Sympathetic Ophthalmia

8

Cindy Ung and Lucy H. Young

Introduction

Sympathetic ophthalmia is a rare, bilateral, diffuse granulomatous form of uveitis that occurs after either surgical or accidental trauma to the uvea of one eye, usually 3 months after injury. The eye sustaining the injury is the "exciting" eye, and the fellow eye is the "sympathizing" eye. Sympathetic ophthalmia has potentially devastating visual consequences if treatment is delayed or inadequate.

The incidence of sympathetic ophthalmia has greatly decreased during the last 30 years as a result of improvements in modern surgical and medical treatments. The only prospective study on the incidence of sympathetic ophthalmia was performed on a small population in UK and Ireland, which shows an incidence of 0.03 per 100,000 people (Kilmartin et al. 2000a). Historically, accidental penetrating trauma was the most common cause of sympathetic ophthalmia, but now surgical trauma, particularly vitreoretinal surgery or secondary operations on predamaged eyes with fresh intraocular hemorrhages, is considered the major risk factor (Chan et al. 1995; Kilmartin et al. 2000a, b; Su and Chee 2006). The current sympathetic ophthalmia risk following vitrectomy might be nearly twice that after external retinal detachment repair and more than twice that of the previously reported 0.06% sympathetic ophthalmia risk after vitrectomy (Gass 1982). Sympathetic ophthalmia can also occur without penetrating eye trauma and has been reported following intravitreal injection (Brouzas et al. 2009), fungal keratitis (Guerriero et al. 2011; Buller et al. 2006), irradiation of choroidal melanoma (Brour et al. 2012), plaque brachytherapy (Ahmad et al. 2007), and laser cyclotherapies (Edwards et al. 2014).

C. Ung · L. H. Young (✉)
Massachusetts Eye and Ear Infirmary, Boston, MA, USA
e-mail: lucy_young@meei.harvard.edu

Pathogenesis

The exact pathogenesis of sympathetic ophthalmia is still unknown. The eye possesses inherent immune privilege with the presence of a blood–retinal barrier at the level of the retinal vascular endothelium and the retinal pigment epithelium (RPE) and the lack of a recognizable lymphatic drainage pathway. The most favored theory is an autoimmune process to an intraocular antigen incited by the breakdown of this blood–retinal barrier and access to the conjunctival lymphatic drainage following a penetrating injury. Rao and coauthors suggested that a wound with uveal prolapse may permit sequestered ocular antigens to sensitize the host and abrogate tolerance to these antigens, resulting in an immunopathologic response and intraocular inflammation (Power and Foster 1995; Rao et al. 1983; Sharp et al. 1984). Evidence for the precise autoantigen responsible in sympathetic ophthalmia is still inconclusive, as retinal S-antigen, melanin-associated antigens, and antigens derived from the RPE and choroid have all been implicated (Marak 1979; Rao et al. 1983; Wong et al. 1971).

Clinical Features

The diagnosis of sympathetic ophthalmia is based on the patient's history and clinical examination. The clinical presentation is variable, and the onset of inflammation in the sympathizing eye is quite often insidious. The time from surgery or trauma to onset of sympathetic ophthalmia has been reported from 5 days to 50 years, with approximately 80% of patients developing symptoms within 3 months and 90% within 1 year (Lubin et al. 1980).

The inflammatory response seen in the anterior chamber is granulomatous with mutton-fat keratic precipitates on the corneal endothelium and findings of an acute anterior uveitis. In the posterior segment, there may be nummular, depigmented, chorioretinitis spots known as Dalen-Fuchs nodules, papillitis, serous retinal detachment, choroiditis, and vitritis

H. G. Yu (ed.), *Inflammatory and Infectious Ocular Disorders*, Retina Atlas, https://doi.org/10.1007/978-981-13-8546-9_8

(Castiblanco and Adelman 2009) (Fig. 8.1). Dalen-Fuchs nodules are frequently located in the midperiphery of the fundus between Bruch's membrane and the retinal pigment epithelium and may not be present in 30–50% of cases (Kilmartin et al. 2000b).

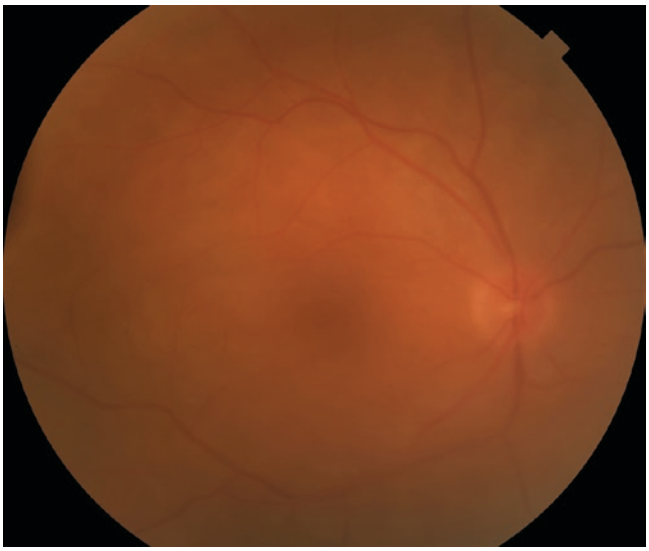

Fig. 8.1 Panuveitis with mild choroidal folds in the right eye of an 81-year-old man, 6 months after vitrectomy and intravitreal antibiotics for endophthalmitis in the left eye following a complicated cataract surgery. He noted gradual loss of vision for a week. Visual acuity was 20/50 in the right eye and light perception in the left eye. Visualization of the fundus was hazy due to 2+ keratic precipitates, anterior chamber inflammation, and mild vitritis. Note edematous and hyperemic disc and multiple light yellow lesions at the level of the retinal pigment epithelium. (Courtesy of Dr. Demetrios Vavvas)

