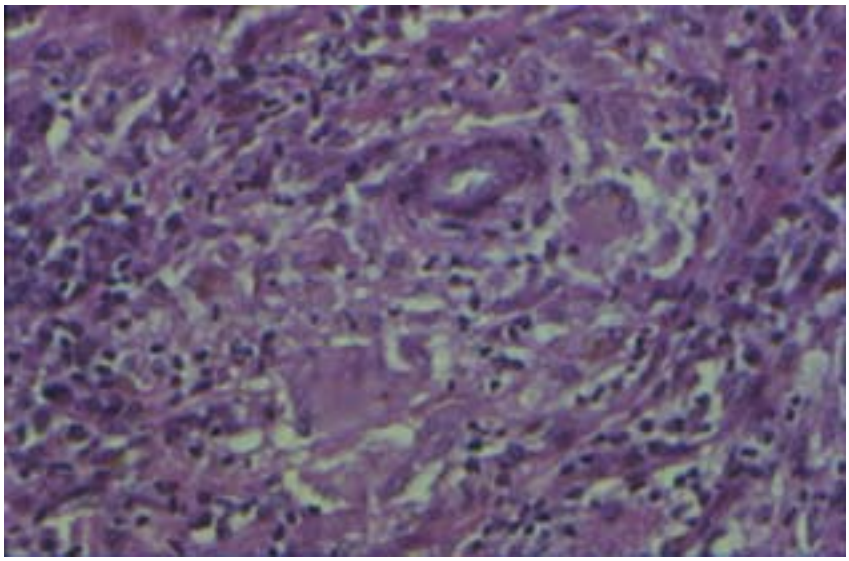

Fig. 16-6. Higher magnification of the uveal infiltrate demonstrating a chronic, granulomatous inflammation consisting of lymphocytes, epithelioid cells, and multinucleated giant cells. (hematoxylin-eosin stain, original magnification x 400).

classically spares the choriocapillaris and retina, and the posterior uvea is generally affected more than the anterior part. The pathological diagnosis depends mainly on the predominant T cell lymphocytic infiltration in the uvea, the early phagocytosis of pigment granules, and the presence of Dalen-Fuchs nodules.[33–35]

The uveal infiltrate consists predominantly of T cells, supporting the concept of a cell-mediated immune reaction (delayed hypersensitivity). Early in the disease, the majority of the T cells are of the helper/inducer subset, with less than 5% to 10% of the cells characterized as B cells, plasma cells, or monocytes.[35,36] In chronic cases, T cells of the suppressor/cytotoxic class predominate.[3,34,37] The change from predominantly helper/inducer T cells in acute disease to suppressor/cytotoxic T cells in the chronic phase is also seen in an animal model of SO, experimental autoimmune uveitis (EAU).[34]

A very specific histopathological finding in SO is that of Dalen-Fuchs nodules, which are clusters of epithelioid cells between the retinal pigment epithelium (RPE) and Bruch's membrane (Figure 16-7). These lesions are often pigmented, especially in chronic disease, and it used to be thought that the cells composing the nodule represented transformed RPE, forming a cagelike framework.[38,39] More recent studies have demonstrated that Dalen-Fuchs nodules are composed of a mixture of well-defined and closely packed epithelioid cells underlying a dome of RPE. Metaplastic cells from the RPE, lymphocytes, and giant cells may occasionally be found within the nodular structure.[7,24,34,35] In the late stages of SO, degenerated RPE can become an important component of the nodules.[3] Light- and electron-microscopic studies[25,26] reveal frequent breaks in Bruch's membrane underlying the nodules.

