Complications in Uveitis

Francesco Pichi
Piergiorgio Neri
Editors

Springer

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"Here's a sigh to those who love me,
And a smile to those who hate;
And whatever sky's above me,
Here's a heart for every fate"

—"To Thomas Moore", Lord Byron

"Talent hits a target no one else can hit;
Genius hits a target no one else can see."

—Arthur Schopenhauer

Foreword

Complication: Latin—to fold together. Complex combination or intricate intermingling

Medicine—a secondary disease, accident or adverse reaction that aggravates an already existing disease

The myriad complications associated with uveitis involve every anatomical part of the eye and surrounding structures. It is a herculean task to not only document and describe these associated complications, but perhaps more importantly to offer concise management options for these often problematic and sometimes devastating problems.

Dr. Pichi and Dr. Neri have put together a book that offers an excellent road map to enable us to diagnose and treat the secondary complications of uveitis. They have been able to "unfold" this complex intermingling of multiple problems providing the practitioner a road map to forecast, to recognize and to appropriately treat these sequelae. Dr. Pichi and Dr. Neri have assembled an excellent group of subspecialists who tackle the complex and often frustrating problem of managing uveitic complications by subdividing these complications anatomically. It is thus easier to diagnose the occurrence of these complications and then be able to offer an appropriate algorithm for treatment. Kudos to Dr. Pichi and Dr. Neri and their co-authors for addressing these complex problems in a concise and organized manner.

Allen Z. Verne
Founding Member of the
American Society of Retina Specialists

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Part I
Cornea Complications in Uveitis

Chapter 1
Band Keratopathy

Alfonso Iovieno, Tony Ng, and Sonia N. Yeung

Introduction

The term band keratopathy refers to band-shaped superficial corneal degeneration that usually involves the interpalpebral area. The degeneration can occur in calcific and non-calcific forms. The disease most commonly intended as band keratopathy implies calcium deposition in the superficial layers of the cornea. Non-calcific superficial corneal depositions, such as those in climatic droplet keratopathy or in the context of gout from urate depositions, are not going to be further discussed in this chapter.

Pathogenesis

Ever since its first description by Dixon in 1948, the disease has remained somewhat mysterious in its pathogenesis [1, 2].

The initial histologic change observed in corneas with band keratopathy is basophilic staining of the epithelial basement membrane, reflecting early calcific change (Fig. 1.1a). This is followed by overt calcium depositions at the level of Bowman layer and the anterior most layers of the stroma. Later changes include Bowman layer fragmentation, deposition of hyaline material within fragmented Bowman layer and corneal fibrosis (Fig. 1.1b) [1, 3]. The calcium granules are commonly extracel-

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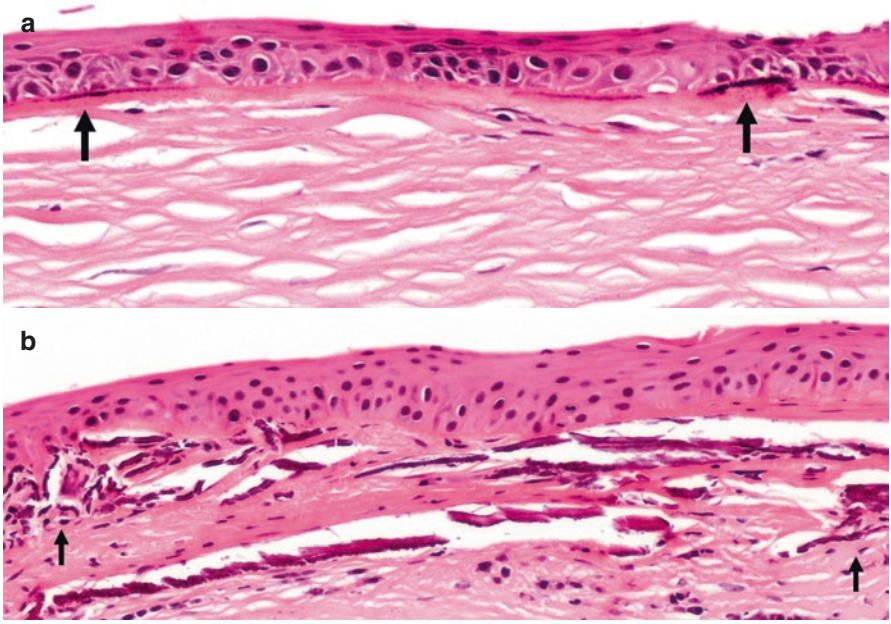

Fig. 1.1 (**a**) Early band keratopathy. There is increased basophilic staining of Bowman's layer (arrows) without overt calcium deposition. (**b**) Advanced band keratopathy. Bowman's layer is widely disrupted by multiple large deposits of calcium; calcified deposits are also present in the anterior stroma (arrows)

lular, with intracellular (intracytoplasmatic and intranuclear) granules also observed in band keratopathy associated with hypercalcemia [4].

In band keratopathy, calcium is found mostly in hydroxyapatite form. Hydroxyapatite is a naturally occurring calcium and phosphate crystal which forms most of the mineral content of dentine, enamel and bones. This compound is very insoluble. The reaction equation of hydroxyapatite is reported below: [5].

$$10Ca(OH)_2 + 6H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18H_2O$$

In conditions of increased pH or abundance of calcium and phosphate, the equilibrium is skewed towards production and consequent deposition of hydroxyapatite. Since the concentration of calcium and phosphate in tears is close to saturation, relatively minor changes in concentration of those ions, tear film osmolarity and pH could trigger the formation of hydroxyapatite and consequent development of band keratopathy [6]. Endothelial damage may also play a role. In edematous corneas there is a reduction in sulfated mucopolysaccharides, known to inhibit ionic binding and calcification [7].

A combination of these factors is likely to be needed to induce development of band keratopathy. In a study by Doughman et al., experimental uveitis in rabbits resulted in band keratopathy only when injection of calciferol (with consequent hypercalcemia) was added. Interestingly, surgical closure of the eyelid prevented

Table 1.1 Ocular and systemic conditions causing band keratopathy divided by putative pathogenetic mechanism

Putative mechanism	Condition
Hypercalcemia	Hyperparathyroidism, osteoporosis, vitamin D intoxication, Paget disease of the bone, metastatic carcinoma to the bone, sarcoidosis, multiple myeloma, milk alkali syndrome, tuberous sclerosis, lupus discoid
Hyperphosphatemia	Renal failure, phosphate containing-eye drops
Increased tear evaporation	Dry eye
Endothelial damage/chronic ocular inflammation	Uveitis, keratitis, silicone oil tamponade, phthisis bulbi, glaucoma, exposure to mercurial vapors or preservatives (thimerosal)
Congenital	Congenital band keratopathy, Norrie's disease

formation of band keratopathy [1, 8]. In another experiment by Odenberger et al., the administration of dihydrotachysterol to rabbits only caused band keratopathy when endothelial damage was also induced [1].

The predilection for the superficial most layers and the interpalpebral area may depend on several factors. Firstly, the structure of Bowman layer may provide a preferential binding site for calcium. Secondly, the interpalpebral zone is more prone to tear evaporation than the rest of the ocular surface, with secondary hyperosmolarity and increase in calcium and phosphate concentration [9]. Moreover, there is an increased carbon dioxide concentration at the corneal surface, due to the predominantly aerobic metabolism of the anterior cornea [1]. This could produce a localized increase in pH compared to the posterior cornea, where anaerobic metabolism and lactate production account for a decrease in pH.

Band keratopathy develops as a non-specific end-point manifestation of several underlying degenerative and inflammatory processes involving the anterior segment, as well as systemic conditions. Most common etiologies include idiopathic, secondary to uveitis and silicone oil tamponade with oil-endothelial touch [10–13]. Table 1.1 shows a list of diseases causing band keratopathy based on the putative underlying mechanism.

Among patients with uveitis, band keratopathy develops in subjects with a chronic course of the disease [14]. Patients affected by juvenile idiopathic arthritis (JIA) associated-uveitis are among the ones at highest risk of band keratopathy, given the long duration of the inflammatory disorder. In these patients, band keratopathy remains a significant cause of vision loss and consequent surgical intervention even in adult age, occurring in as many as 42% of individuals with JIA [15].

Clinical Features

Band keratopathy usually develops over a long period of time, although acute onset has been described following intracameral tissue plasminogen activator [16]. The common initial presentation occurs at the extreme periphery of the cornea at 3 and 9

o'clock in the interpalpebral region. The peripheral calcium plaques have sharply demarcated outer edges and a billowed inner border. There is usually an intervening clear space between the plaque and the sclerocorneal limbus, thought to be caused by either the lack of Bowman layer in this area or the clearance of calcium provided by the limbal vasculature (Fig. 1.2a). The plaques are initially grayish in color usually progressing to chalky white over time. The development of the plaque is centripetal and the central cornea usually remains clear until later stages. Cases of primary central development of band keratopathy have also been described [17]. It is sometimes possible to identify intervening pores within the context of the band, thought to be secondary to penetrating corneal nerves through the Bowman layer (Fig. 1.2b). In the fully developed form, the band can occupy the entirety of the interpalpebral space and can maintain the aspect of a regular gray-white subepithelial haze or become irregularly placoid with marked surface unevenness (Fig. 1.3a, b).

Visual symptoms associated with band keratopathy include photophobia, glare and reduced visual acuity in eyes that retain visual potential. The corneal epithelium is raised and scarcely adherent to the underlying band. Therefore, patients commonly develop foreign body sensation as well as symptoms of recurrent corneal erosions. The occurrence of infectious keratitis secondary to superinfected chronic epithelial defects is not uncommon.

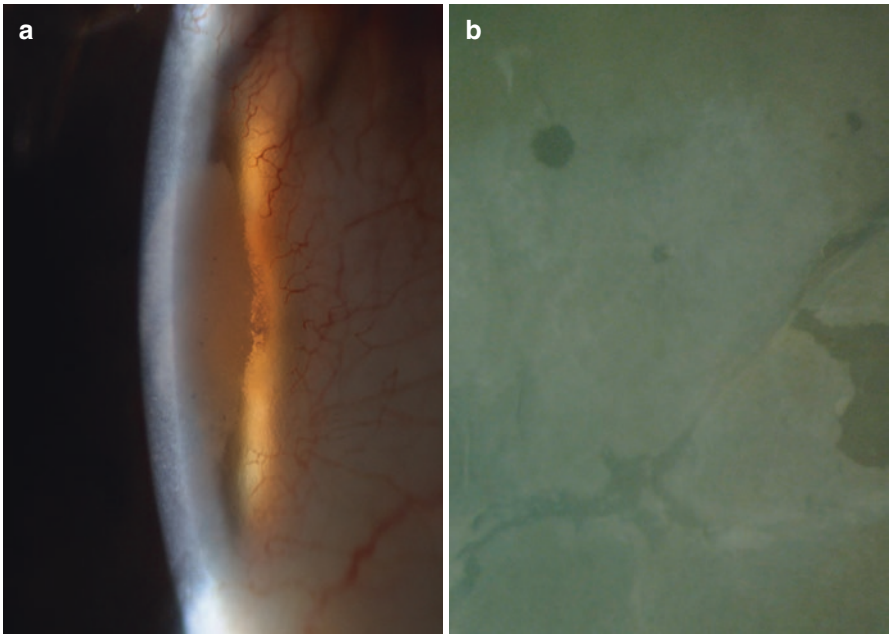

Fig. 1.2 (**a**) clear intervening space between the band keratopathy plaque and the sclerocorneal limbus. (**b**) Scattered round pores through the extension of the calcium plaque, thought to be formed by trespassing corneal nerves

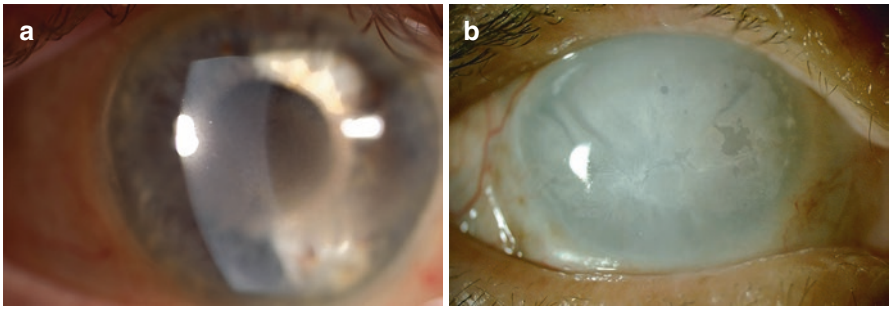

Fig. 1.3 (**a**) Band keratopathy presenting as interpalpebral subepithelial haze. (**b**) Band keratopathy as a chalky, placoid opacity with surface irregularity

Differential diagnosis of band keratopathy includes other corneal degenerations with calcium deposition such as calcareous degeneration and reticular degeneration of Koby, which can be considered rare variants of band keratopathy. In calcareous degeneration, calcium deposits are not limited to the superficial layers of the cornea but are present throughout the entire corneal tissue with potential solitary involvement of the posterior stroma, full-thickness deposits and sparing of the Bowman layer [18]. This rare keratopathy can be associated with bone formation elsewhere in the eye. Similar to band keratopathy, calcareous degeneration affects diseased eyes, especially when chronic epithelial defects are present [19]. It has also been described in association with abundant use of phosphate-based artificial tears for non-healing epithelial defects [20]. Calcareous degeneration can occur more rapidly than band keratopathy.

Reticular degeneration of Koby is an even rarer corneal degeneration where calcium deposits present in a reticular shape at the level of Bowman layer underlying a brownish discoloration of the cornea epithelium secondary to iron deposition [21].

As mentioned above, non-calcified band keratopathy can also occur in climatic droplet keratopathy (also known as spheroidal degeneration or Labrador keratopathy) and urate keratopathy associated with gout.

Corneal dystrophies involving the Bowman layer and anterior stroma such as Reis-Bücklers, Thiel-Behnke, granular and Schnyder's dystrophy can sometimes resemble band keratopathy. The feathery gray microcystic whorls of Lisch dystrophy could also be misinterpreted as calcific bands [22]. Bilateral involvement, preferential central distribution and lack of associated ocular or systemic associations can help differentiate these conditions.

Diagnosis of band keratopathy is essentially clinical and does not require additional testing. In large case series, one of the most common causes of band keratopathy was found to be idiopathic, accounting for about 25–35% of cases [13, 23]. Serum electrolytes, renal function testing and urinalysis should be considered in all idiopathic cases.

Management

As affected patients are often asymptomatic, conservative management can be considered. The limited visual potential and ocular comorbidities often do not justify surgical intervention. Artificial tears and a bandage contact lens with topical antibiotic coverage can sometimes be used as temporizing measures in symptomatic patients. In addition, when associated with systemic disease causing hypercalcemia, early band keratopathy can sometimes be reversed by treating the underlying condition [24, 25].

The mainstay of treatment for band keratopathy is mechanical removal of the calcium deposits. The standard technique consists of a superficial keratectomy with utilization of ethylenediaminetetraacetic acid (EDTA), a calcium-chelating agent, at a concentration of 0.5 mol/l (0.5–1.5%). Removal of the calcifications and superficial keratectomy without EDTA, although possible in eyes with limited visual potential, is usually not advised as it is more likely to result in incomplete removal and an uneven corneal surface with limited visual improvement [26].

The procedure is classically performed under topical anesthesia, although general anesthesia may be required for pediatric patients. It is usually conducted in a procedure room with the aid of a surgical microscope, although it could be undertaken also at the slit lamp [27]. Total timing of the procedure is usually between 10 and 20 min. It can at times be quite time-consuming and tedious depending on the extension and density of the plaque. Briefly, the cornea is de-epithelialized either mechanically with a blade or spear swab (after soaking with balanced salt solution) or using 20% ethanol. Then, EDTA is applied on the cornea either by using a photorefractive keratectomy corneal well as a reservoir or just spear swabs repeatedly soaked in EDTA solution. EDTA soaking time can be variable and depends on the extension of the calcium deposits. Following EDTA treatment, calcifications can either be mechanically removed using forceps, scraped off with surgical blades (usually a no.15 or no.69 blade) or gently dissected using blunt dissection corneal instruments. EDTA application is usually repeated several times to remove all the calcium deposits. It is particularly useful, once superficial calcifications have been removed, to use a truncated spear swab soaked in EDTA in a rubbing fashion onto the cornea to slowly eliminate all residual calcium from the Bowman layer without violating it. The end-point of the procedure is the identification of a clear corneal plane with visualization of the anterior chamber. Copious irrigation with balanced salt solution should be conducted throughout the surgery. At the end of the procedure, a bandage contact lens is usually applied and topical antibiotics, corticosteroids and unpreserved artificial tears are prescribed postoperatively. Oral analgesics are often necessary to account for post-operative pain in the 1–2 days following the procedure.

The procedure is usually straightforward with limited potential complications. When performed with sharp instruments, removal of the calcifications and superficial keratectomy could result in an irregular corneal plane with potential stromal scarring and suboptimal visual acuity. EDTA treatment would only eliminate the

calcium deposits, leaving any underlying corneal scar untreated. The procedure should be carefully considered in patients with potential delayed epithelial healing (neurotrophic keratopathy, limbal stem cells deficiency, etc.), as post-operative non-resolving epithelial defects and indolent ulcers could occur. If necessary, in these cases, a temporary tarsorrhaphy or amniotic membrane grafting may be of benefit to expedite the healing process.

Band keratopathy has the tendency to recur after surgical removal. Recurrence rate ranges between 15% and 30%, on average within 1–2 years after treatment [13, 23]. Nonetheless, only about 5% of recurring cases would require a second surgical intervention [13].

Phototherapeutic keratectomy (PTK) has also been investigated as a potential primary treatment modality for band keratopathy. The two larger series published on PTK produced similar results. In a study by O'Brart et al., 122 eyes were treated with a single photoablation zone PTK [28]. Significant improvement in symptoms and vision was reported, with a recurrence rate around 8% within mean follow-up of 12 months. About a quarter of the patients reported a post-surgical average hyperopic shift of 1.4 diopters at 6 months. In another study by Stewart and Morrel, treatment with PTK produced an improvement in vision in 55% of the treated eyes with visual potential and an improvement in symptoms in 85% of the treated eyes with no visual potential [29]. Interestingly, this study described a significant post-operative myopic shift.

PTK has the advantage of being less time consuming and more standardized compared to mechanical removal with EDTA. Laser platforms though do not have the ability to discriminate between corneal tissue and calcifications, possibly producing an irregular residual corneal surface. The use of masking agents partially counteracts for the uneven ablation profile. In addition, excimer laser is largely ineffective on large or irregular calcium deposits. In both the abovementioned series, large and irregular band keratopathies required mechanical removal of the calcifications prior to PTK treatment [28, 29]. When considering PTK, the issue of refractive change in eyes with visual potential should also be taken into account. Hyperopic and myopic shift could both occur. Lastly, whilst post-surgical results do not seem to differ, PTK has significantly higher costs compared to standard superficial keratectomy with EDTA.

The use of amniotic membrane has been advocated by some authors in the surgical management of band keratopathy. The well-known epitheliotrophic and anti-inflammatory properties of amniotic membrane account for the popular and versatile use of this tissue in ocular surface surgery [30]. Amniotic membrane does not have any effect on calcium depositions and should not be considered as a primary treatment. In a study by Anderson et al., amniotic membrane grafting was performed after superficial keratectomy for band keratopathy with or without the use of EDTA [31]. Symptoms improved in all patients and 93% of patients re-epithelialized within 15 days. Other authors have reported cases amniotic membrane grafting into a lamellar bed with fibrin glue in cases of band keratopathy with stromal involvement [32, 33]. Im and co-workers also described a series of band keratopathy

patients treated with a combination of superficial keratectomy with EDTA, PTK and amniotic membrane grafting [34].

The use of amniotic membrane did not seem to have a significant impact on the post-operative course and is therefore not routinely recommended. In cases where delayed epithelialization is expected due to ocular surface disorders, amniotic membrane graft should be considered to prevent chronic epithelial defects and reduce post-operative complications.

References

1. O'Connor GR. Calcific band keratopathy. Trans Am Ophthalmol Soc. 1972;70:58–81.
2. Dixon J. In: Churchill J, editor. Diseases of the eye. London; 1848. p. 114.
3. Cursino JW, Fine BS. A histologic study of calcific and noncalcific band keratopathies. Am J Ophthalmol. 1976;82(3):395–404.
4. Berkow JW, Fine BS, Zimmerman LE. Unusual ocular calcification in hyperparathyroidism. Am J Ophthalmol. 1968;66(5):812–24.
5. Bouyer E, Gitzhofer F, Boulos MI. Morphological study of hydroxyapatite nanocrystal suspension. J Mater Sci Mater Med. 2000;11(8):523–31.
6. Huth SW, Hirano P, Leopold IH. Calcium in tears and contact lens wear. Arch Ophthalmol. 1980;98(1):122–5.
7. Quantock AJ, Meek KM, Brittain P, Ridgway AE, Thonar EJ. Alteration of the stromal architecture and depletion of keratan sulphate proteoglycans in oedematous human corneas: histological, immunochemical and X-ray diffraction evidence. Tissue Cell. 1991;23(5):593–606.
8. Doughman DJ, Olson GA, Nolan S, Hajny RG. Experimental band keratopathy. Arch Ophthalmol. 1969;81(2):264–71.
9. Mathers W. Evaporation from the ocular surface. Exp Eye Res. 2004;78(3):389–94.
10. Nascimento H, Yasuta MK, Marquezan MC, Salomão GHA, González D, Francesconi C, et al. Uveitic band keratopathy: child and adult. J Ophthalmic Inflamm Infect. 2015;5(1):1–4.
11. Morphis G, Irigoyen C, Eleuteri A, Stappler T, Pearce I, Heimann H. Retrospective review of 50 eyes with long-term silicone oil tamponade for more than 12 months. Graefes Arch Clin Exp Ophthalmol. 2012;250(5):645–52.
12. Federman JL, Schubert HD. Complications associated with the use of silicone oil in 150 eyes after retina-vitreous surgery. Ophthalmology. 1988;95(7):870–6.
13. Al-Hity A, Ramaesh K, Lockington D. EDTA chelation for symptomatic band keratopathy: results and recurrence. Eye. 2018;32(1):26–31.
14. Ozdal PC, Berker N, Tugal-Tutkun I. Pars planitis: epidemiology, clinical characteristics, management and visual prognosis. J Ophthalmic Vis Res. 2015;10(4):469–80.
15. Oray M, Khachatryan N, Ebrahimiadib N, Abu Samra K, Lee S, Foster CS. Ocular morbidities of juvenile idiopathic arthritis-associated uveitis in adulthood: results from a tertiary center study. Graefes Arch Clin Exp Ophthalmol. 2016;254(9):1841–9.
16. Moisseiev E, Gal A, Addadi L, Caspi D, Shemesh G, Michaeli A. Acute calcific band keratopathy: case report and literature review. J Cataract Refract Surg. 2013;39(2):292–4.
17. Cogan DG, Henneman PH. Diffuse calcification of the cornea in hypercalcemia. N Engl J Med. 1957;257(10):451–3.
18. Bordin GL, Dornelles F, Martins JA, Magalhaes OA. Primary calcareous degeneration of the cornea. Indian J Ophthalmol. 2017;65(10):1027–30.
19. Lavid FJ, Herreras JM, Calonge M, Saornil MA, Aguirre C. Calcareous corneal degeneration: report of two cases. Cornea. 1995;14(1):97–102.

20. Lake D, Tarn A, Ayliffe W. Deep corneal calcification associated with preservative-free eye-drops and persistent epithelial defects. Cornea. 2008;27(3):292–6.
21. Perry HD, Leonard ER, Yourish NB. Superficial reticular degeneration of koby. Ophthalmology. 1985;92(11):1570–3.
22. Lisch W, Steuhl KP, Lisch C, Weidle EG, Emmig CT, Cohen KL, et al. A new, band-shaped and whorled microcystic dystrophy of the corneal epithelium. Am J Ophthalmol. 1992;114(1):35–44.
23. Najjar DM, Cohen EJ, Rapuano CJ, Laibson PR. EDTA chelation for calcific band keratopathy: Results and long-term follow-up. Am J Ophthalmol. 2004;137(6):1056–64.
24. Galor A, Leder HA, Thorne JE, Dunn JP. Transient band keratopathy associated with ocular inflammation and systemic hypercalcemia. Clin Ophthalmol. 2008;2(3):645–7.
25. MILLER S. Band-keratopathy with a report of a case of Fanconi's syndrome with calcium deposits in the cornea. Trans Ophthalmol Soc U K. 1958;78:59–69.
26. Bee CR, Koenig LR, Hwang ES, Koenig SB. Removal of calcific band keratopathy without ethylenediaminetetraacetic acid (EDTA) in eyes with limited visual potential. Clin Ophthalmol. 2018;12:1895–9.
27. Jhanji V, Rapuano CJ, Vajpayee RB. Corneal calcific band keratopathy. Curr Opin Ophthalmol. 2011;22(4):283–9.
28. O'Brart DPS, Gartry DS, Lohmann CP, Patmore AL, Muir MGK, Marshall J. Treatment of band keratopathy by excimer laser phototherapeutic keratectomy: Surgical techniques and long term follow up. Br J Ophthalmol. 1993;77(11):702–8.
29. Stewart OG, Morrell AJ. Management of band keratopathy with excimer phototherapeutic keratectomy: Visual, refractive, and symptomatic outcome. Eye. 2003;17(2):233–7.
30. Jirsova K, Jones GLA. Amniotic membrane in ophthalmology: properties, preparation, storage and indications for grafting—a review. Cell Tissue Bank. 2017;18(2):193–204.
31. Anderson DF, Ophth FRC, Prabhasawat P, Alfonso E, Tseng SCG. Amniotic membrane transplantation after the primary surgical management of band keratopathy. Cornea. 2001;20(4):354–61.
32. Esquenazi S, Rand W, Velazquez G, Grunstein L. Novel therapeutic approach in the management of band keratopathy using amniotic membrane transplantation with fibrin glue. Ophthalmic Surg Lasers Imaging. 2008;39(5):418–21.
33. Young SK, Young SS, Jae CK. New treatment for band keratopathy: superficial lamellar keratectomy, EDTA chelation and amniotic membrane transplantation. J Korean Med Sci. 2004;19(4):611–5.
34. Im S-K, Lee K-H, Yoon K-C. Combined ethylenediaminetetraacetic acid chelation, phototherapeutic keratectomy and amniotic membrane transplantation for treatment of band keratopathy. Korean J Ophthalmol. 2010;24(2):73–7.

Chapter 2
Limbal Stem Cell Deficiency in Inflammatory Disorders

Paolo Rama

Introduction

The corneal epithelium undergoes regular turn-over throughout the migration of cells from the limbus, where the corneal epithelial stem cells (LSCs) reside in the basal layer [1–4]. Disorders that damage the limbal area may cause limbal stem-cell deficiency (LSCD) (Fig. 2.1).

Impairment of the limbal stem-cell compartment causes corneal epithelial turn-over breakdown, resulting in damage to the corneal epithelium, which will ultimately repair itself due to conjunctiva migration onto the cornea [5–7].

Conjunctival migration, or "conjuctivalization", is a compensatory repair mechanism that protects the cornea from infection, stromal ulceration, melting, and perforation. While it provides the cornea with a stable and protective superficial layer, it is often accompanied by persistent inflammation, severe visual impairment, and other symptoms.

Lamellar and/or penetrating keratoplasty cannot be used successfully in these cases as donor corneal epithelium is replaced by that of the recipient within months. In the presence of corneal epithelial stem-cell compartment deficiency, donor graft re-epithelialisation will not take place, with subsequent epithelial defects and the ultimate recurrence of conjunctivalization, and the risk of rejection and failure (Fig. 2.2).

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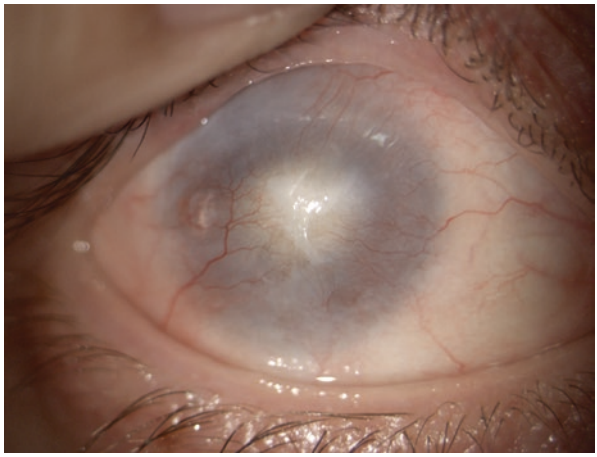

Fig. 2.1 Corneal neovascular pannus, "conjunctivalization", after alkali burn injury

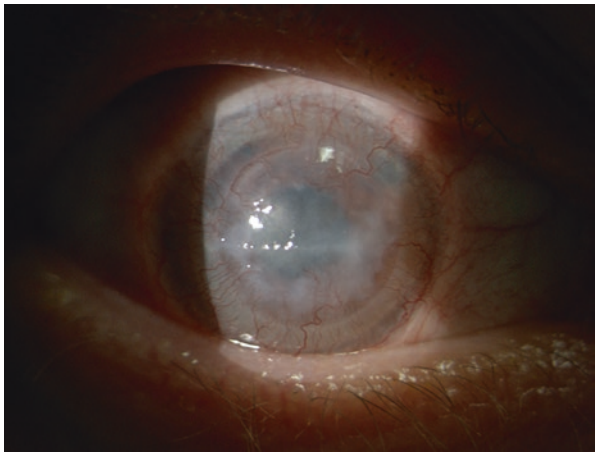

Fig. 2.2 Failed penetrating keratoplasty with recurrence of conjunctivalization due to limbal stem cell deficiency secondary to chemical burn

Causes of LSCD

Numerous ocular or systemic disorders can lead to LSCD, including congenital diseases (e.g. aniridia), acquired diseases due to chemical injuries, toxicity, infections [5–7], and inflammatory diseases, such as mucous membrane pemphigoid (Fig. 2.3) [7–9], Stevens-Johnson syndrome (Fig. 2.4) [7, 10], graft-versus-host disease (Fig. 2.5) [11], vernal and atopic keratoconjunctivitis [7–13]. Such diseases may not only damage the limbus, but also the eyelids, conjunctiva, corneal nerves, stroma and lacrimal system. Ocular surface disease is the most appropriate term for such a complex disorder [7].

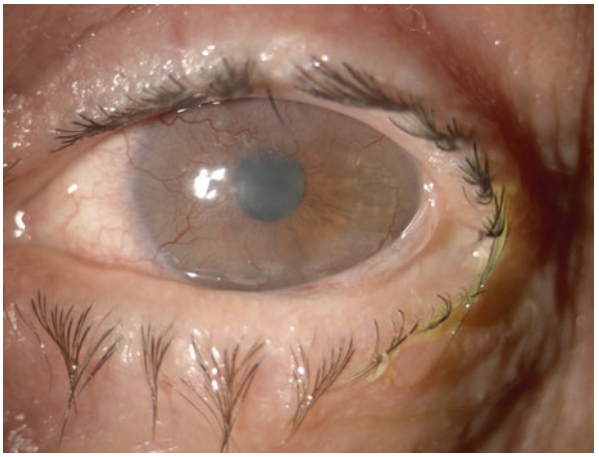

Fig. 2.3 Mucous membrane pemphigoid

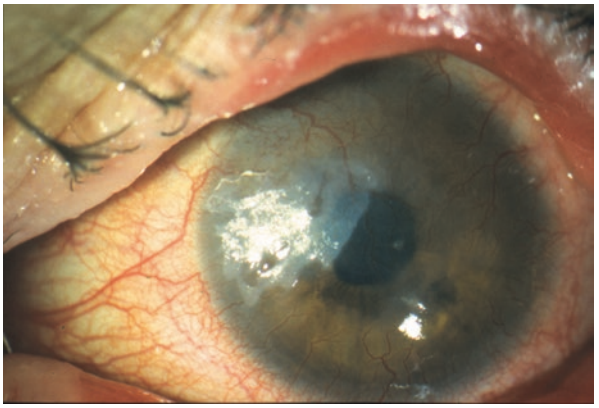

Fig. 2.4 Stevens-Johnson

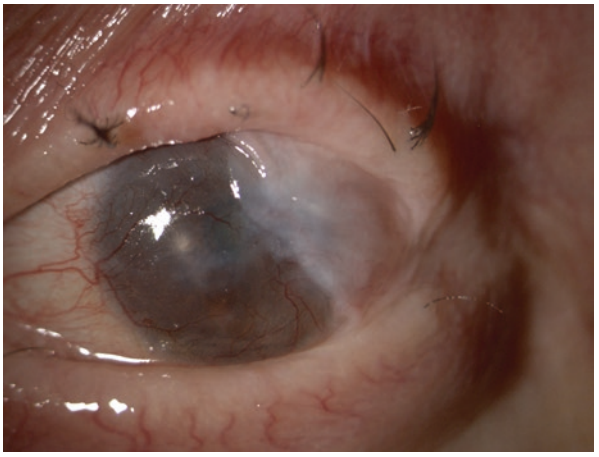

Fig. 2.5 Graft-versus-host disease

Surgical Treatment

Stem-cell transplantation to treat LSCD is a step in the reconstruction of the ocular surface, while lamellar or penetrating corneal grafting will finally restore corneal transparency, leading to the recovery of visual capacity.

Limbal Reconstruction with Stem Cells

Source of Stem Cells

The source of stem cells is typically classified as autologous (donor and recipient are the same subject) and allogeneic (donor and recipient are different subjects).

Unilateral or partial bilateral LSCDs can be treated with autologous limbal stem cells (LSCs), while total bilateral deficiency requires allogeneic LSCs, or other sources of autologous cells such as oral epithelial stem cells.

Autologous Limbal Stem-Cell Transplantation

– **Conjunctival limbal autograft (CLAU).** Unilateral limbal stem-cell deficiency has been successfully treated for years by directly grafting a portion of the healthy limbal tissue taken from the contralateral eye (Fig. 2.6) [14–16]. Some concerns exist regarding potential donor-eye risks [17]: although few reports show the consequences related to harvesting [18], patients are often unenthusiastic about having the "good" eye touched, together with the great responsibility felt by surgeons. Moreover, further limbus harvesting of following possible failure is not advisable.