Imaging

Fluorescein angiography (FA) is also useful in evaluating posterior segment involvement. In the acute phase of sympathetic ophthalmia, the FA typically demonstrates multiple hyperfluorescent sites of leakage at the level of the retinal pigment epithelium in the early phase followed by pooling of fluorescein dye in the detached areas (Fig. 8.2). In severe cases, these foci may consolidate with pooling of dye beneath the areas of exudative neurosensory detachment (Castiblanco and Adelman 2012). Dalen-Fuchs nodules may be hyper- or hypofluorescent depending on the integrity of the overlying RPE (Chang and Young 2011). The optic nerve may also demonstrate leakage in the later stages (Fig. 8.3). Optical coherence tomography (OCT) is helpful in demonstrating choroidal thickening in the posterior pole with or without exudative retinal detachment (Fig. 8.4).

Indocyanine green angiography (ICGA) is a useful diagnostic adjunct to confirm diagnosis and monitor response to therapy (Moshfeghi et al. 2005). Two patterns have been described. Hypofluorescence during the intermediate and late phase may correlate with chorioretinal atrophy. When there is active choroiditis, ICGA shows multiple hypocyanescent areas during the intermediate phase and not in in the late phase (Bernasconi et al. 1998). These are believed to represent focal, choroidal, inflammatory infiltrates (Fig. 8.5). B-scan ultrasonography can also be used to reveal choroidal thickening (Fig. 8.6).

Autofluorescence is a noninvasive imaging modality that can be useful in patients with sympathetic ophthalmia. Speckled areas of hypoautofluorescence resembling leopard spots can be seen in previous areas of exudative detachment. Over time, depigmentation of the RPE can occur (Fig. 8.7).

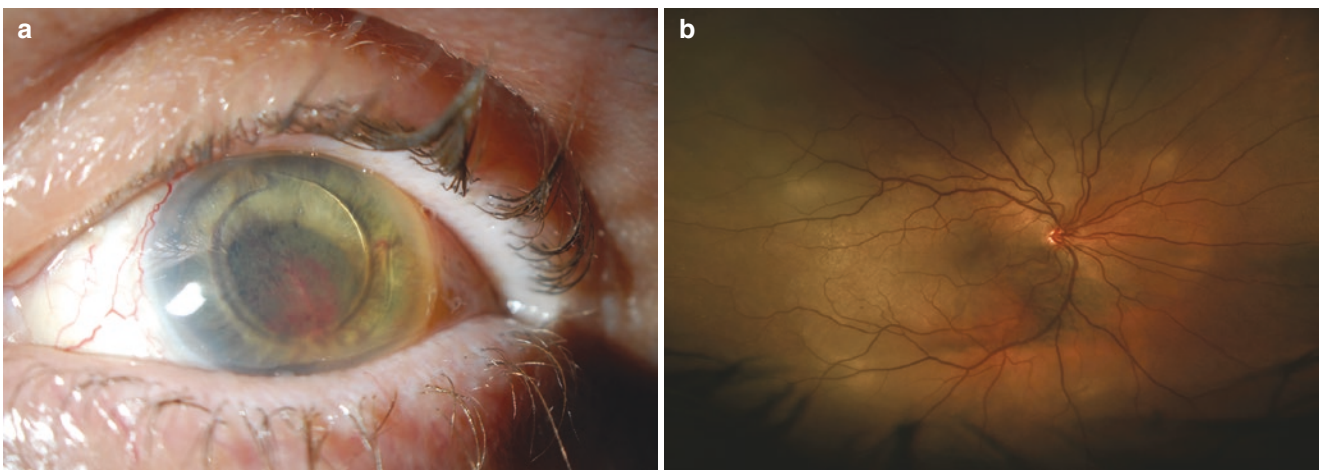

Fig. 8.2 Panuveitis with exudative retinal detachment in the right eye of a 54-year-old man, 6 months after surgical repair of zone 3 ruptured globe followed shortly by two vitreoretinal procedures for retinal detachment associated with giant tear. Visual acuity was 20/400 in the right eye and light perception in the left eye. (**a**) The left eye is pre-phthisical. (**b**) Note shallow exudative retinal detachment throughout the posterior pole extending to mid-periphery. (**c**, **d**) Fluorescein angiography shows multiple pinpoint areas of leakage in the early phase followed by increasing pooling of the dye in the detached areas