A zonal granulomatous reaction to the lens (phacoanaphylactic endophthalmitis, phacoantigenic uveitis, lens-induced uveitis) is often found in cases of SO (Figure 16-8). In one series it was found in 23% of 170 documented cases.[40] In a review of 100 cases of SO from the files of the Armed Forces Institute of Pathology, Washington, DC,[12] 14 cases were associated with phacoanaphylactic endophthalmitis (22% of the 46 eyes enucleated before 1950, compared with only 7% of the 54 eyes enucleated after 1950). This decline in the associated incidence of phacoanaphylactic endophthalmitis and SO has been demonstrated in several other reports. In a retrospective analysis[41] of 144 cases of phacoanaphylactic endophthalmitis from 1970 to 1988, only 4 cases (2.6%) of SO were diagnosed. In another series[42] of 105 cases of SO that spanned the years 1913 to 1978 and that contained 48 cases of phacoantigenic uveitis (46%), only 1 case of the 48 was detected after 1949. The authors of this latter study[42] attribute the decline in incidence to the introduction of corticosteroid therapy and the more-complete treatment that lens injuries currently receive.

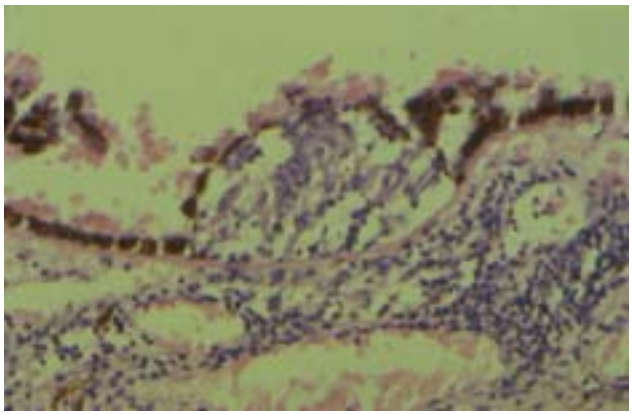

Fig. 16-7. High magnification of a Dalen-Fuchs nodule. This is a very specific histopathological finding in sympathetic ophthalmia, consisting of clusters of epithelioid cells between the retinal pigment epithelium (RPE) and Bruch's membrane (hematoxylin-eosin stain, original magnification x 800).

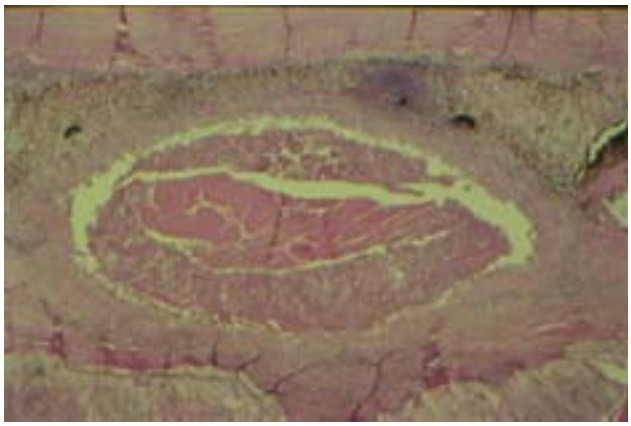

Fig. 16-8. A zonal granulomatous reaction to the lens (phacoanaphylactic endophthalmitis, phacoantigenic uveitis, lens-induced uveitis) is often found in sympathetic ophthalmia (hematoxylin-eosin stain, original magnification x 40).

PATHOGENESIS

Ever since SO was first described, physicians have speculated about a mechanism that could explain how an injury to one eye could result in inflammation of both. Writers in the 19th century hypothesized that the inflammation was propagated along the optic nerves and chiasm from one eye to the other; others suggested the trigeminal nerve as the route of transmission.[1]

Hypersensitivity Reaction Theories

That the disorder might represent a hypersensitivity reaction was first suggested in 1903, with uveal pigment proposed as the offending antigen.[6,43] The characteristic phagocytosis of melanin seen on histopathological examination would support a possible role for the pigment, but the experimental evidence for this is weak, and melanin generally is considered to be nonantigenic. However, investigators during the early 1990s described an insoluble uveal melanin preparation that can produce an inflammation limited to the uvea in immunized animals, and later workers reported that spontaneous recurrences of the inflammation occurred that were reminiscent of human SO.[3]

Uveal or retinal antigens other than melanin might be involved. Certainly the finding that uveal injury is an almost constant precursor to the development of SO makes the uvea a prime suspect. Uveal tissue alone is weakly antigenic, but its antigenicity can be increased with staphylococcal toxin or complete Freund's adjuvant.[44–47] Although this type of immunization produces a severe uveitis in guinea pigs and monkeys, it is nongranulomatous and does not resemble human SO. Antiuveal antibodies have been reported[48] in a high percentage of individuals with SO, and enhanced transformation of peripheral lymphocytes has been found[49] following exposure to homologous uveoretinal antigen. Others[44] consider the presence of circulating antibodies to uvea to merely represent a nonspecific result of tissue injury.