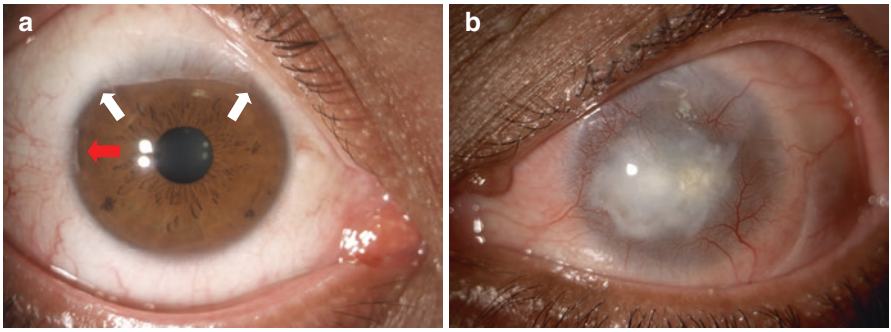

Fig. 2.6 (**a**) Limbal biopsy for CLAU (white arrows) Small limbal biopsy (red arrow) for CLET after failure of the previous CLAU. (**b**) Fellow eye: recurrence of conjunctivalization after failed autologous CLAU

– **Autologous Cultivated Limbal Epithelial Transplantation (CLET)**
To overcome risks for the donor eye, much effort has been made to develop a technique to reduce biopsy dimension using cell expansion in culture. The pioneering work of Rheinwald and Green showed that it was possible to culture a layer of stratified squamous epithelium with stem cells taken from a small skin biopsy [19]. Some years later, cultivated skin grafts were successfully used to treat severe-burn patients [20]. Based on this proof-of-concept, the same procedure was used to prepare autologous grafts of cultivated corneal epithelium with stem cells obtained from a 1–2 mm^2 limbal biopsy Fig. 2.6) [4, 21]. Since 1998, more than 270 grafts have been transplanted in various centres throughout Italy, with long-term stability reported in more than 150 patients, and with a success rate in 70–80% of cases (Fig. 2.7) [22, 23]. In February 2015, this therapy was approved by the European Medicine Agency (EMA) for the treatment of corneal burns (Holoclar®). Two recent publications summarize the history of CLET, from discovery to clinical approval, including the regulatory aspects [24, 25]. A pre-requisite for CLET is the presence of a small area of preserved limbus (2–3 mm), which is biopsied, expanded in culture, and transplanted onto the LSCD-affected eye. Ex-vivo stem-cell expansion is a complex, time consuming, and expensive procedure, but it has several advantages compared with traditional limbal grafting: fewer risks for the donor eye, the possibility to treat partial bilateral LSCD, and the possibility to re-graft following eventual failure.
– **Simple limbal epithelial transplantation (SLET)**. In 2012, Sangwan described a novel technique which claimed to combine the advantages of both CLAU and CLET. From a small limbal biopsy, several pieces of limbal tissue are placed on the recipient corneal surface covered by amniotic membrane [26, 27]. Compared to CLAU, a smaller amount of donor limbal tissue is harvested. Compared to CLET, it is much faster and less expensive. However, the long-term effectiveness of the technique is still under evaluation, and there is a need for further comparison with other techniques, both in terms of clinical outcome and the subsequent success of keratoplasty, when needed. The idea of directly transplanting small pieces

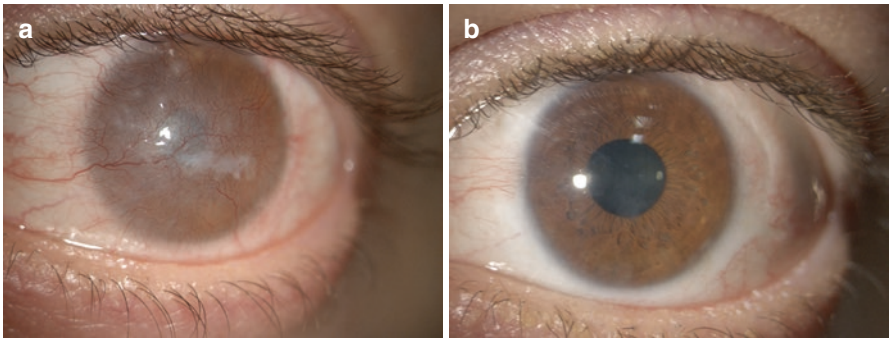

Fig. 2.7 (**a**) Limbal stem deficiency after unilateral chemical burn. (**b**) Six months after autologous CLET

of limbal tissue, claiming that it might support "in-vivo expansion of epithelial cells", is fascinating: it is a "simple", inexpensive, and fast way to treat cases of limbal stem-cell deficiency. As well as cutting costs, it would avoid the complicated regulatory-related rules of ex-vivo expansion procedures. However, some concerns do exist. First of all, stem cells from the small limbal pieces might migrate onto the recipient surface to find their homing. This might promote differentiation: it has not yet been proven that TA cells can re-differentiate into a stem-cell state. Moreover, amniotic membrane (AM) can, at the same time, prevent or promote the correct engraftment and survival of the stem cells [28]: AM can integrate or be digested, and the fate of limbal biopsies is thus not predictable.

Allogeneic Limbal Stem-Cell Transplantation

Allogeneic limbal grafts may come from a deceased donor or from living relatives, and the surgical procedure can be either CLAU, SLET, or CLET.

The major disadvantage of allogeneic limbal stem cell transplantation is the risk of rejection, with the need for prolonged systemic immunosuppression and the possibility of late failure.

In the literature, contrasting results have been reported on the use of allogeneic keratolimbal grafts, with an overall success rate of 73% [17]. Both clinical successes and failures have been observed in the presence of systemic immunosuppressive therapy [29–31], while positive clinical results have been reported in the absence of immunosuppression [32, 33] and/or in the absence of allogeneic cell survival [34, 35].

A recent publication on allogeneic cultivated limbal stem-cell transplantation (CALET) reports a case-series of 6 eyes that showed graft rejection up to 8 years after limbal allograft [36]. The Authors suggest that prolonged and tailored systemic immunosuppression, guided by an organ transplant team, should be maintained. However, they also report that, despite appropriate immunosuppressive treatment, two thirds of their patients developed some degree of failure. Others have performed DNA analysis on 19 samples of recipient corneal epithelium collected after CALET, finding, as previously reported, no persistence of donor DNA after 3 months [34, 35, 37]. They raise provocative questions as to what may be the origin of regenerated epithelium, and whether long-term immunosuppression following CALET is required in examined patients. In the absence of demonstrated surviving donor cells, a possible explanation for clinical success is that patients with non-total limbal stem-cell deficiency were included, and the grafted allogeneic limbal cells might have induced modification of the microenvironment, and promoted proliferation of the patient's own dormant stem cells, whose progeny gradually replaces donor cells. While remaining in situ in the injured eye, these limbal cells are evidently unable to

generate corneal epithelium, both because of the lack of a suitable microenvironment for multiplication, and because of fibrotic obstruction to their migration over the cornea.

Allogeneic limbal stem cells may represent an option for patients with bilateral total LSCD. However, questions remain regarding long-term efficacy, the best regimen of systemic immunosuppression to prevent rejection, and the explanation as to how the cornea improves in certain cases despite non-detectable donor DNA in the patient's epithelium.

Cultivated Autologous Oral Epithelial Transplantation (COMET)

The use of autologous cultivated oral epithelium was proposed in the beginning of 2000 as an alternative to allogeneic limbal grafts for the treatment of bilateral LSCD [38–40]. Several protocols have been proposed to cultivate the cells, although most the studies used amniotic membrane as a substrate/carrier ([41]. Utheim recently reviewed the results of 20 studies involving 242 patients [42]. Success was reported around 70%, although varying inclusion criteria and definitions of success were used in the different studies. Moreover, follow-up was very short, with only two studies reporting results after more than three years. Lastly, peripheral neovascularisation was reported after COMET, which is clearly explained by the great angiogenic properties of the oral epithelium. In conclusion, COMET seems to be a safe procedure able to provide a stable epithelium and reduce inflammation, albeit still not able to prevent recurrence of vessel migration onto the cornea in total LSCDs.

Conclusions

Limbal stem-cell deficiency caused by inflammatory disorders is a challenging problem. Severe acute or chronic inflammation can often cause damage not only to the limbal stem cells but also to other components of the ocular surface, such as the eyelids, conjunctiva, lacrimal system, and nerves. Precise evaluation of damage is crucial, and step-by-step treatment should be planned. The systemic disease must be kept under control with systemic treatment, as should ocular inflammation. A "minimum" of tear film should be present. Eyelid malposition and conjunctival scarring should firstly be surgically corrected. For limbal stem cell deficiency, in the presence of unilateral or partial bilateral damage, cultivated autologous limbal stem-cell transplantation is probably the safest and best procedure. For total bilateral LSCD, allogeneic limbal stem-cell transplantation or autologous oral epithelium have been proposed, but doubts still persist regarding the long-term survival, stability, and avascularity of the epithelium.

References

1. Schermer A, Galvin S, Sun TT. Differentiation-related expression of a major 64K corneal keratin in vivo and in culture suggests limbal location of corneal epithelial stem cells. J Cell Biol. 1986;103:49–62.
2. Cotsarelis G, Cheng SZ, Dong G, Sun TT, Lavker RM. Existence of slow-cycling limbal epithelial basal cells that can be preferentially stimulated to proliferate: implications on epithelial stem cells. Cell. 1989;57:201–9.
3. Tseng SC. Concept and application of limbal stem cells. Eye. 1989;3:141–57.
4. Pellegrini G, Golisano O, Paterna P, et al. Location and clonal analysis of stem cells and their differentiated progeny in the human ocular surface. J Cell Biol. 1999;145:769–82.
5. Dua HS, Azuara-Blanco A. Limbal stem cells of the corneal epithelium. Surv Ophthalmol. 2000;44:415–25.
6. Shortt AJ, Secker GA, Notara MD, et al. Transplantation of ex vivo cultured limbal epithelial stem cells: a review of techniques and clinical results. Surv Ophthalmol. 2007;52:483–502.
7. Deng SX, Borderie V, Chan CC, et al. Global consensus on definition, classification, diagnosis, and staging of limbal stem cell deficiency. Cornea. 2019;38:364–75.
8. Le Q, Xu J, Deng SX. The diagnosis of limbal stem cell deficiency. Ocul Surf. 2018;16:58–69.
9. Eschle-Meniconi ME, Ahmad SR, Foster CS. Mucous membrane pemphigoid: an update. Curr Opin Ophthalmol. 2005;16:303–7.
10. Puangsricharern V, Tseng SC. Cytologic evidence of corneal diseases with limbal stem cell deficiency. Ophthalmology. 1995;102:1476–85.
11. Sivaraman KR, Jivrajka RV, Soin K, et al. Superior limbic keratoconjunctivitis-like inflammation in patients with chronic graft-versus-host disease. Ocul Surf. 2016;14:393–400.
12. Sangwan VS, Jain V, Vemuganti GK, Murthy SI. Vernal keratoconjunctivitis with limbal stem cell deficiency. Cornea. 2011;30:491–6.
13. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology. 2002;109:1159–66.
14. Kenyon KR, Tseng SC. Limbal allograft transplantation for ocular surface disorders. Ophthalmology. 1989;96:709–22.
15. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. Trans Am Ophthalmol Soc. 1996;94:677–743.
16. Frucht-Pery J, Siganos CS, Solomon A. Limbal cell autograft transplantation for severe ocular surface disorders. Graefes Arch Clin Exp Ophthalmol. 1998;236:582–7.
17. Baylis O, Figueiredo F, Henein C, et al. 13 years of cultured limbal epithelial cell therapy: a review of the outcomes. J Cell Biochem. 2011;112:993–1002.
18. Jenkins C, Tuft S, Lui C, Buckley R. Limbal transplantation in the management of chronic contact lens-associated epitheliopathy. Eye. 1993;7:629–33.
19. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. Cell. 1975;6:331–43.
20. Gallico GG 3rd, O'Connor NE, Compton CC, et al. Permanent coverage of large burn wounds with autologous cultured human epithelium. N Engl J Med. 1984;311:448–51.
21. Pellegrini G, Traverso CE, Franzi AT, et al. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. Lancet. 1997;349:990–3.
22. Rama P, Matuska S, Paganoni G, et al. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010;363:147–55.
23. Pellegrini G, Rama P, Matuska S, et al. Biological parameters determining the clinical outcome of cultures of autologous limbal stem cells. Regen Med. 2013;8:553–67.
24. Pellegrini G, Rama P, Di Rocco A, et al. Concise review: hurdles in a successful example of limbal stem cell-based regenerative medicine. Stem Cells. 2014;32:26–34.
25. Pellegrini G, Lambiase A, Macaluso C, et al. From discovery to approval of an advanced therapy medicinal product-containing stem cells, in the EU. Regen Med. 2016;11:407–20.

26. Sangwan VS, Basu S, Macneil S, et al. Simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency. Br J Ophthalmol. 2012;96:931–4.
27. Sangwan VS, Sharp JAH. Simple limbal epithelial transplantation. Curr Opin Ophthalmol. 2017;28:382–6.
28. Dietrich-Ntoukas T, Hofmann-Rummelt C, Kruse FE, Schlötzer-Schrehardt U. Comparative analysis of the basement membrane composition of the human limbus epithelium and amniotic membrane epithelium. Cornea. 2012;31:564–9.
29. Djalilian AR, Mahesh SP, Koch CA, Nussenblatt RB, Shen D, Zhuang Z, Holland EJ, Chan CC. Survival of donor epithelial cells after limbal stem cell transplantation. Invest Ophthalmol Vis Sci. 2005;46:803–7.
30. Mills RA, Coster DJ, Williams KA. Effect of immunosuppression on outcome measures in a model of rat limbal transplantation. Invest Ophthalmol Vis Sci. 2002;43:647–54.
31. Ilary L, Daya SM. Long-term outcomes of keratolimbal allografts for the treatment of severe ocular surface disorders. Ophthalmology. 2002;109:1278–84.
32. Kwitko S, Marinho D, Barcaro S, et al. Allograft conjunctival transplantation for bilateral ocular surface disorders. Ophthalmology. 1995;102:1020–5.
33. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P. Limbal allografting from related live donors for corneal surface reconstruction. Ophthalmology. 1999;107:411–2.
34. Henderson TR, Coster DJ, Williams KA. The long-term outcome of limbal allografts: the search for surviving cells. Br J Ophthalmol. 2001;85:604–9.
35. Daya SM, Watson A, Sharpe JR, et al. Outcomes and DNA analysis of ex vivo expanded stem cell allograft for ocular surface reconstruction. Ophthalmology. 2005;112:470–7.
36. Eslani M, Haq Z, Movahedan A, et al. Late acute rejection after allograft limbal stem cell transplantation: evidence for long-term donor survival. Cornea. 2017;36:26–31.
37. Chen P, Zhou Q, Wang J, et al. Characterization of the corneal surface in limbal stem cell deficiency and after transplantation of cultured allogeneic limbal epithelial cells. Graefes Arch Clin Exp Ophthalmol. 2016;254:1765–77.
38. Nakamura T, Endo K, Cooper LJ, et al. The successful culture and autologous transplantation of rabbit oral mucosal epithelial cells on amniotic membrane. Invest Ophthalmol Vis Sci. 2003;44:106–16.
39. Nakamura T, Kinoshita S. Ocular surface reconstruction using cultivated mucosal epithelial stem cells. Cornea. 2003;22:S75–80.
40. Nishida K, Yamato M, Hayashida Y, et al. Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. N Engl J Med. 2004;351:1187–96.
41. Utheim TP. Concise review: transplantation of cultured oral mucosal epithelial cells for treating limbal stem cell deficiency-current status and future perspectives. Stem Cells. 2015;33:1685–95.
42. Utheim TP, Utheim ØA, Khan QE, Sehic A. Culture of oral mucosal epithelial cells for the purpose of treating limbal stem cell deficiency. J Funct Biomater. 2016;7:2–18.

Chapter 3
Herpetic Corneal Opacities

Luigi Fontana

Pathogenesis

Herpes Simplex viral keratitis is one of the most common infectious causes of corneal blindness [1, 2] involving 0.1% of the general population and inducing significant reduction in vision in 1 out 6 of the affected patients [2]. The incidence is 8.4 cases 100.000 people and the prevalence is 149 cases every 100.000 individuals. These figures are probably underestimated as the disease is underdiagnosed. Ocular disease is more commonly caused by type 1 rather than type 2 Herpes Simplex Virus (HSV). Exposure to HSV type 1 (HSV-1) usually occurs during childhood from contact with oral lesions and secretions. Following the primary infection, that remains undetected in the majority of patients, the virus, due to its neurotropism, enters the peripheral nerves and travels along the neurons in a retrograde direction to reach the peripheral ganglia, including the trigeminal and cervical ganglia, where it remains in the neuronal nuclei for the life span of the patient. In the general population older than 60 years serum and ganglia positivity is found in 90–100% of cases [3]. The cornea itself may also represents a site of host latent HSV. After a variable period of latency, virus reactivation may occur due to several factors that are somewhat related to the immune regulatory system such as high stress and systemic disease [4]. Liesegang et al. [3] in a large epidemiological study addressed the risk of first recurrence as high as 36% at 5 years and 63% after 20 years from the first episode. After first recurrence the probability of a second episode is 70–80%. In the Herpetic Eye Disease Study [5] the recurrence probability after the first episode was 18% within two years.

The clinical sequelae of HSV infection are largely a result of recurrent disease and immunologic response associated with each episode.

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Clinical Forms

Infectious Epithelial Keratitis

Dendritic and Geographic Epithelial Keratitis

Most common presentation of HSV corneal involvement is the dendritic ulcer. This is characterized by a lineal epithelial lesion with dichotomous branching and terminal bulbs with swollen epithelial borders that contain replicating virus. Typically, the epithelial lesion stains with fluorescein in the center and with rose Bengal in the borders (Fig. 3.1a). The area around the lesion is hyposensitive due to compromised nerve endings. Despite viral suppression with treatment and healing of the ulcer, the cornea epithelium may appear abnormally irregular for several weeks as consequence of the nerve damage and topical antivirals toxicity.

Occasionally an initial dendritic ulcer may enlarge and expand forming a geographic ulcer (Fig. 3.1b). Characteristics are similar to the linear ulcer as the center of the ulcer depleted of cells stains with fluorescein and the swollen margins characterized by dead epithelial cells stain with rose Bengal. Possible causes are a long-standing untreated dendritic ulcer or prolonged use of topical steroids. Geographic epithelial ulcer may be more frequently seen in immunocompromised patients.

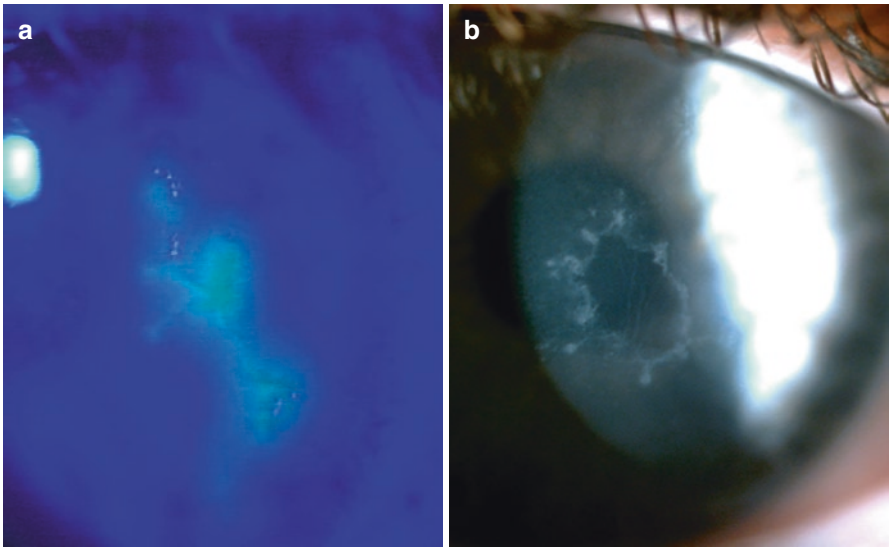

Fig. 3.1 Dendritic (**a**) and geographic (**b**) epithelial keratitis

Marginal Keratitis

Represents a form of epithelial keratitis due to replicating virus infection where the proximity to the limbus induces a peculiar clinical aspect (Fig. 3.2). Compared to the dendritic ulcer, marginal ulcers are associated with more active inflammation derived from the limbal vessels with inflammatory white blood cells and stromal necrosis . Treatment is with topical antivirals and topical steroid to suppress the immune reaction (Fig. 3.3a, b).

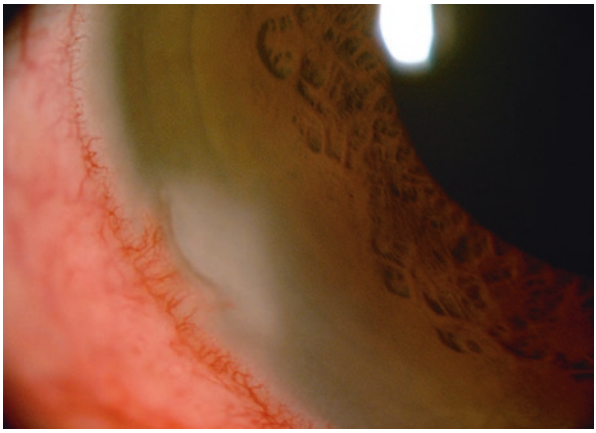

Fig. 3.2 Marginal keratitis with focal perikeratic hyperemia, stromal infiltration with ulceration

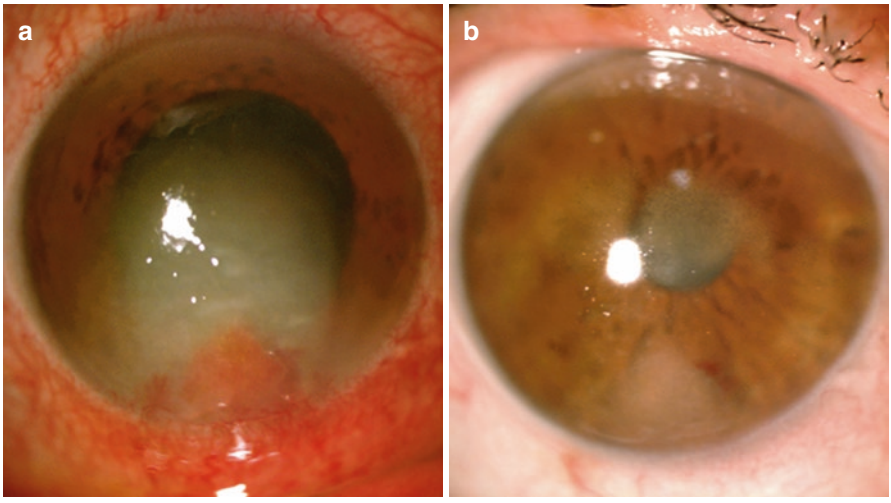

Fig. 3.3 Marginal keratitis before (**a**) and after treatment (**b**). In figure a peripheral corneal vascularization with stromal edema and cells infiltration is evident. After treatment (**b**) vascularization and edema regressed

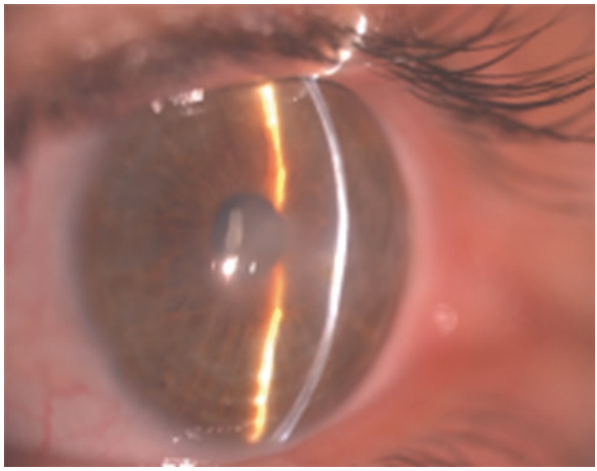

Fig. 3.4 Anterior stromal scarring with thinning following epithelial keratitis

Corneal Opacities After Infectious Epithelial Keratitis

A potentially sight-threatening complication of epithelial keratitis is stromal scarring. Stromal opacities may range from faint to dense and diffuse opacities involving the anterior stroma (Fig. 3.4). Loss of transparency may be accompanied by thinning due to stromal melting. Opacities may appear in the form of multiple round leucoma that resemble the distribution of the epithelial dendrites and are often called as "footprints". The severity and the number of recurrences are correlated with the risk of development of opacities.

Another possible complication of epithelial keratitis is the involvement of the stroma by infectious or immune disease.

Stromal Keratitis

Necrotizing Stromal Keratitis

It is a rare, although very severe, ulceration of the corneal stroma due to the direct invasion of replicating virus with secondary host response, leading to destructive stromal inflammation, caused by the release of collagenolytic enzymes (Fig. 3.5). The clinical features may be multiple and may mimic the features of other forms of infectious keratitis (bacterial or fungal).

Immune Stromal Keratitis

It is an inflammation occurring within the stroma (interstitial keratitis) with an immunologic etiology. The inflammation is a consequence of retained virus antigen within the corneal stroma, triggering an antigen antibody reaction. Its frequency is

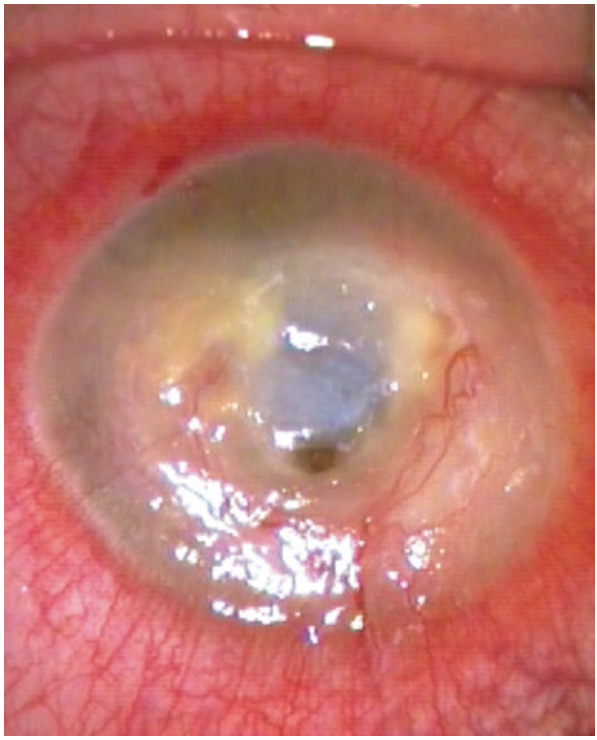

Fig. 3.5 Necrotizing keratitis showing large stromal ulceration, vascularization with lipid keratopathy and descemetocele

relatively high (21–48%) [6–8] and tends to increase with time following infectious keratitis first event. Common clinical feature is intrastromal inflammation with edema, cells infiltration and immune complexes deposition, frequently developing in presence of an intact corneal epithelium. Immune complexes deposits may assume the shape of a ring (Wesley ring), localized in mid stroma of the central or paracentral cornea. Oftentimes corneal involvement is accompanied by anterior uveitis with keratic precipitates. Inflammation recurrences are the cause of stroma vascularization with lipid deposition and stromal scarring and band keratopathy, causing loss of vision (Fig. 3.6).

Endothelitis

May develop in three different clinical forms (focal, diffuse, linear) characterized by more or less extensive involvement of the corneal endothelial surface (Fig. 3.7a, b). Etiology is uncertain but it is thought to be immunologic as this clinical form is associated with iritis, keratic precipitates, trabeculitis, and favorably responds to topical and systemic steroids. It is characterized by stromal and epithelial edema localized or diffuse (Fig. 3.8), associated with raised intraocular pressure in the

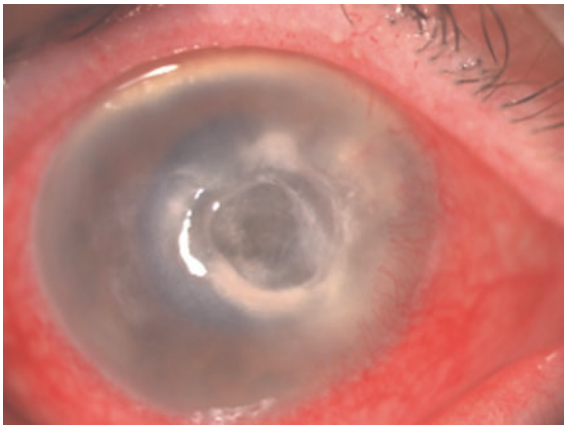

Fig. 3.6 Immune stromal keratitis showing stromal infiltration with edema and central neurotrophic ulcer

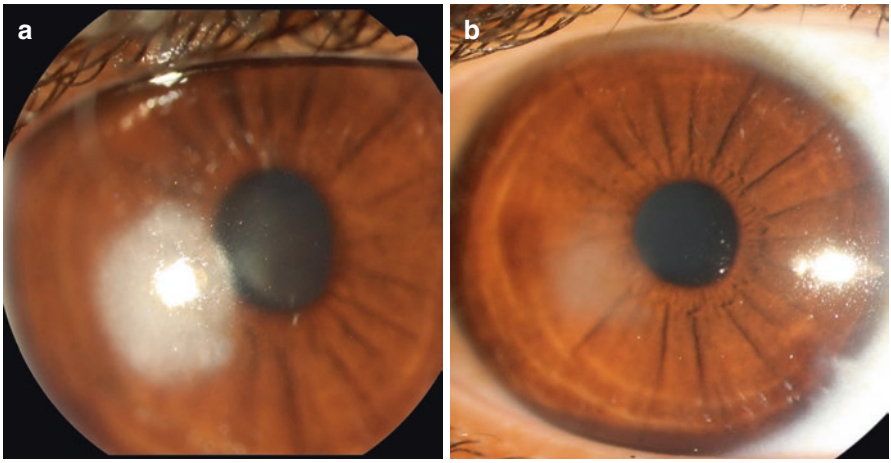

Fig. 3.7 Focal endothelitis before (**a**) and after treatment (**b**)

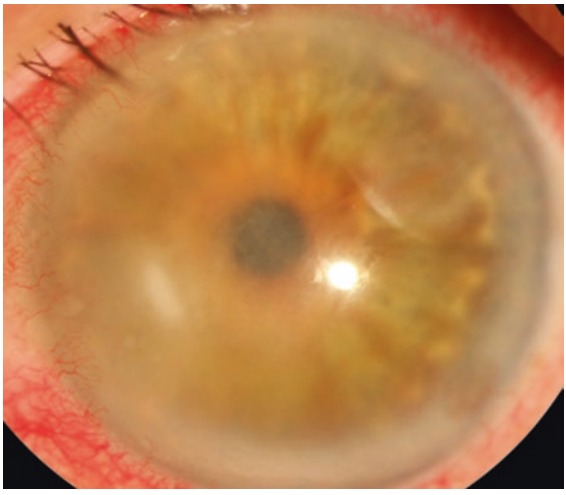

Fig. 3.8 Diffuse endothelitis showing stromal end epithelial edema and opacification

cases with extensive involvement. Onset of endothelitis may occur time after an epithelial involvement episode sometimes asymptomatic.

Endothelial cells damage is the result of endothelial cells inflammatory involvement and may cause transient or irreversible corneal decompensation due to extensive endothelial cells loss.

Treatment Management of Herpes Simplex Virus Keratitis (HSVK)

Infectious Epithelial Keratitis

Preferred treatment: topical acyclovir ointment or ganciclovir gtt 5 times/day until healing (usually 5–7 days), then TID for 7 days.

Alternative treatment: trifluridine gtt 2 h/day until healing (usually 5–7 days), then 5 times/day for 7 days.

Systemic antivirals have demonstrated to be equally effective for the treatment of epithelial lesions and may be employed as alternative treatment to topical antiviral in those cases of lack of compliance to topical treatment (children).

Adults:

- acyclovir 400 mg 5 times/day until healing, then 400 mg BD for 1 month or longer period if high risk
- valacyclovir 500 mg BD until healing, then 500 mg OD for 1 month or longer period if high risk
- famcyclovir 250 mg BD until healing, then 125 mg BD for 1 month or longer period if high risk

Children:

- acyclovir suspension <40 kg 20 mg/kg QID until healing, then 20 mg/kg BD for 1 month or longer period if high risk
- children >40 kg adult regimen

Immune Stromal Keratitis/Endothelitis

Topical steroids (dexamethasone, betamethasone, prednisolone) 4–8 times/day slowly tapered according to the clinical response. Treatment should be prolonged at minimal dosage (once/day or once/every other day) in order to avoid rapid recurrence. In case of recurrence treatment should be repeated and then tapered and maintained for a longer period of time.

Cyclosporin A (0.5–2%) gtt or tacrolimus (0.1%) gtt may be used as alternative treatment to steroids in case of steroid intraocular pressure response.

Systemic antiviral treatment:

- acyclovir 400 mg 5 times/day for 5 days, then 400 mg BD for prolonged time according to the risk of recurrence.

– valacyclovir 500 mg BD for 5 days, then 500 mg OD for prolonged time according to the risk of recurrence.
– famcyclovir 250 mg BD for 5 days, then 125 mg BD for prolonged time according to the risk of recurrence.

Necrotizing Stromal Keratitis

Systemic antiviral treatment:

– acyclovir 800 mg 5 times/day until healing of the corneal ulcer, then 400 mg BD for prolonged time according to the risk of recurrence.
– valacyclovir 1 g TID until healing of the corneal ulcer, then 500 mg OD for prolonged time according to the risk of recurrence.
– famcyclovir 500 mg TID until healing of the corneal ulcer, then 250 mg BD for prolonged time according to the risk of recurrence.

Topical steroids (dexamethasone, betamethasone, prednisolone) 4–8 times/day slowly tapered according to the clinical response. Treatment should be prolonged at minimal dosage (once/day or once/every other day) in order to avoid rapid recurrence. In case of recurrence treatment should be repeated and then tapered and maintained for a longer period of time.

In case of impending perforation (descemetocele):

– Amniotic membrane multilayer graft
– Conjunctival flap
– Cyanoacrilate gluing
– Tarsorraphy

Treatment of Corneal Opacities Following HSVK

Treatment of severe corneal opacities following HSVK may require partial or full thickness surgical excision of the opaque cornea and the implant of corneal graft from a donor. Deep anterior lamellar keratoplasty (DALK) may only be applied to those cases where corneal opacity is localized to the anterior 2/3 of the stroma whereas for the remaining cases penetrating keratoplasty (PK) may be preferred in order to re-establish cornea transparency. Keratoplasty may be often associated to cataract surgery as recurrent inflammation promote the development of lens opacities. The advantage of DALK over PK in patients with HSV leucoma is mainly ascribable to the lower risk of rejection derived from an endothelial sparing technique and to the better long term prognosis in terms of graft survival.

In order to reduce the risk of recurrence a maintenance therapy with acyclovir 400 mf BD (or valacyclovir 500 mg OD) and topical dexamethasone 0.1% gtt. BD in order to reduce the risk of rejection [9]. Prophylactic treatment may be maintained indefinitely with annual renal function testing.

References

1. Liesegang TJ, Melton J III, Daly PJ, et al. Epidemiology of ocular herpes simplex. Arch Ophthalmol. 1989;107:1155–9.
2. Scott T. Epidemiology of herpetic infection. Am J Ophthalmol. 1957;43:134–8.
3. Liesegang TJ. Herpes Simplex Virus epidemiology and ocular importance. Cornea. 2001;20(1):1–13. Review
4. Wilhelmus KR, Coster DJ, Donovan HC, et al. Prognostic indicators of herpetic keratitis: analysis of five-year observation period after corneal ulceration. Arch Ophthalmol. 1981;89:1578–82.
5. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes Simplex Virus eye disease. N Engl J Med. 1998;339:300–6.
6. Williams HP, Falcon MG, Jones BR. Corticosteroid in the management of herpetic eye disease. Trans Ophthalmol Soc UK. 1977;97:341–4.
7. Wilhelmus KR. Diagnosis and management of herpes simplex stromal keratitis. Cornea. 1987;6:286–91.
8. Kobayashi S, Ishizu M. Electron microscopic demonstration of viral particles in keratitis. Jpn J Ophthalmol. 1972;16:247–50.
9. Barney NP, Foster CS. Prospective randomized trial of oral acyclovir after penetrating keratoplasty for herpes simplex keratitis. Cornea. 1994;13:232–6.

Part II
Iris Complications in Uveitis

Chapter 4
Iris Complications in Uveitis

Alexander Chen, Careen Y. Lowder, and Angela Bessette

Peripheral Anterior Synechiae

Peripheral anterior synechiae (PAS) refer to adhesions that extend from the iris to the peripheral cornea. PAS arise from inflammation due to a variety of etiologies including uveitis, trauma and intraocular surgery [1]. In the context of uveitis, intraocular inflammation leads to the release of fibrinogen and resultant formation of fibrin and synechiae [2]. Factors that may predispose to PAS formation include a narrow angle and granulomatous inflammation [3]. PAS are typically visualized and diagnosed with gonioscopy, but anterior segment OCT can also be used [2]. In uveitic eyes, PAS may be most commonly found in the inferior angle [4]. Other studies have found that PAS are more common in the superior angle, but may have included patients with PAS due to primary angle closure [5]. PAS can lead to secondary angle glaucoma (open and closed angle subtypes).