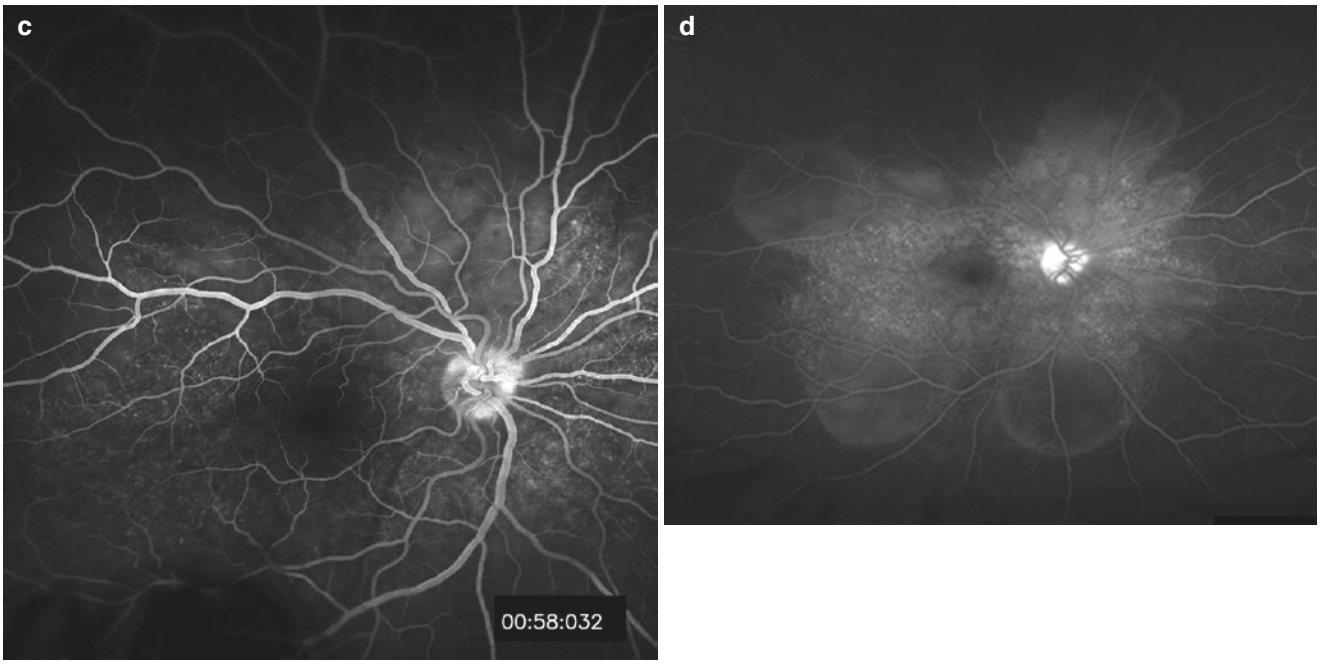

Fig. 8.2 (continued)