Evidence for Autoimmunity Role

There is persuasive evidence that clinical sympathetic ophthalmitis may represent an autoimmune response to antigens derived from the retinal photoreceptor layer.[50] Sera from patients with SO showed mild to moderate staining of the outer segments of the photoreceptors using an indirect immunoperoxidase technique.[51] Retinal extracts are highly antigenic and easily produce retinouveitis in experimental animals. Four of the potential retinal antigens are rhodopsin, retinal soluble antigen (S-antigen), interphotoreceptor retinoid binding protein, and recoverin.[3]

The most extensively studied of these has been S-antigen. EAU induced in animals by immunization with S-antigen is considered to be a model for the human ocular condition, resembling SO both clinically and in its response to therapy.[52–54] Cell-mediated immunity to the retinal S-antigen has been demonstrated in animals.[53] To date, however, circulating anti-S-antigen antibodies have not been detected in the sera of humans with SO.[51]

Specific epitopes of another retinal protein, interstitial retinoid binding protein (IRBP), are also capable of eliciting uveitis. Peptide fragments containing these epitopes, as well as IRBP itself, produce experimental autoimmune uveitis in Lewis rats.[55] Other recent immunohistochemical investigations suggest that SO is mediated by delayed T cell hypersensitivity directed at surface membrane antigens shared by photoreceptors, RPE cells, and choroidal melanocytes.[34] Interestingly, some of the antigens used to produce an experimental model of SO in animals (S-antigen, IRBP) also cause an inflammatory disease of the pineal gland. As yet no evidence has been reported for pineal gland involvement in human disease.[56]

The absence of lymphatics within the eye may play an important role in the pathogenesis of SO. Normally, intraocular antigens circulate to the blood and spleen, bypassing local lymph nodes, which may result in the induction of blocking antibodies or suppressor cells in the spleen. However, in cases of penetrating ocular trauma, these antigens drain directly into the regional lymph nodes, permitting the initiation of a cell-mediated immune response.[3,57] Thus, a key step in the development of SO may be the exposure of uveoretinal antigens to the conjunctival lymphatics. Simultaneously, bacteria (eg, *Propionibacterium acnes*), viruses, and other infectious agents can enter the eye through the wound, and this exposure might serve as an adjuvant to induce or up-regulate the inflammatory process.

Association With HLA Types

SO has been associated with certain human leukocyte antigen (HLA) types. For example, HLA-A11 has been reported[58] in patients with histopathologically proved SO; the relative risk in the disease group, compared with the control group, was 11. In another study[59] of the VKH syndrome and SO, strong associations of VKH with HLA-DR4 and HLA-DRw53 were found; the strongest associations observed were with HLA-DQw3. The small number of patients with SO in this latter study[59] precluded statistical analysis; nevertheless, similar HLA associations were noted. HLA class II loci (ie, HLA-DR, HLA-DQ, HLA-DP) appear to be especially important in immune responses mediated through T helper cells, because the surface molecules coded by these genes interact directly with antigen and with the T cell receptor in the regulation of immune responses.