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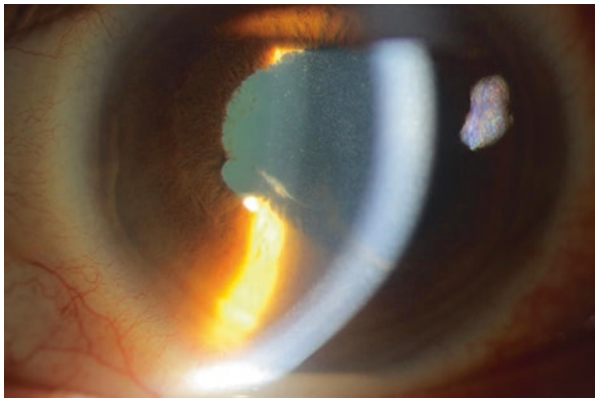

Fig. 4.1 Posterior synechiae have formed in hypopyon uveitis secondary to fungal endophthalmitis. (Photo courtesy of Careen Lowder, M.D., Ph.D.)

Posterior Synechiae

Posterior synechiae are adhesions that extend from the posterior surface of the iris to anterior surface of the intraocular lens or vitreous. Posterior synechiae are typically visualized on slit lamp examination (see Fig. 4.1). There may be a higher risk of formation of posterior synechiae when associated with granulomatous inflammation [3]. Extensive posterior synechiae can precipitate angle closure glaucoma by closing all aqueous out flow and push the peripheral iris forward (iris bombe) [2]. This is frequently associated with 360 degrees of posterior synechiae adhesions, referred to as seclusio pupillae [6]. In addition, narrowing of the angle from posterior synechiae can predispose to formation of peripheral anterior synechiae [7].

The presence or absence of posterior synechiae can be helpful in the diagnostic workup of uveitis. Absence of posterior synechiae is associated with Fuchs heterochromic iridocyclitis and rubella associated uveitis [8, 9]. The presence of posterior synechiae upon presentation may be associated with a higher rate of visual complications in specific uveitic disease entities such as HLA-B27 associated uveitis [10].

Topical Medical Management of Iris Synechiae

Steroids and cycloplegics are the mainstays in topical medical management of iris synechiae. Given the risks of extension of PAS and posterior synechiae, one important goal of uveitis management is breaking and preventing formation of synechiae. Steroids are often necessary for decreasing intraocular inflammation, resulting in decreased synechial formation. Topical steroid treatment typically involves use of difluprednate or prednisolone acetate. For severe cases, oral steroids, such as prednisone, should also be used.

Mydriasis can be achieved with a cholinergic sphincter paralysis or sympathomimetic dilator. Cycloplegics are useful for treating ciliary spasm in addition to breaking existing synechiae [11]. Use of a cycloplegic agent with a sympathomimetic dilator such as phenylepinephrine is necessary if maximal mydriasis is desired. Anterior chamber depth needs to be considered in the choice of a mydriatic or cycloplegic agent. Synechiae formation in an eye with a normal depth anterior chamber is rare with full mydriasis. However, a shallow anterior chamber may predispose to synechial formation despite full mydriasis [2]. In such cases, a treatment regimen that enables the pupil to still be mobile such as cyclopentolate or homatropine may be preferable [12].

Intracameral Management of Iris Synechiae

In cases where high-dose oral and topical steroids and cycloplegics are not effective, there are case reports of the successful use of intracameral tissue plasminogen activator to dissolve fibrinous membranes and break posterior synechiae [13]. Doses of tissue plasminogen activator ranging from 6 to 25 μg/0.1 mL have been reported to dissolve post-surgical fibrinous membranes following cataract surgery, vitrectomy, and glaucoma filtering procedures [14–16]. An increased risk of hyphema was reported in patients following glaucoma surgery administered the 25 μg dose. A dose of 6–12.5 μg may mitigate this risk [16]. Figure 4.2 illustrates an example of the rapid resolution of organized fibrin following an injection of intracameral tissue plasminogen activator. It should be noted that while intracameral tissue plasminogen activator may be helpful for acute fibrin formation and recently-formed synechiae, it is not useful for breaking chronic synechiae.

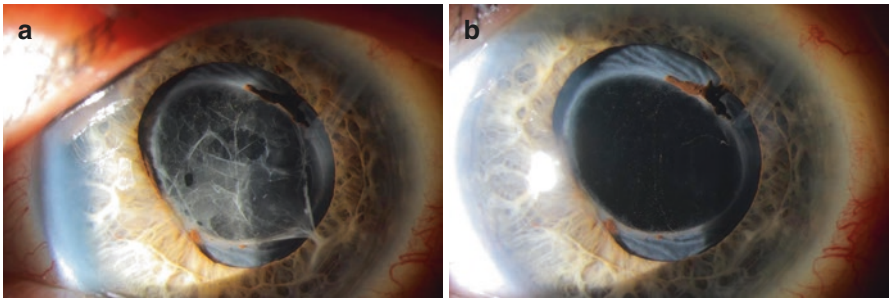

Fig. 4.2 (**a**) An organized fibrinous reaction in a patient with chronic panuveitis 4 weeks following combined cataract and Baerveldt implant. (**b**) The same patient 30 min following intracameral injection of 0.05 mL of tissue plasminogen activator (12.5 μg/0.1 mL). (Photo courtesy of Careen Lowder, M.D., Ph.D.)

Intrasurgical Management of Iris Synechiae

There are primarily two reasons to address iris synechiae surgically: to treat secondary angle closure glaucoma and to achieve adequate visualization for cataract surgery. In eyes with recently-formed and extensive PAS, goniosynechiolysis can be performed to open the angle and lower intraocular pressure. This can be combined with a surgical iridectomy or other glaucoma surgeries, such as the placement of a drainage device. Goniosynechiolysis is generally less effective for chronic PAS [17].

Posterior synechiae may also prevent adequate visualization and access for cataract surgery. Synechiolysis is often required in uveitic eyes undergoing cataract surgery. This can usually be achieved with blunt dissection under viscoelastic protection using either the viscoelastic cannula or a cyclodialysis spatula [18]. In the case of a fibrotic membrane, sharp dissection using the cystotome or a small gauge needle (such as a 30 gauge) may be necessary to access the pupillary margin. Once the synechiae are broken, attention should be turned to achieving adequate pupillary dilation. Gentle stretching of the pupillary margin may be required if it is sufficiently fibrotic. Iris hooks or a pupil expansion ring, such as the Malyugin ring, may be used to achieve and maintain adequate pupillary dilation [18]. Oetting et al. described a modified technique using iris hooks in a diamond configuration with one hook placed under the main incision [19]. This technique is particularly effective in reducing iris prolapse through the main wound and damage to the iris from the phacoemulsification tip. The decision to use iris hooks or a Malyugin ring will depend on surgeon preference. Advantages to iris hooks include reduced risk of iris prolapse and smaller profile in shallow anterior chambers, but disadvantages include the creation of multiple incisions and they can be time consuming to insert [18]. Rings can be inserted through the main incision, but are bulkier and may provide less control of the sub-incisional iris.

Iris Atrophy Associated with Viral Uveitis

Iris atrophy is a complication of uveitic inflammation commonly associated with viral etiologies. Inflammation can lead to ischemia and atrophy of one or more layers of the iris [2]. The pattern of iris atrophy can vary from a focal to generalized pattern. Sectoral iris atrophy has previously been described as a hallmark of varicella zoster virus uveitis although polymerase chain reaction studies have found HSV to be a significant cause as well [2]. In contrast, rubella virus and cytomegalovirus are two important causes of diffuse iris atrophy [20, 21].

References

1. Anderson DR. Pathology of the glaucomas. Br J Ophthalmol. 1972;56(3):146–57.
2. Jones N. Uveitis Second edition. 2nd ed. London: JP Medical Publishers; 2013. p. 1–382. http://www.jpmedpub.com
3. Moorthy RS, Mermoud A, Baerveldt G, Minckler DS, Lee PP, Rao NA. Glaucoma associated with uveitis. Surv Ophthalmol. 1997;41:361–94.
4. Sng CCA, Ang M, Barton K. Uveitis and glaucoma: new insights in the pathogenesis and treatment. In: Progress in brain research. 1st ed. Amsterdam: Elsevier B.V; 2015. p. 243–69. https://doi.org/10.1016/bs.pbr.2015.06.008.
5. Lee JY, Kim YY, Jung HR. Distribution and morphology of peripheral anterior synechiae in primary-angle closure glaucoma. Korean J Ophthalmol. 2006;20:104–8.
6. Siddique SS, Suelves AM, Baheti U, Foster CS. Glaucoma and Uveitis. In: Survey of ophthalmology, vol. 58. Amsterdam: Elsevier Inc; 2013. p. 1–10. https://doi.org/10.1016/j.survophthal.2012.04.006.
7. Bodh SA, Kumar V, Raina UK, Ghosh B, Thakar M. Inflammatory glaucoma. Oman J Ophthalmol. 2011;4(1):3–9.
8. Agrawal R, Murthy S, Sangwan V, Biswas J. Current approach in diagnosis and management of anterior uveitis. Indian J Ophthalmol. 2010;58(1):11–9.
9. de Visser L, Braakenburg A, Rothova A, de Boer JH. Rubella virus-associated uveitis: clinical manifestations and visual prognosis. Am J Ophthalmol. 2008;146(2):292–7.
10. Loh AR, Acharya NR. Incidence rates and risk factors for ocular complications and vision loss in HLA-B27-associated uveitis. Am J Ophthalmol. 2010;150(4):534–42. .e2. https://doi.org/10.1016/j.ajo.2010.04.031.
11. Foster CS, Kothari S, Anesi SD, Vitale AT, Chu D, Metzinger JL, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol. 2016;61(1):1–17.
12. American Academy of Ophthalmology. Basic and clinical science course, 2018-2019. San Francisco: American Academy of Ophthalmology; 2018.
13. Skolnick CA, Fiscella RG, Tessler HH, GoldsteinDA. Tissue plasminogen activator to treat impending pupillary block glaucoma in patients with acute fibrinous HLA-B27 positive iridocyclitis. Am J Ophthalmol. 2000;129:363–6.
14. Moon J, Chung S, Myong Y, et al. Treatment of postcataract fibrinous membranes with tissue plasminogen activator. Ophthalmology. 1992;99:1256–9.
15. Jaffe GJ, Abrams GW, Williams GA, Han DP. Tissue plasminogen activator for postvitrectomy fibrin formation. Ophthalmology. 1990;97:184–9.
16. Lundy DC, Sidoti P, WinarkoT MD, Heuer DK. Intracameral tissue plasminogen activator after glaucoma surgery: indications, effectiveness, and complications. Ophthalmology. 1996;103:274–82.
17. Sng CCA, Barton K. Mechanism and management of angle closure in uveitis. Curr Opin Ophthalmol. 2015;26:121–7.
18. Henderson BA. Essentials of Cataract Surgery. Thorofare, NJ: Slack; 2014.
19. Oetting TA, Omphroy LC. Modified technique using iris retractors in clear corneal cataract surgery. J Cataract Refract Surg. 2002;28(4):596–8.
20. Groen-Hakan F, Babu K, Tugal-Tutkun I, Pathanapithoon K, de Boer JH, Smith JR, et al. Challenges of diagnosing viral anterior uveitis. Ocul Immunol Inflamm. 2017;25(5):710–20.
21. Chan NSW, Chee SP. Demystifying viral anterior uveitis: a review. Clin Exp Ophthalmol. 2019;47(3):320–33.

Part III
Lens Complications from Uveitis

Chapter 5
Lens Complications in Uveitis

Jennifer Lee and Debra A. Goldstein

Pathogenesis of Cataract in Uveitis Patients

Cataracts are one of the most common complications seen in uveitis patients. There are multiple factors contributing to cataract development, of which the inherent ocular inflammation plays the most significant role [1]. Specifically, the anatomic location of inflammation, duration of disease, and rates of relapse are strongly linked to its development. Therefore, it is not surprising that cataracts are found most frequently in patients with panuveitis, followed by chronic anterior uveitis, intermediate uveitis, and posterior uveitis [1]. Cataracts are especially prevalent in pediatric patients who present with pathology at a younger age, have more chronic disease, and may be more difficult to examine and to treat [2]. The treatment of uveitis also increases the propensity for cataract development as steroids in any form promote posterior subscapular opacification, and children may be more susceptible to the cataractogenic effects of steroids [3, 4]. Immunomodulatory therapies have gained popularity in recent years as an alternative to chronic steroids and do not increase the risk for cataracts [5]. Like their non-uveitis counterparts, uveitis patients can have age-related lens changes [6], and may require intraocular surgery such as pars plana vitrectomy that contribute to cataract formation. The biochemical mechanism of cataractogenesis in the setting of inflammation is not known.

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Table 5.1 Risks for and outcomes of cataract surgery in various uveitic entities

Disease	Estimated incidence of cataract formation	Surgical outcomes, Vision of 20/40 or better
Fuchs heterochromic iridocyclitis	64–75% [7–11]	85% [12]
Juvenile idiopathic arthritis	11–80% [4, 7, 13–15]	70% [16]
HLA-B27 uveitis	5–28% [17–19]	
Pars planitis	35–47% [20]	71% [12]
Behçet disease	12–57% [7, 21–23]	36–50% [7]
Vogt-Koyanagi-Harada Syndrome	40–56% [7]	49% [12]
Sympathetic ophthalmia	32% [24]	56% [12]
Ocular toxoplasmosis	4–10% [7, 25, 26]	90%[a] [27]
Herpetic uveitis	26.6–40% [7, 18]	36.8% [7]

[a]Without central scar

Uveitis Etiologies Associated with Cataract Development

All types of uveitis can promote cataract formation. Infectious etiologies include syphilis, toxoplasmosis, tuberculosis, and herpetic diseases. Systemic diseases associated with inflammation and cataracts include HLA-B27-associated diseases, Juvenile idiopathic arthritis, Behçet and sarcoidosis. Reported incidences and visual outcomes are listed in Table 5.1.

Prevention of Cataract Development in Uveitis Patients

Aggressive control of intraocular inflammation and judicious use of topical, periocular, and oral corticosteroids reduce the risk of cataract development. For refractory cases, early substitution of steroids with immunomodulatory therapy leads to control of chronic inflammation, reduction in corticosteroid burden, and delays visually significant cataract progression [28].

Preoperative Management

A detailed preoperative evaluation is essential to selecting the appropriate patient for surgery. A thorough ophthalmic exam, appropriate imaging, and review of the patient's history are necessary to estimate the visual potential, to determine appropriate surgical technique, and to optimize the timing of surgery. The type of uveitis greatly influences preoperative and intraoperative strategies. For example, surgery in a JIA patient is more challenging compared to a Fuchs uveitis patient due to more

abnormal intraocular anatomy and greater inflammatory response. Moreover, the surgeon must assess the patient's ability to access and administer medications and adhere to postoperative instructions.

Indications for Cataract Surgery

Cataract surgery is indicated in the following scenarios: [29].

- Phacoantigenic uveitis
- Cataract that limits view to the fundus in patients with suspected posterior segment pathology and in patients undergoing posterior segment surgery
- Visually significant cataract is an eye with potential for visual improvement

Timing of Surgery

Once the decision to proceed with cataract surgery is made, complete control of inflammation should be maintained for three months prior to surgery. Excellent preoperative control has been associated with reduction in postoperative CME and rebound inflammation [30–32]. Three months is generally accepted for all forms of uveitis except for Behçet disease. In these cases, a higher rate of recurrence have been reported if active disease is present within 12 months of surgery [33]. Therefore, some authors recommend delaying surgery in these patients, if possible, until at least 6 months of quiescence is achieved [34].

In the pediatric population, timing is important because cataracts can develop at an amblyogenic age. Children are also more likely to have higher rates of undesirable surgical complications as compared to adults. Therefore, timing of the cataract surgery must balance amblyogenic risks with surgical risks. Amongst children with uveitis, JIA patients have the poorest visual outcomes compared to those with other forms of uveitis (e.g. pars planitis). This finding is likely related to their younger age of onset, asymptomatic presentation, and more robust inflammatory response [30, 35, 36].

Evaluating Vision Potential

A thorough ophthalmic exam is required to identify potential ocular co-morbidities. This may reveal the need for combined or staged procedures and address patient expectations regarding visual prognosis.

Pre-existing posterior segment disease such as macular ischemia or optic neuropathy portends a worse prognosis. Ocular pathologies that should be addressed perioperatively are listed in Table 5.2.

Table 5.2 Ocular pathologies and perioperative management

Pathology	Indication	Management	Additional
Band keratopathy	Obstructs view to the anterior chamber	Disodium Ethylenediaminetetraacetic acid (EDTA) chelation	If possible, chelation should be performed pre-operatively. The epithelium should be healed prior to proceeding with cataract surgery. If necessary, chelation may be performed at the time of cataract surgery
Cystoid macular edema (CME)	CME must be minimized prior to surgery for all types of uveitis	Perioperative systemic steroids may be administered if the patient has active or prior CME. Intraoperative intravitreal triamcinolone acetonide (Triesence, TA) 4 mg in 0.1 mL [37, 38] or preoperative dexamethasone 0.7 mg intravitreal implant (Ozurdex, Allergan, Irvine, CA, USA) are reasonable alternatives [39]	
Elevated intraocular pressure (IOP)	IOP must be controlled prior to surgery	Medical management of ocular hypertension consist of topical antiglaucoma drops. This can be escalated to oral carbonic anhydrase inhibitors. If pressure is still uncontrolled on maximum medical therapy, consider staged or combined surgical procedure with cataract surgery	Gonioscopy should be performed to elucidate the etiology of elevated IOP, which can range from pupillary block, secondary angle closure from peripheral synechiae, or corticosteroid response. Avoid laser trabeculoplasty in patients with anterior uveitis

Other common ocular findings include corneal scarring, corneal neovascularization, reduced corneal sensation, endothelial disease from herpetic uveitis, fragile angle vessels, peripheral anterior synechiae (Image 5.1), posterior synechiae (Images 5.1 and 5.2), pupillary membranes, ciliary body atrophy, hypotony, vision obstructing vitreous opacities, macular scar, epiretinal membrane, macular ischemia, choroidal neovascularization, optic neuropathy, glaucoma, and retinal detachment. In children, additional complications include amblyopia and strabismus [36].

Beyond the clinical exam, additional investigations are helpful to detect pathology. Ancillary tests and diagnostic pathologies are listed in Table 5.3.

Image 5.1 6 year old juvenile idiopathic arthritis patient with poorly controlled inflammation, and excessive use of topical corticosteroids. There is a white cataract, extensive posterior synechiae, and a shallow anterior chamber

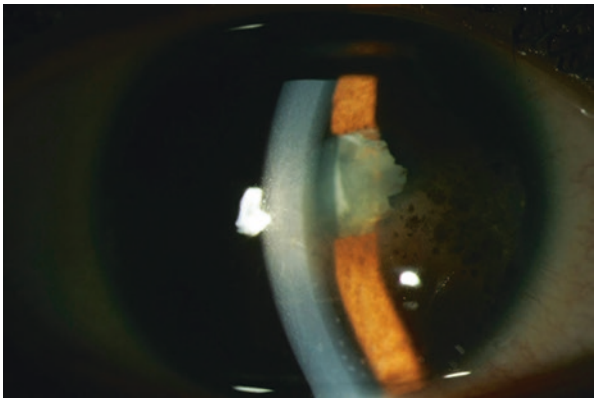

Image 5.2 Juvenile idiopathic arthritis cataract with posterior synechiae, band keratopathy, and inferior keratic precipitates

Table 5.3 Ancillary testing

Ancillary testing	Evaluation
Optical coherence tomography	Macular edema, macular hole, epiretinal membrane, optic nerve pathology
Fluorescein angiography	Macular ischemia, macular edema, choroidal neovascularization, optic nerve leakage, retinal vasculitis, posterior segment disease activity
Ultrasonography[a]	Ciliary body atrophy, retinal detachment, choroidal thickening or detachment

[a]Must be done when there is no view to the posterior segment

Control of Inflammation

There is no standardized protocol for controlling preoperative inflammation. It must be tailored to the patient's underlying uveitis and treatment history. A wide range of immunosuppressive therapies can be utilized from corticosteroids to antimetabolites, T-cell activation inhibitors, biologics, or alkylating agents. A variety of delivery systems for corticosteroids are available such as topical drop, subconjunctival injection, subtenon injection, intravitreal injection, steroid containing short or long acting implants and systemic oral medication. Switching to immunomodulating therapy is generally recommended if more than 5–10 mg of prednisone or its equivalent is required for more than 3 months, if inflammation persists after 1 month of high dose corticosteroids, or if unacceptable side effects arise [40].

Non-infectious Uveitis

In the perioperative period, most specialists will provide prophylactic or escalated doses of anti-inflammatory medications. Prophylaxis is typically initiated two to seven days prior to surgery and slowly tapered after cataract surgery [5, 41, 42]. For patients already on chronic oral corticosteroids, a stress dose should be added on the day of surgery [43]. When inflammation is not completely controlled, but cataract surgery is urgently required, intravenous methylprednisolone may be administered prior to or during surgery [8]. If there is systemic corticosteroid intolerance (e.g. diabetes mellitus) and no contraindications to local therapy (e.g. steroid response), subtenon or intravitreal triamcinolone acetonide (TA) or a short acting intravitreal steroid implant are reasonable alternatives for pre-operative management of inflammation.

For patients on chronic topical steroids, dosing may be increased to once every one to two hours prior to surgery [43].

Lastly, not all patients with uveitis need perioperative steroids. Patients with a single remote history of isolated anterior uveitis can usually be spared additional corticosteroids. Patients with FHI may also do well with no additional perioperative steroids.

Infectious Uveitis

For toxoplasmosis uveitis, the use of empiric anti-parasitic drugs is controversial. Additionally, the best medical regimen for prophylaxis has not been established. The risk of reactivation ranges from zero percent [44] to 36% [27], therefore the decision to start treatment is within the surgeon's discretion. Prophylaxis is commonly used when the lesion is vision threatening (i.e. within the macula or close to the optic nerve). Options include double-strength trimethoprim-sulfamethoxazole, pyrimethamine alone, pyrimethamine with sulfadiazine, azithromycin and atovaquone [5, 27].

For herpetic uveitis, oral acyclovir or valacyclovir may be started one week prior to surgery [5, 45].

Surgical Treatment

The surgical treatment for uveitic cataracts is complicated. Surgeons are often faced with significant structural abnormalities. Visibility through the cornea may be reduced by the presence of scars, band keratopathy, or neovascularization from chronic inflammation. Access to the crystalline lens may be limited by a miotic pupil, posterior synechiae, or pupillary membranes. Successful removal of the crystalline lens may be challenged by weak zonules, cyclitic membranes, and vitreous opacities reducing the red reflex.

General Approach and Technique

Most patients will undergo cataract surgery under monitored anesthesia care. However, additional regional anesthesia through peribulbar or retrobulbar block is generally recommended if significant iris manipulation is anticipated. This strategy eliminates ocular movement thereby creating a more stable surgical environment. This also maximizes patient comfort, as uveitic cataracts may require longer surgical time and manipulation of sensitive intraocular tissue.

The standard for cataract extraction is phacoemulsification with in-the-bag intraocular lens placement. This technique is associated with reduced postoperative inflammation, cystoid macular edema, epiretinal membrane, and posterior synechiae [43, 46–48].

Whenever possible, there should be minimal manipulation of intraocular tissues. During phacoemulsification, reducing the average phaco time also minimizes postoperative inflammation, corneal endothelial trauma, posterior capsular rupture and subsequent loss of nuclear fragments/vitreous loss.

Managing a Small Pupil and an Abnormal Iris

There are many causes of small pupils in uveitis patients. External and intrinsic disease of the iris can limit its size, manipulability, and therefore access to the lens. In addition to being floppy and atrophic, the iris may be occluded by membranes or adherent to the crystalline lens and/or peripheral corneal endothelium.

Some surgeons advocate dissection of PAS using viscoelastic material, using the cannula tip to sweep the iris away from the cornea. However, this is not always helpful, and may result in further damage to the peripheral iris.

Posterior synechiae may be addressed with gentle dissection using dispersive or cohesive viscoelastic material and by manual separation using the viscoelastic cannula, iris spatula, cyclodialysis spatula, or Kuglen hooks [43, 49]. If the edges of the pupil cannot be freed anteriorly, then a posterior approach via a peripheral iridotomy to introduce a cyclodialysis spatula can be done to lyse adhesions. For fibrotic membranes at the pupillary margin, the sheet of tissue can be cut with a scissors, and peeled off with microforceps.

Once the iris is free of adhesions and membranes, the pupil may remain miotic. Dilation can then be accomplished using intracameral preservative free epinephrine, iris hooks or pupil expansion devices such as Malyugin ring (Microsurgical Technologies, Redmond, WA, USA). Iris hooks are ideal in eyes with shallow anterior chambers or very atrophic irides. In general, surgeons should minimize iris manipulation as it promotes intraoperative floppiness, iris prolapse, bleeding, iris tattering and inflammation.

A surgical peripheral iridectomy can be considered in eyes with chronic flare or eyes that required extensive iris manipulation, although this is rarely required.

Beyond the Small Pupil

Once the cataract is adequately exposed, capsular dyes such as trypan blue provide good contrast for making a capsulorhexis. Ideally, smooth continuous curvilinear capsulorhexis of at least 5 mm should be fashioned. A small rhexis size or ragged capsular edges will increase the risk of capsular phimosis and synechiae [46]. (Image 5.4).

In cases of zonular weakness, capsular tension devices may be inserted to help center the IOL, stabilize the capsular bag, and reduce the risk of future capsular phimosis.

Intraocular Lens Considerations

With improvement in lens design and biomaterial, modern intraocular lenses (IOL) are now routinely placed in almost all patients with uveitis. The ideal placement is in the intact capsular bag. If the posterior capsule is violated, ciliary sulcus placement with a 3-piece IOL is also acceptable [50]. If there is inadequate anterior capsular rim support for sulcus placement, a scleral fixated IOL can be placed. Iris sutured or anterior chamber placement should be avoided as this may result in greater postoperative inflammation. In our experience, aphakia should be considered in cases of preoperative 360° of posterior synechiae, poor compliance, difficult to control inflammation, dense flare and hypotony. Should a lens be placed in these conditions, there is high risk for intraocular lens cocooning (Image 5.3).

A single piece acrylic IOL is the ideal lens choice for uveitic eyes. Acrylic outperforms silicone, poly methyl methacrylate (PMMA), and heparin-surface-modified PMMA in rates of PCO formation, inflammation relapse, and postoperative CME [51–53]. Hydrophobic and hydrophilic acrylic lenses have similar rates of postoperative complications such as macular edema, inflammation, corneal edema, and IOL decentration [54]. A long-term study comparing the two biomaterial have

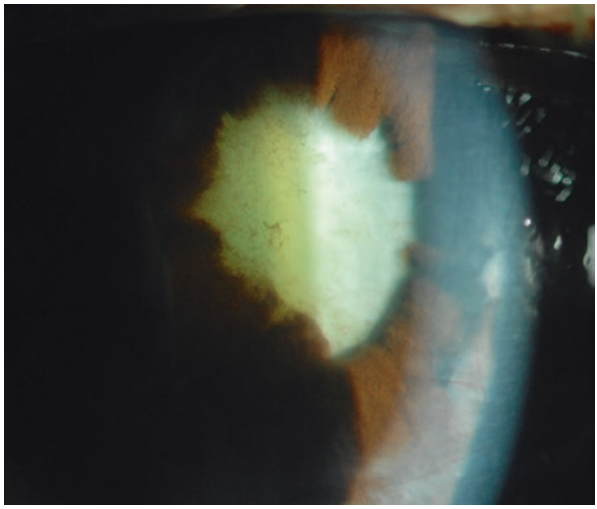

Image 5.3 This patient had a lens placed, apparently in the capsular bag. Dense inflammatory membranes formed, "cocooning" the intraocular lens. There is 360° of posterior synechiae as well as very anterior peripheral anterior synechiae (PAS)

shown that hydrophilic acrylic has better uveal biocompatibility, quantified as the least amount of cellular reaction on the IOL surface, but a higher rate of PCO compared to hydrophobic acrylic [55]. Multifocal lenses are discouraged because they reduce contrast sensitivity in patients with uveitis who may have coexisting macular or vitreous pathology [8, 56].

Pars Plana Vitrectomy

In patients with visually significant vitreous opacities, pars plana vitrectomy (PPV) can be offered as a combined procedure to optimize vision outcomes [57]. This can also improve intraocular inflammation and comorbid CME. Retinal detachments and epiretinal membranes can also be addressed simultaneously with combined cataract and vitreoretinal surgery.

Intraoperative Medications

The addition of steroids during surgery can reduce anticipated postoperative inflammation, need for post-operative steroids, and risk of CME. These strategies include adding dexamethasone to the infusion fluid, intravenous methylprednisolone, subtenon or intravitreal triamcinolone acetonide, intracameral dexamethasone, and short-acting dexamethasone intravitreal implants [12, 37, 38, 53, 58, 59].

Special Consideration in the Pediatric Population

The management of pediatric cataracts is controversial. Not only is the surgery technically challenging, but there may also be inaccuracies in biometry and opposing views regarding primary IOL implantation.

First, the decision to implant an IOL again requires proper patient selection, which needs to account for the type of uveitis, age of the child, and perioperative control of inflammation. With modern phacoemulsification, improved lens biocompatibility, use of immunomodulating therapy, and complete disease quiescence preoperatively, cataract surgery with primary IOL placement can be successful in children [30, 36, 60–62]. An intraocular lens is also a better option for amblyopia therapy. Aphakic children may not be able to tolerate optical correction with contact lenses or spectacles. However, others advise against IOL implantation [49, 63]. The presence on an IOL is thought to incite an inflammatory response and serve as a scaffold for secondary and cyclitic membranes [64, 65]. There is also a higher risk of secondary glaucoma [63]. Therefore, there is no consensus for primary lens implantation [66], although most surgeons will implant an IOL in children with well controlled uveitis.

Children are also more likely to develop posterior capsular opacification (PCO), independent of their uveitis status. As well, laser capsulotomy may be difficult to perform in young uncooperative children. Therefore, if a child is younger than six to eight years old, a primary posterior capsulotomy ± limited anterior vitrectomy should be considered at the time of surgery.

Post-operative Management

Postoperative care is equally as important as preoperative care. Close follow up and aggressive control of inflammation is critical, especially for younger patients who have a more robust inflammatory response. Medications initiated or increased preoperatively should be tapered slowly based upon clinical examination and ancillary testing. In recent years, advancement in pharmacology in the form of immunologic agents and steroid delivery vehicles have greatly expanded our armamentarium for postoperative management.

Management of Post-operative Complications

Early Complications

Recurrent Uveitis

Persistent or recurrent uveitis can reverse an initially good visual outcome. Inflammation can result in posterior synechiae to the anterior capsule or IOL, PAS, ciliary or pupillary membranes, CME, hypotony, and epiretinal membrane (ERM).

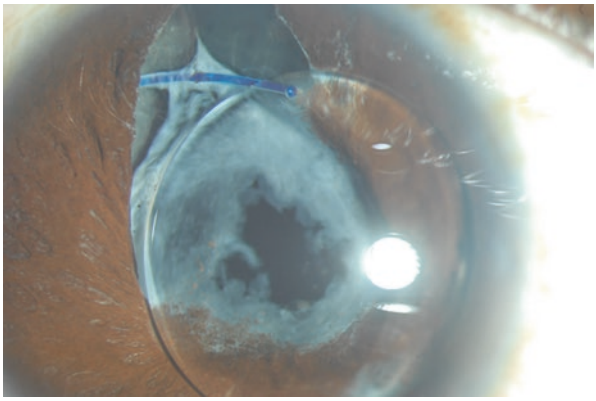

Image 5.4 Dislocated 3-piece intraocular lens with pupil capture. The IOL was apparently placed into the ciliary sulcus at the time of cataract surgery, but intraocular inflammation in this uveitis patient was not well controlled in the peri-operative period

Each of these complications can independently generate more complications. For example, pupillary membranes can distort the iris and cocoon or displace the IOL (Image 5.4), and ciliary body membranes can lead to ciliary body detachment and permanent hypotony (refer to late complications for more details). Therefore, post-operative inflammation needs to be identified early and be treated aggressively.

Cystoid Macular Edema

In cases of CME, inflammatory mediators interrupt the normal function of the retinal pigment epithelium and lead to fluid accumulation. Therefore, therapy is targeted at managing the inflammation. The first line of treatment is often intensive topical steroid and topical NSAID therapy. Periocular or intravitreal triamcinolone acetonide may also be used [37, 38, 54, 57, 67]. In up to half of the cases, triamcinolone only provides temporary resolution, and the CME relapses when the drug wears off [68]. Longer duration intravitreal fluocinolone acetonide implants (Retisert, Bausch& Lomb, Rochester, NY, USA, Yutiq, Eyepoint Pharmaceuticals, Watertown, MA, USA) [69] and the shorter-acting dexamethasone implant (Ozurdex, Allergen, Irvine, CA, USA) provide a more lasting resolution of CME. Unfortunately, longer exposure and higher doses of steroids are associated with intraocular pressure (IOP) rise, and may necessitate chronic antihypertensive drops or glaucoma surgery for pressure control [38, 54, 57, 69]. For patients intolerant to steroids, alternative agents include anti-angiogenic intravitreal injections such as bevacizumab [70, 71], systemic carbonic anhydrase inhibitors [72], and interferon alpha [73].

Acute Ocular Hypertension and Hypotony

An acute rise in IOP is often seen in the immediate postoperative period because of inflammatory debris, retained lens material or ophthalmic viscoelastic. IOP spikes can be addressed by releasing aqueous from the anterior chamber, increasing corticosteroids, starting anti-glaucoma drops, and/or systemic oral carbonic anhydrase inhibitors [67].

Low IOP can be problematic as well, and has been associated with inflammation, prostaglandin-mediated increase in uveoscleral outflow, supraciliary or suprachoroidal effusion. It is unclear if surgery is an independent risk factor for hypotony or if it is the underlying uveitis that predisposed the patient to both cataract formation and hypotony [74]. Raising IOP involves treatment targeted towards reducing intraocular inflammation.

Retinal Complications

Vitreous hemorrhage and retinal detachment are rare complications more often reported in patients with intermediate, posterior, and panuveitis. Non-clearing vitreous hemorrhages and retinal detachments require additional surgery and should be addressed by a vitreoretinal surgeon.

Like all routine cataract cases, uveitic eyes undergoing cataract surgery are also at risk for endophthalmitis. Currently, there are no studies that demonstrate an increased risk of endophthalmitis for the uveitis population.

Delayed Complications

Capsular and IOL Complications

Posterior capsular opacification (PCO) occurs in 34.3–81.7% of uveitis cases [75]. If the PCO becomes significant, it can be lasered with a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, using as little energy as possible in order to minimize the inflammatory response [49, 53, 67]. Importantly, the uveitis must be quiescent before proceeding. Nd:YAG is also effective for removal of giant cell IOL deposits [76].

As discussed previously, capsular phimosis and capsular membranes are manifestations of chronic inflammation. Phimosis can be treated using a Nd:YAG laser to make radial cuts on the fibrotic rim to prevent further capsular shrinking. Capsular membranes can also be lasered, but may reform in the setting of uncontrolled inflammation. Surgical removal may be required if the membranes become dense.

IOL—dislocation is a rare complication. Early dislocation is due to intraoperative loss of capsular integrity or zonular dehiscence. Over time, even in uncomplicated cases, the zonules can slowly dehisce leading to in-the-bag IOL dislocation. Correcting the dislocation depends on the degree of dislocation. Treatment options include observation, IOL removal, in-the-bag IOL re-fixation, and 4-point sutured scleral-fixated IOL [77].