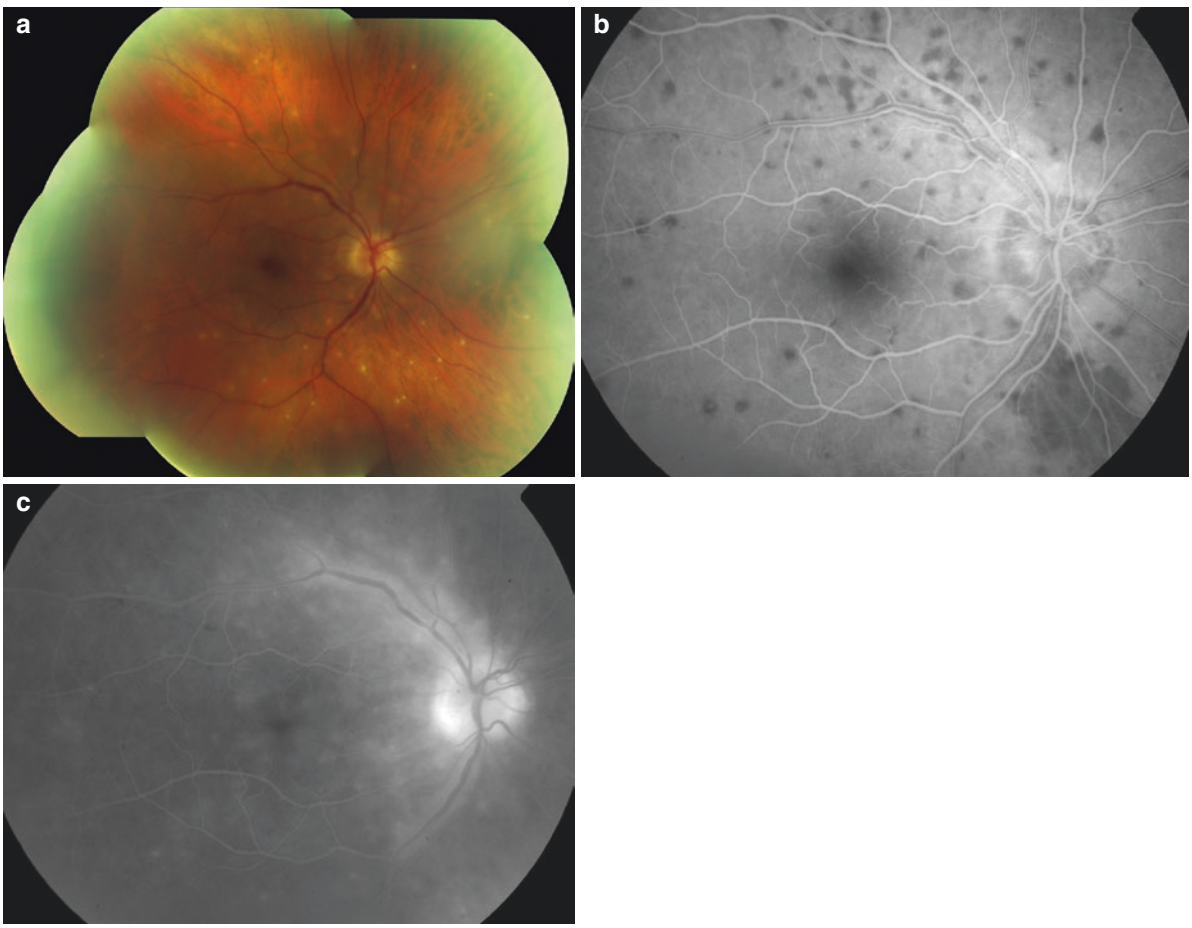

Fig. 8.3 Posterior uveitis in the right eye of a 69-year-old man, 9 months after surgical repair of a ruptured globe of the left eye. He noted blurry vision and floaters for few days. Visual acuity was 20/20 in the right eye and no light perception in the left eye. (**a**) Note multiple creamy yellow chorioretinal lesions around the hyperemic and edematous optic disc. (**b**) These hypopigmented spots are multifocal choroidal granulomas which obstruct the choriocapillaris and appear nonfluorescent early on fluorescein angiography. (**c**) Later angiograms show staining of these lesions, low-grade vasculitis, and papillitis. Multiple atrophic spots developed throughout the fundus 5 years after management with prednisone and immunotherapy. Visual acuity was 20/30-2. (Courtesy of Dr. George Papaliodis)