Possible Role of Bacterial Antigens

Although the association with trauma, exposure of uveal tissue, and characteristic granulomatous inflammatory process is suggestive of a possible infective process, no confirmation of a causative organism has been reported to date. A causal role has been proposed for *Mycobacterium tuberculosis*, *Bacillus subtilis*, *Rickettsia*, and various viruses, and although infectious agents are sporadically isolated, none have fulfilled Koch's postulates.[60–62] In fact, it has long been known that SO rarely occurs in cases with endophthalmitis.[63] More likely, biological products (eg, a bacterial cell wall), which may be present in the wound, could act as immunostimulators and thereby up-regulate a local immune response. As has been noted above, although uveal tissue itself is only weakly antigenic, its antigenicity can be increased with staphylococcal toxin or complete Freund's adjuvant.[45–47]

It is tempting to hypothesize that the perforating ocular injury permits several events to take place. The first is that drainage of a uveal or a retinal antigen, or both, occurs through the conjunctival lymphatics, an event that does not occur under normal conditions. The second is that small amounts of adjuvant, such as bacterial cell wall or other immunostimulators, enter the eye through the perforation. These products then may upgrade profoundly the local immune response, causing it to bypass certain inherent suppressor mechanisms in genetically prone individuals. This phenomenon then leads to the inflammatory response that ultimately becomes the clinical entity recognized as SO.[64]

DIFFERENTIAL DIAGNOSIS

The major consideration in the differential diagnosis is VKH syndrome, a disease that has many features in common with sympathetic uveitis. Patients with the VKH syndrome have no history of trauma and typically have bilateral localized serous detachments of the retina, findings that are not typically seen in SO. VKH syndrome is also more prevalent in certain racial and ethnic groups. Despite these differences, the only clear distinctions between VKH and SO are (1) the history of trauma in SO and (2) the very rare occurrence of central nervous system symptoms and pigmentary changes in SO, findings that are often seen in VKH syndrome. In the typical case of SO, no laboratory studies are necessary for diagnosis. Should it be necessary to differentiate SO from VKH syndrome, a lumbar puncture should be performed early in the course of the disease. This reveals a pleocytosis in 84% of VKH cases, with mostly lymphocytes and monocytes present.[65]

Other causes of a bilateral, granulomatous panuveitis, such as sarcoidosis, pars planitis, and certain infections, are usually fairly easy to differentiate from SO on history and clinical examination. The association between SO and lens-induced uveitis has been mentioned above.[12,40,41] Either disease may occur alone, and both may be present in the same eye. This association is much greater than we would expect by chance alone and strengthens the hypothesis that lens-induced uveitis and SO are both immunological in nature. If lens-induced uveitis is present, then surgical removal of the lens or lens fragments should be considered.

TREATMENT

Enucleation

As stated above, the earliest method for the prevention of SO was to induce a suppurative inflammation in the injured eye. This treatment was well known to veterinary surgeons,[1,9,63] but for obvious reasons is not appropriate for humans. The classic method to prevent SO remains enucleation of the

injured eye before the other eye develops disease. The role of enucleation was borrowed from veterinary surgery by Wardrop in 1818, put into clinical practice by Prichard in 1851, and fully established in ophthalmological routine as a measure of proven value by Critchett in 1863.[1] Enucleation of an injured eye within 2 weeks of injury almost always prevents the development of SO but is not an absolute preventive measure: SO does occasionally develop after enucleation. Of the 18 cases of SO from the Moorfields Eye Hospital, London, England, 1 (5.5%) occurred in a patient whose injured eye was enucleated before the onset of disease,[66] and of the 29 cases from the Armed Forces Institute of Pathology, 2 (6.9%) occurred after enucleation of the traumatized eyes.[67,3]

Evisceration is not an acceptable alternative to enucleation. SO can occur after evisceration, probably as a result of remaining uveal tissue in the scleral emissary channels. It would seem prudent not to perform eviscerations except perhaps in cases of endophthalmitis or in patients whose general condition is very poor, who thus may not be able to withstand the more-involved enucleation procedure.[17,68]

If there is reasonable doubt regarding the visual potential of an injured eye, then every effort should be made to preserve it. With aggressive immunosuppressive therapy, good vision may be retained in an exciting eye, sometimes better vision than in the sympathizing eye.[7] Careful microsurgical management of the wound, with prompt closure of all penetrating injuries, is an effective—although not absolute—measure for avoiding the development of SO. Uveal incarceration into the wound must be avoided.

Once definite signs of disease have started in the second eye, enucleation of the injured eye, except when it is blind or painful, is of little or no value and may be inadvisable. A review[69] of 257 cases of histopathologically proven SO indicated no benefit to the sympathizing eye from enucleation of the exciting eye, whether performed briefly before, concomitant with, or subsequent to the development of SO at various intervals following injury.