Late Ocular Hypertension and Hypotony

Delayed or persistent ocular hypertension may be due to peripheral anterior synechiae or a steroid response. Therefore, all patients should undergo gonioscopy to assess for angle abnormalities. For steroid responders with persistent inflammation, every effort should be made to wean off steroids and to start immunomodulating medications. Extensive PAS can close the angle, necessitating filtering glaucoma surgery to lower the IOP. Ultimately, chronically high pressures can lead to secondary glaucomatous optic neuropathy.

On the opposite spectrum, late hypotony is another dreaded complication. Left untreated, the eye is at risk for choroidal effusion, macular edema, and phthisis. Hypotony is a consequence of ongoing inflammation which promotes the development of cyclitic membranes that damage the ciliary epithelium and place tension on the ciliary body. This can lead to tractional detachment of the ciliary body and increased uveal scleral flow. Ultrasound biomicroscopy can be used to identify the presence of epiciliary membranes, ciliary body detachment, and ciliary body atrophy. In the presence of atrophy, silicone oil has been successfully used to raise IOP, although this effect may not be long-lived [78]. In cases of epiciliary tissue or tractional detachment, a pars plana vitrectomy approach can be used to remove the membranes, again, with variable success [79, 80].

Conclusion

In the era of modern phacoemulsification, most uveitis patients have excellent visual outcomes if the following conditions are met: appropriate patient selection, strict control of preoperative inflammation, careful surgical planning, early detection and care of postoperative complications. With expansion of immunomodulating therapies, surgical outcomes will continue to improve, particularly in the pediatric population.

References

1. Blum-Hareuveni T, Seguin-Greenstein S, Kramer M, et al. Risk factors for the development of cataract in children with uveitis. Am J Ophthalmol. 2017;177:139–43.
2. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. Ophthalmology. 2004;111(12):2299–306.
3. Sijssens KM, Rothova A, Van De Vijver DA, Stilma JS, De Boer JH. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol. 2007;144(4):574–9.

4. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436–41.
5. Van Gelder RN, Leveque TK. Cataract surgery in the setting of uveitis. Curr Opin Ophthalmol. 2009;20(1):42–5.
6. Conway MD, Stern E, Enfield DB, Peyman GA. Management of cataract in uveitis patients. Curr Opin Ophthalmol. 2018;29(1):69–74.
7. AlBloushi AF, Alfawaz AM, Al-Dahmash SA, et al. Incidence, risk factors and surgical outcomes of cataract among patients with uveitis in a University Referral Hospital in Riyadh, Saudi Arabia. Ocul Immunol Inflamm. 2018:1–9. [epub ahead of print].
8. Agrawal R, Murthy S, Ganesh SK, Phaik CS, Sangwan V, Biswas J. Cataract surgery in uveitis. Int J Inflamm. 2012;2012:548453.
9. Accorinti M, Spinucci G, Pirraglia MP, Bruschi S, Pesci FR, Iannetti L. Fuchs' heterochromic iridocyclitis in an Italian tertiary referral centre: epidemiology, clinical features, and prognosis. J Ophthalmol. 2016;2016:1458624.
10. Tugal-Tutkun I, Guney-Tefekli E, Kamaci-Duman F, Corum I. A cross-sectional and longitudinal study of Fuchs uveitis syndrome in Turkish patients. Am J Ophthalmol. 2009;148(4):510–5.
11. Yang P, Fang W, Jin H, Li B, Chen X, Kijlstra A. Clinical features of Chinese patients with Fuchs' syndrome. Ophthalmology. 2006;113(3):473–80.
12. Mehta S, Linton MM, Kempen JH. Outcomes of cataract surgery in patients with uveitis: a systematic review and meta-analysis. Am J Ophthalmol. 2014;158(4):676–92. e677
13. Clarke SL, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol Online J. 2016;14(1):27.
14. Suelves AM, Lamba N, Meese HK, et al. Nuclear cataract as an early predictive factor for recalcitrant juvenile idiopathic arthritis-associated uveitis. J AAPOS. 2016;20(3):232–8. e231
15. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology. 1997;104(2):236–44.
16. Ganesh SK, Sudharshan S. Phacoemulsification with intraocular lens implantation in juvenile idiopathic arthritis. Ophthalmic Surg Lasers Imaging. 2010;41(1):104–8.
17. Power WJ, Rodriguez A, Pedroza-Seres M, Foster CS. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. Ophthalmology. 1998;105(9):1646–51.
18. Hoeksema L, Los LI. Visual prognosis and ocular complications in herpetic versus HLA-B27- or ankylosing spondylitis-associated anterior uveitis. Ocul Immunol Inflamm. 2016;24(3):302–12.
19. Yang P, Wan W, Du L, et al. Clinical features of HLA-B27-positive acute anterior uveitis with or without ankylosing spondylitis in a Chinese cohort. Br J Ophthalmol. 2018;102(2):215–9.
20. Ozdal PC, Berker N, Tugal-Tutkun I. Pars planitis: epidemiology, clinical characteristics, management and visual prognosis. J Ophthalmic Vis Res. 2015;10(4):469–80.
21. Davatchi F, Chams-Davatchi C, Shams H, et al. Adult Behcet's disease in Iran: analysis of 6075 patients. Int J Rheum Dis. 2016;19(1):95–103.
22. Sachdev N, Kapali N, Singh R, Gupta V, Gupta A. Spectrum of Behcet's disease in the Indian population. Int Ophthalmol. 2009;29(6):495–501.
23. Tugal-Tutkun I, Urgancioglu M. Childhood-onset uveitis in Behcet disease: a descriptive study of 36 cases. Am J Ophthalmol. 2003;136(6):1114–9.
24. Ganesh SK, Sundaram PM, Biswas J, Babu K. Cataract surgery in sympathetic ophthalmia. J Cataract Refract Surg. 2004;30(11):2371–6.
25. Friedmann CT, Knox DL. Variations in recurrent active toxoplasmic retinochoroiditis. Arch Ophthalmol. 1969;81(4):481–93.
26. Mets MB, Holfels E, Boyer KM, et al. Eye manifestations of congenital toxoplasmosis. Am J Ophthalmol. 1997;123(1):1–16.
27. Bosch-Driessen LH, Plaisier MB, Stilma JS, Van der Lelij A, Rothova A. Reactivations of ocular toxoplasmosis after cataract extraction. Ophthalmology. 2002;109(1):41–5.

28. Gregory AC 2nd, Kempen JH, Daniel E, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: The Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology. 2013;120(1):186–92.
29. Rojas B, Foster CS. Cataract surgery in patients with uveitis. Curr Opin Ophthalmol. 1996;7(1):11–6.
30. Quinones K, Cervantes-Castaneda RA, Hynes AY, Daoud YJ, Foster CS. Outcomes of cataract surgery in children with chronic uveitis. J Cataract Refract Surg. 2009;35(4):725–31.
31. Jancevski M, Foster CS. Cataracts and uveitis. Curr Opin Ophthalmol. 2010;21(1):10–4.
32. Belair ML, Kim SJ, Thorne JE, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol. 2009;148(1):128–35. e122
33. Matsuo T, Takahashi M, Inoue Y, Egi K, Kuwata Y, Yamaoka A. Ocular attacks after phacoemulsification and intraocular lens implantation in patients with Behcet disease. Ophthalmologica. 2001;215(3):179–82.
34. Hu K, Lei B, Kijlstra A, et al. Male sex, erythema nodosum, and electroretinography as predictors of visual prognosis after cataract surgery in patients with Behcet disease. J Cataract Refract Surg. 2012;38(8):1382–8.
35. BenEzra D, Cohen E. Cataract surgery in children with chronic uveitis. Ophthalmology. 2000;107(7):1255–60.
36. Ganesh SK, Mistry S. Phacoemulsification with intraocular lens implantation in pediatric uveitis: a retrospective study. Ocul Immunol Inflamm. 2018;26(2):305–12.
37. Dada T, Dhawan M, Garg S, Nair S, Mandal S. Safety and efficacy of intraoperative intravitreal injection of triamcinolone acetonide injection after phacoemulsification in cases of uveitic cataract. J Cataract Refract Surg. 2007;33(9):1613–8.
38. Okhravi N, Morris A, Kok HS, et al. Intraoperative use of intravitreal triamcinolone in uveitic eyes having cataract surgery: pilot study. J Cataract Refract Surg. 2007;33(7):1278–83.
39. Larochelle MB, Smith J, Dacey MS. Dexamethasone intravitreal implant in the treatment of uveitic macular edema in the perioperative cataract setting: a case series. Am J Ophthalmol. 2016;166:149–53.
40. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130(4):492–513.
41. Quek DT, Jap A, Chee SP. Risk factors for poor visual outcome following cataract surgery in Vogt-Koyanagi-Harada disease. Br J Ophthalmol. 2011;95(11):1542–6.
42. Elgohary MA, McCluskey PJ, Towler HM, et al. Outcome of phacoemulsification in patients with uveitis. Br J Ophthalmol. 2007;91(7):916–21.
43. Mehta S, Kempen JH. Cataract surgery in patients with uveitis. Int Ophthalmol Clin. 2015;55(3):133–9.
44. Heringer GC, Oueghlani E, Dell'Omo R, Curi AL, Orefice F, Pavesio CE. Risk of reactivation of toxoplasmic retinitis following intraocular procedures without the use of prophylactic therapy. Br J Ophthalmol. 2014;98(9):1218–20.
45. Sykakis E, Karim R, Parmar DN. Management of patients with herpes simplex virus eye disease having cataract surgery in the United Kingdom. J Cataract Refract Surg. 2013;39(8):1254–9.
46. Estafanous MF, Lowder CY, Meisler DM, Chauhan R. Phacoemulsification cataract extraction and posterior chamber lens implantation in patients with uveitis. Am J Ophthalmol. 2001;131(5):620–5.
47. Foster RE, Lowder CY, Meisler DM, Zakov ZN. Extracapsular cataract extraction and posterior chamber intraocular lens implantation in uveitis patients. Ophthalmology. 1992;99(8):1234–41.
48. Ram J, Gupta A, Kumar S, Kaushik S, Gupta N, Severia S. Phacoemulsification with intraocular lens implantation in patients with uveitis. J Cataract Refract Surg. 2010;36(8):1283–8.
49. Chan NS, Ti SE, Chee SP. Decision-making and management of uveitic cataract. Indian J Ophthalmol. 2017;65(12):1329–39.

50. Holland GN, Van Horn SD, Margolis TP. Cataract surgery with ciliary sulcus fixation of intraocular lenses in patients with uveitis. Am J Ophthalmol. 1999;128(1):21–30.
51. Alio JL, Chipont E, BenEzra D, Fakhry MA. International ocular inflammation Society SGoUCS. Comparative performance of intraocular lenses in eyes with cataract and uveitis. J Cataract Refract Surg. 2002;28(12):2096–108.
52. Papaliodis GN, Nguyen QD, Samson CM, Foster CS. Intraocular lens tolerance in surgery for cataracta complicata: assessment of four implant materials. Semin Ophthalmol. 2002;17(3-4):120–3.
53. Chiu H, Dang H, Cheung C, et al. Ten-year retrospective review of outcomes following phacoemulsification with intraocular lens implantation in patients with pre-existing uveitis. Can J Ophthalmol. 2017;52(2):175–80.
54. Roesel M, Heinz C, Heimes B, Koch JM, Heiligenhaus A. Uveal and capsular biocompatibility of two foldable acrylic intraocular lenses in patients with endogenous uveitis--a prospective randomized study. Graefes Arch Clin Exp Ophthalmol. 2008;246(11):1609–15.
55. Abela-Formanek C, Amon M, Kahraman G, Schauersberger J, Dunavoelgyi R. Biocompatibility of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses in eyes with uveitis having cataract surgery: long-term follow-up. J Cataract Refract Surg. 2011;37(1):104–12.
56. Leung TG, Lindsley K, Kuo IC. Types of intraocular lenses for cataract surgery in eyes with uveitis. Cochrane Database Syst Rev. 2014;3:CD007284.
57. Androudi S, Ahmed M, Fiore T, Brazitikos P, Foster CS. Combined pars plana vitrectomy and phacoemulsification to restore visual acuity in patients with chronic uveitis. J Cataract Refract Surg. 2005;31(3):472–8.
58. Gupta A, Ram J, Gupta A, Gupta V. Intraoperative dexamethasone implant in uveitis patients with cataract undergoing phacoemulsification. Ocul Immunol Inflamm. 2013;21(6):462–7.
59. Jinagal J, Gupta G, Agarwal A, et al. Safety and efficacy of dexamethasone implant along with phacoemulsification and intraocular lens implantation in children with juvenile idiopathic arthritis associated uveitis. Indian J Ophthalmol. 2019;67(1):69–74.
60. Lam LA, Lowder CY, Baerveldt G, Smith SD, Traboulsi EI. Surgical management of cataracts in children with juvenile rheumatoid arthritis-associated uveitis. Am J Ophthalmol. 2003;135(6):772–8.
61. Nemet AY, Raz J, Sachs D, et al. Primary intraocular lens implantation in pediatric uveitis: a comparison of 2 populations. Arch Ophthalmol. 2007;125(3):354–60.
62. Grajewski RS, Zurek-Imhoff B, Roesel M, Heinz C, Heiligenhaus A. Favourable outcome after cataract surgery with IOL implantation in uveitis associated with juvenile idiopathic arthritis. Acta Ophthalmol. 2012;90(7):657–62.
63. Magli A, Forte R, Rombetto L, Alessio M. Cataract management in juvenile idiopathic arthritis: simultaneous versus secondary intraocular lens implantation. Ocul Immunol Inflamm. 2014;22(2):133–7.
64. Harper SL, Foster CS. Intraocular lens explantation in uveitis. Int Ophthalmol Clin. 2000;40(1):107–16.
65. Adan A, Gris O, Pelegrin L, Torras J, Corretger X. Explantation of intraocular lenses in children with juvenile idiopathic arthritis-associated uveitis. J Cataract Refract Surg. 2009;35(3):603–5.
66. Phatak S, Lowder C, Pavesio C. Controversies in intraocular lens implantation in pediatric uveitis. J Ophthalmic Inflamm Infect. 2016;6(1):12.
67. Kosker M, Sungur G, Celik T, Unlu N, Simsek S. Phacoemulsification with intraocular lens implantation in patients with anterior uveitis. J Cataract Refract Surg. 2013;39(7):1002–7.
68. Androudi S, Letko E, Meniconi M, Papadaki T, Ahmed M, Foster CS. Safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema. Ocul Immunol Inflamm. 2005;13(2-3):205–12.
69. Williams GA, Haller JA, Kuppermann BD, et al. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. Am J Ophthalmol. 2009;147(6):1048–54.

70. Bae JH, Lee CS, Lee SC. Efficacy and safety of intravitreal bevacizumab compared with intravitreal and posterior sub-tenon triamcinolone acetonide for treatment of uveitic cystoid macular edema. Retina. 2011;31(1):111–8.
71. Soheilian M, Rabbanikhah Z, Ramezani A, Kiavash V, Yaseri M, Peyman GA. Intravitreal bevacizumab versus triamcinolone acetonide for refractory uveitic cystoid macular edema: a randomized pilot study. J Ocul Pharmacol Ther. 2010;26(2):199–206.
72. Whitcup SM, Csaky KG, Podgor MJ, Chew EY, Perry CH, Nussenblatt RB. A randomized, masked, cross-over trial of acetazolamide for cystoid macular edema in patients with uveitis. Ophthalmology. 1996;103(7):1054–62. discussion 1062-1053
73. Fardeau C, Simon A, Rodde B, et al. Interferon-alpha2a and systemic corticosteroid in monotherapy in chronic uveitis: results of the randomized controlled BIRDFERON study. Am J Ophthalmol. 2017;177:182–94.
74. Sen HN, Drye LT, Goldstein DA, et al. Hypotony in patients with uveitis: the multicenter uveitis steroid treatment (MUST) trial. Ocul Immunol Inflamm. 2012;20(2):104–12.
75. Okhravi N, Lightman SL, Towler HM. Assessment of visual outcome after cataract surgery in patients with uveitis. Ophthalmology. 1999;106(4):710–22.
76. Iwase T, Tanaka N. Reiterative membranous proliferation with giant-cell deposits on hydrophobic acrylic intraocular lenses after triple procedures in eyes with cataracts and uveitis. Cutan Ocul Toxicol. 2010;29(4):306–11.
77. Ganesh SK, Sen P, Sharma HR. Late dislocation of in-the-bag intraocular lenses in uveitic eyes: An analysis of management and complications. Indian J Ophthalmol. 2017;65(2):148–54.
78. Kapur R, Birnbaum AD, Goldstein DA, et al. Treating uveitis-associated hypotony with pars plana vitrectomy and silicone oil injection. Retina. 2010;30(1):140–5.
79. Gupta N, Punjabi OS, Steinle NC, Singh RP. Rate of hypotony following 25-gauge pars plana vitrectomy. Ophthalmic Surg Lasers Imaging Retina. 2013;44(2):155–9.
80. de Smet MD, Gunning F, Feenstra R. The surgical management of chronic hypotony due to uveitis. Eye. 2005;19(1):60–4.

Chapter 6
The Repair of Dislocated Intraocular Lenses and the Placement of Secondary Intraocular Lenses in the Setting of Uveitis

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Introduction

This chapter will focus on techniques for the repair of dislocated intraocular lenses (IOLs) and placement of secondary IOLs in eyes with uveitis. As there are many different procedures, materials, and IOL types used for repair and replacement of IOLs, not all can be covered in one chapter. Instead, we will focus on well-established principles and approaches. A primary focus will be on the challenges imposed by uveitis.

A particular focus on the repair of dislocated IOLs and the placement of secondary IOLs in the setting of uveitis is warranted for several reasons. First, uveitis may impose some limitations on what procedures and materials can be used out of concern for inciting inflammation. Second, due to the inherent complexity of cataract surgery in eyes with uveitis, it is more likely that surgical complications will occur. Third, there are a subset of uveitis patients that surgeons have elected to leave aphakic following cataract surgery due to concerns over primary IOL placement and the potential to exacerbate uveitis. Subsequently, some of these patients may have had their uveitis brought under control and as a result, have become candidates for secondary IOL placement. And forth, even with uncomplicated cataract surgery and successful placement of an implant within the capsular bag, uveitic eyes appear to be at higher risk for progressive zonulopathy and in-the-bag, late IOL dislocation. It is to the topic of IOL dislocation that we first direct our attention.

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IOL Displacement and Dislocation

IOL dislocation may occur as a result of surgical complications or underlying diseases of zonulopathy. Although diseases such as pseudoexfoliation and Marfan's garner much of the attention in this area, uveitis is underappreciated in its contribution to this challenging surgical problem. The two major contributory factors to IOL dislocation in pseudoexfoliation—capsule phymosis and zonulopathy—are also major features of uveitis. In general, the cumulative risk for IOL dislocation increases with time from surgery. Because of the fact that the indication for the use of IOLs in many subtypes of uveitis had a delayed start until modern anti-inflammatory therapies and strict perioperative control of uveitis became available, it is likely that a significant cohort of uveitis patients presenting with IOL dislocation is on the horizon.

Early Versus Late Dislocation

There is a bimodal distribution of IOL dislocation following cataract surgery [1]. Early dislocation is defined as occurring within 3 months of surgery and often manifests as a result of inadequate fixation within the capsular bag. The majority of such dislocations are the result of surgical complications resulting in damage to the capsular bag or zonules, or from failure of both haptics to remain within the capsular bag—a significant problem associated with can-opener type capsulorrhexis [1–3]. The rate of early IOL dislocation has decreased since the advent of the continuous curvilinear capsulorrhexis because the optic is supported by 360° of capsular overlap [1, 3].

Late dislocation is defined as occurring 3 or more months after uncomplicated surgery, with a mean interval of 6.9 to 8.5 years, and some cases presenting a decade or more following surgery [1]. The majority of late dislocation cases involve the entire IOL-bag complex as a unit and are thus described as 'in-the-bag' dislocations. The etiology of late IOL dislocation may be multifactorial, with potential contributions from preoperative risk factors for zonulopathy or capsule contraction syndrome, as well as surgical stress on zonules and postoperative trauma [4].

In up to 90% of reviewed cases of late IOL dislocation, there is an identified underlying diagnosis [1, 4]. Diseases associated with zonular insufficiency are major contributors, including pseudoexfoliation [1, 3–11], which accounts for more than 50% of cases, as well as uveitis [5, 7–9, 12, 13, 18–20], high axial myopia [8, 13, 14], retinitis pigmentosa [3, 8, 13, 15], and connective tissue disorders [4] such as Marfan's syndrome, homocystinuria, hyperlysinemia, Ehler-Danlos syndrome, scleroderma, and Weill-Marchesani syndrome. Trauma is also a significant cause of late dislocation [1, 3, 5, 7, 9, 16], including eye rubbing from atopic dermatitis [17], surgical trauma from pars plana vitrectomy [3, 9, 13], and possible association with YAG laser capsulotomy [11].

A developing issue in cataract surgery is the observation that an increasing number of patients are presenting with late-onset IOL dislocation [1, 4, 6]. This has led to suggestions that we are witnessing an emerging epidemic [4, 18–20]. The title of a recent editorial from the Journal of Cataract and Refractive Surgery, "In-the-bag intraocular lens dislocation: A ticking time bomb", illustrates the potential severity of this developing problem [21]. It is unclear whether the observed increase in late IOL dislocations is the merely the result of the increase in volume of cataract surgery performed over the past several decades [6, 22], or if the incidence of late dislocation is truly rising.

There are several lines of evidence supporting the argument that the incidence of late dislocation is indeed rising. Epidemiological evidence includes a population-based study from South-Eastern Norway (a region encompassing 56% of the national population) where cataract surgery data from all patients in the region was available for analysis [11]. The investigators found that the frequency of late in-the-bag dislocation increased in a statistically-significant fashion over the course of the 6-year study period, with four times as many dislocations presenting in the last year of the study as compared to the first. Convincing anecdotal evidence comes from surveys of ophthalmologists, which reveal a rise in the incidence of late dislocation [4, 23]. Additional evidence comes from pathologic analysis. Of the explanted IOLs submitted to the Intermountain Ocular Research Center for pathologic investigation, the number and proportion of in-the-bag late dislocations has risen dramatically and the majority of these submissions have evident zonular insufficiency [9].

An estimate of the dislocation rate for the general population is provided from a retrospective analysis of 14,471 cataract surgeries performed over a 29-year period (1980–2009) (n = 14,771) in a well-defined population of Olmsted County, Minnesota, U.S.A [6]. The cumulative risk of late IOL dislocation was 0.1% at 5 years, 0.1% at 10 years, 0.2% at 15 years, 0.7% at 20 years, and 1.7% at 25 years following cataract surgery [6]. The strengths of this study derive from the large, stable, and well-defined population of Olmsted County. Virtually all medical data from this population of 124,277 individuals has been captured in a linked medical record system that has been validated across multiple studies. Although the prevalence of pseudoexfoliation in Minnesota is unknown, it likely considerably lower than that of a high-prevalence pseudoexfoliation population such as Sweden [6]. Thus, this study provides baseline dislocation rates against which data from high-risk populations (such as pseudoexfoliation and uveitis) can be compared. In this Olmsted County population at relatively low-risk for IOL dislocation, the incidence of dislocation was found to be stable over time. This latter finding underscores the point that the reported rising incidence of late in-the-bag dislocations comes from high-risk populations [9, 11].

An estimate of the dislocation risk for a high-prevalence pseudoexfoliation population was determined in a prospective investigation of 810 cataract surgery patients from a defined-population in Northern Sweden where 40% of patients undergoing cataract surgery have pseudoexfoliation [22]. The study revealed a 10-year cumulative risk for in-the-bag dislocation of 1%—ten times higher than the 10-year timepoint for the general population estimate from the Olmsted County study, above [6].

Capsular Fibrosis and the Anterior Capsular Contraction Syndrome

Following most routine phacoemulsification cases, there is a limited amount of capsular fibrosis that causes the capsular bag to constrict around the IOL [24, 25]. This is manifest by the observation that in the presence of a continuous curvilinear capsulorrhexis, the diameter of the capsulorhexis opening normally decreases a small amount following surgery. Capsular fibrosis accounts for the fact that, with the passage of time, capsular bags are often more difficult to reopen for IOL exchange procedures.

Once capsular fibrosis is sufficiently established—generally 90 days after primary phacoemulsification—subsequent capsular procedures can be performed without significant concern for propagation of radial capsular tears that could result in dislocation of the IOL from the capsular bag. Examples include YAG laser capsulotomy and suture-repair of dislocated in-the-bag IOLs, in which needles and suture can be passed through sufficiently-fibrosed capsular bags and around haptics or capsular tension rings in order to secure IOL-bag complexes to the sclera.

While a small amount of capsular fibrosis is normal, exuberant anterior capsular fibrosis can be a pathologic condition associated with capsular phimosis. Such excessive fibrosis is known as the anterior capsular contraction syndrome [26]. The pathogenesis of anterior capsule contraction syndrome condition is poorly understood. The onset is fairly rapid following cataract surgery, occurring within several weeks to months following the procedure. A possible explanation is that breakdown of the blood-aqueous barrier releases inflammatory cytokines, resulting in monocyte and T-cell activation, and promoting fibrous metaplasia and proliferation of residual lens epithelial cells leading to purse-string contracture of the capsular bag [4].

Capsule contraction syndrome appears to be a pathologic byproduct of the continuous curvilinear capsulorrhexis. It is interesting to note that late in-the-bag IOL dislocation was unreported prior to the introduction of the continuous curvilinear capsulorhexis in 1983 [4, 27, 28]. A small capsulorhexis opening may exacerbate the sphincter effect [1, 4, 24, 29].

Anterior capsular contraction syndrome is associated with several conditions, including pseudoexfoliation syndrome [26, 30], undifferentiated uveitis [26, 31], pars planitis [26], Behcet's syndrome [32], retinitis pigmentosa [15, 33], diabetes mellitus [34, 35], and myotonic dystrophy [36]. In the setting of intact zonules, capsule contraction syndrome may not result in IOL displacement or dislocation. However, in conditions associated with concurrent zonulopathy, capsule contraction syndrome can lead to traction-induced zonular dehiscence and IOL dislocation [4, 6, 9, 26]. Thus, there is essentially a two-hit hypothesis, where zonulopathy and capsule contraction syndrome act in concert to lead to IOL dislocation. Both pseudoexfoliation and uveitis can give rise to zonulopathy and capsule contraction syndrome, and as will be demonstrated, both may have comparable rates of IOL dislocation.

Progression from Partial to Total Dislocation

It is the general consensus among investigators that without surgical intervention, all partially dislocated in-the-bag IOLs will eventually completely dislocate into the posterior segment [10, 11]. For this reason, surgical intervention is generally recommended at the first sign of inferior IOL dislocation [10, 11].

With early detection of dislocation, less invasive surgical procedures can be performed, often by suture-fixating the existing IOL-bag complex to the sclera via an anterior segment approach [11]. Delaying surgery may require pars plana vitrectomy and IOL retrieval from the posterior segment combined with more complex techniques to suture the existing IOL-bag complex to the sclera, or require IOL exchange [11].

In a large series of pseudoexfoliation patients in South-Eastern Norway with dislocated in-the-bag IOLs that were managed with early intervention where possible (n = 81), the majority of the dislocated IOLs were managed via an anterior segment approach (91.3%), either by IOL repositioning in the majority of cases (67.6%) or by IOL exchange surgery (32.4%) [11]. Anterior segment repositioning surgery consisted of scleral fixation performed by passing prolene suture through fibrosed capsular bags and around the haptics via an ab externo approach (discussed later in this chapter). Of eyes that underwent IOL dislocation repair via an anterior segment approach, vitreous loss occurred in 10% of eyes that underwent IOL repositioning surgery versus 78.3% of eyes that underwent IOL exchange (two eyes from the IOL exchange group developed retinal detachment). Seven eyes (8.6%) in the cohort required a pars plana vitrectomy approach because of total dislocation of the IOL-capsular bag complex into the posterior segment. The investigator's preferred surgical technique for total dislocation was to elevate the IOL-bag complex via pars plana vitrectomy and then perform scleral fixation rather than IOL exchange. The authors concluded that surgical repair should be performed within one month of diagnosis of IOL partial dislocation in order to avoid complete dislocation into the vitreous cavity, and that scleral suturing of the existing IOL-bag complex rather than IOL exchange results in fewer complications.

The first signs of zonular instability following cataract surgery may be displacement of the IOL, which is predominantly in an inferior direction and manifests with a gap between the pupillary margin and the superior edge of the optic [10, 37], or with pseudophakodonesis, which can be categorized as mild, moderate, or severe [22]. Utilizing Scheimpflug images (Pentacam), Østern et al. have provided quantitative evidence for progressive downward shift of IOLs over time in patients with pseudoexfoliation and dislocation, thus emphasizing the need for timely intervention [37]. An advantage of Scheimpflug imaging for the detection of dislocation is its utility in the face of poor pupillary dilation where the optic edge may not be visible [37], as often occurs in pseudoexfoliation and uveitis.

Lorente et al. have suggested a 4-grade dislocation classification scheme for which they recommend surgical intervention at grade 2 and above [10]. Grade 1

consists of pseudophakodonesis. In Grade 2 dislocation, the IOL-bag complex dislocates inferiorly, with the superior edge of IOL located above the visual axis. There is a slight decrease in visual acuity. In Grade 3 dislocation, the superior edge of IOL is below the visual axis, with resultant severe decrease in visual acuity. In Grade 4 dislocation, all of the zonules are broken and the IOL is dislocated into vitreous cavity with severe decrease in visual acuity.

Several authors have reported that IOL dislocation in one eye is associated with an increased risk for dislocation in the opposite eye, and thus advocate for increased monitoring of the fellow eye [1, 3, 11]. Østern et al. reported that 9.1% of pseudoexfoliation patients with late IOL dislocation in one eye developed dislocation in the fellow eye, with a 4-month gap between surgeries [11]. Jacobsson et al. reported an 18% rate of bilateral dislocation in a high-prevalence pseudoexfoliation population in Sweden [8].

Uveitis and Late Dislocation

Uveitis patients may have an underlying predisposition to zonular weakness and dehiscence [12, 38]. The major site of inflammation in intermediate uveitis is the in the vitreous; however, intermediate uveitis was first described as “chronic cyclitis” by Fuchs in 1908 [39]. Indeed inflammation frequently involves the peripheral retinal vasculature and may extend to the pars plicata and ciliary body, resulting in disinsertion of zonules [38, 40]. As previously mentioned, a dysfunctional blood-aqueous barrier, along with activation and migration of inflammatory cells, is a hallmark of intraocular inflammation that may stimulate epithelial cell proliferation and may underlie the etiology of the anterior capsule contraction syndrome in uveitis [40]. A dysfunctional blood-aqueous barrier has been proposed to underlie late IOL dislocation in retinitis pigmentosa [15]. Additional support for the hypothesis that uveitis can induce zonulopathy comes from case reports of spontaneous dislocation of crystalline lenses in uveitis patients [41, 42].

A retrospective review of all uveitis patients that underwent cataract surgery at a referral uveitis clinic in Chennai, Tamil Nadu, India over a 18 year period (n = 581) revealed 11 eyes with late IOL dislocation (1.89%) [38]. The mean time from surgery to dislocation was 11.24 years. All 11 eyes with dislocation had chronic intermediate uveitis. One patient in the series developed bilateral dislocation. This rate of dislocation is considerably higher than that of the general population data reported from Olmstead County (discussed above) where the cumulative risk for dislocation was 0.2% at 15 years and 0.7% at 20 years (the years spanning the 18-year study period in the Tamil Nadu study). Of course, such a comparison is not statistically valid for a variety of reasons, including that the Tamil Nadu data is not from a defined population and thus subject to inclusion bias, and because potential differences in surgical technique between studies may influence the rate of dislocation.

At the Manchester Uveitis Clinic in the United Kingdom, a retrospective review of 1056 uveitis patients that underwent uncomplicated cataract surgery over a

13-year period revealed that six patients (0.57%) developed late in-the-bag IOL dislocation [12]. All of the dislocated IOLs in this study had clinically evident anterior capsular fibrosis, suggesting that anterior capsular contraction syndrome may underlie IOL dislocation in uveitis in this population. The mean time from surgery to dislocation was 10.3 years (range 5–13 years). Although the prevalence of dislocation in the setting of uveitis in the Manchester study (0.57% over 13 years) is not as high as that reported from Chennai (1.89% over 18 years), this rate is almost three times higher than the general population data from Olmsted County, where the cumulative risk for dislocation was 0.1% at 10 years and 0.2% at 15 years (the years spanning the 13-year study period in the Manchester study).

Although the available data for IOL dislocation in uveitis is limited, it appears that the rate of dislocation is higher than the general population and is perhaps be comparable to that of a high-prevalence pseudoexfoliation population. Moreover, it is possible that uveitis shares with pseudoexfoliation a propensity towards developing zonulopathy and capsule contraction syndrome, which appear to act in concert to give rise to late IOL dislocation.

Avoidance of Late IOL Dislocation

There are many techniques and interventions that can be made to avoid late IOL dislocation. It is of obvious importance that one should perform high-quality surgery, with particular attention to minimizing intraoperative stress on zonules. However, postoperative inflammation may sabotage even the most elegantly performed surgery. If, as suggested, inflammation is a risk factor for the development of capsule contraction syndrome and zonulopathy, then it is imperative that inflammation be strictly controlled, both in the perioperative period and over the long term in chronic uveitis patients.

There are a number of surgical interventions that can be made to reduce the risk of late dislocation. First, the risk of developing the capsule contraction syndrome may be decreased by avoiding the creation of small-diameter capsulorrhexi [24, 29]. If a capsulorhexis is too small, its size can be easily enlarged at the end of surgery [23]. With single-piece acrylic IOLs placed within the bag and with viscoelastic filling the anterior chamber, a small capsular nick is made at the capsulorhexis margin with a cystatome or microscissors. Capsulorhexis forceps are then used to create a larger rhexis using the optic as a sizing guide to achieve approximately 1 mm of capsular overlap. If a three-piece IOL is to be used, then the capsulorhexis should be enlarged prior to IOL insertion using Vasavada's spatula technique [43], as the tension from the haptics expanding the bag could otherwise induce a radial tear.

During surgical cases, great care should be taken to minimize intraoperative zonular stress. Various techniques can be utilized. With relatively soft lenses such as those found in younger uveitis patients, the lenses can be prolapsed into the anterior chamber during hydrodissection. With denser lenses in the setting of zonular insuf-

ficiency, the use of multiple hydrodissection waves can facilitate nuclear rotation with minimal zonular stress, and nuclear chopping techniques can also reduce zonular tension [44].

The choice of IOL type and material used during primary cataract surgery may impact the risk for late dislocation. Silicone IOLs, and in particular plate-haptic silicone IOLs, are known to induced capsular fibrosis and increase the risk for capsule contraction [1, 31, 45, 46]. Moreover, silicone lenses are not good choices for patients that may require subsequent complex pars plana vitrectomy due to adverse interaction with silicone oil and intravitreal gases, both of which may result in reduced lens transparency. Stiff polymethyl methacrylate (PMMA) IOLs, particularly of the one-piece variety, may counteract the contractile force that capsular contraction places on zonules. However, because of the fact that PMMA optics are non-foldable and thus require larger corneal incisions, their use has fallen out of favor. Of the more popular foldable options, three-piece IOLs with acrylic optics and relatively stiff PMMA haptics may resist capsule contraction more than one-piece acrylic IOLs [4, 23, 45]. Although hydrophilic acrylic IOLs have the advantage of better uveal biocompatibility in comparison to hydrophobic acrylic IOLs, this difference has not proven to be clinically significant. More important is capsular biocompatibility, for which hydrophobic acrylic IOLs hold an established advantage [46]. Hydrophobic acrylic is stiffer than hydrophilic acrylic, and thus is better able to withstand capsular bag contraction [47]. A comparison of two common and similar hydrophobic acrylic single-piece IOLs, the AcrySof SN60WF (Alcon Laboratories, Inc., Fort Worth, TX, USA) and the Tecnis ZCB00 (Abbott Medical Optics Inc., Santa Ana, CA, USA) found a significant reduction in the incidence of anterior capsule contraction syndrome in favor of the ZCB00 IOL [48]. This was attributed to stiffer haptic design in the ZCB00 that better resisted contractile forces.