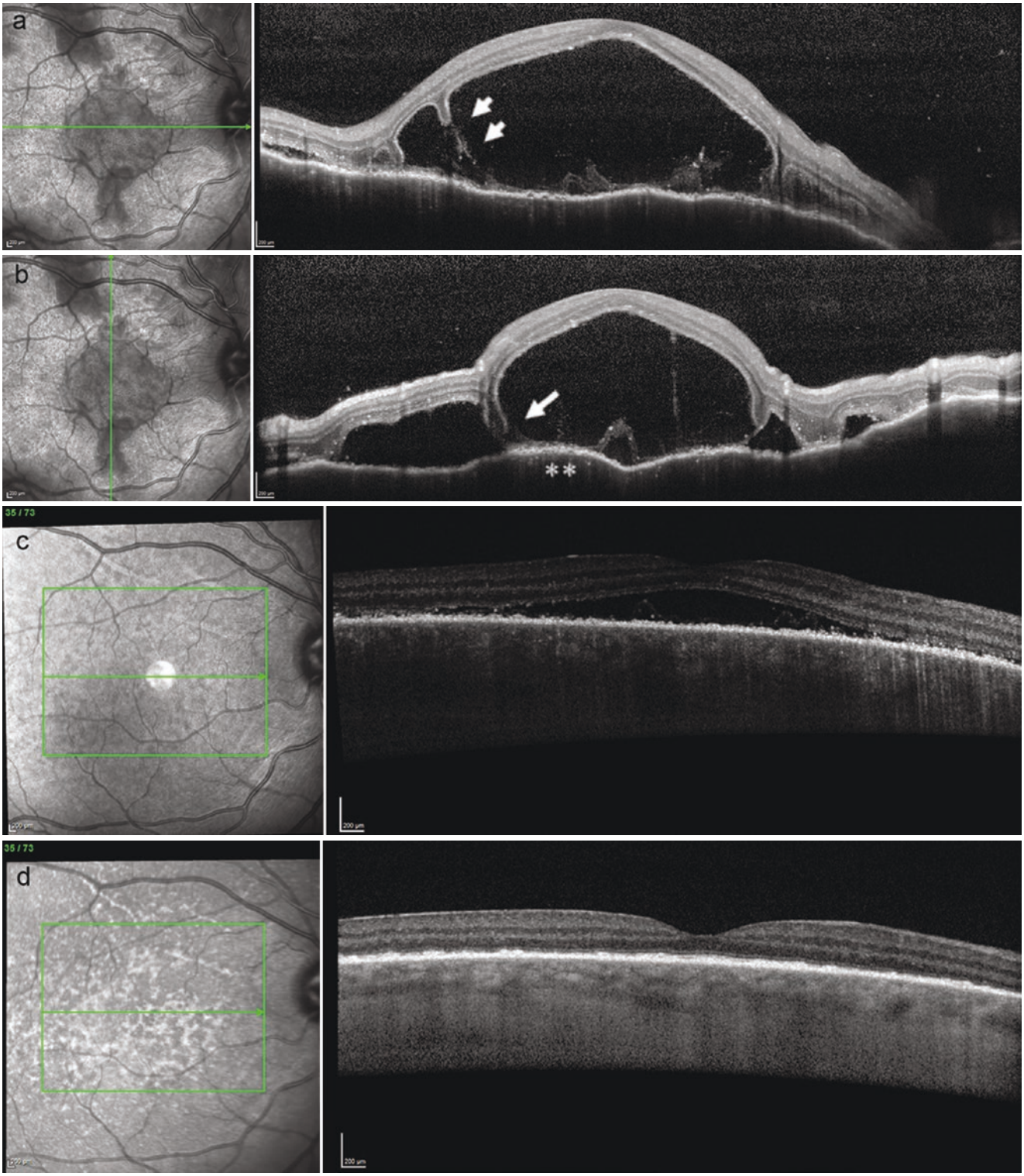

Fig. 8.4 Optical coherence tomography (OCT) images of the right eye. (**a**) OCT horizontal scan image shows a serous retinal detachment with subretinal septa and reflective dots consistent with fibrin in the subretinal fluid (SRF). The subretinal septa cross the detachment dividing it into pockets (arrows). (**b**) OCT vertical scan image shows thick choroid with loss of physiologic vascular pattern (white asterisks) and subretinal choroidal folds. (**c**) OCT shows reduced SRF after two doses of IV solumedrol. (**d**) OCT shows resolved SRF and improved choroidal vascular pattern 10 days after steroid pulse therapy

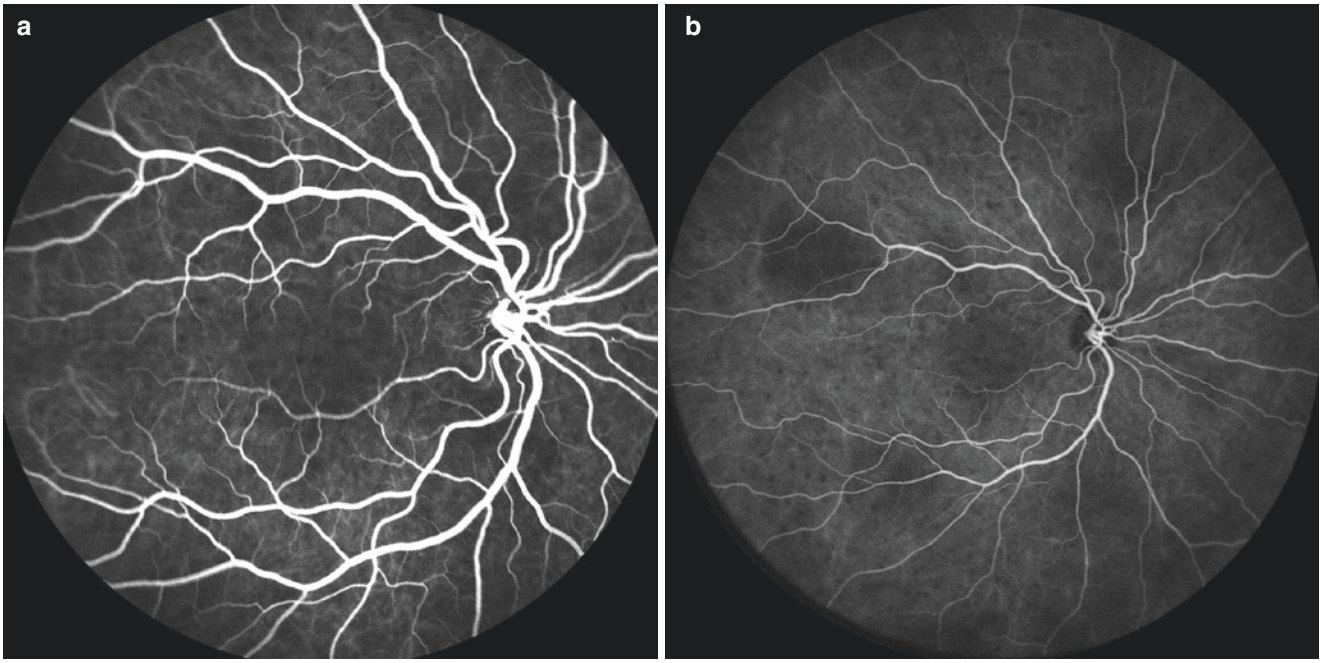

Fig. 8.5 Indocyanine angiography (ICGA) shows fuzziness of stromal vessels and multiple hypocyanescent spots (early phase, **a**) remaining up to the late angiographic phase (**b**) indicating full thickness choroidal granulomas