Some investigators,[42] however, have suggested that enucleation within 2 weeks after symptoms of SO have begun might improve the visual prognosis. Significantly fewer recurrences of inflammatory disease in patients who underwent early enucleation have been reported,[3] but there was no improvement in ultimate visual acuity. In a retrospective clinicopathological study[70] of 30 cases of SO, early enucleation of the exciting eye was associated with a benign clinical course: visual acuity better than 20/50 and fewer and milder relapses than eyes that underwent late enucleation. This remains a very controversial subject, with strong arguments for and against enucleation as a therapeutic measure.[70–73] It is probably advisable not to enucleate an eye with any visual potential. Enucleation should be reserved for those eyes with no light perception or perhaps with only bare light perception. There have been reports[74] of cases of sympathetic uveitis that showed sudden recovery of a sympathizing eye without enucleating the injured eye, even after a long period of unresponsiveness to corticosteroids.

Corticosteroids

Once SO has developed, the systemic therapy of first choice remains corticosteroids, and the inflammation usually responds rapidly. Corticosteroids have revolutionized the treatment of this disease. Before the use of corticosteroids the visual prognosis was generally poor, and approximately 70% of the eyes became permanently blind.[31] Now the prognosis is markedly better. Makley and Azar[75] found that 9 (64%) of 14 treated patients attained 20/60 vision or better, Lubin and colleagues[42] noted that 13 (72%) of 18 treated patients achieved 20/50 vision or better, and Reynard and colleagues[70] reported that 18 (82%) of 22 treated patients had 20/50 vision or better.

Large doses of corticosteroids should be given early in the course of the disease and continued for at least 6 months after apparent resolution of inflammation. In adults, oral doses as high as 100 to 200 mg of prednisone are suggested for the first week.[15] The initiating dose can be reduced by approximately 5 mg/wk—so long as the inflammatory activity remains controlled—to a maintenance dose of 5–10 mg/d.[7] Patients on systemic steroids require regular monitoring of their blood pressure and blood glucose levels. Infection needs to be ruled out before initiating systemic corticosteroids.

Although corticosteroids are very effective in the treatment of SO, they cannot prevent the development of the disease. Several reports[3,49,76] have demonstrated that SO may develop despite the use of systemic or topical corticosteroids.

Immunosuppressive Agents

In some patients, corticosteroid drugs alone are ineffective (which is unusual in SO), or too high a dose is necessary to achieve control (a more com-

mon problem). Additionally, medical problems and systemic or ophthalmological complications may prevent their protracted use by some patients, such as those with diabetes mellitus, uncontrolled glaucoma, or psychological problems. In these individuals, alternative treatment with immunosuppressive agents can effectively suppress inflammation, allowing a reduction of corticosteroid therapy to a nontoxic level.

The recommended agents are usually cyclosporin A (5 mg/kg/d) in patients younger than approximately 40 years or azathioprine (2 mg/kg/d in three divided doses) in older patients.[7,77] Because eyes with SO are usually infiltrated with numerous activated T cells, cyclosporine, a potent inhibitor of T cell function, can be a very effective therapeutic agent. The recommended dosages for a combination of cyclosporine and steroids are cyclosporin A (3–5 mg/kg/d) and prednisone (15–20 mg/d).[3,77] Renal function tests (eg, blood urea nitrogen, creatinine) should be monitored regularly in patients taking cyclosporine.