Meticulous cortical cleanup and removal of lens epithelial cells from the posterior aspect of the anterior capsule via capsule polishing techniques has been demonstrated to reduce the extent of the anterior capsule contraction syndrome and increase the stability of the IOL with respect to tilt, decentration, and postoperative refraction [4, 49, 50].

There is some controversy as to whether capsular tension rings (CTRs) can reduce the incidence of late dislocation. In theory, the use of capsular tension rings may counteract the contractile forces generated by capsule contraction, and thus reduce the stress placed on zonules. In practice, however, capsule contraction syndrome [51–53] and late dislocation [54, 55] have been reported in association with the use of capsular tension rings, thus leading some to conclude that capsular tension rings do not prevent late dislocation [10]. Despite these concerns, in cases of limited zonulolysis, standard capsular tension rings have been demonstrated to provide support [56]. However, in the presence of significant intraoperative zonular instability, scleral-sutured (eyelet modified) capsular tension rings or capsular tension segments should be considered [57]. Placement of standard capsular tension rings in these precarious cases may be inappropriate [54].

An alternative to the use of modified capsular tension rings in the face of zonular instability is to place a three-piece IOL in the sulcus and posteriorly capture the

optic through the capsulorhexis opening. Advantages of sulcus-placement combined with posterior optic capture include, (a) anchoring the IOL to the sulcus rather than the bag, thus significantly reducing the risk for late dislocation, (b) prevention of lateral movement of the IOL within the sulcus, (c) centering the optic within the visual axis, and (d) displacing the optic a bit more posteriorly into the capsular bag and thus reducing the risk for the anterior edge of the optic chaffing the posterior iris. Some advocate the prophylactic use of sulcus-placed three piece IOLs combined with posterior optic capture in all eyes at risk for capsule contraction syndrome, regardless of whether or not intraoperative zonular instability is manifest [1].

Postoperatively, if capsule contraction syndrome is beginning to develop, early intervention can be made using the Nd:YAG laser to create multiple radial [25] or circular [58] relaxing incisions in the anterior capsule. In a randomized, prospective trial, superiority of the circular approach has been reported [58]. Alternatively, the femtosecond laser can be utilized to create precise circular openings and relieve contractile tension in cases of capsular phimosis [59]. As discussed further below, if the IOL is displaced as the result of capsule contraction syndrome, then the patient can be brought to the operating room where the fibrotic material is removed by peeling it out of the bag, and in this manner the bag can be completely reconstituted [60, 61]. In addition to managing anterior capsule contraction, the argument can be made that posterior capsule opacification also places contraction-induced stress on zonules, particularly in pseudoexfoliation, and that early YAG laser capsulotomy may be indicated [1].

Complications of Intraocular Lens Malposition

The complications associated with IOL malposition generally fall into one of three categories: Degraded optical performance, incitement of the uveitis-glaucoma-hyphema syndrome, or in the case of anterior chamber IOLs, corneal decompensation. IOL decentration and tilt introduce optical aberrations that often decrease the quality of vision. Holladay has demonstrated that greater than 15° of tilt introduces higher-order aberrations that cannot be corrected with spectacles [62]. Modern IOL design incorporates wavefront-corrected IOLs with negative asphericity in order to improve optical performance by lowering spherical and higher order aberrations [63]. However, a variety of optical models predict that the optical performance of negatively aspheric IOLs is significantly degraded as a result of IOL decentration or tilt, and that older spherical designs perform better under such circumstances [64, 65]. Thus, spherical IOLs should be considered when IOL displacement is anticipated [63, 65].

IOL decentration and tilt are potential issues with IOL refixation surgery and secondary IOL placement. With respect to sulcus-fixated IOLs, the ASCRS Cataract Clinical Committee states [65], “it appears inadvisable to implant a wavefront-corrected negatively aspheric IOL if centration within 0.5–0.8 mm cannot be

achieved. Based on limited data, it appears that up to one-third to one half of sulcus-fixated IOLs may exceed this level".

Properly-sized and correctly-placed anterior chamber IOLs and sulcus-placed, three-piece IOLs can remain well-centered without tilt or movement and are often well-tolerated. On the other hand, undersized anterior chamber and sulcus IOLs are subject to decentration, tilt, and movement, which can lead to the uveitis-glaucoma-hyphema (UGH) syndrome and—in the case of anterior chamber IOLs—progressive endothelial cell loss due to IOL contact with the cornea. Oversized anterior chamber IOLs may result in iris tuck, pupil ovalization, angle erosion, and pain, and also induce the UGH syndrome.

Surgical Management of Aphakia and Intraocular Lens Complications in Uveitic Eyes

Traditionally, the term "secondary IOL" refers to the clinical scenario where patients are left aphakic at the time of primary surgery and an IOL is placed during a secondary procedure. Now that surgical aphakia is less common, a more contemporary use of the term may also refer to an IOL exchange procedure. Nevertheless, although surgical aphakia is less common in the modern era, there are times where it is appropriate, including some cases of chronic uveitis in which inflammation is difficult to control and where there is concern that primary IOL placement may exacerbate inflammation, in fellow eyes of uveitis patients in which IOLs have been poorly tolerated, following IOL explantation for endophthalmitis, or following complicated cataract surgery where capsular support is unavailable. As discussed further below, primary placement of anterior chamber IOLs is relatively contraindicated for many subtypes of uveitis. Moreover, proper sizing of anterior chamber IOLs in relation to the diameter of the anterior chamber is crucial in order to avoid complications; this necessity often dictates delaying primary placement of an anterior chamber IOL.

The array of surgical IOL challenges that face the cataract surgeon in uveitic eyes can be placed into three broad categories: (1) repair or exchange of dislocated IOLs (either in-the-bag with poor zonular support or out-of the bag secondary to bag damage), (2) IOL exchange of damaged or poorly-tolerated IOLs (e.g., due to incitement of uveitis or the uveitis-glaucoma-hyphema syndrome, wrong IOL power, dysphotopsias, etc.), and (3) placement of secondary IOLs in aphakic eyes.

Management options include a large variety of techniques and IOL categories. Given the vast number of surgical options in the published literature, not all can possibly be covered here. An additional caveat is that very little has been published on the use of secondary IOLs in uveitis. The few publications that are available are generally retrospective in nature and are thus subject to systemic biases related to patient selection and long-term follow-up. Given the paucity of publications on the topic, conclusions are often inferred from other lines of investigation, including the incitement of inflammation in non-uveitic patients.

The ideal location for IOL placement in uveitic eyes is within the capsular bag, as this eliminates IOL interaction with highly reactive uveal tissue [66]. In practice, however—when placement of the IOL within the capsular bag is not an option—the remaining choices for IOL placement generally result in some IOL or suture interaction with the uvea, with varying degree and propensity to incite inflammation.

Secondary IOL techniques can be divided into five categories: (1) anterior chamber IOLs, (2) sulcus-placed IOLs, (3) optic capture, (4) iris-fixated IOLs (both iris-claw and iris-sutured IOLs), and (5) scleral fixation. Of these, iris-fixated IOLs will not be reviewed here due to the fact that this approach remains contraindicated in uveitis due to risk of inducing iritis. Suffice it to say that iris-fixation is gaining favor in non-uveitis cases, particularly via the retropupillary approach using the Ophtec Artisan Aphakia iris clip IOL [10, 67].

Perioperative Management Considerations in Uveitis

The remainder of this chapter addresses the repair of dislocated IOLs and the placement of secondary IOLs in eyes with uveitis. Other chapters in this book address the medical management and surgical challenges associated with primary cataract surgery in uveitis patients. Suffice to say, many of the same management principles apply to uveitis patients undergoing dislocated IOL repair and secondary IOL placement including, (a) that patients be adequately evaluated and managed from an inflammatory and infectious disease standpoint prior to surgery, (b) that eyes be without signs of active uveitis for at least three months prior to surgery on a stable anti-inflammatory regimen if necessary, (c) that that patients undergo appropriate perioperative anti-inflammatory medical treatment in an effort to reduce the risk of potential structural complications, such as CME, during this period [68], and (d) that significant postoperative inflammation, when present, be addressed early and aggressively. The need for a definitive uveitis diagnosis, even if idiopathic, and a tailored approach to intraocular inflammation underscores the importance involving experienced uveitis practitioners in the perioperative management of these patients.

Surgical management considerations include the fact that surgical risks may be considerably higher in uveitis patients, including the possibility of inducing cystoid macular edema, intractable uveitis, and even phthisis—particularly in eyes with poorly controlled or active inflammation or that have undergone multiple prior surgeries. The fact that inflammatory control is central to surgical success cannot be overstated.

Before performing secondary IOL surgery, consideration should be given as to whether non-surgical refractive options may suffice, even if the refractive state is not ideal. If the patient can tolerate contact lenses or aphakic glasses, then surgery can be avoided. If the plan is to proceed with surgery, then visual potential should be ascertained from subjective refraction, and all potential preoperative structural damage, especially diseases of the macula or optic nerve, must be thoroughly docu-

mented and treated, with explanation provided to the patient regarding postoperative visual potential and expectations.

The least invasive surgical options should be considered first in uveitic eyes. For example, it is generally more efficient and less invasive to repair partially and completely dislocated IOLs with refixation approaches that utilize small incisions rather than to perform IOL exchange procedures. IOL exchange is associated with a higher rate of vitreous loss and retinal detachment [11], and, depending upon surgical technique and IOL type, may require a larger wounds, which reduce endothelial cell count, produce greater postoperative astigmatism, and require longer healing and visual recovery time.

Given the inherent refractive uncertainty following placement of secondary IOLs—in particular scleral-fixated IOLs—patients should be counseled that they will likely need glasses following surgery. The greater uncertainty in final refraction is due to variance in effective lens position, the potential to introduce astigmatism from suture-closure of large corneal wounds, as well as the potential for IOL tilt with scleral fixation. If the plan is for a scleral-fixated IOL, then a target postoperative refraction of approximately −1.00 to −1.50 diopters should be considered in order to avoid hyperopia.

Reopening and Repositioning IOLs Within the Capsular Bag

Fibrosis of the capsular bag may lead to IOL decentration or tilt within the bag, or even partial or full expulsion of IOLs out of the bag. Utilizing careful dissection with viscoelastic and blunt spatulated instruments, fibrosed bags can often be completely reopened, allowing for IOL repositioning, IOL exchange, or secondary IOL placement in aphakic eyes [69]. Reyntjens et al. demonstrated that surgical removal of a ring of fibrotic tissue from phimotic bags allows for reconstitution of a normally round capsulorhexis, and that capsular bags can return to normal dimensions [61]. As noted previously, the femtosecond laser can be utilized to create precise circular openings and relieve contractile tension in cases of capsular phimosis [59].

When the bag and zonules are intact, reopening and resurrecting the fibrosed capsular bag should be considered in uveitic eyes, because virtually all other approaches to IOL fixation and secondary IOL placement involve uveal contact with the IOL or suture material.

In the clinical setting of pseudophakic visual disturbance, is imperative to rule-out the possibility that IOL decentration or tilt is the culprit before proceeding with YAG laser capsulotomy because an open posterior capsule may complicate lens repositioning [69].

If the IOL has prolapsed out of the capsular bag, then consideration should be given to reopening the capsular bag and repositioning the IOL, followed by rotating the IOL to find the best haptic support and then suturing all corneal wounds, as fluid

egress is a major culprit for IOL prolapse. Pupillary constriction with Miochol can also help retain the IOL within the capsular bag prior to suturing wounds.

Optic Capture

Optic capture is relatively easy and quick to perform, largely avoids many of the potential complications associated with other IOL fixation techniques [70], and minimizes IOL contact with uveal tissue. Optic capture can be used for repositioning out-of-the-bag dislocations, IOL exchange, placement of secondary IOLs, and management of capsular complications during primary cataract surgery. The requirements for optic capture are intact zonular support and a round opening in either the anterior or posterior capsule that is smaller than the optic. In secondary procedures, if the capsulorhexis opening is fibrotic and too small (perhaps from phimosis), then it can be enlarged either with a vitrector or micro-scissors. Virtually any single piece or three-piece IOL can be used for optic capture as long as it is not of a plate-haptic design [71].

The term 'optic capture' implies that the optic and haptics are placed on opposite sides of the capsular opening. Posterior optic capture is most commonly used when a three-piece IOL is placed in the sulcus and the optic is gently positioned through the capsulorhexis opening by pushing on the edge of the optic located 90° from a haptic and then pushing on the opposite side of the optic. Another application of posterior optic capture utilizes the posterior capsule. If an appropriately-sized opening is made in the posterior capsule, the haptics can either be placed in the sulcus or in the bag, and the optic then is delivered posteriorly through the posterior capsulorhexis. A third approach is anterior (or reverse) optic capture, where the optic is oriented anterior to the haptics. The most common approach is to place the IOL in the bag (even if the posterior capsule is torn) and then lift the optic through the anterior capsulorhexis opening. A dispersive viscoelastic is used when the posterior capsule is open in order to compartmentalize vitreous.

Almost any combination of optic and haptic positioning can be used: The optic or haptics can be placed anterior to the anterior capsule, posterior to the posterior capsule, or between the anterior and posterior capsule [71]. The only exception is that the haptics of single-piece acrylic, square-edged IOLs should never be placed in the sulcus utilizing a posterior optic capture configuration due to the risk of complications that include pigment dispersion, hemorrhage, and cystoid macular edema [65]. However, the optic of single-piece acrylic IOLs can be safely placed in the sulcus while the haptics remain posterior to the anterior capsule through the use of anterior optic capture [72] as described above. Anterior optic capture has been reported to be successful in pediatric patients with chronic uveitis [73]. Note that anterior optic capture allows for placement of single-piece acrylic toric or multifocal IOLs in the setting of an open posterior capsule (although multifocal IOLs are strictly contraindicated in uveitis).

Sulcus-Placement of Intraocular Lenses

In a case series published in 1999, Holland reported that ciliary sulcus fixation of rigid single-piece and three-piece polymethylmethacrylate IOLs during primary cataract surgery in patients with uveitis is relatively safe, with no evidence for increased postoperative inflammation or intraocular pressure, and a reduced risk for posterior synechiae formation [74]. The report was retrospective and an in-the-bag IOL control group was absent. To our knowledge, there are no published studies on the use of modern three-piece acrylic IOLs for sulcus placement in uveitic eyes. Furthermore, at the time of this writing, there are no FDA-approved IOLs for sulcus implantation, and thus the use of sulcus-placed IOLs is off-label in the United States.

Approximately one-third to one-half of sulcus-fixated IOLs without optic capture experience enough tilt and decentration to generate significant adverse spherical and other higher order aberrations. As previously mentioned, if IOL centration within 0.5 to 0.8 mm cannot be achieved, then consideration should be given for the use of spherical IOLs [65], which have less induced optical aberrations with decentration. Silicone IOLs should be avoided if vitreous loss is encountered and retinal detachment is possible, or if future vitrectomy is anticipated due to uveitis, because of the risk for decreased IOL clarity as a result of interaction with silicone oil or expansile gas.

In 2009, the American Society of Cataract and Refractive Surgery (ASCRS) Cataract Clinical Committee published a Special Report warning against sulcus-placement of single-piece acrylic IOLs [65]. This report also made recommendations for backup IOL implantation following posterior capsular rupture, including the recommendation that sulcus-placed, three-piece IOLs should not make contact with the posterior iris, and that three-piece IOLs should be sized correctly such that the haptics make contact with the ciliary sulcus tissue in order to provide secure fixation and avoid lateral IOL movement within the sulcus space. Without secure fixation, the optic may become decentered, tilt, or move within the sulcus space, potentially inducing uveitis, bleeding, and pigment dispersion [65].

The ASCRS recommendation is to combine sulcus-placement of three-piece IOLs along with posterior optic capture, as the latter procedure stabilizes the IOL, obviates the need for the haptics to make contact with the ciliary sulcus, centers the optic within the visual axis, places a capsular barrier between the anterior optic edge and the posterior iris surface (thus avoiding posterior synechiae formation, which is a significant complication in uveitis), and moves the optic more posteriorly—as reflected by the fact that the IOL power does not have to be adjusted from that for in-the-bag placement [75].

If optic capture is not possible, then the ASCRS recommendation is to use three-piece IOLs that are large enough for the haptics to touch the apex of the ciliary sulcus and thus prevent lateral subluxation, tilt, or movement [65]. Unfortunately, there is no way to directly measure or indirectly estimate the sulcus diameter [65]. Complicating the problem further is the fact that the sulcus diameter varies in dif-

ferent meridians [65]. Without optic capture, the recommendation is to use the longest available three-piece IOL (ideally 13.5 mm or longer, and definitely no shorter than 13.0 mm) with a minimum 6.0 mm optic, thin-looped haptics that angulate posteriorly, and rounded anterior IOL edges [65].

A potential downside of posterior optic capture in uveitis patients is increased risk of posterior synechiae formation between the iris and the capsulorhexis edge. Topical mydriatic agents as well as topical/systemic anti-inflammatory treatments may help avoid this complication. In the setting of uveitis, some advocate for capsulorrhexi that are larger than the optic in order to avoid posterior synechiae formation with the capsule. Optic capture, however, requires capsulorrhexi that are smaller than the optic. A solution to this dilemma may be to first create a relatively small capsulorhexis. If surgery is uncomplicated and an IOL is successfully placed within the capsular bag, then the capsulorhexis can be enlarged as previously described. If the capsulorhexis is enlarged such that there is no optic overlap, then wounds should be sutured in order to minimize fluid egress and thus minimize the possibility that the optic will prolapse out of the capsular bag.

A remaining question regarding sulcus placement of three-piece IOLs in uveitis is whether haptic contact with the uveal tissue of the ciliary sulcus will induce inflammation. In a study of inflammation induced by sulcus-placed, three-piece IOLs, 22 non-uveitis patients with sulcus-placed IOLs were examined by ultrasound biomicroscopy (UBM) and laser flare meter [76]. Fellow eyes with in-the-bag IOL placement served as controls. UBM demonstrated that of the 22 eyes with sulcus-placed IOLs, 19 had well-placed haptics in the sulcus and all 19 of these eyes had optic-iris touch. In the three remaining eyes, the haptics were malpositioned, with one haptic against the ciliary body while the other was in the ciliary sulcus. In 2 of these latter eyes, there was no optic-iris touch, and in the third eye, only minimal optic-iris touch. Control eyes with in-the-bag IOL placement had no optic-iris touch. Mean anterior chamber flare was significantly higher in eyes with optic-iris touch ($p < 0.05$). This finding is intriguing because it suggests that although optic-iris touch incites inflammation, haptic-sulcus contact may not. If true, then perhaps inflammation could be avoided if sulcus-supported IOLs are designed with increased posterior vault such that optic-iris touch is eliminated.

Even in situations where sulcus-placed, three-piece IOLs are properly-sized and stable, pupillary constriction and dilatation may result in friction between the optic and iris, with resultant uveal irritation and inflammation. This is particularly true for optics that have a square-edge design. Atropine-induced mydriasis may alleviate the rubbing in such cases and assist in establishing a diagnosis. If the uveitis resolves, then pupillary constriction and dilatation may be the culprit. If the patient can tolerate long-term dilation, then this approach may provide a solution. Otherwise, an IOL repositioning or exchange may be necessary.

IOL power is reduced in most eyes undergoing sulcus implantation, with the exception of long eyes that require low power IOLs. There are two approaches to IOL power adjustment for sulcus fixation. Hill provides a table at his website based on theoretic calculation of IOL power adjustment [77]. Alternatively, the axial length can be considered along with the calculated IOL power, which may modify

results slightly, particularly in short eyes [78]. As mentioned, Millar recommends no power adjustment with optic capture [75].

Anterior Chamber Intraocular Lenses

The use of anterior chamber IOLs in uveitis patients is controversial. To our knowledge, there are only three published reports on the topic [66, 79, 80], which are discussed in greater detail, below. Suffice it to say at the outset that although these studies conclude that the use of anterior chamber IOLs in uveitis is relatively safe, they can be criticized for being retrospective in design, of small size, and with short follow-up duration.

It is our belief that the safe use of anterior chamber IOLs in uveitis patients remains unproven and is thus relatively contraindicated out of concern for inciting uveitis, particularly persistent low-grade inflammation that may require lens explantation. Alternative IOL fixation techniques are likely to induce less chronic inflammation and should be considered first. That said, some types of uveitis—for example, birdshot retinochoroidopathy and Fuchs heterochromic iridocyclitis—may tolerate anterior chamber IOLs better than more aggressive forms of anterior uveitis such as those associated with juvenile idiopathic arthritis or HLA-B27. Thus, anterior chamber IOLs may remain an alternative for some patients who cannot tolerate aphakia or contact lenses provided one proceeds with caution and with full awareness of the risks, potential complications, and the lack of reliable long-term data on the safety of using anterior chamber IOLs in uveitis. The remainder of this section will focus on the use of anterior chamber IOLs in general, and will review the three aforementioned publications on anterior chamber IOL use in uveitis.

Overall, the use of anterior chamber IOLs is declining as popularity has increased in sulcus-placed, three-piece IOLs as well as in new iris and scleral fixation techniques. Despite this shift away from anterior chamber IOL usage, there is support in the literature for equivalency in outcomes between anterior chamber IOLs and other IOL fixation techniques in non-uveitis patients. Much of the concern surrounding the use of anterior chamber IOLs stems from older designs that were associated with high rates of UGH syndrome, pseudophakic bullous keratopathy, and cystoid macular edema [65]. Design improvements that have led to better outcomes include the development of flexible, open-looped haptics, the addition of anterior vault to the optic in order to reduce iris contact, and availability in multiple sizes.

Despite improvements in design, anterior chamber IOLs remain relatively contraindicated in eyes with shallow anterior chambers, glaucoma, peripheral anterior synechiae, large iris defects, and endothelial dysfunction or low endothelial cell counts. As previously discussed, we believe that uveitis is also a relative contraindication for anterior chamber IOL use—particularly in eyes with chronic uveitis and in eyes with quiescent potentially fulminant anterior uveitis such as juvenile idiopathic arthritis and HLA-B27.

A 2003 Ophthalmic Technology Assessment Report from the American Academy of Ophthalmology (AAO) reviewed 43 articles with evidence-rating of III or higher on the subject of IOL implantation in the absence of capsular support. The report compared the use of modern, open-loop anterior chamber IOLs, scleral-sutured IOLs, and iris-sutured posterior chamber IOLs [81]. Their conclusion was that use of any of the three options is supported by the literature, and none has been demonstrated to be superior. It is important to note that the report does not address secondary IOL placement in uveitic eyes.

With respect to anterior chamber IOLs, the AAO report concludes, "Modern open-loop AC IOLs are not susceptible to the unacceptably high rates of corneal endothelial decompensation, secondary glaucoma, and CME associated with closed-loop AC IOLs. In the series analyzing open-loop AC IOLs individually or comparing them to scleral or iris-sutured PC IOLs, there was no evidence to suggest that visual outcomes were less satisfactory with open-loop AC IOLs [81]". Again, the reader is cautioned that this conclusion is not generalizable to uveitic eyes.

Support for the use of anterior chamber IOLs in the setting of chronic uveitis comes primarily from three small retrospective reports. In a review of same-surgeon phacoemulsification procedures in uveitis patients performed over a 6-year period (n = 631), Suelves' et al. identified 18 eyes that received anterior chamber IOLs [66]. These were aged-matched to 18 patients from the same uveitis cohort that received in-the-bag, posterior chamber IOLs. There was no significant difference in postoperative complications between the two groups, with the exception of a higher rate of posterior capsular opacification in the posterior chamber IOL group. The authors conclude, "In uveitic eyes with inadequate capsule support, anterior chamber IOL implantation was safe and effective in providing satisfactory improved corrected distance visual acuity without a significant increase in long-term complications compared with eyes that had posterior chamber IOL placement".

In Suelves et al.'s second publication on the use of anterior chamber IOLs in uveitis, 17 patients with a history of chronic uveitis that received anterior chamber IOLs were compared to 23 non-uveitis patients that also received anterior chamber IOLs [79]. Five-year, retrospective follow-up data was available for analysis. Although the risk for epiretinal membrane formation was higher in the uveitis group, the rate of uveitis flare-ups attributable to the presence of an anterior chamber IOL was comparable to the control group ($p < .001$). The authors conclude, "In uveitic eyes with inadequate capsular support, anterior chamber IOL implantation restored visual function without a significant increase in long-term postoperative complications compared with eyes that had no history of uveitis."

Tao and Hall have also reported on the successful use of anterior chamber IOLs in a small retrospective series of uveitis patients that experienced late in-the-bag IOL dislocations and underwent pars plana vitrectomy with IOL explantation [80]. Three of the four cases that were explanted received anterior chamber IOLs, and these IOLs were well tolerated.

Proper anterior chamber IOL sizing reduces the risk for complications [65]. IOLs that are too large in diameter may induce uveal inflammation and pain from iris tuck and angle erosion. IOLs that are too small are subject to movement, which

can lead to iridocyclitis and progressive endothelial cell loss secondary to contact with the corneal endothelium. Undersized anterior chamber IOLs that undergo rotation may result in a haptic passing through the (required) iridectomy causing ciliary body irritation and inflammation.

Anterior chamber IOLs are manufactured in a range of diameters. To achieve proper sizing of anterior chamber IOLs, 1 mm is generally added to the white-to-white measurement [65]. The white-to-white measurement should be made on the same axis as the surgical incision for IOL insertion. For example, if the incision for IOL placement is temporal and the IOL is to be placed in the horizontal meridian, then the horizontal white-to-white measurement should be utilized for anterior chamber IOL size determination. However, adding 1 mm to the white-to-white distance is inaccurate in some patients and can lead to under- or oversizing of anterior chamber IOLs [65]. White-to-white measurement has been demonstrated to have poor correlation [82, 83] to technologies that directly measure the anterior chamber diameter, including ultrasound [82] and optical coherence tomography [84]. Therefore, in the absence of such technology, intraoperative sizing cannot depend solely upon white-to-white measurement. Once the anterior chamber IOL is placed, it should be visually and manually assessed to confirm that it fits well within the anterior chamber [65].

Scleral-Fixation

Scleral fixation is a complex topic. There are a large variety of published techniques with no conclusive data to guide our procedure choices. The techniques are generally more complex and time-consuming than most other secondary IOL options, and often involve more risk including the possibility for retinal detachment and suprachoroidal hemorrhage. In addition, there is potential for significant postoperative refractive error due to variability in effective lens position as well as potential for IOL tilt and decentration.

The many surgical variables in scleral fixation present a series of choices: Which anatomic fixation site should be utilized (ciliary sulcus, pars plicata, or pars plana)? Should a sutured-IOL approach be undertaken, or should sutureless intrascleral fixation be performed? If a sutured-approach is undertaken, which strategy should be used for accurate anatomic suture placement—ab interno or ab externo? If ab interno, should endoscopy be employed? Should scleral-fixation be combined with anterior or pars plana vitrectomy? Should the capsular bag should be left in place or removed? Should the current IOL be salvaged or exchanged? In addition, there are a several choices of suture material and a variety of techniques for dealing with exposed knots.

There are three potential sites for suture-fixation to the sclera: From anterior to posterior, these are the ciliary sulcus (anterior pars plicata), the ciliary body (posterior pars plicata), and the pars plana. Potential advantages of ciliary sulcus suture-fixation include the fact the sulcus is an anatomic recess that may serve as

a landing spot for haptics and thus may help stabilize IOLs with respect to tilt. In addition, sulcus placement may reduce the variability of effective lens position that is otherwise associated with scleral fixation. However, as described below, achieving accurate ciliary sulcus placement without specialized equipment is unlikely.

In a study of 20 patients (40 haptics) that received a suture-fixated IOL utilizing an ab externo docking needle approach with the target of ciliary sulcus placement, ultrasound biomicroscopy revealed that 22 (55.0%) of the haptics were located in the sulcus, 11 (27.5%) anterior to the sulcus, and 7 (17.5%) posterior to the sulcus [85]. In another investigation comparing ab interno and ab externo techniques, ultrasound biomicroscopy revealed that both procedures performed poorly, with successful sulcus placement in only 31% of cases with ab externo fixation and 29% with ab interno fixation, a difference was not statistically significant [86]. Another large study confirmed the same problems associated with an ab externo suture-fixation approach, but noted a significant improvement when ab interno fixation was performed with three-port vitrectomy utilizing endoscopic visualization of haptic placement in the ciliary sulcus [87].

The surgical challenge in ciliary-sulcus suture-fixation is that many commonly performed ab interno and ab externo techniques are essentially blind procedures, where the location of the internal sclerostomy site for suture fixation is hidden behind the iris. Utilizing UBM, Sugiura et al. have carefully analyzed the measurement challenges and surgical issues associated with precise haptic placement in the ciliary sulcus [88]. The authors provide convincing evidence that blind ab interno and ab externo attempts at ciliary sulcus fixation are highly inaccurate and should be abandoned [88]. When the haptics are not well-seated in the apex of the sulcus, IOL tilt and decentration with resultant high astigmatism and higher order visual aberrations are often the result [65, 87, 88]. Inflammation and bleeding are also significant potential complications of poor haptic localization [76, 87, 88]. If the sclerostomy is too anterior, then the haptic may end up embedded in the root of the iris, while the optic makes contact with the iris, increasing the risk for iritis, bleeding, cystoid macular edema, and optic capture. On the other hand, if the sclerostomy is located posterior to the apex of the ciliary sulcus, then as described by Sugiura, “the haptics would be fixated over the ciliary processes, which can result in them becoming lodged obliquely in the valleys between the tips of the ciliary processes, causing significant and irreversible IOL tilt and decentration” [88].

For ab interno fixation without endoscopic visualization, Sugiura et al. recommend use of a specialized needle injection device that has a custom-shaped tip that fits snugly within the ciliary sulcus, thus optimizing suture passage through the apex of the sulcus (Ciliary Sulcus Pad Injector, Duckworth & Kent Ltd) [88]. For ab externo approaches, the authors recommend pars plana suture fixation (rather than ciliary sulcus fixation), with the creation of sclerotomies 3.0 mm posterior to the limbus, thus completely avoiding the iris and the highly vascular pars plicata with its associated ciliary processes, allowing the haptics to rest against a relatively smooth internal surface that is less likely to induce tilt and decentration.

With intrascleral fixation, haptics are inserted into intrascleral tunnels that are created parallel to the limbus. As such, the use of sutures is avoided, and haptics are not resting on the uneven inner surface of the pars plicata (as is the case for sutured IOLs). Rather, the haptics are embedded in the sclera and as such there is the potential to reduce the amount of tilt associated with standard pars plicata suture fixation. In fact, a low and acceptable level of IOL tilt with intrascleral fixation has been demonstrated [89, 90]. When such fixation is posterior to the iris root and anterior to the pars plana the term 'pars plicata fixation' can be applied [91]. Examples include Agarwal's intrascleral glued-haptic fixation technique which utilizes scleral tunnels located 1.5 mm posterior to the limbus [92], and Yamane's intrascleral flanged-haptic fixation technique which utilizes scleral tunnels located 2.0 mm posterior to the limbus [93].

The use of intrascleral fixation has been reported in patients with uveitis [94]. Todorich et al. performed complete three-port pars plana vitrectomy with total removal of the capsule in five patients with uveitic entities that included HLA-B27-associated uveitis, sarcoidosis, rheumatoid arthritis, psoriatic arthritis, and idiopathic posterior uveitis. Intrascleral fixation of three-piece acrylic IOLs with PMMA haptics (model Alcon MA60AC) was performed using a sutureless transconjunctival approach at a position measured 2 mm posterior to the limbus. The patients had good uveitis control following surgery with no escalation of baseline therapy. The IOLs were well-fixated without dislocation, and there was no scleral thinning, erosion, or melting.

Suture suspension techniques offer another form of scleral fixation that do not necessarily involve haptics resting against internal ocular structures. In the case of late in-the-bag dislocations, the entire IOL-bag complex can be sutured to the sclera, thus avoiding IOL exchange [11]. This is possible because fibrosis of the capsular bag allows suture passage around a haptic without inducing radial capsular tears that could result in IOL dislocation from the bag. In addition, capsular fibrosis prevents the suture from slipping laterally along the haptic, effectively acting like an eyelet, thus assisting in IOL centration and reducing the potential for IOL tilt during scleral suturing procedures. Because the haptics are tucked inside the typically contracted capsular bag, the overall diameter of the bag-IOL complex is relatively small (particularly if the IOL is a one-piece acrylic lens) and the haptics are less likely to interact with the uneven pars plicata surface.

Chan et al. have described a suture-fixation technique for the repair of dislocated in-the-bag IOLs that uses an ab externo-inserted, bent 26-gauge hypodermic needle to pierce the capsular bag and then receive the long needle of a 9-0 Prolene suture that is passed across the anterior chamber [95]. A major advantage of this approach is that only a few corneal incisions are necessary, thus allowing the surgeon to work within a relatively closed system. In most cases, anterior vitrectomy is not necessary and the potential for vitreous loss and retinal detachment is reduced as compared to pars plana vitrectomy and IOL exchange. It is possible that the success of such two-point fixation relies upon an intact vitreous face to minimize IOL tilt.

Hoffman et al. have added a potential improvement on this technique through the creation of scleral pockets that originate at the limbus and which eliminate the need

for conjunctival dissection and scleral flap creation [96]. Conserving conjunctiva for future possible glaucoma surgery is advantageous. However, care must be taken to inform future surgeons of the placement of the hidden scleral sutures. Both techniques involve pars plicata fixation. In the Chan technique, sclerotomies are made 1.5 mm posterior to the limbus, whereas in the Hoffman pocket technique, sclerotomies are placed 1.0 mm posterior to the limbus.

Pars plana fixation can be used with sutured [62] or intrascleral [97] fixation approaches. With respect to suture-fixation, moving the fixation site more posteriorly avoids the potential problem of IOL tilt secondary to haptic contact with the ciliary processes [88] and reduces the risk for intraoperative hemorrhage, corneal endothelial damage, and postoperative optic capture [97, 98]. Potential risks include inducing retinal detachment and suprachoroidal hemorrhage. However, in a comparison of ciliary sulcus and pars plana locations for scleral suture fixation, Ma et al. found that the pars plana location as safe and effective as the ciliary sulcus, and also found that intraocular lens dislocation ($p = .001$) and pupillary capture ($p = .041$) occurred less frequently as compared to the ciliary sulcus group [98]. An additional advantage of pars plana fixation at a point measured 3 mm posterior to the limbus is that this point approximates "in-the-bag" IOL power choice [99].

Reduced IOL tilt and improved IOL centration may be achieved with four-point fixation. Multipoint fixation may be more important in eyes that are unicameral following vitrectomy, as two-point, scleral-fixated IOLs may be more likely to rotate without vitreous support. The Bausch and Lomb Akreos AO60 lens has four haptics, each containing an eyelet. Terveen et al. reported on the use of 9-0 polypropylene (Prolene) and polytetrafluoroethylene (Gore-Tex) (off label) for four-point scleral fixation of this IOL in 37 eyes [100]. The IOLs were folded and inserted through 3.5–4.0 mm limbal corneal incisions, and were secured through the pars plicata at a position measured 2.5 mm posterior to the limbus. The authors report 97% of eyes had improved vision with a minimal complication profile. There was a relatively low rate of vitreous hemorrhage and cystoid macular edema which the authors attributed to suture suspension of the relatively small IOL (10.5 mm diameter) and avoidance of haptic irritation of uveal tissue. Morkin and Patterson reported on delivery of the Akreos AO60 IOL through a 2.75 mm limbal corneal incision using a Monarch C cartridge [101]. The IOLs were secured through the pars plana, at a position measured 3.5 mm posterior to the limbus. One potential drawback of the Akreos AO60 lens is that its particular hydrophilic acrylic material is subject to opacification with exposure to gas and air as might occur with endothelial keratoplasty and retinal detachment procedures [102], or with exposure to silicone oil tamponade [103].