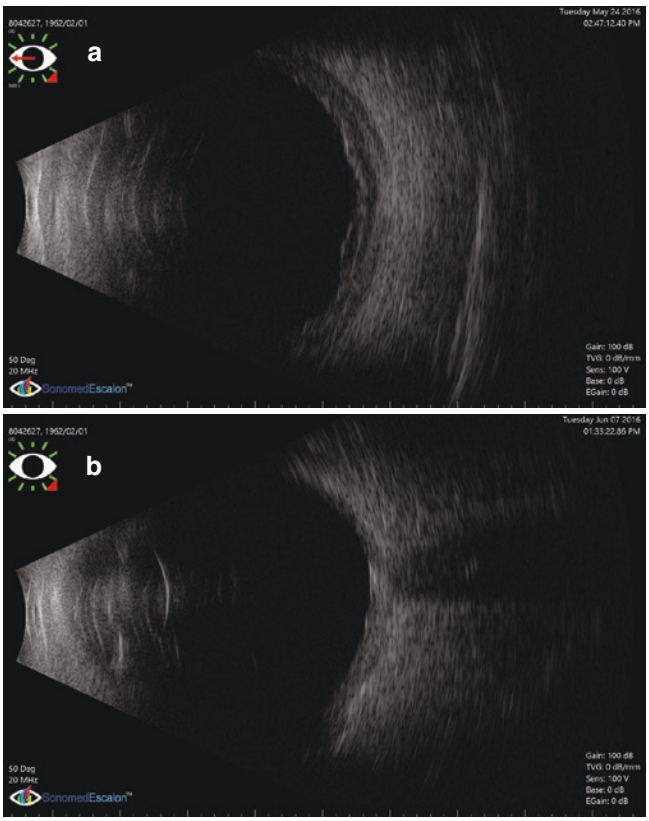

Fig. 8.6 B-scan ultrasonography of the right eye shows choroidal thickening posteriorly with an overlying membranous interface corresponding to the exudative retinal detachment (**a**) and 10 days after IV solumedrol, the choroidal layer remains thickened but the exudative retinal detachment is resolved (**b**)

Differential

Other causes of bilateral granulomatous inflammation include Vogt–Koyanagi–Harada syndrome (VKH), sarcoidosis, phacoanaphylactic uveitis, chronic idiopathic uveitis, infectious granulomatous uveitis (bacterial and fungal) such as that occurs in tuberculosis and syphilis, and intraocular lymphoma. VKH in particular can have a similar presentation to sympathetic ophthalmia and may have Dalen-Fuchs nodules. These patients with VKH do not have a history of ocular injury and have systemic manifestations of VKH such as deafness, poliosis, and vitiligo.

Although there are no specific laboratory studies to establish the diagnosis of sympathetic ophthalmia, it is important to rule out the presence of other diseases with focused clinical studies. These include PPD skin testing, chest radiography, measurement of serum angiotensin-converting enzyme, lysozyme, RPR and FTA-Abs, and possibly lumbar puncture.

Prevention and Management

Surgical Treatment

The classic teaching has been that enucleation within 14 days after ocular injury protects the second eye from the development of sympathetic ophthalmia (Albert and Diaz-Rohena 1989). The protective role of enucleation has been largely