Other agents have been advocated for the treatment of intractable SO. Some authors[78,79] have advocated high-dose, short-term chlorambucil. Because chlorambucil is well absorbed from the gastrointestinal tract, it has the advantage of oral administration. With chlorambucil, corticosteroids can often be completely discontinued, whereas with cyclosporine they are often required, especially if the dose of cyclosporine needs to be decreased because of renal toxicity.[78] Methotrexate is another potentially useful drug and has the advantage of a weekly dosing schedule.[7]

IMPLICATIONS FOR MILITARY MEDICINE

Eye injuries will continue to be of major significance in combat. The incidence of eye injuries sustained by US forces has increased 18-fold since the Civil War, reaching 9% in the Vietnam War.[80] Conflicts since Vietnam have continued to demonstrate the increasing frequency of battlefield ocular injuries, reaching 13% of the patient volume at a major combat support hospital during the ground phase of the Persian Gulf War.[81] Therefore, soldiers are at continued risk for ocular injury and for subsequent development of SO. Prevention of eye injuries remains the best means to eliminate the risk of SO, and this fact lends further support to the argument for improved development, deployment, and use of eye armor.

Once a penetrating eye injury has occurred, however, trained ophthalmologists should promptly and meticulously close it. This procedure requires that ophthalmologists be present in the theater of operations, along with specialized equipment such as the operating microscope and microsurgical instruments. The dramatic decrease in the incidence of SO since the American Civil War—despite the overall increase in the incidence of ocular injuries—can be largely attributed to the advances in the management of traumatized eyes on the battlefield.

It must be stressed that enucleation should be considered only in those cases where the visual prognosis is nil and the eye is irreparable (Figure 16-9). Eyes with any potential vision should *not* be

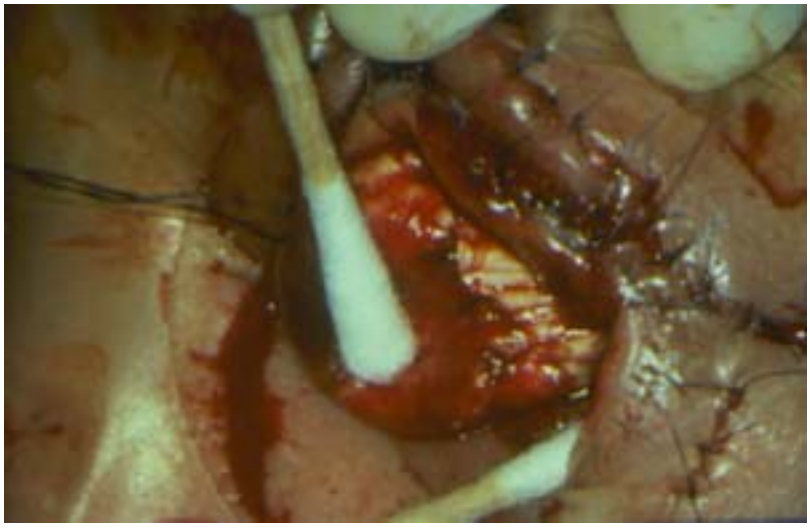

Fig. 16-9. This irreparably injured eye required enucleation to prevent the development of sympathetic ophthalmia. Such enucleations should be performed within 2 weeks of injury. This eye had no light perception (NLP) vision. Photograph: Courtesy of Francis G. La Piana, MD, Colonel, Medical Corps, US Army (Ret), Washington, DC.

enucleated. Enucleation, like the surgical care of penetrating eye injuries, also requires the presence of fully trained and competent ophthalmologists in the theater of operations. During the Vietnam War, a number of unnecessary enucleations occurred because the patients were managed by nonophthalmologists or by only partially trained ophthalmic surgeons.[82]

Careful follow-up should be afforded to all patients with penetrating eye injuries. The early signs and symptoms of SO must be carefully watched for, and, if the disease does develop, prompt and aggressive therapy must be initiated under the direction of an ophthalmologist.

SUMMARY

SO is a rare, bilateral, granulomatous uveitis, usually associated with a perforating eye injury. The exact cause is unknown, but it is believed to be related to an autoimmune response to retinal or uveal antigens or both. A severely injured eye with no prognosis for vision should be enucleated within 2 weeks of injury to prevent SO. The disease usually responds rapidly to corticosteroid therapy, but recalcitrant cases may require the addition of other immunosuppressive agents.

The highest incidence of SO has occurred in eyes injured on the battlefield; therefore, this disorder is of particular importance to military ophthalmologists, who should be present in the theater of operations. With modern microsurgical management of ocular injuries, the incidence of this disorder has dramatically decreased in the 20th century.

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