Another IOL option for scleral fixation is the Alcon CZ70BD, a polymethylmethacrylate (PMMA) lens with one eyelet on each haptic. Snyder and Perez have demonstrated that effective four-point fixation with minimal tilt can be achieved with the CZ70BD through the use of Gore-Tex CV-8 suture combined with a girth hitch suturing technique [104]. Moreover, their technique allows for fine tuning of IOL centration through alignment of Purkinje reflexes. A disadvantage is that this large, non-foldable PMMA IOL requires a 7.0 mm scleral tunnel wound. On the

positive side, the PMMA material is not subject to opacification and thus a good choice for eyes that are at risk for retinal detachment or might need future pars plana vitrectomy or endothelial keratoplasty.

An interesting question is whether—in select uveitis cases—the capsular bag should be removed and scleral fixation performed in order to help control potential complications related to postoperative inflammation. In these cases, complete pars plana vitrectomy with excision of the capsule, cortex, and zonules is preferred as it removes scaffolding for proliferation and fibrosis, and thereby reduces ciliary body traction that may otherwise cause postoperative hypotony. Such an approach may deliver better anatomic results, and may result in reduced postoperative inflammation and improved visual outcomes.

As part of a 71-patient, retrospective case-series on scleral-fixation using pars plana vitrectomy with endoscopic guidance for ciliary sulcus IOL placement, Olsen and Pribila reported on the management of nine adult and pediatric patients with uveitis [105]. All patients had the vitreous base shaved and capsular remnants and zonules removed. One child underwent initial vitrectomy and lensectomy in a quiet eye, with IOL placement into the capsular bag. Postoperatively, despite aggressive uveitis management, a dense cyclitic membrane formed and hypotony maculopathy ensued. The capsular bag and cyclitic membrane were excised, and the IOL was explanted and replaced with a scleral-fixated IOL. The patient's eye recovered 20/70 vision. The fellow eye was managed with primary removal of the lens and capsule, along with scleral-fixation of an IOL; the outcome was excellent (20/25 vision). A second pediatric patient in this series had juvenile idiopathic arthritis-related uveitis and the same pars plana vitrectomy and scleral-fixation approach to cataract surgery was successfully undertaken. The authors conclude that complete vitrectomy with excision of the capsule, cortex, and zonules removes scaffolding for fibrosis and reduces inflammation, ultimately improving visual outcome [105].

In a study of adult patients with exudative uveitis (mostly sarcoidosis and Vogt-Koyanagi-Harada syndrome), Secchi performed a prospective trial in which Group A consisted of 12 patients that underwent intracapsular cataract extraction combined with anterior vitrectomy and pars plana scleral-fixation of IOLs, and Group B consisted of 12 patients that underwent extracapsular phacoemulsification with in-the-bag or sulcus IOL implantation [106]. With follow-up time of at least seven years, Secchi found that total removal of the lens and capsular bag combined with anterior vitrectomy resulted in significantly better outcomes with respect to vision and inflammatory complications. The author concluded poor outcomes "might sometimes be predicted prior to surgery", and that better uveitis outcomes may be achieved in at-risk patients with total removal of the lens and capsule combined with scleral-fixation of IOLs. According to Secchi, candidates for total removal of the lens and capsule include patients with exudative uveitis and patients with poor outcome secondary to uveitis complications in the first eye [106].

With regards to the options for suture material in scleral fixation, there are two major concerns. The first is the long-term risk for suture breakage and resultant IOL dislocation, and the second concern is the risk for externalized knots or suture tips eroding through conjunctiva and the subsequent threat for endophthalmitis. 10-0 polypropylene suture (Prolene) has traditionally been a popular choice for scleral

fixation, but there are now many reports of its risk for long-term degradation and breakage [62]. In 2006, Vote et al. reported that 28% of patients that underwent scleral fixation with 10-0 Prolene developed broken sutures, and the mean interval between fixation and breakage was 50 ± 28 months [107]. It has been recommended that 10-0 Prolene be completely avoided for scleral fixation of IOLs [108]. Instead, 9-0 Prolene and 7-0 polytetrafluoroethylene suture (Gore-Tex) should be considered, given their greater tensile strength and resistance to degradation. There have been no reports of Gore-Tex suture breakage [108]. Nevertheless, there is some reluctance to use of 7-0 Gore-Tex because of a manufacturer's label warning against use in the eye. As a result of this warning label, some hospitals and institutions in the US prohibit its use for intraocular surgery [109]. On the other hand, polypropylene is approved for intraocular use. Recently 8-0 Prolene has reported as an alternative suture for scleral fixation [109].

The surgical management of knots and suture tips in order to prevent conjunctival erosion is very important in order to reduce the risk for endophthalmitis, as transscleral suture tracks are potential conduits for bacteria to enter the eye. Traditionally, knots are either rotated into sclerotomies or placed under scleral flaps. Alternatives include coverage with Tutoplast, the use of Hoffman pockets [96], or tucking the knot within a scleral groove [110]. Brown is credited with developing an innovative solution for burying the entire suture within sclera at a pars plana location without the use of scleral flaps, which from the perspective of endoophthalmitis avoidance, may be safer than solely burying the knot while leaving the suture lying between the conjunctiva and sclera [111, 112]. The knots formed with 7-0 Gore-Tex can be difficult to rotate into sclerotomies, and the force used to achieve rotation may loosen the knot to the extent that it unravels. Thus, the knots should not be trimmed until they are rotated into the sclera (so that they can be re-tightened if they unravel). In addition, the knots of 7-0 Gore-Tex can be tied with a 2-1-1 configuration in order to reduce knot size [104]. One of the advantages of using 8-0 Prolene is that it forms smaller knots that are easier to rotate as compared to 7-0 Gore-Tex [109].

Conclusion

With significant improvement in uveitis diagnosis and treatment over the past several decades, cataract surgery in uveitis patients has become increasingly safe and efficacious. In the modern era, approximately 50% of uveitis patients undergo cataract surgery, and almost all receive an IOL [12, 113]. As this cohort of pseudophakic patients ages, we can expect an increased number of uveitis patients will present with late IOL dislocation, particularly given recent reports that suggest that the prevalence of late dislocation in uveitis is under appreciated [12, 38].

Similar to pseudoexfoliation, uveitis has two risk factors that act in concert to contribute to the development of late in-the-bag IOL dislocation. The first is a propensity toward the development of zonulopathy [12, 15, 40–42], and the second, capsule contraction syndrome, is well-established in uveitis patients [26, 31, 32]. The risk for late dislocation may be reduced through strict perioperative control of

inflammation, including control of low-grade, chronic postoperative inflammation. The employment of careful surgical techniques during primary cataract surgery that minimize placement of stress on zonules, and the use of meticulous cortical cleanup combined with anterior capsular polishing may also lower the risk for development of zonulopathy and capsule contraction syndrome, and thus reduce the risk for late in-the-bag IOL dislocation.

The surgical management of aphakia and IOL complications in uveitis is challenging. Many established approaches may exacerbate underlying inflammatory disease. In addition, patients may be at higher risk for secondary complications including glaucoma, cystoid macular edema, and corneal decompensation. In the setting of intact capsule support with a round capsulorhexis (either anterior or posterior), optic capture appears to be reasonable approach in uveitic eyes. Both scleral suture-fixation techniques and intrascleral haptic-fixation techniques hold promise to reduce the incidence of postoperative complications. Pars plana fixation minimizes IOL contact with the iris and ciliary body, and thus may reduce the risk for intraoperative bleeding and postoperative inflammation. There is a paucity of high-quality, published literature on the topic to guide decision-making. For these reasons, it behooves the practitioner to carefully evaluate patients and to tailor surgical approaches on a case-by-case basis.

References

1. Ascaso FJ, Huerva V, Grzybowski A. Epidemiology, etiology, and prevention of late IOL-capsular bag complex dislocation: review of the literature. J Ophthalmol. 2015;2015:1–7.
2. Böke WR, Krüger HC. Causes and management of posterior chamber lens displacement. J Am Intraocul Implant Soc. 1985;11(2):179–84.
3. Hayashi K, Hirata A, Hayashi H. Possible predisposing factors for in-the-bag and out-of-the-bag intraocular lens dislocation and outcomes of intraocular lens exchange surgery. Ophthalmology. 2007;114(5):969–75.
4. Gimbel HV, Condon GP, Kohnen T, Olson RJ, Halkiadakis I. Late in-the-bag intraocular lens dislocation: Incidence, prevention, and management. J Cataract Refract Surg. 2005;31(11):2193–204.
5. Krėpštė L, Kuzmienė L, Miliauskas A, Janulevičienė I. Possible predisposing factors for late intraocular lens dislocation after routine cataract surgery. Medicina (Kaunas). 2013;49(5):37.
6. Pueringer SL, Hodge DO, Erie JC. Risk of late intraocular lens dislocation after cataract surgery, 1980–2009: a population-based study. Am J Ophthalmol. 2011;152(4):618–23.
7. Gross JG, Kokame GT, Weinberg DV. In-the-bag intraocular lens dislocation. Am J Ophthalmol. 2004;137(4):630–5.
8. Jakobsson G, Zetterberg M, Sundelin K, Stenevi U. Surgical repositioning of intraocular lenses after late dislocation: complications, effect on intraocular pressure, and visual outcomes. J Cataract Refract Surg. 2013;39(12):1879–85.
9. Davis D, et al. Late in-the-bag spontaneous intraocular lens dislocation. Ophthalmology. 2009;116(4):664–70.
10. Lorente R, et al. Management of late spontaneous in-the-bag intraocular lens dislocation: retrospective analysis of 45 cases. J Cataract Refract Surg. 2010;36(8):1270–82.
11. Østern AE, Sandvik GF, Drolsum L. Late in-the-bag intraocular lens dislocation in eyes with pseudoexfoliation syndrome. Acta Ophthalmol. 2014;92(2):184–91.

12. Steeples LR, Jones NP. Late in-the-bag intraocular lens dislocation in patients with uveitis. Br J Ophthalmol. 2015;99(9):1206–10.
13. Matsumoto M, et al. Spontaneous dislocation of in-the-bag intraocular lens primarily in cases with prior vitrectomy. Eur J Ophthalmol. 2012;22(3):363–7.
14. Fernández-Buenaga R, et al. Late in-the-bag intraocular lens dislocation requiring explantation: risk factors and outcomes. Eye. 2013;27(7):795–802.
15. Hayashi K, Hayashi H, Matsuo K. Anterior capsule contraction and intraocular lens dislocation after implant surgery in eyes with retinitis pigmentosa. Ophthalmology. 1998;105(7):1239–43.
16. Zech J-C, Tanniére P, Denis P, Trepsat C. Posterior chamber intraocular lens dislocation with the bag. J Cataract Refract Surg. 1999;25(8):1168–9.
17. Yamazaki S, Nakamura K, Kurosaka D. Intraocular lens subluxation in a patient with facial atopic dermatitis. J Cataract Refract Surg. 2001;27(2):337–8.
18. Dillon AB, Myung JS, Tran KM, Tseng JJ, Wald KJ. A modified iris suture technique for in-the-bag intraocular lens dislocation. Retina. 2017;37(4):789–92.
19. J. Passut, EyeWorld|Mastering IOL dislocation, 2012. https://www.eyeworld.org/article-mastering-iol-dislocation. Accessed Jan 02 2019.
20. R. O'hEineachain, Looming epidemic, EuroTimes. Accessed Feb 01 2016.
21. Srinivasan S. In-the-bag intraocular lens dislocation: a ticking time bomb. J Cataract Refract Surg. 2019;45(3):259–60.
22. Mönestam EI. Incidence of dislocation of intraocular lenses and pseudophakodonesis 10 years after cataract surgery. Ophthalmology. 2009;116(12):2315–20.
23. Chang DF. Prevention of bag-fixated IOL dislocation in pseudoexfoliation. Ophthalmology. 2002;109(11):1951–2.
24. Joo C-K, Shin J-A, Kim J-H. Capsular opening contraction after continuous curvilinear capsulorhexis and intraocular lens implantation. J Cataract Refract Surg. 1996;22(5):585–90.
25. Kimura W, Yamanishi S, Kimura T, Sawada T, Ohte A. Measuring the anterior capsule opening after cataract surgery to assess capsule shrinkage. J Cataract Refract Surg. 1998;24(9):1235–8.
26. Davison JA. Capsule contraction syndrome. J Cataract Refract Surg. 1993;19(5):582–9.
27. Gimbel HV, Neuhann T. Development, advantages, and methods of the continuous circular capsulorhexis technique. J Cataract Refract Surg. 1990;16(1):31–7.
28. Apple DJ, et al. Complications of intraocular lenses. A historical and histopathological review. Surv Ophthalmol. 1984;29(1):1–54.
29. Kato S, et al. Risk factors for contraction of the anterior capsule opening after cataract surgery. J Cataract Refract Surg. 2002;28(1):109–12.
30. Hayashi H, Hayashi K, Nakao F, Hayashi F. Anterior capsule contraction and intraocular lens dislocation in eyes with pseudoexfoliation syndrome. Br J Ophthalmol. 1998;82(12):1429–32.
31. Lüke C, Dietlein TS, Jacobi PC, Konen W, Krieglstein GK. Massive anterior capsule shrinkage after plate-haptic silicone lens implantation in uveitis. J Cataract Refract Surg. 2001;27(2):333–6.
32. Alintaş AGK, Dal D. Capsule contraction syndrome in Behcet's disease. Int J Ophthalmol. 2010;3(4):358–60.
33. Shatriah I, Jin-Poi T, Khairy-Shamel ST, Zunaina E. Rapid anterior capsular contraction after phacoemulsification surgery in a patient with retinitis pigmentosa. Clin Ophthalmol. 2013;7:839.
34. Hayashi H, Hayashi K, Nakao F, Hayashi F. Area reduction in the anterior capsule opening in eyes of diabetes mellitus patients. J Cataract Refract Surg. 1998;24(8):1105–10.
35. Kato S, et al. Anterior capsular contraction after cataract surgery in eyes of diabetic patients. Br J Ophthalmol. 2001;85(1):21–3.
36. Hansen SO, Crandall AS, Olson RJ. Progressive constriction of the anterior capsular opening following intact capsulorhexis. J Cataract Refract Surg. 1993;19(1):77–82.
37. Østern AE, Sandvik GF, Drolsum L. Positioning of the posterior intraocular lens in the longer term following cataract surgery in eyes with and without pseudoexfoliation syndrome: Acta Ophthalmologica 2012. Acta Ophthalmol. 2014;92(3):253–8.

38. Ganesh S, Sen P, Sharma H. Late dislocation of in-the-bag intraocular lenses in uveitic eyes: an analysis of management and complications. Indian J Ophthalmol. 2017;65(2):148.
39. Hogan MJ, Kimura SJ, O'Connor GR. Peripheral retinitis and chronic cyclitis in children. Trans Ophthalmol Soc U K. 1965;85:39–52.
40. Brilakis HS, Lustbader JM. Bilateral dislocation of in-the-bag posterior chamber intraocular lenses in a patient with intermediate uveitis. J Cataract Refract Surg. 2003;29(10):2013–4.
41. Rapkin JS, Bogorad DD. Bilateral dislocation of the crystalline lens in a patient with presumed syphilitic uveitis. Henry Ford Hosp Med J. 1986;34(3):207–10.
42. Belfort R, et al. Spontaneous lens subluxation in uveitis. Am J Ophthalmol. 1990;110(6):714–6.
43. Vasavada A, Desai J, Singh R. Enlarging the capsulorhexis. J Cataract Refract Surg. 1997;23(3):329–31.
44. Jacob S. Different methods of chopping in cataract surgery. Curr Opin Ophthalmol. 2019;30(1):25–38.
45. Werner L, Pandey SK, Escobar-Gomez M, Visessook N, Peng Q, Apple DJ. Anterior capsule opacification: a histopathological study comparing different IOL styles. Ophthalmology. 2000;107(3):463–71.
46. Özyol P, Özyol E, Karel F. Biocompatibility of intraocular lenses. Turk J Ophthalmol. 2017;47(4):221–5.
47. Bellucci R. An introduction to intraocular lenses: material, optics, haptics, design and aberration. In: Güell JL, editor. ESASO course series, vol. 3. Basel: S. KARGER AG; 2013. p. 38–55.
48. Hartman M, Rauser M, Brucks M, Chalam K. Evaluation of anterior capsular contraction syndrome after cataract surgery with commonly used intraocular lenses. Clin Ophthalmol. 2018;12:1399–403.
49. Hanson RJ, Rubinstein A, Sarangapani S, Benjamin L, Patel CK. Effect of lens epithelial cell aspiration on postoperative capsulorhexis contraction with the use of the AcrySof intraocular lens: randomized clinical trial. J Cataract Refract Surg. 2006;32(10):1621–6.
50. Wang D, et al. The effect of anterior capsule polishing on capsular contraction and lens stability in cataract patients with high myopia. J Ophthalmol. 2018;2018:1–7.
51. Moreno-Montañés J, Sánchez-Tocino H, Rodriguez-Conde R. Complete anterior capsule contraction after phacoemulsification with acrylic intraocular lens and endocapsular ring implantation. J Cataract Refract Surg. 2002;28(4):717–9.
52. Waheed K, Eleftheriadis H, Liu C. Anterior capsular phimosis in eyes with a capsular tension ring. J Cataract Refract Surg. 2001;27(10):1688–90.
53. Sudhir RR, Rao SK. Capsulorhexis phimosis in retinitis pigmentosa despite capsular tension ring implantation. J Cataract Refract Surg. 2001;27(10):1691–4.
54. Werner L, Zaugg B, Neuhann T, Burrow M, Tetz M. In-the-bag capsular tension ring and intraocular lens subluxation or dislocation. Ophthalmology. 2012;119(2):266–71.
55. Scherer M, Bertelmann E, Rieck P. Late spontaneous in-the-bag intraocular lens and capsular tension ring dislocation in pseudoexfoliation syndrome. J Cataract Refract Surg. 2006;32(4):672–5.
56. Price FW, Mackool RJ, Miller KM, Koch P, Oetting TA, Johnson AT. Interim results of the United States investigational device study of the Ophtec capsular tension ring. Ophthalmology. 2005;112(3):460–5.
57. Weber CH, Cionni RJ. All about capsular tension rings. Curr Opin Ophthalmol. 2015;26(1):10–5.
58. Elmohamady MN, Elhabbak A, Gad EA. Circular YAG laser anterior capsulotomy for anterior capsule contraction syndrome. Int Ophthalmol. 2019;39(11):2497–503.
59. Gerten G, Schultz M, Oberheide U. Treating capsule contraction syndrome with a femtosecond laser. J Cataract Refract Surg. 2016;42(9):1255–61.
60. Koizumi K, Watanabe A, Koizumi N, Kinoshita S. Peeling the fibrous membrane from the anterior capsule for capsulorhexis contraction after phacoemulsification in aphakic patients. J Cataract Refract Surg. 2002;28(10):1728–32.

61. Reyntjens B, Tassignon M-JBR, Van Marck E. Capsular peeling in anterior capsule contraction syndrome. J Cataract Refract Surg. 2004;30(4):908–12.
62. Stem MS, Todorich B, Woodward MA, Hsu J, Wolfe JD. Scleral-fixated intraocular lenses: past and present. J Vitreoretin Dis. 2017;1(2):144–52.
63. Devgan U. Aspheric intraocular lenses. In: Fishkind WJ, editor. Phacoemulsification and intraocular lens implantation. Stuttgart: Thieme; 2017.
64. Montés-Micó R, Ferrer-Blasco T, Cerviño A. Analysis of the possible benefits of aspheric intraocular lenses: review of the literature. J Cataract Refract Surg. 2009;35(1):172–81.
65. Chang DF, et al. Complications of sulcus placement of single-piece acrylic intraocular lenses. J Cataract Refract Surg. 2009;35(8):1445–58.
66. Suelves AM, Kruh JN, Aznar-Peña I, Siddique SS, Foster CS. Long-term safety and visual outcomes of anterior chamber intraocular lens implantation in patients with a history of chronic uveitis. J Cataract Refract Surg. 2012;38(10):1777–82.
67. Artisan Aphakia|Ophtec. https://www.ophtec.com/products/cataract-surgery/iols/artisan-aphakia. Accessed Jan 19 2019.
68. Bélair M-L, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol. 2009;148(1):128–35. e2.
69. Fine IH, Hoffman RS. Late reopening of fibrosed capsular bags to reposition decentered intraocular lenses. J Cataract Refract Surg. 1997;23(7):990–4.
70. Brunin G, et al. Secondary intraocular lens implantation: complication rates, visual acuity, and refractive outcomes. J Cataract Refract Surg. 2017;43(3):369–76.
71. Gimbel HV, DeBroff BM. Intraocular lens optic capture. J Cataract Refract Surg. 2004;30(1):200–6.
72. Jones JJ, Oetting TA, Rogers GM, Jin GJC. Reverse optic capture of the single-piece acrylic intraocular lens in eyes with posterior capsule rupture. Ophthalmic Surg Lasers Imaging. 2012;43(6):480–8.
73. Kemp PS, et al. Cataract surgery in children with uveitis: retrospective analysis of intraocular lens implantation with anterior optic capture. J Pediatr Ophthalmol Strabismus. 2015;52(2):119–25.
74. Holland GN, Horn SDV, Margolis TP. Cataract surgery with ciliary sulcus fixation of intraocular lenses in patients with uveitis. Am J Ophthalmol. 1999;128(1):10.
75. Millar ERA, Allen D, Steel DHW. Effect of anterior capsulorhexis optic capture of a sulcus-fixated intraocular lens on refractive outcomes. J Cataract Refract Surg. 2013;39(6):841–4.
76. Amino K, Yamakawa R. Long-term results of out-of-the-bag intraocular lens implantation. J Cataract Refract Surg. 2000;26(2):266–70.
77. W. Hill Capsular Bag vs. Ciliary Sulcus—Calculating IOL Power|East Valley Ophthalmology. doctor-hill.com. https://www.doctor-hill.com/iol-main/bag-sulcus.htm. Accessed Mar 17 2019.
78. Dubey R, Birchall W, Grigg J. Improved refractive outcome for ciliary sulcus-implanted intraocular lenses. Ophthalmology. 2012;119(2):261–5.
79. Suelves AM, Siddique SS, Schurko B, Foster CS. Anterior chamber intraocular lens implantation in patients with a history of chronic uveitis: five-year follow-up. J Cataract Refract Surg. 2014;40(1):77–81.
80. Tao LW, Hall A. In-bag dislocation of intraocular lens in patients with uveitis: a case series. J Ophthalmic Inflamm Infect. 2015;5:10.
81. Wagoner MD, Cox TA, Ariyasu RG, Jacobs DS, Karp CL, American Academy of Ophthalmology. Intraocular lens implantation in the absence of capsular support: a report by the American Academy of Ophthalmology. Ophthalmology. 2003;110(4):840–59.
82. Reinstein DZ, Archer TJ, Silverman RH, Rondeau MJ, Coleman DJ. Correlation of anterior chamber angle and ciliary sulcus diameters with white-to-white corneal diameter in high myopes using artemis VHF digital ultrasound. J Refract Surg. 2009;25(2):185–94.

83. Piñero DP, Plaza Puche AB, Alió JL. Corneal diameter measurements by corneal topography and angle-to-angle measurements by optical coherence tomography: evaluation of equivalence. J Cataract Refract Surg. 2008;34(1):126–31.
84. Goldsmith JA, et al. Anterior chamber width measurement by high-speed optical coherence tomography. Ophthalmology. 2005;112(2):238–44.
85. Sewelam A, Ismail AM, El Serogy H. Ultrasound biomicroscopy of haptic position after transscleral fixation of posterior chamber intraocular lenses. J Cataract Refract Surg. 2001;27(9):1418–22.
86. Kamal AM, Hanafy M, Ehsan A, Tomerak RH. Ultrasound biomicroscopy comparison of ab interno and ab externo scleral fixation of posterior chamber intraocular lenses. J Cataract Refract Surg. 2009;35(5):881–4.
87. Sasahara M, Kiryu J, Yoshimura N. Endoscope-assisted transscleral suture fixation to reduce the incidence of intraocular lens dislocation. J Cataract Refract Surg. 2005;31(9):1777–80.
88. Sugiura T, Kaji Y, Tanaka Y. Anatomy of the ciliary sulcus and the optimum site of needle passage for intraocular lens suture fixation in the living eye. J Cataract Refract Surg. 2018;44(10):1247–53.
89. Kumar DA, Agarwal A, Packialakshmi S, Agarwal A. In vivo analysis of glued intraocular lens position with ultrasound biomicroscopy. J Cataract Refract Surg. 2013;39(7):1017–22.
90. Kumar DA, Agarwal A, Agarwal A, Chandrasekar R, Priyanka V. Long-term assessment of tilt of glued intraocular lenses. Ophthalmology. 2015;122(1):48–55.
91. Narang P, Agarwal A. Clinical outcomes of pars plicata anterior vitrectomy: 2-year results. Indian J Ophthalmol. 2015;63(9):699.
92. Agarwal A, Kumar DA, Jacob S, Baid C, Agarwal A, Srinivasan S. Fibrin glue–assisted sutureless posterior chamber intraocular lens implantation in eyes with deficient posterior capsules. J Cataract Refract Surg. 2008;34(9):1433–8.
93. Yamane S, Sato S, Maruyama-Inoue M, Kadonosono K. Flanged Intrascleral Intraocular Lens Fixation with Double-Needle Technique. Ophthalmology. 2017;124(8):1136–42.
94. Todorich B, Thanos A, Yonekawa Y, Thomas BJ, Abbey AM, Faia LJ. Transconjunctival sutureless intrascleral fixation of secondary intraocular lenses in patients with uveitis. Ocul Immunol Inflamm. 2018;26(3):456–60.
95. Chan CC, Crandall AS, Ahmed IIK. Ab externo scleral suture loop fixation for posterior chamber intraocular lens decentration: clinical results. J Cataract Refract Surg. 2006;32(1):121–8.
96. Hoffman RS, Fine IH, Packer M. Scleral fixation without conjunctival dissection. J Cataract Refract Surg. 2006;32(11):1907–12.
97. Miyamoto N, Yamakawa M, Akimoto M. Intrascleral fixation of an intraocular lens through the pars plana prevents corneal endothelial damage. Case Rep Ophthalmol. 2019;10:53–60.
98. Ma DJ, Choi HJ, Kim MK, Wee WR. Clinical comparison of ciliary sulcus and pars plana locations for posterior chamber intraocular lens transscleral fixation. J Cataract Refract Surg. 2011;37(8):1439–46.
99. Khan MA, et al. Combined pars plana vitrectomy and scleral fixation of an intraocular lens using gore-tex suture: one-year outcomes. Retina. 2018;38(7):1377–84.
100. Terveen DC, Fram NR, Ayres B, Berdahl JP. Small-incision 4-point scleral suture fixation of a foldable hydrophilic acrylic intraocular lens in the absence of capsule support. J Cataract Refract Surg. 2016;42(2):211–6.
101. Morkin MI, Patterson M. Scleral-sutured intraocular lenses: single-surgeon technique for suture-preloaded intraocular lens insertion through a small-incision corneal wound. J Cataract Refract Surg. 2019;45(2):121–4.
102. Kalevar A, Dollin M, Gupta RR. Opacification of scleral-sutured akreos ao60 intraocular lens after vitrectomy with gas tamponade: case series. Retin Cases Brief Rep. 2017 Sep 27. https://doi.org/10.1097/ICB.0000000000000634. [Epub ahead of print].
103. Gregori NZ, Echegaray JJ, Flynn HW Jr. Opacification of Akreos hydrophilic acrylic lens after retinal detachment repair with silicone oil tamponade: a case report. Ophthalmol Ther. 2019;8(2):341–5.

104. Snyder ME, Perez MA. Tiltless and centration adjustable scleral-sutured posterior chamber intraocular lens. J Cataract Refract Surg. 2014;40(10):1579–83.
105. Olsen TW, Pribila JT. Pars plana vitrectomy with endoscope-guided sutured posterior chamber intraocular lens implantation in children and adults. Am J Ophthalmol. 2011;151(2):287–96. e2.
106. Secchi AG. Cataract surgery in exudative uveitis: effectiveness of total lens removal, anterior vitrectomy, and scleral fixation of PC IOLs. Eur J Ophthalmol. 2008;18(2):220–5.
107. Vote BJ, Tranos P, Bunce C, Charteris DG, Da Cruz L. Long-term outcome of combined pars plana vitrectomy and scleral fixated sutured posterior chamber intraocular lens implantation. Am J Ophthalmol. 2006;141(2):308–12. e1.
108. Roach L. Gore-Tex: An alternative for fixation sutures. EyeNet Magazine. 2016.
109. John T, Tighe S, Hashem O, Sheha H. New use of 8-0 polypropylene suture for four-point scleral fixation of secondary intraocular lenses. J Cataract Refract Surg. 2018;44(12):1421–5.
110. Slade DS, Hater MA, Cionni RJ, Crandall AS. Ab externo scleral fixation of intraocular lens. J Cataract Refract Surg. 2012;38(8):1316–21.
111. K. B. Editor Senior Associate, It's (Not) in the Bag: IOL Fixation. https://www.reviewofophthalmology.com/article/its-not-in-the-bag-iol-fixation. Accessed Jun 06 2019.
112. The Review of Ophthalmology, Scleral Fixation 3 13 IOL Removal. https://www.youtube.com/watch?time_continue=5&v=8IvbYhU2aXI.
113. Elgohary MA, et al. Outcome of phacoemulsification in patients with uveitis. Br J Ophthalmol. 2007;91(7):916–21.

Part IV
Ciliary Processes Complications from Uveitis

Chapter 7
Ciliary Processes Complications from Uveitis

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UBM for Evaluation of Ciliary Processes

Topographic Anatomy of the Ciliary Body

The ciliary body (CB) is one of the three portions of the uveal tract, otherwise known as the vascular layer of the eye; the other two structures in this system are represented by the iris and the choroid. It is composed of several layers including the ciliary muscle, a layer of vessels and ciliary processes, the basal lamina, the ciliary epithelium, and the internal limiting membrane, with its apex contiguous to the

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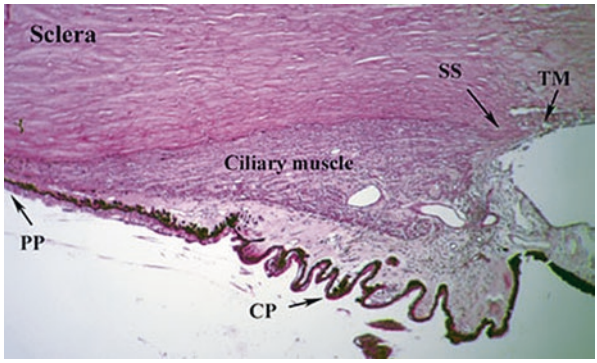

Fig. 7.1 Histology of human ciliary body. *CP* ciliary processes, *TM* trabecular meshwork, *CM* ciliary muscle, *SS* scleral spur, *PP* pars plana

choroid and the base close to the iris. CB extends from the ora serrata posteriorly to the scleral spur anteriorly, with the internal surface in contact with the vitreous cavity and the external counterpart facing the sclera through the supraciliary space. Its main function is aqueous humor (AH) production being totally involved in aqueous humor dynamics; however, CB is also helping in the accommodation process, trabecular outflow dynamics, secretion of hyaluronic acid to the vitreous, and formation of blood-aqueous barrier. In the adult eye, the anterior-posterior length of the ciliary body ranges between 4.5–5.2 mm nasally and 5.6–6.3 mm temporally [1]. The anterior third of the CB is represented by the pars plicata (about 2 mm wide) consisting of approximately 70 ciliary processes (CPs) that are meridionally arranged and project from the anterior portion of the CB, whose surface is estimated to be 6 cm^2, for ultrafiltration and active fluid transport, as the actual site of aqueous production, while the posterior two thirds are represented by the pars plana (PP) (about 4 mm wide), which continues with the choroid at the ora serrata [2]. PP is usually not pigmented uniformly and the posterior zonular fibers take their origin from a band of this structure. The vitreous base gains attachment to the epithelium of the PP over a band extending forward from the ora. The suspensory ligaments of the lens, whose distance from the processes is 0.5 mm, are found between CPs (Fig. 7.1).

Ciliary Muscle

The ciliary muscle consists of two main portions: the longitudinal and the circular fibers, which attach the CB to the limbus at the scleral spur, while the circular fibers occupy the anterior and inner portions of the ciliary body and run parallel to the limbus [3]. One-third of the ciliary muscle has been described as radial fibers, which connects the longitudinal and circular fibers. The supraciliary layer consists of melanocyte and fibroblast rich tissue and collagen strands, derived from the longitudinal layer of the ciliary muscle. The space this layer may create under pathological conditions, such as CB detachment, may be well delineated with UBM.

Vascular Supply

The major arterial circle, which is found near the root of the iris, is predominantly supplied by two long posterior ciliary arteries originating from the ophthalmic artery, which anastomose with the anterior ciliary arteries at the CB. Blood is mainly drained by the vortex veins. The major arterial circle and the intramuscular vascular circle supply the inner and outer part of the ciliary muscle respectively. The major arterial circle is the immediate vascular supply of the iris and CPs [4].

Nerve Supply

The major innervation is provided by ciliary nerve branches, forming a rich parasympathetic plexus. Sensory innervation is derived from the nasociliary nerve. There are also sympathetic fibers, originating from the superior cervical ganglion, reaching the ciliary muscle via the long ciliary nerve.

The Structure of the Ciliary Processes

The ciliary processes (CPs) are the most vascular region of the whole eye. The vascular core consists of veins and capillaries. Each CP is supplied by an artery derived from the vascular plexus, springing from the major arterial circle. The anterior ciliary process arterioles supply the anterior and marginal aspects of the major CPs. The capillary endothelium is fenestrated and permeable to plasma proteins. The ciliary stroma consists of irregularly arranged bundles of collagen fibrils, vascular tissue and melanocytes. The stroma of the CB is separated from the ciliary epithelium by the forward continuation of the Bruch's membrane. The inner surfaces of the CPs and PP are lined by two layers of outer pigmented and inner non-pigmented epithelium apposed apex to apex, originating from the invagination of the optic cup during embryogenesis. These different epithelia are joined together by zonulae occludentes, gap junctions, desmosomes and puncta adherentia, which are a hallmark of the secretory function of the processes [5]. The tight junctions give birth to a selectively impermeable barrier to macromolecular tracers and permeable towards small ions [6]. The outer pigmented cell layer is the forward continuation of the retinal pigmented epithelium (RPE), and the non-pigmented cells are the forward continuation of the neural retina.

The Principle and Techniques of UBM

In the past three decades, UBM, a type of ocular ultrasound developed by Pavlin, Michael, and Foster, has shown its efficacy in the evaluation of the pathophysiology of the anterior segment [7–9]. The term ultrasound biomicroscopy (UBM) is applied

to this technique due to its similarities to optical biomicroscopy, and the fact that it also allows acquiring and viewing real-time high-resolution images of the anterior segment under magnification. The UBM system uses a piezoelectric co-polymer transducer attached to a microprocessor controlled RF signal generator to convert electrical signals into ultrasound waves of a specific high frequency. Ultrasound waves pass through the various tissues of the eye at varying speeds and are reflected back at different intervals, depending on the density of the tissues. Commercially available UBM systems use a 50 MHz transducer in order to get high resolution and penetration. The resolution of 50 MHz is 40 μm and the depth is 4 mm. The patient is to be placed in a supine posture. After instillation of topical anesthetic drops, a scleral cup of appropriate size is inserted. Currently, UBM can be performed through the employment of various techniques, such as linear, sector and arc scan. Each technique is performed through an immersion bath.