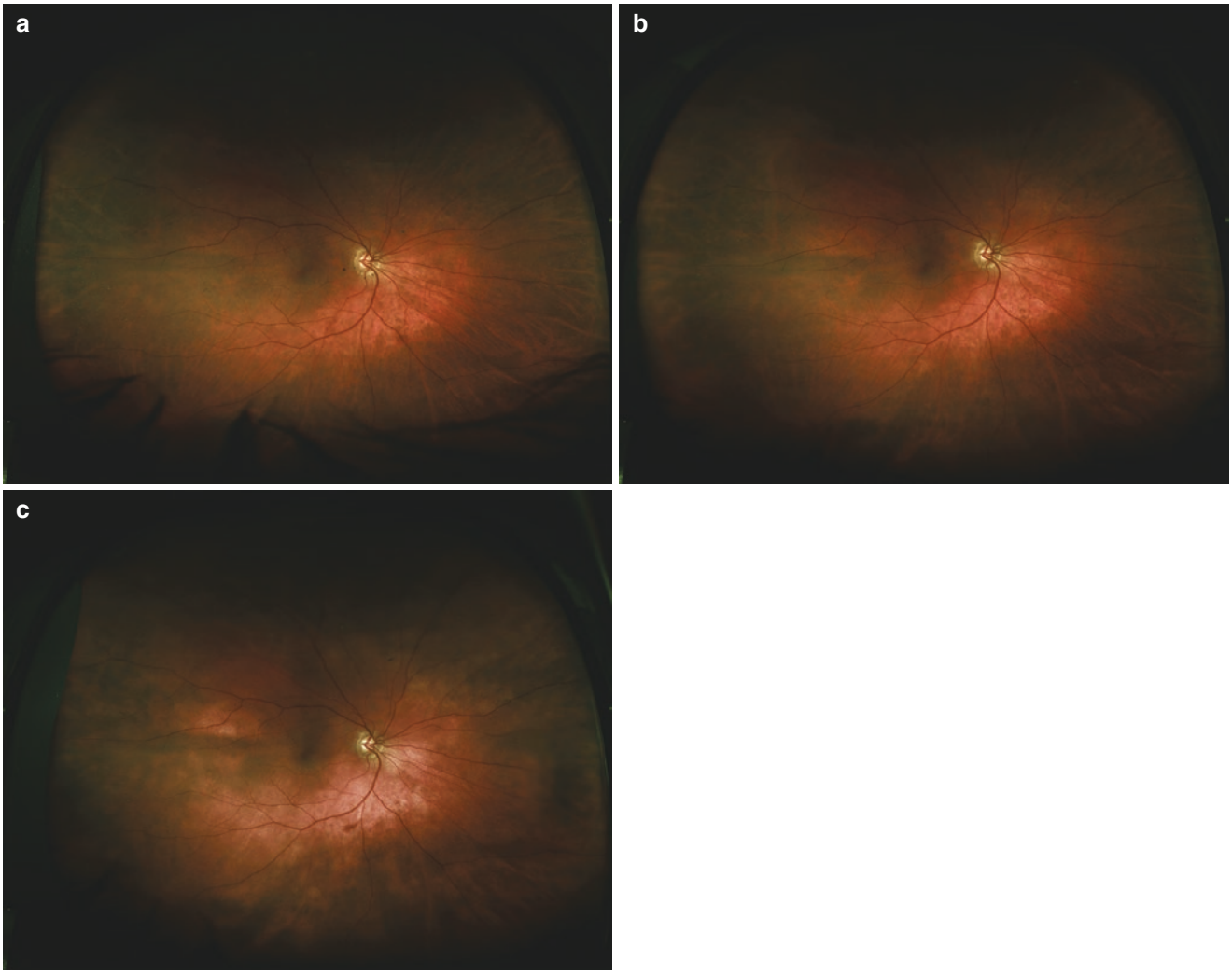

Fig. 8.7 (**a**–**c**) Color fundus photographs over a year period revealing depigmentation of the RPE

unproven and generally discouraged unless open globe repair is deemed impossible at the time of injury (Manandhar 2011).

Controversy still exists regarding enucleation of the exciting eye once sympathetic ophthalmia has commenced. Although Lubin et al. published data that early enucleation of the exciting eye after the onset of sympathetic ophthalmia yields better vision in the sympathizing eye (Lubin et al. 1980), this has not been supported by more recent studies (Reynard et al. 1983). Enucleation should not be performed in the exciting eye with vision because not uncommonly, the exciting eye may be the one with the better vision (Moshfeghi et al. 2000; Gasch et al. 2000).

Medical Treatment

Immunosuppressive therapy is the mainstay of treatment. The initial approach, in most cases, should be with corticosteroids. Systemic corticosteroids are recommended on a daily basis, beginning with a high dose of a short-acting agent (1.0–1.5 mg/kg/day prednisone). If the disease is severe, intravenous pulse steroid therapy (1.0 g/day × 3 days) followed by oral prednisone can be considered (Hebestreit et al. 1997). Therapeutic efficacy should be evaluated at 3 months. If corticosteroid therapy is effective, then a slow taper should be initiated (Table 8.1).

Patients who become resistant to corticosteroids or develop side effects may be candidates for therapy with other immunosuppressive agents such as chlorambucil, cyclophosphamide, azathioprine, or cyclosporine. Cyclosporine has been used at 5 mg/kg/day, tapering to a maintenance dose of 1 mg/kg/day with regular monitoring of blood pressure and renal function. Azathioprine, at a dose of 50 mg three times a day, has also been used effectively in combination with low-dose corticosteroids with blood count monitoring (Hakin et al. 1992). Mycophenolate dosage has been 1 g b.i.d. Chlorambucil has a risk of infertility and secondary

Table 8.1 Treatment for sympathetic ophthalmia

Initial therapy
High-dose corticosteroid (prednisone 1–2 mg/kg/day) for 3 months
If severe, IV solumedrol 1 g/day for 3 days followed by oral prednisone
If no response/side effects
Cyclosporine 5 mg/kg/day with 1 mg/kg/day taper
Azathioprine 50 mg three times a day
Mycophenolate 1 g twice a day
Chlorambucil 2 mg/day

malignancies and should be reserved for elderly patients who have failed other options. Collaborative management with an internist, rheumatologist or hematologist is advisable.

Early diagnosis and initiation of treatment can yield good visual results (Kilmartin et al. 2000a). Chan and associates reported 16 of 32 patients achieving 20/40 or better vision after immunosuppressive treatment for sympathetic ophthalmia (Chan et al. 1995).

References

Ahmad N, Soong TK, Salvi S, Rudle PA, Rennie IG. Sympathetic ophthalmia after ruthenium plaque brachytherapy. Br J Ophthalmol. 2007;91(3):399–401. https://doi.org/10.1136/bjo.2006.102384.

Albert DM, Diaz-Rohena R. A historical review of sympathetic ophthalmia and its epidemiology. Surv Ophthalmol. 1989;34(1):1–14.

Bernasconi O, Auer C, Zografos L, Herbort CP. Indocyanine green angiographic findings in sympathetic ophthalmia. Graefes Arch Clin Exp Ophthalmol. 1998;236(8):635–8.

Brour J, Desjardins L, Lehoang P, Bodaghi B, Lumbroso-Lerouic L, Dendale R, Cassoux N. Sympathetic ophthalmia after proton beam irradiation for choroidal melanoma. Ocul Immunol Inflamm. 2012;20(4):273–6. https://doi.org/10.3109/09273948.2012.689072.