Indication of UBM in Uveitis

UBM is a high-frequency ultrasound device which uses frequencies in the range of 35–50 MHz, allowing for the analysis of the retro-iridal space and PP, areas that are occult to the usual visual examination techniques [10]. The evaluation of those structures is of outmost importance in uveitic entities, where the inflammatory process is suspected to be involved principally in these anatomical landmarks. In contrast to anterior segment OCT, UBM seems to penetrate the pigmented epithelium of the iris even when dioptric means are opaque. UBM systems are able to evaluate all segments of the anterior segment including cornea, irido-corneal angle, anterior chamber, iris, CB and lens. UBM is useful in a variety of clinical applications, from cataract and refractive surgery to glaucoma, uveitis, tumors and ocular trauma [11, 12]. Moreover, intraocular inflammatory conditions such as pars planitis snow banks, supra-ciliary effusions, cyclitic membranes, and CB detachments can be visualized through the use of UBM.

UBM Scanning of the Ciliary Body

In the normal eye, the cornea, anterior chamber, posterior chamber, iris, CB, and the anterior lens surface can be easily recognized. The CB can be seen clearly on UBM (Figs. 7.2 and 7.3). Changes in the posterior chamber, CB, and its surrounding tissues are scarcely evaluated in vivo using the conventional techniques. UBM has shown its efficacy as an additional diagnostic tool leading to a more precise management of uveitis cases where the primary site of inflammation is located in the anterior uveal structures and anterior vitreous, such as acute anterior uveitis (AAU) and intermediate uveitis (IU) [10]. In particular, UBM allows for a real-time imaging of the ciliary region, including structures not otherwise visible, as well as provides a

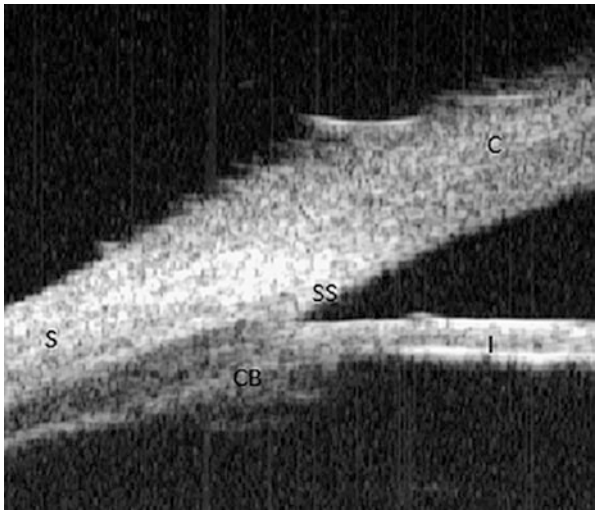

Fig. 7.2 Radial UBM scan showing angle structures in a healthy eye: *C* cornea, *S* sclera, *SS* scleral spur, *CB* ciliary body, *I* iris

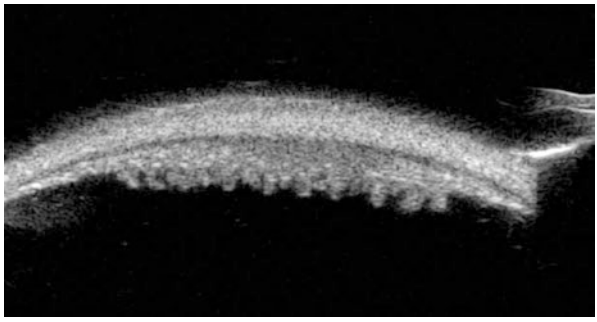

Fig. 7.3 Longitudinal UBM scan showing the ciliary processes (CP) in a healthy eye. (*Courtesy*: Prof. Biljana Kuzmanović Elabjer, Zagreb, Croatia)

digital image from which morphometric measurements can be readily made. In cases of severe inflammation in the anterior chamber, the observation of the anterior surface of the vitreous is scarce, rendering it difficult to differentiate between iritis and iridocyclitis. During acute iridocyclitis, the iris and CB become thickened due to swelling with blunting of CPs (Figs. 7.4, 7.5, 7.6, and 7.7). The involvement of the CB is a hallmark of AAU, whereas slit-lamp microscopy hinders the retroiridial inflammation in the majority of patients. In a paper of Saavedra et al., UBM was employed for the evaluation of the length of CPs in patients with acute and chronic uveitis. In patients affected by chronic, diffuse, and aggressive forms of intraocular inflammation the length of the CPs was estimated to be shorter [13]. Another study from the same center showed that UBM employment was useful in the evaluation of the anatomical changes of CPs in uveitic eyes and ocular hypotony. Moreover, measurements of CPs in the study group showed that the highest average value was 591.6 μm in the temporal quadrant of control eyes, whereas the lowest average measure was 307.7 μm in the inferior quadrant of aggressive uveitis. Whereas in the 68 healthy eyes of the control group, the mean length of the ciliary processes was

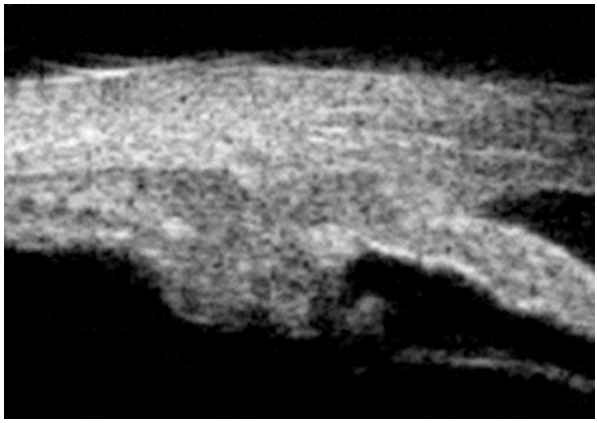

Fig. 7.4 Longitudinal UBM scan showing edema of the CB in an acute anterior uveitis (AAU) case

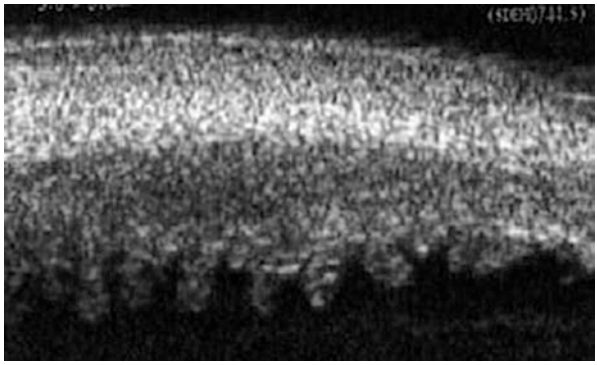

Fig. 7.5 Image showing inflated CPs in a case of iridocyclitis (AAU)

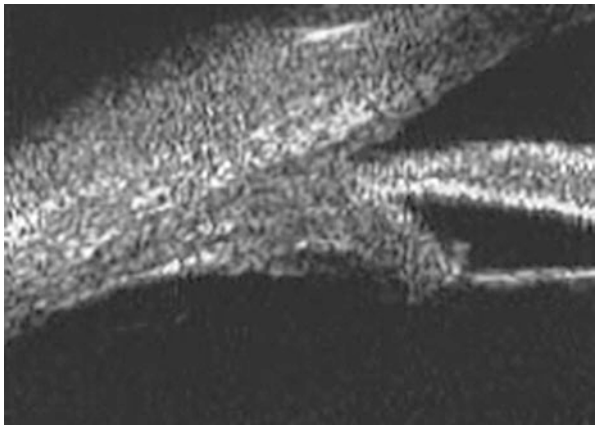

Fig. 7.6 Radial UBM scan showing resolution of CB edema (patient Fig. 7.4) after 6 weeks of therapy

568 ± 23.1 μm, mirroring the findings of previous measurements in normal subjects of glaucoma trials [27]. Overall, the physiological difference in the ciliary CPs' length that was found in the various quadrants of the control group, was reflected in uveitic eyes too, with the temporal ones longer and the inferior ones shorter as

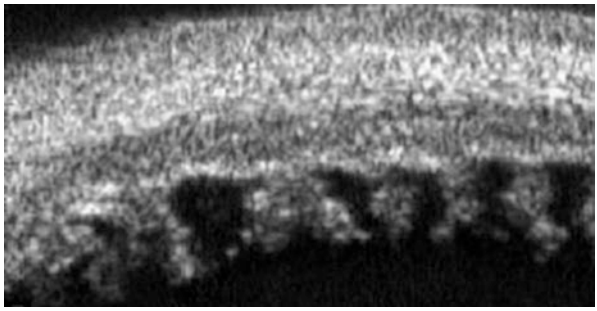

Fig. 7.7 Longitudinal UBM scan shows normal CPs (patient Fig. 7.5)

compared to CPs in the remaining quadrants. No statistically significant difference in the measurements of the control group was found between the eyes of healthy subjects and healthy eyes of uveitis patients. In a recent work of Ahn JK, important data were reported regarding the morphology of CB and PP in patients with AAU or pars planitis and the comparison of UBM parameters according to the anatomic locations of uveitis, human leukocyte antigen (HLA)-B27 status, and recurrence [14]. The mean ciliary thickness at 2 mm near the pars plicata in the AAU patients was significantly higher than that of the contralateral eyes and the pars planitis patients in the acute phase, while at 3 mm near the PP the authors noticed no difference between the two groups. HLA-B27 positivity in AAU patients is considered an important prognostic factor regarding the severity of uveitis as compared with HLA-B27 negative cases. In attendance to Peizeng Y et al., UBM represents a useful diagnostic tool for the evaluation of anterior and posterior chamber iris and ciliary body edema and exudates in eyes with anterior uveitis [15]. UBM analysis indicated that treatment should be continued for a longer period and should not be based on the inflammatory changes disclosed by slit-lam biomicroscopy.

Vogt-Koyanagi-Harada (VKH) disease is associated with important morphologic changes of the anterior segment as reported by Tran VT and Ahn JK [10, 16]. Acute VKH disease frequently displays ciliary effusions associated with angle closure, while in the recurrent phase of VKH, UBM disclosed a marked involvement of the CB and PP. In an article dealing with the clinical features of Fuchs' uveitis (FU) in Chinese patients, the authors provided interesting evidence through the employment of UBM, showing CB edema and inflammatory exudates [17]. The most common lesions disclosed with UBM in patients affected by IU were vitreous condensations or membranes of various configurations (Fig. 7.8) mainly located over the peripheral retina and PP [18]. When IU diagnosis is not definitive, UBM might represent the examination of choice in order to elucidate the clinical condition [8].

Ciliary Body Cysts

Morphological changes of the anterior uveal structures occurring during inflammatory conditions have been frequently reported since the advent of UBM. The main inflammatory changes affecting the CB are stromal edema and exudates due to

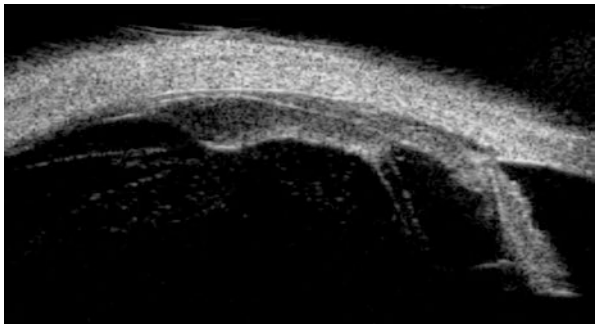

Fig. 7.8 Longitudinal UBM scan showing condensation over the pars plana (PP) in pars planitis affecting a 5-year-old patient. (*Courtesy*: Prof. Biljana Kuzmanović Elabjer, Zagreb, Croatia)

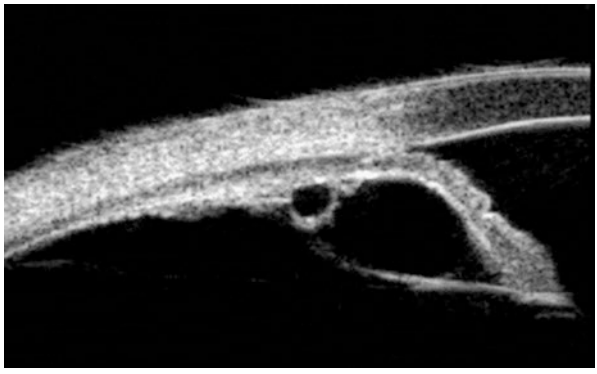

Fig. 7.9 Longitudinal UBM scan of a CB cyst at the iridociliary junction and one between ciliary processes. (Courtesy: Prof. Biljana Kuzmanović Elabjer, Zagreb, Croatia)

blood–aqueous barrier disruption which is markedly pronounced in AAU, CB atrophy from chronic or severe uveitis or inflammatory CB detachment in ocular hypotony, as well as CB granulomas as in the case of ocular tuberculosis (TB) [10, 15]. The clinical findings from a North American center reported UBM findings of 14 eyes affected by anterior uveitis before and after treatment. They reported new echographic data other than stromal edema of the CB, which were represented by the discovery of epithelial cysts located at the iridociliary junction and at the anterior portion of the CB with a maximal diameter of 1000 μm. Epithelial cysts were discovered in 1/3 of uveitic patients and were more frequent in non-granulomatous uveitis [19]. CB epithelial cysts are associated with the non-pigmented epithelium of the CB with a usually benign clinical course with the exception of secondary closed-angle glaucoma as a complication, while PP cysts are mostly acquired and lie between the epithelial layers (Figs. 7.9, 7.10, and 7.11). Histologically, the pigmented cysts are filled with a clear fluid and are lined by epithelial cells showing all the characteristics of mature pigment epithelium [20]. UBM characterized these cysts to have no internal reflectivity and to be mostly thin-walled. There are reports of CB cysts associated with multiple myeloma [21, 22]. A Japanese study by Kunimatsu et al. reported the UBM findings in a large series of 232 healthy eyes [23]. UBM disclosed CB cysts in more than half of the patients with the favorite location being the inferior and temporal quadrants of the aforementioned structure. In attendance to this work, the high percentage of CB cysts compared with other

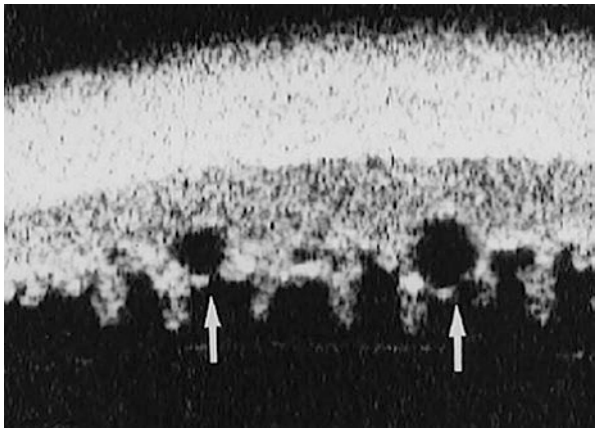

Fig. 7.10 Longitudinal UBM scan showing two cysts located between the ciliary villosities

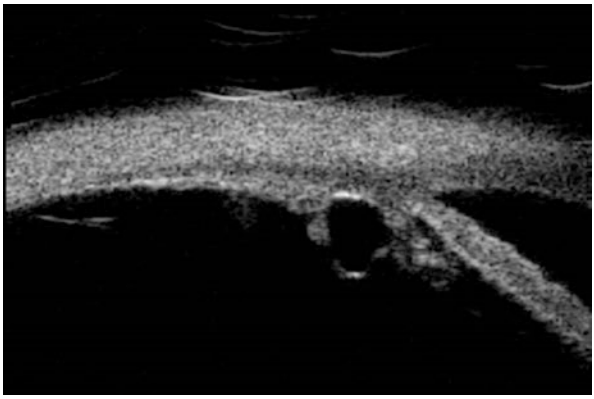

Fig. 7.11 Longitudinal UBM scan of a cyst between ciliary processes. (Courtesy: Prof. Biljana Kuzmanović Elabjer, Zagreb, Croatia)

studies may be justified by the age distribution and UBM acquiring technique. Regarding the pathogenesis of these cystic structures in the CB during an inflammatory condition Gentile et al. speculate that uveitic eyes might be more predisposed to cyst formation as fluid finds it easier to penetrate the interepithelial space after the healing of the CB stromal edema. However, cyst formation between CPs still remains unexplained [19]. In cases with Toxocara uveitis Tran et al. have reported a pseudocystic pattern of vitreous degeneration disclosed by UBM [10]. In these cases, UBM findings seem to have a high yield of sensitivity and specificity.

Ciliary Processes Atrophy

Ocular hypotension refers to a persistent intraocular pressure (IOP) of less than 6 mm Hg, with the most serious side effects such as disk edema, hypotonous maculopathy, and even phthisis bulbi occurring at an IOP below 4 mm Hg [24]. Multiple etiologies and mechanisms such as long-standing retinal detachment, ocular trauma, previous

vitreous surgery, proliferative vitreoretinopathy (PVR), and chronic uveitis are summoned together in order to induce chronic ocular hypotony [25, 26]. The correct distinction between conditions that lead to reduced aqueous production and those causing increased aqueous outflow is of critical importance with regard to the therapeutic options. UBM efficacy in the diagnosis and management of the chronic ocular hypotony has been widely reported in the imaging of CP atrophy, CB detachment, cyclitic membranes [10, 27–29]. Factors related to ocular hypotony in inflammatory conditions are unique and able to determine the acute or chronic nature of uveitis. Supraciliary or suprachoroidal effusions, prostaglandin-mediated increased uveoscleral outflow, or ciliary body shutdown represent the main causes of hypotony in hyperacute uveitis, which seems to be reversible once inflammation is controlled [30, 36]. Hypotony associated with chronic uveitis, a condition often present in a relatively quiet eye, may be caused by the development of inflammatory cyclitic membranes (Fig. 7.12), which may lead to tractional CB detachment (Fig. 7.13), increasing

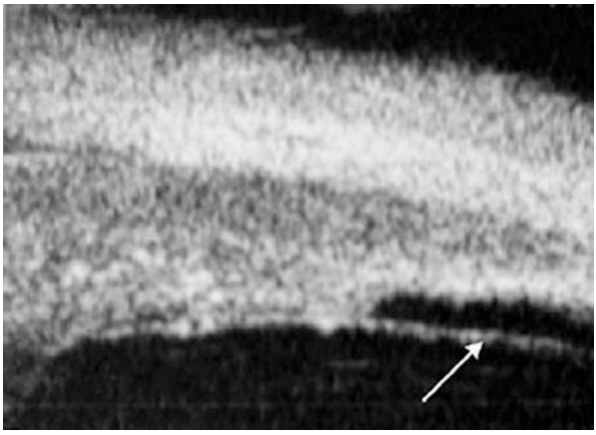

Fig. 7.12 Radial UBM scan showing a cyclitic membrane (arrow) attached to the CB

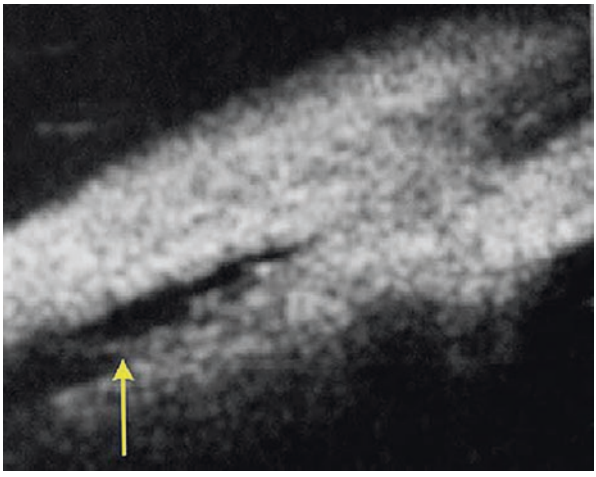

Fig. 7.13 Radial UBM scan showing CB detachment

AH outflow and by direct damage toward the secretory ciliary epithelium decreasing AH production thus leading to permanent atrophy of CPs (Figs. 7.14 and 7.15) [31–34]. Therapeutical options employed in ocular hypotony include loco-regional corticosteroid therapy, topical ibopamine, pars plana vitrectomy (PPV) with or without intraocular gas or silicone oil [35–39]. Roters et al. evaluated the usefulness of UBM in elucidating the causes of ocular hypotony in 60 patients, where 1/3 were affected by CB atrophy and cyclitic membranes of the CB [40]. They reported that all patients with cyclitic membranes had additional CB atrophy, making it difficult to have a proper classification. In their study, UBM proved to be a very important diagnostic tool in 75% of the hypotonic eyes, pointing out two main types of hypotony: (a) CB dysfunction, and (b) CB detachment. These conditions are difficult to distinguish because dysfunction may also result in detachment and vice versa [41]. Describing the successful surgical outcomes of 15 eyes with chronic hypotony due to uveitis, with or without CB atrophy, Gupta et al. highlighted the importance of a precise differential diagnosis between acute and chronic hypotony, with the former being associated with cells and flare, and the latter presenting with poor visual acuity, low IOP, posterior synechiae, absent iris bombé despite extensive posterior synechiae, cataract, band-shaped keratopathy, and the eventual presence or absence of cells [42]. Preoperatively UBM showed cyclitic membranes in 100% (9/9) of available eyes and CPs atrophy plus cyclitic membrane in 66% (6/9) of eyes. These findings were fully confirmed intraoperatively, showing a high yield of sensitivity for UBM. Concluding,

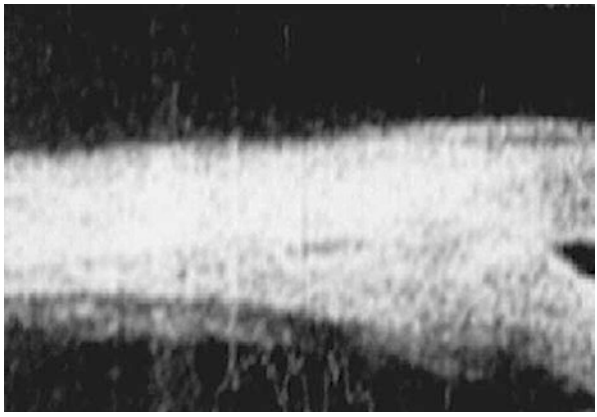

Fig. 7.14 Radial UBM scan showing thinning of the ciliary body depicting CB atrophy

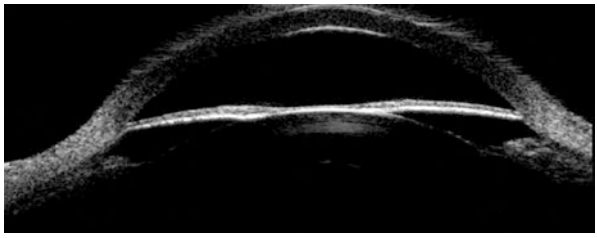

Fig. 7.15 Radial UBM scan of a chronic uveitis showing iris and ciliary body atrophy and pupillary membrane. (*Courtesy: Prof. Biljana Kuzmanović Elabjer, Zagreb, Croatia*)

the authors state that in uveitic eyes with intact CPs PPV and the surgical removal of cyclitic membranes are sufficient to restore IOP post-operatively, otherwise silicone oil tamponade may be required in order to have a significant rise in IOP. In uveitic eyes with ocular hypotony, CB abnormalities were detected by UBM in 80–83% of eyes [10, 28]. In attendance to Tran et al., the addition of UBM analysis in uveitic eyes associated with hypotony represented a major contribution that influenced treatment in 10 out of 12 patients [10]. The authors reported 2 patients with hypotony due to cyclitic membranes where subsequent surgery was recommended, complete CB atrophy in 2 patients where cataract surgery was not performed because of the high risk of phthisis development. Other reported UBM features included iris and CB dialysis, uveal effusion syndrome, and an inflammatory CB detachment. In another study by Kapur and associates, 12 eyes of 10 patients with uveitis-associated hypotony were treated with pars plana vitrectomy (PPV) and silicone oil infusion [43]. IOP was modestly elevated in most patients in this series in which six eyes had an IOP of 5 mm Hg or higher at 6 months and one third of eyes had an IOP of 5 mm Hg or more at 1 year. A recent paper by Dayani et al. reported the surgical outcomes of 13 eyes affected by panuveitis related ocular hypotony that were managed with PPV, placement of a fluocinolone acetonide implant, and silicone oil tamponade [44]. It was reported that 10 out of 13 eyes had a preoperative IOP of 0 mm Hg, poor vision, and a longstanding history of hypotony. The authors emphasized the space-occupying properties of silicone oil tamponade and its role in sequestering the inflammatory mediators that can adversely affect aqueous production in the CB. In attendance to this study, the addition of the fluocinolone acetonide implant provided extra benefits regarding the postoperative reduction of the immunomodulatory therapy in 45% of the eyes [44]. Da Costa et al. investigated the relationship between the length of CPs as measured by UBM and the duration, localization and severity of uveitis [27]. With the most common etiology being idiopathic uveitis they reported that recurrent, aggressive and diffuse uveitis led to significant damage of the CPs mainly in the inferior quadrant, and described a reduction of the CPs in hypotonic eyes. This finding is presumed to be secondary to the majority of inflammatory processes becoming more aggressive inferiorly. Most of the patients with flat ciliary processes in this cohort had aggressive uveitis with 4+ cells either in the anterior chamber or in the vitreous. This is in accordance with previous findings which have shown that hypotony is much more frequently seen among individuals with long-standing disease. In those eyes, an intensive anti-inflammatory treatment may prevent the development of hypotony. Univariate logistic regression analysis found a higher hypotony risk in patients with CPs length lower than 425.23 μm in at least 2 quadrants, or lower than 371.36 μm in one quadrant. In a multivariable logistic regression analysis, the bilaterality of uveitis was not independently associated with the onset of ocular hypotony during the course of uveitis [27].

In eyes where the chronic inflammatory process is mainly located in the CB, the damage might still be reversible, such as in the case of ocular hypotony from Cidofovir, especially in those receiving intravitreal therapy of four or more injections [45, 46].

Key Points

1. UBM employs high frequency ultrasounds, providing high resolution reproducible images of the cross sectional anterior segment anatomy.
2. Pupillary dilation and clear dioptric media are not required to perform this examination.
3. UBM has shown its efficacy as an additional diagnostic tool leading to a more precise management of uveitis cases, where the primary site of inflammation is located in the anterior uveal structures.
4. UBM employment is useful in the evaluation of the anatomical changes of CPs in uveitic eyes.
5. UBM is helpful in discerning between CB dysfunction and/or detachment in uveitic eyes with chronic hypotony.
6. Following intraocular pressures alone may be insufficient to assess ciliary process status, and UBM may be used as an indicator of long-term prognosis in uveitis patients.
7. Dependence on a skilled operator and the fact that it requires direct contact with the eye, represent two main limitations of UBM.

References

1. Aiello AL, Tran VT, Rao NA. Postnatal development of the ciliary body and pars plana. A morphometric study in childhood. Arch Ophthalmol. 1992;110(6):802–5.
2. Bron AJ, Tripathi RC, Tripathi BJ. The choroid and uveal vessels. In: Bron AJ, Tripathi RC, Tripathi BJ, editors. Wolff's anatomy of the eye and orbit. 8th ed. London: Chapman & Hall Medical; 1997. p. 371–410.
3. Rohen JW, Schachtschabel DO, Berghoff K. Histoautoradiographic and biochemical studies on human and monkey trabecular meshwork and ciliary body in short-term explant culture. Graefes Arch Clin Exp Ophthalmol. 1984;221(5):199–206.
4. Funk RH, Rohen JW. Scanning electron microscopic study of episcleral arteriovenous anastomoses in the owl and cynomolgus monkey. Curr Eye Res. 1996;15(3):321–7.
5. Raviola G. The fine structure of the ciliary zonule and ciliary epithelium with special regard to the organization and insertion of the zonular fibrils. Investig Ophthalmol. 1971;10(11):851–69.
6. Coca-Prados M. The blood-aqueous barrier in health and disease. J Glaucoma. 2014;23:S36–S8.
7. Pavlin CJ, Michael DS, Foster FS. Subsurface ultrasound microscopic imaging of the intact eye. Ophthalmology. 1990;97:224–50.
8. Klaeger AJ, Tran VT, Hiroz CA, Morisod L, Herbort CP. Use of ultrasound biomicroscopy, indocyanine green angiography and HLA-B51 testing as adjunct methods in the appraisal of Behçet's uveitis. Int Ophthalmol. 2004;25:57–63.
9. Ritch R, Vessani RM, Tran HV, Ishikawa H, Tello C, Liebmann JM. Ultrasound biomicroscopic assessment of zonular appearance in exfoliation syndrome. Acta Ophthalmol Scand. 2007;85:495–9.
10. Tran VT, LeHoang P, Herbort CP. Value of high-frequency ultrasound biomicroscopy in uveitis. Eye. 2001;15:23–30.
11. Dada T, Gadia R, Sharma A, Ichhpujani P, Bali SJ, Bhartiya S, Panda A. Ultrasound biomicroscopy in glaucoma. Surv Ophthalmol. 2011;56(5):433–50.
12. Silverman RH. High-resolution ultrasound imaging of the eye—a review. Clin Exp Ophthalmol. 2009;37(1):54–67.

13. Saavedra E, Socci da Costa D, Sculley L, Lowder CY. Ultrasound Biomicroscopy (UBM) of Ciliary Processes in Uveitis. Poster session presented at: ARVO Annual Meeting Abstract. Invest Ophthalmol Vis Sci. 2003;44:695.
14. Ahn JK, Jeong IY. Ultrasound biomicroscopy in anterior uveitis. Ophthalmology. 2008;115(10):1851.
15. Peizeng Y, Qianli M, Xiangkun H, Hongyan Z, Li W, Kijlstra A. Longitudinal study of anterior segment inflammation by ultrasound biomicroscopy in patients with acute anterior uveitis. Acta Ophthalmol. 2009;87(2):211–5.
16. Ahn JK. Morphologic changes in the anterior segment in patients with initial-onset or recurrent Vogt-Koyanagi-Harada disease. Ocul Immunol Inflamm. 2010;18(4):314–8.
17. Yang P, Fang W, Jin H, Li B, Chen X, Kijlstra A. Clinical features of Chinese patients with Fuchs' syndrome. Ophthalmology. 2006;113(3):473–80.
18. Häring G, Nölle B, Wiechens B. Ultrasound biomicroscopic imaging in intermediate uveitis. Br J Ophthalmol. 1998;82(6):625–9.
19. Gentile RC, Liebmann JM, Tello C, Stegman Z, Weissman SS, Ritch R. Ciliary body enlargement and cyst formation in uveitis. Br J Ophthalmol. 1996;80(10):895–9.
20. Yanoff M, Fine BS. Ocular pathology: cyst of the iris and anterior ciliary body (pars plicata). 5th ed. Philadelphia: Mosby; 2002. p. 317–9.
21. Baker TR, Spencer WH. Ocular findings in multiple myeloma. A report of two cases. Arch Ophthalmol. 1974;91(2):110–3.
22. Ruprecht KW, Heinrich T, Nauman GOH. Augeun Allgemeinkrankheiten. In: Nauman GOH un Mitarbeiter: Pathologie des Auges. 2. Auflage, vol. 1523. New York: Springer Verlag, Berlin Heidelberg; 1997.
23. Kunimatsu S, Araie M, Ohara K, Hamada C. Ultrasound biomicroscopy of ciliary body cysts. Am J Ophthalmol. 1999;127(1):48–55.
24. Pederson JE. Hypotony. In: Tasman W, Jaeger EA, editors. Duane's clinical ophthalmology. Philadelphia, PA: Lippincott-Raven; 1999. p. 1–8.
25. Schubert HD. Postsurgical hypotony: relationship to fistulization, inflammation, chorioretinal lesions, and the vitreousm. Surv Ophthalmol. 1996;41:97–125.
26. Fine HF, Biscette O, Chang S, et al. Ocular hypotony: a review. Compr Ophthalmol Updat. 2007;8:29–37.
27. Da Costa DS, Lowder C, de Moraes HV Jr, Oréfice F. The relationship between the length of ciliary processes as measured by ultrasound biomicroscopy and the duration, localization and severity of uveitis. Arq Bras Oftalmol. 2006;69(3):383–8.
28. Roters S, Szurman P, Engels BF, Bartz-Schmidt KU, Krieglstein GK. Ultrasound biomicroscopy in chronic ocular hypotony: its impact on diagnosis and management. Retina. 2002;22(5):581–8.
29. Tran VT, LeHoang P, Mermoud A, Herbort CP. Intraocular hypotony: use of ultrasound biomicroscopy (UBM) for differential diagnosis and its schematic representation. Klin Monatsbl Augenheilkd. 2000;216(5):261–4.
30. Roe R, Branco BC, Cunningham ET Jr. Hypotony maculopathy in a patient with HLA-B27-associated uveitis. Ocul Immunol Inflamm. 2008;16(3):107–8.
31. Lewis H, Aaberg TM. Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy. Am J Ophthalmol. 1991;111:15–9.
32. Zarbin MA, Michels RG, Green WR. Dissection of epiciliary tissue to treat chronic hypotony after surgery for retinal detachment with proliferative vitreoretinopathy. Retina. 1991;11(2):208–13.
33. Tran VT, Mermoud A, Herbort CP. Appraisal and management of ocular hypotony and glaucoma associated with uveitis. Int Ophthalmol Clin. 2000;40(2):175–203.
34. Kim HC, Hayashi A, Shalash E, de Juan E Jr. A model of chronic hypotony in the rabbit. Graefes Arch Clin Exp Ophthalmol. 1998;236:69–74.
35. Jonas JB, Vossmerbaeumer U, Kamppeter BA. Chronic prephthisical ocular hypotony treated by intravitreal triamcinolone acetonide. Acta Ophthalmol Scand. 2004;82(5):637.

36. De Smet MD, Gunning F, Feenstra R. The surgical management of chronic hypotony due to uveitis. Eye (Lond). 2005;19(1):60–4.
37. Morse LS, McCuen BW 2nd. The use of silicone oil in uveitis and hypotony. Retina. 1991;11(4):399–404.
38. Pivetti-Pezzi P, Da Dalt S, La Cava M, Pinca M, De Gregorio F, Virno M. Ibopamine treatment in chronic hypotony secondary to long-lasting uveitis. A case report. Eur J Ophthalmol. 2000;10(4):332–4.
39. Virno M, De Gregorio F, Pannarale L, Arrico L. Topical ibopamine and corticosteroids in the treatment of post surgery ocular hypotony. Int Ophthalmol. 1996;20(1):147–50.
40. Roters S, Engels BF, Szurman P, Krieglstein GK. Typical ultrasound biomicroscopic findings seen in ocular hypotony. Ophthalmologica. 2002;216(2):90–5.
41. Coleman DJ. Evaluation of ciliary body detachment in hypotony. Retina. 1995;15:312–8.
42. Gupta P, Gupta A, Gupta V, Singh R. Successful outcome of pars plana vitreous surgery in chronic hypotony due to uveitis. Retina. 2009;29(5):638–43.
43. Kapur R, Birnbaum AD, Goldstein DA, et al. Treating uveitis-associated hypotony with pars plana vitrectomy and silicone oil injection. Retina. 2010;30(1):140–5.
44. Dayani PN, Chow J, Stinnett SS, Jaffe GJ. Pars plana vitrectomy, fluocinolone acetonide implantation, and silicone oil infusion for the treatment of chronic, refractory uveitic hypotony. Am J Ophthalmol. 2011;152(5):849–56. e1. https://doi.org/10.1016/j.ajo.2011.04.035.
45. Taskintuna I, Rahhal FM, Rao NA, Wiley CA, Mueller AJ, Banker AS, De Clercq E, Arevalo JF, Freeman WR. Adverse events and autopsy findings after intravitreous cidofovir (HPMPC) therapy in patients with acquired immune deficiency syndrome (AIDS). Ophthalmology. 1997;104(11):1827–36. discussion 1836-7
46. Davis JL, Taskintuna I, Freeman WR, Weinberg DV, Feuer WJ, Leonard RE. Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. Arch Ophthalmol. 1997;115(6):733–7.