Brouzas D, Koutsandrea C, Moschos M, Papadimitriou S, Ladas I, Apostolopoulos M. Massive choroidal hemorrhage after intravitreal administration of bevacizumab (Avastin) for AMD followed by contralateral sympathetic ophthalmia. Clin Ophthalmol. 2009;3:457–9.

Buller AJ, Doris JP, Bonshek R, Brahma AK, Jones NP. Sympathetic ophthalmia following severe fungal keratitis. Eye (Lond). 2006;20(11):1306–7. https://doi.org/10.1038/sj.eye.6702156.

Castiblanco CP, Adelman RA. Sympathetic ophthalmia. Graefes Arch Clin Exp Ophthalmol. 2009;247(3):289–302. https://doi.org/10.1007/s00417-008-0939-8.

Castiblanco C, Adelman RA. Imaging for sympathetic ophthalmia: impact on the diagnosis and management. Int Ophthalmol Clin. 2012;52(4):173–81. https://doi.org/10.1097/IIO.0b013e318265d5c7.

Chan CC, Roberge RG, Whitcup SM, Nussenblatt RB. 32 cases of sympathetic ophthalmia. A retrospective study at the National Eye Institute, Bethesda, Md., from 1982 to 1992. Arch Ophthalmol. 1995;113(5):597–600.

Chang GC, Young LH. Sympathetic ophthalmia. Semin Ophthalmol. 2011;26(4–5):316–20. https://doi.org/10.3109/08820538.2011.588658.

Edwards TL, McKelvie P, Walland MJ. Sympathetic ophthalmia after diode laser cyclophotocoagulation: now an issue in informed consent. Can J Ophthalmol. 2014;49(4):e102–4. https://doi.org/10.1016/j.jcjo.2014.05.005.

Gasch AT, Foster CS, Grosskreutz CL, Pasquale LR. Postoperative sympathetic ophthalmia. Int Ophthalmol Clin. 2000;40(1):69–84.

Gass JD. Sympathetic ophthalmia following vitrectomy. Am J Ophthalmol. 1982;93(5):552–8.

Guerriero S, Montepara A, Ciraci L, Monno R, Cinquepalmi V, Vetrugno M. A case of sympathetic ophthalmia after a severe acanthamoeba keratitis. Eye Contact Lens. 2011;37(6):374–6. https://doi.org/10.1097/ICL.0b013e3182128e93.

Hakin KN, Pearson RV, Lightman SL. Sympathetic ophthalmia: visual results with modern immunosuppressive therapy. Eye (Lond). 1992;6(Pt 5):453–5. https://doi.org/10.1038/eye.1992.95.

Hebestreit H, Huppertz HI, Sold JE, Dammrich J. Steroid-pulse therapy may suppress inflammation in severe sympathetic ophthalmia. J Pediatr Ophthalmol Strabismus. 1997;34(2):124–6.

Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. Br J Ophthalmol. 2000a;84(3):259–63.

Kilmartin DJ, Dick AD, Forrester JV. Sympathetic ophthalmia risk following vitrectomy: should we counsel patients? Br J Ophthalmol. 2000b;84(5):448–9.

Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia. A clinicopathologic review of 105 cases (1913–1978). Ophthalmology. 1980;87(2):109–21.

Manandhar A. Sympathetic ophthalmia: enucleation or evisceration? Nepal J Ophthalmol. 2011;3(2):181–7. https://doi.org/10.3126/nepjoph.v3i2.5274.

Marak GE Jr. Recent advances in sympathetic ophthalmia. Surv Ophthalmol. 1979;24(3):141–56.

Moshfeghi DM, Moshfeghi AA, Finger PT. Enucleation. Surv Ophthalmol. 2000;44(4):277–301.

Moshfeghi AA, Harrison SA, Ferrone PJ. Indocyanine green angiography findings in sympathetic ophthalmia. Ophthalmic Surg Lasers Imaging. 2005;36(2):163–6.

Power WJ, Foster CS. Update on sympathetic ophthalmia. Int Ophthalmol Clin. 1995;35(1):127–37.

Rao NA, Robin J, Hartmann D, Sweeney JA, Marak GE Jr. The role of the penetrating wound in the development of sympathetic ophthalmia experimental observations. Arch Ophthalmol. 1983;101(1):102–4.

Reynard M, Riffenburgh RS, Maes EF. Effect of corticosteroid treatment and enucleation on the visual prognosis of sympathetic ophthalmia. Am J Ophthalmol. 1983;96(3):290–4.

Sharp DC, Bell RA, Patterson E, Pinkerton RM. Sympathetic ophthalmia. Histopathologic and fluorescein angiographic correlation. Arch Ophthalmol. 1984;102(2):232–5.

Su DH, Chee SP. Sympathetic ophthalmia in Singapore: new trends in an old disease. Graefes Arch Clin Exp Ophthalmol. 2006;244(2):243–7. https://doi.org/10.1007/s00417-005-0009-4.

Wong VG, Anderson R, O'Brien PJ. Sympathetic ophthalmia and lymphocyte transformation. Am J Ophthalmol. 1971;72(5):960–6.