Part V
Glaucoma Complications in Uveitis

Chapter 8
Hypertensive Uveitis

Francesco Pichi and Scott D. Smith

Joseph Beer in 1813 was credited with the recognition of glaucoma as a complication of uveitis [1]. This common and often severe complication of intraocular inflammation led to the inclusion of uveitic glaucoma as a separate entity in the first modern classification of secondary glaucoma by Priestly Smith in 1891 [2]. Numerous eponymous uveitic syndromes associated with elevated intraocular pressure (IOP) have since been described, including Fuchs uveitis syndrome (FUS) in 1906 [3] and Posner-Schlossman syndrome in 1948 [4].

The natural tendency in uveitis is for the IOP to decrease during acute inflammatory episodes. In experimental uveitis in monkeys, aqueous production has been reported to drop by 50% in the acute phase, with a four-fold rise in uveoscleral outflow and a net reduction in IOP [5].

In a minority of patients with severe or chronic anterior segment inflammation, chronic ocular hypotony can develop from irreversible ciliary body damage (see Chap. 1). Chronically low IOP in the absence of active inflammation is a sign of poor prognosis.

However, in many patients, a reduction in aqueous production is outweighed by a concomitant increase in outflow resistance. The resultant IOP level thus depends on the fine balance between these two opposing pathological influences. Elevated IOP has been reported to affect 5–19% of uveitis patients [6]. Elevated IOP can be acute or chronic, but does not always lead to glaucomatous damage. According to different series [6–8], glaucomatous damage occurs in 13–25% of patients with hypertensive uveitis without significant differences between viral and non-viral etiologies.

Elevated IOP and glaucoma have been described more frequently in certain uveitis entities, such as juvenile idiopathic arthritis (JIA), sarcoidosis, Vogt-Koyanagi-

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Harada (VKH) syndrome, sympathetic ophthalmia, syphilis, and toxoplasmosis. Viral uveitis, including rubella virus infection associated with a clinical diagnosis of Fuchs uveitis and anterior uveitis due to herpes virus infection (herpes simplex virus (HSV), herpes zoster virus (VZV), and cytomegalovirus (CMV)), is another uveitis group also frequently associated with elevated IOP and glaucoma [7–11].

A major issue in hypertensive uveitis is to evaluate the relative roles of inflammation and corticosteroid-response in the elevation of IOP. In addition, the detection of glaucoma may be influenced by uveitic changes, as structural damage due to uveitis may affect the visual field and inflammatory optic disc swelling may also obscure the assessment of glaucomatous optic nerve and retinal nerve fiber layer changes.

Despite more effective treatments for uveitis such as immunosuppression and biologics, more effective topical ocular hypotensive drugs that achieve better IOP control, advances in surgical technique including anti-fibrotic agents and newer aqueous shunt devices, uveitic glaucoma remains one of the least predictable forms of secondary glaucoma in terms of treatment outcomes, both medical and surgical.

IOP elevation in uveitis patients may have different origins: trabeculitis, obstruction of the trabecular meshwork, pupillary block due to posterior synechiae, or steroid-induced [6].

Inhibition of Access to Trabecular Meshwork

Angle-Closure

Angle-closure may occur in uveitis as a result of pupillary block, forward movement of the iris lens diaphragm, peripheral anterior synechiae (PAS), and occasionally due to neovascularization.

Peripheral Anterior Synechiae

Peripheral anterior synechiae may differ in appearance, distribution and speed of development in uveitis compared with primary angle-closure (PAC) glaucoma. While PAS are probably more common in uveitis with anatomically narrow angles, bridging PAS, which are particularly characteristic of uveitis, may develop in eyes with wide open drainage angles. These are peripheral synechiae that bridge from the peripheral iris to Schwalbe's line (Fig. 8.1) and therefore differ in appearance from other types of PAS. Uveitic PAS may also differ in location from PAC. In the latter, the angle is often narrowest superiorly and PAS preferentially form in this area. In uveitis, inflammatory cells precipitating inferiorly may cause iris contraction and PAS inferiorly in the presence of an open superior angle. It is important to note that irido-trabecular apposition may form permanent adhesions more rapidly in uveitis than in PAC.

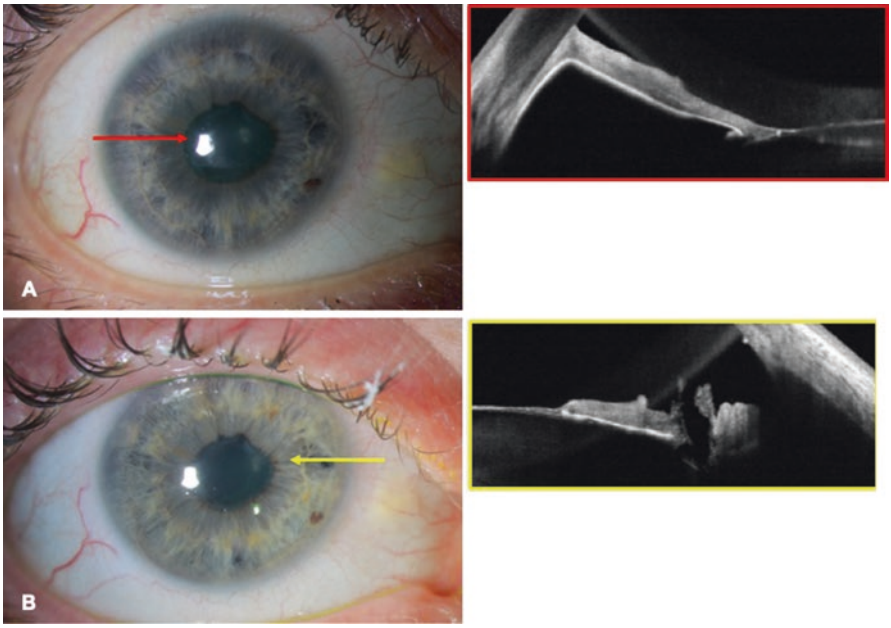

Fig. 8.1 Panel (**a**) shows iris bombé in a patient with HLA-B27 anterior uveitis with irido-corneal apposition and ocular hypertension. The closed angle can be confirmed by anterior segment-optical coherence tomography (red square). After YAG laser iridotomy the iris bombé resolved (**b**) and the angle opened (yellow square)

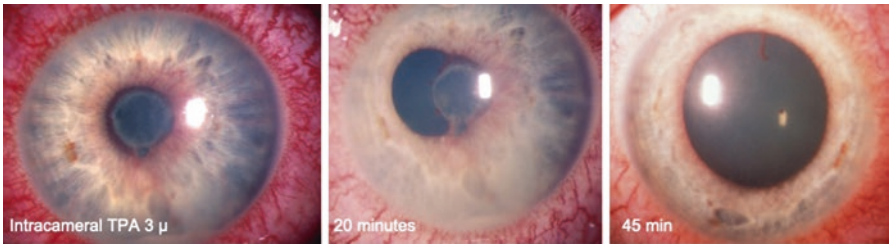

Fig. 8.2 Fibrin occluding the pupil in a patient with active HLA-B27 anterior uveitis that resolved with intracameral injection of 3 µg tissue plasminogen activator

HLAB27

HLAB27-associated entities, with their frequent presence of fibrin in the anterior chamber (Fig. 8.2), are particularly likely to result in synechiae.

JIA

Although corticosteroid treatment is a common cause of ocular hypertension in young patients, 17% of patients are reported to have developed glaucoma independent of steroid responsiveness [12]. Because the uveitis often remains

asymptomatic for long periods, many cases are diagnosed following slit-lamp screening of children for uveitis after the onset of arthritis. Glaucoma develops in almost a quarter of patients and may be particularly difficult to control. As most eyes historically have been aphakic by the time glaucoma was diagnosed, progressive synechial angle-closure has been observed as the main cause.

Iris Bombé

Pupillary block in patients with uveitis may be particularly dramatic. Unlike the pupillary block that is the precipitating factor in many cases of acute primary angle closure, pupillary block in uveitis usually develops from complete seclusion of the pupil by posterior synechiae (Fig. 8.3), which completely isolates the posterior chamber from the anterior chamber. This results in a dramatic forward ballooning of the iris (Fig. 8.3b), often in the presence of a relatively deep central anterior chamber (Fig. 8.3a). Uveitic pupillary block also differs from PAC in that it may occur in pseudophakic, as well as phakic eyes, as a result of the development of posterior synechiae between the anterior lens capsule and pupil margin even in the pseudophakic eye.

Neovascularization of the Iris and Angle

Neovascularization due to uveitis alone is uncommon. However, uveitis affecting the posterior segment may result in retinal ischemia with resultant increased vascular endothelial growth factor production.

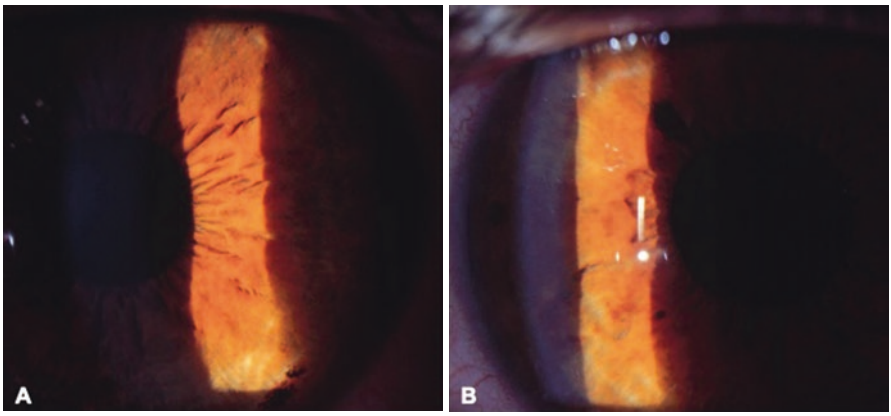

Fig. 8.3 Forward ballooning of the iris in a patient with pupillary block in chronic inactive uveitis (**a**). The central anterior chamber is still relatively deep (**b**)

Acute Retinal Necrosis (ARN)

High intraocular pressure may be a presenting feature of ARN, mostly caused by VZV and HSV infections. The management of ARN requires the use of intraocular and systemic antivirals and also topical steroids. IOP-lowering drugs are also used in cases with elevated IOP. The mechanism of IOP elevation is generally considered to be trabeculitis.

Behçet's Disease

This systemic, inflammatory disorder induces a widespread occlusive vasculitis. In a report of Behçet's disease in a Turkish population, secondary glaucoma occurred in 10.9% [13]. The main glaucoma subtypes were neovascular glaucoma, followed by steroid-induced glaucoma, open-angle glaucoma and chronic angle-closure glaucoma secondary to pupil block. Glaucoma accounts for almost 80% of Behçet's-related visual loss [14].

Sarcoidosis

Granulomatous uveitis (Fig. 8.4) is the most common ocular manifestation of this idiopathic, multisystem, inflammatory disorder, occurring in 74% of patients with ocular involvement. Inflammation may be acute or chronic. The latter form is usually bilateral and is strongly associated with cataract and glaucoma. In one retrospective Japanese series of 1099 uveitis patients, sarcoidosis had the second highest prevalence of secondary glaucoma (34%) after Posner-Schlossman syndrome [15]. Mechanisms of neovascular glaucoma include inflammatory lesions compressing the optic nerve and causing vein occlusion (Fig. 8.4). One histopathological study

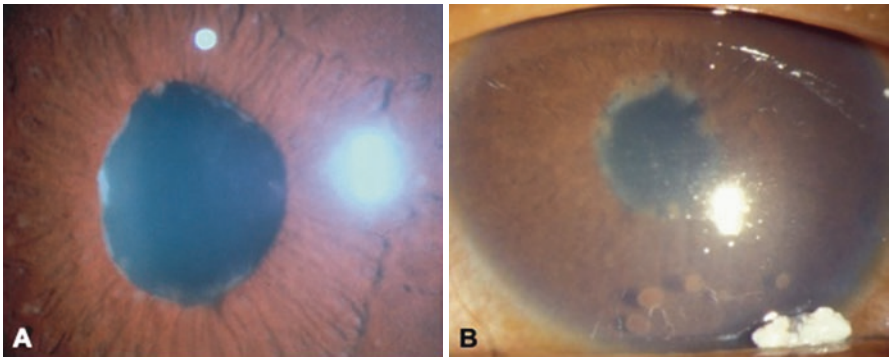

Fig. 8.4 Appearance of hypertensive anterior uveitis secondary to sarcoidosis, with iris nodules (**a**) and mutton-fat keratic precipitates (**b**)

documented inflammatory changes in the inner and outer walls of Schlemm's canal [16]. Standard medical therapy and filtration or glaucoma implant surgery are the preferred treatments. Particular characteristic features that may be associated with IOP elevation are sarcoid nodules on the face of the ciliary body band on gonioscopy. These may be easily missed if careful gonioscopy is not performed.

Forward Movement of the Lens-Iris Diaphragm

In cases of marked posterior segment inflammation such as posterior scleritis, angle-closure may develop without pupillary block. The key distinguishing feature from pupillary block is the very shallow central anterior chamber.

Phacomorphic changes are not uncommon in uveitis and may result in either type of angle-closure, though pupillary block tends to be the more common mechanism.

Vogt-Koyanagi-Harada Disease

Optic disc hyperemia and edema are common findings. Secondary glaucoma is common, occurring in 30–40% of patients [17] (Fig. 8.5). Pupil block-induced angle-closure and secondary angle-closure due to choroidal effusions are important causes of raised IOP. In VKH disease, elevated IOP requiring surgical or medical treatment has been reported in approximately 40% of patients in one series with equal numbers having open-angle and angle-closure mechanisms [17]. Although medical therapy is used initially to lower IOP, surgical intervention is frequently indicated, in the form of laser and surgical iridotomy, antimetabolite-augmented filtration surgery, and/or shunt surgery [17]. Trabeculectomy success in VKH is relatively poor and almost invariably requires subsequent aqueous shunt implantation. On the other hand, VKH patients seem to achieve low pressures with tube

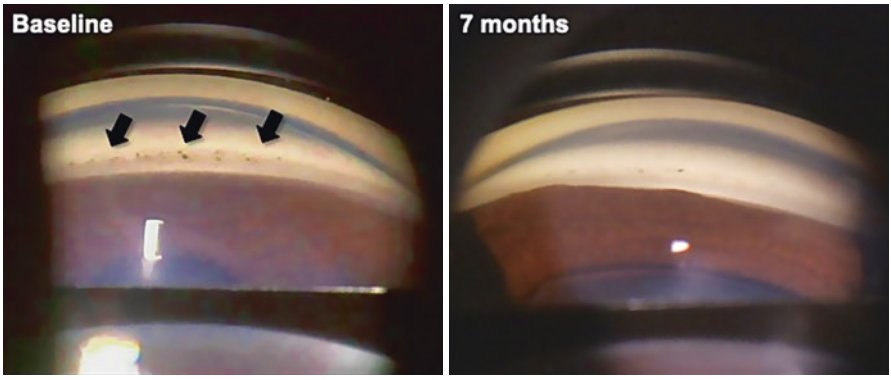

Fig. 8.5 Depigmentation of the angle in active Vogt-Koyanagi-Harada syndrome

shunts, often requiring a smaller device (e.g., Ahmed Glaucoma Valve or Baerveldt 250), rather than one with a larger plate.

Sympathetic Ophthalmia

Uveitic glaucoma may develop in this rare ocular inflammatory condition, which in many ways resembles VKH syndrome. The mechanisms resulting in glaucoma are similar, including synechial angle closure, iris bombé, and ciliary body infiltration with consequent secondary angle-closure. In one study with long-term follow-up, glaucoma was present in 43% of cases [18]. Management of both the inflammation and IOP elevation is difficult and the disease carries a poor prognosis.

Blockage of Trabecular Meshwork by Cells or Debris

Alterations in aqueous humor composition influence aqueous viscosity and hence outflow. Reduced outflow in the presence of elevated flare is not immediately reversible when aqueous returns to normal, and Epstein has suggested that this may be due to protein sequestration in the trabecular meshwork [19]. Aqueous protein concentration, in the presence of an intact blood-aqueous barrier, is usually less than 1% of that in serum [20]. In anterior uveitis, protein leakage into the aqueous from the inflamed ciliary body and iris results in a higher protein concentration, approaching serum levels. A negative association between outflow facility and aqueous flare has been reported [21]. Whether this is the result of increased viscosity, protein sequestration or even reduced function from altered perfusion is uncertain. Polymorphonuclear leukocytes have been observed to infiltrate the trabecular meshwork in animal studies [22]. Pigment and cellular debris deposited in the trabecular meshwork of patients with uveitis have an uncertain effect on outflow. In pigmentary glaucoma, pigment deposition does not seem to elevate the IOP by mechanical obstruction alone, and in uveitis it is probable that pigment and cellular debris lead to loss of the normal trabecular cell population and eventual loss of architecture as is seen in pigmentary glaucoma [23].

Lens-Induced Uveitis

Some lens-related disorders result in acute or chronic uveitis with a high incidence of glaucoma.

Phacoanaphylactic endophthalmitis is an uncommon form of chronic intraocular inflammation in which disruption of the lens capsule leads to varying degrees of inflammation with endophthalmitis and hypopyon in extreme cases.

Phacolytic glaucoma is a separate entity in which IOP elevation results from trabecular outflow obstruction in eyes with lens protein leakage from a hypermature

cataract. Typically, engorged macrophages and lens protein particles are seen in the anterior chamber slit beam on examination, giving the appearance of suspended particles larger than cells floating in the aqueous. These may settle and only be visible when the patient moves the eye back and forth to the extremes of gaze. In both of these conditions, trabecular outflow is believed to be compromised by the accumulation of cells in the trabecular meshwork [24–28]. As a rule, lens removal usually leads to a reduction in the degree of inflammation and improved IOP control.

Chronic Retinal Detachment (Schwartz Syndrome)

In chronic retinal detachment (Schwartz syndrome) the presence of a longstanding rhegmatogenous retinal detachment may result in the release of photoreceptor outer segments that exit the subretinal space through the retinal break to eventually reach the trabecular meshwork and produce increased IOP.

Increase in Trabecular Meshwork Outflow Resistance

Trabeculitis

Direct trabecular meshwork inflammation may also cause trabecular dysfunction, and this may be the mechanism of IOP elevation in Posner-Schlossman syndrome and herpetic keratouveitis, where minimal anterior segment inflammation may be associated with very high IOP levels. Certain cytokines, such as transforming growth factor-ß2 (TGF-ß2), have a role in regulating trabecular cell function and extracellular matrix composition in the normal eye. A potent immunosuppressant, TGF-ß2 is notably reduced or absent in eyes with inflammation [29]. Interleukin-1 (IL-1) may cause extracellular matrix degradation through activation of matrix metalloproteinases resulting in increased uveoscleral outflow [30]. Other cytokines may cause trabecular meshwork cell depopulation, either by direct cytotoxicity or by inducing cell migration away from the meshwork, thereby increasing resistance to aqueous flow through the conventional pathway.

Secondary glaucoma is a frequent complication of uveitis associated with HSV- or VZV-induced inflammation. In one report based on a tertiary referral practice, [11] the prevalence of secondary glaucoma was actually higher in HSV (58%) than VZV (38%) patients.

Herpes Simplex Virus

Anterior uveitis has been reported in approximately 4% of eyes with HSV infection [31]. Although ocular hypertension is a frequent finding, glaucoma is less common, affecting 10% of cases overall [32, 33]. However, glaucoma has been observed in a

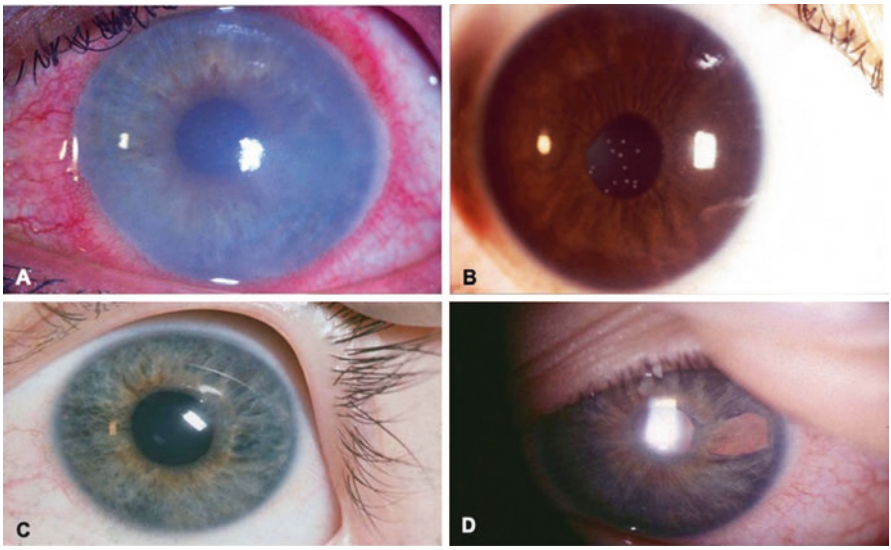

Fig. 8.6 Clinical appearance of hypertensive anterior uveitis secondary to herpes simplex virus, with corneal stromal involvement (**a**), keratic precipitates (**b**), and iris stromal sub-atrophy (**c**), better highlighted with transillumination (**d**)

much higher percentage (up to 80%) of severe cases of herpetic keratouveitis, and, in general, glaucoma is more likely if corneal disease extends to the stroma (Fig. 8.6a). In one retrospective review of 50 eyes with herpetic eye disease, 96% of those who presented with ocular hypertension had stromal keratitis [29]. Additionally, no patients with isolated dendritic or amoeboid ulcers developed ocular hypertension. The clinical diagnosis is important to suspect in patients with focal corneal stromal edema with underlying keratic precipitates (Fig. 8.6b). The initial management reduces viral activity and intraocular inflammation through the concomitant use of topical antiviral agents, such as acyclovir, and topical steroids. In most cases, the IOP normalizes once the intraocular inflammation has subsided without the need for long-term topical ocular hypotensive agents. However, approximately 10% of cases have persistently elevated IOP warranting long-term medical therapy and occasionally surgical intervention [29, 33].

Varicella Zoster Virus

Intraocular complications occur commonly in patients with herpes zoster ophthalmicus [6, 11]. As with HSV-related uveitis, trabeculitis and trabecular obstruction are thought to be the main mechanisms causing ocular hypertension and glaucoma [34]. Prompt treatment with systemic antiviral therapy reduces the likelihood and severity of ocular complications, including uveitis and secondary ocular hypertension [35]. However, the mainstay of anti-inflammatory treatment is with

corticosteroids. There is usually very good response to the use of topical steroids, typically carried out under systemic antiviral cover. Systemic steroids are usually not required in such cases.

Posner-Schlossman Syndrome (Glaucomatocyclitic Crisis)

Posner-Schlossman syndrome (PSS) is a uveitic disorder characterized by discrete episodes of mild, unilateral anterior uveitis in association with a profound rise in IOP (often to 40–60 mmHg). There may be recurrent episodes, although the frequency can vary considerably. Other typical features include slight blurring of vision, haloes, and mild ocular discomfort which is disproportionate to the degree of ocular hypertension. Examination reveals corneal edema, fine white keratic precipitates, very mild anterior uveitis, and an open anterior chamber angle. Iris hypochromia and anisocoria may be evident. Patients are usually between 20 and 50 years of age, and typically only one eye is affected. The natural history of these episodes of inflammation is now rarely observed, but was reported by Posner and Schlossman to last from a few hours to a month, although rarely more than 2 weeks [36]. During this time there is believed to be a reduction in aqueous outflow and an increase in aqueous production [37]. In between crises aqueous outflow is normal. Because CMV has shown to induce this disease, oral valganciclovir has been beneficial, but a proper study is needed to confirm this observation and determine the risks and benefits of this strategy [38]. Antivirals in combination with topical steroids and topical or systemic aqueous suppressants tend to achieve good results. Topical apraclonidine has been reported to be particularly effective in acute attacks [39]. Although medical treatment successfully controls IOP in the majority of cases, occasionally, surgery is required, in which case filtration surgery is the surgical procedure of choice [36, 40].

Fuchs Uveitis Syndrome

The main clinical features of FUS are unilateral iris changes (Fig. 8.7a), mild anterior uveitis, cataract, vitreous floaters, and glaucoma. FUS is another type of uveitis that is often associated with elevated IOP. Although IOP elevation is not as profound as in Posner-Schlossman syndrome, glaucomatous optic neuropathy may not be detected early and significant visual loss is not uncommon. The prevalence of glaucoma in FUS has ranged from 13% to 59% in a number of series, with higher prevalence observed with longer follow-up [41–45]. Many patients with FUS develop elevated IOP following cataract surgery. Although this might lead one to suspect a causal relationship, it is quite likely that the presence of floaters followed by cataract and eventually glaucoma is the natural sequence of events in many patients with this condition. Onset typically occurs insidiously between 20 and 40 years of age, with floaters usually as the first symptoms, though the condition probably remains asymptomatic for some time. Fine stellate keratic precipitates are very typical (Fig. 8.7b, c), but not pathognomonic for FUS, while the presence of

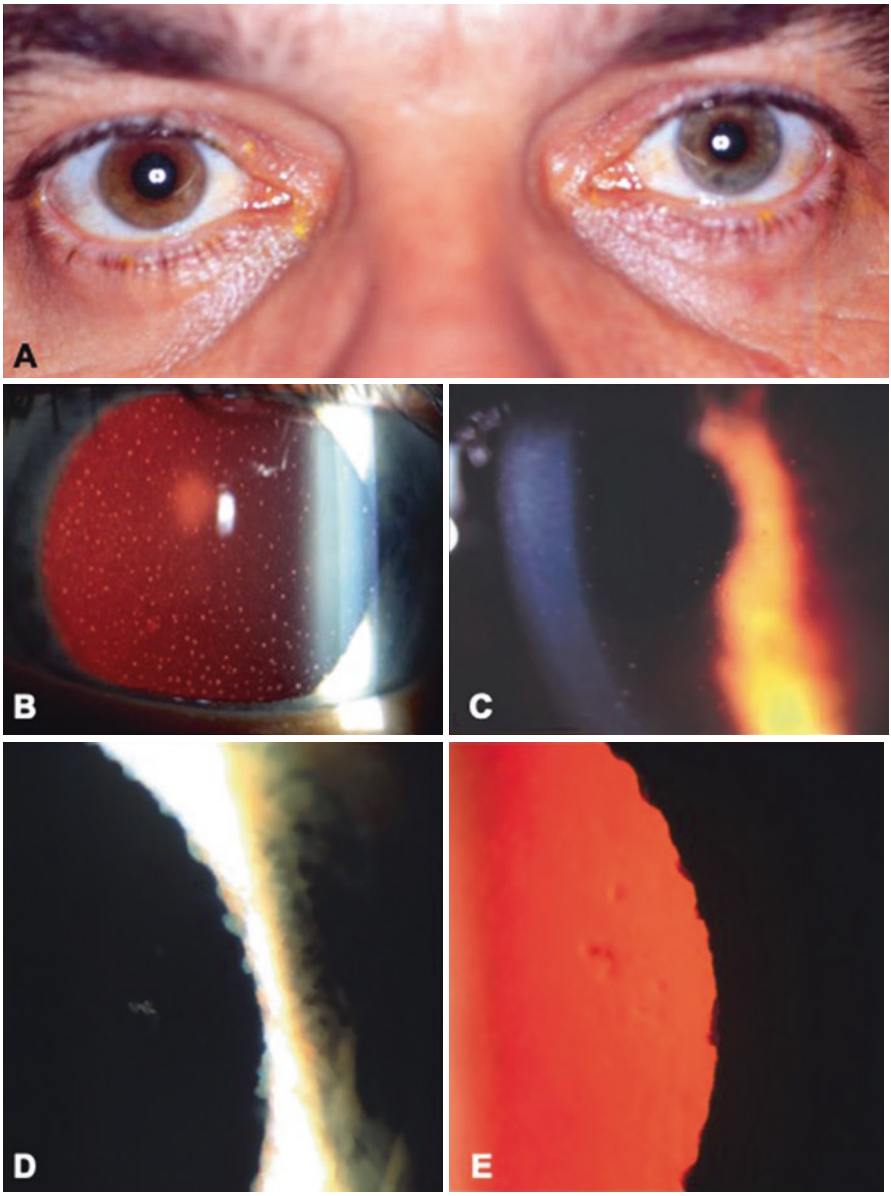

Fig. 8.7 Heterochromia in a patient with Fuchs uveitis (**a**). Fine stellate keratic precipitates (**b**, **c**) are typical but not pathognomonic for Fuchs; multiple iris nodules along the pupillary margin (**d**, **e**) can help make the diagnosis

heterochromia is not particularly diagnostic, and is not always easy to detect. Subtle iris stromal changes, visible on detailed slit lamp examination, and particularly angle changes visible on gonioscopy, are much more reliable. It is essential to differentiate FUS from other types of uveitis as corticosteroid treatment is of little

benefit and may exacerbate the IOP elevation. It is important to compare the normal and abnormal eyes. Blue-eyed patients with FUS will often have a moth-eaten type of loss of posterior iris pigment epithelium that results in dramatic patchy iris transillumination on slit-lamp retro-illumination. This is usually not seen in brown eyes with FUS, presumably due to a thicker anterior stroma. Brown-eyed patients will more often demonstrate multiple iris nodules which also help make the diagnosis (Fig. 8.7d, e). These may be present along the pupillary margin or on the anterior iris surface. Additionally, iris stromal changes result in a particular texture to the iris that can differ considerably from the fellow eye.

FUS patients do not develop posterior synechiae, but do sometimes develop a fibrotic pupillary margin. Gonioscopy is essential in confirming the diagnosis. A remarkable finding is the absence of pigment deposition in the drainage angle in the eyes with marked iris transillumination. Unlike pigmentary glaucoma and glaucoma secondary to other types of uveitis in which pigment is lost from the iris, in FUS, none appears to be deposited in the trabecular meshwork. A possible explanation for this is a very low rate of iris pigment loss such that pigment never accumulates in the angle. Small new vessels may be seen traversing the drainage angle on gonioscopy, and these are so characteristic that they represent a strong confirmatory sign that the diagnosis is FUS. The angle is typically open and devoid of PAS even in cases of established glaucoma. The recent demonstration of chronic rubella virus activity within the eye as the likely etiological agent in FUS has led to the presumption that FUS will become less common in countries where there is a widespread uptake of rubella vaccination by the population [46, 47]. Preliminary evidence suggests that the incidence of FUS is declining in the USA as the generation who have had rubella vaccination reaches the typical age of onset of FUS [48]. The impact of rubella vaccination on this condition will be more apparent as populations in other western countries where rubella vaccination was introduced later than in the USA also reach the age of maximum risk of onset of FUS [48]. In contrast to other forms of uveitis-related IOP elevation with active inflammation, steroid therapy has little beneficial effect on IOP and may induce a steroid response. Conventional medical and surgical measures are required in cases of uncontrolled IOP. Several reports have documented a high rate of surgical intervention in FUS patients. However, the success rates appear to be less favorable than in non-uveitic eyes [49]. This underscores the importance of the role for antimetabolites in filtration surgery or the use of a glaucoma drainage device in these cases.

Delayed Corticosteroid Response

Corticosteroid-induced IOP changes have been linked to most methods of administration including transcutaneous inhalers, nasal sprays, oral and parenteral administration, though most cases occur following topical application or periocular or intraocular injection. The IOP response following topical application is proportional to the strength of the steroid and is highest with dexamethasone sodium 0.1% and

prednisolone acetate 1%. Fluorometholone 0.1% and rimexolone 1% have less effect on IOP than other topical corticosteroid agents [50], but also have lower efficacy for the treatment of intraocular inflammation. The IOP response of the normal individual to topical dexamethasone has been classified into three groups by Armaly [51, 52]. In about two-thirds a low response (≤5 mmHg elevation) develops within 4 weeks of treatment. One-third exhibit an intermediate response (6–15 mmHg), and approximately 5% develop a response of >15 mmHg (high response). In the last group, the average IOP often increases by up to 8 mmHg within the first week. Children are particularly sensitive to the effects of steroids. The hypertensive response to topical steroids in children occurs earlier and with greater frequency than in adults and is often more severe [53]. Glaucoma and a positive family history of glaucoma increase the likelihood of a steroid-induced IOP response. In one study [54], 50% of normal volunteers developed a pressure rise within 6 weeks of treatment with topical betamethasone. In contrast, an impressive 92% of primary open angle glaucoma patients developed a rise in pressure to >31 mmHg. The use of inhaled steroids has also been associated with elevated IOP and glaucoma [55, 56], and patients with a family history of glaucoma appear to have an elevated risk [57]. Typically, steroid-induced IOP elevation in those who are genetic non-responders takes several weeks to develop. Systemic steroids can also cause a rise in IOP [58], usually developing insidiously over a prolonged period. Stopping steroids usually returns the IOP to normal, but this may also take several weeks to occur.

Corticosteroids reduce aqueous outflow by an effect on extracellular matrix turnover and cytoskeletal alterations in the trabecular meshwork cells themselves. Steroids may also affect IOP by altering the expression of myocilin mRNA. Mutations in MYOC are associated with a small proportion of cases of open-angle glaucoma, usually juvenile in onset [59]. Although the exact function of myocilin remains unknown, its presence appears to influence trabecular meshwork function. Mechanical stretching of the trabecular meshwork and exposure to corticosteroids cause induction of myocilin expression. Whether IOP elevation following exposure to steroids is due to the effect of myocilin or whether myocilin is produced in response to the IOP elevation is uncertain [60]. MYOC gene mutations do not appear to be associated with steroid-induced pressure elevation, at least in an animal model [60].

Increased Episcleral Venous Pressure

Scleritis

Scleritis is a chronic inflammatory eye disease with a potentially poor clinical outcome. Common secondary complications are scleral melting, keratitis, cataract, and also elevated IOP. Glaucoma incidence varies in the literature between 9 and 19 %. The pathogenesis of this pressure increase is not clearly defined in scleritis patients. In addition to morphological changes in the trabecular outflow pathway, increased scleral or episcleral vein pressures may be involved.

The rate of secondary elevated IOP is highest in patients with necrotizing scleritis. IOP increase predominantly in the early phase of scleritis and during the acute phase of inflammation, which is in contrast to IOP elevation in uveitis patients, but supporting the role for effective anti-inflammatory treatment in these patients.

Conclusion

Ocular hypertension and secondary glaucoma are common sequelae of intraocular inflammation, and in this chapter we discussed the mechanisms of IOP elevation in uveitis. IOP elevation in idiopathic uveitis generally occurs as a result of the combined effects of inflammation in the anterior segment, angle closure, and corticosteroid treatment, the degree of IOP elevation often depending on the severity or chronicity of exposure to the above factors in combination with the individual's own genetic susceptibility to corticosteroid-induced IOP elevation.

On the other hand, there are certain specific clinical uveitis syndromes such as FUS, herpetic keratouveitis, and Posner-Schlossman syndrome in which IOP elevation and the risk of glaucoma may be disproportionately high in comparison to the degree of inflammation. It is difficult to ascertain the precise incidence of ocular hypertension in various types of uveitis, except in conditions such as Posner-Schlossman syndrome where IOP elevation is a fundamental diagnostic criterion, consequently occurring in 100% of cases. Control of IOP is therefore an integral part of the management of these conditions.

In Chap. 10 Uveitic Glaucoma, its diagnoses and management (both medical and surgical) will be discussed.

References

1. Beer J. Die Lehre v. d. Augenkrankheiten. Vienna. 1813;1:633.
2. Smith P. The pathology and treatment of glaucoma. London: J & A Churchill; 1891.
3. Fuchs E. Uber Komplikationen der Heterochromie. Z Augenheilkd. 1906;15:191.
4. Posner A, Schlossman A. Syndrome of recurrent attacks of glaucoma with cyclitic symptoms. Arch Ophthalmol. 1948;39:517–33.
5. Toris CB, Pederson JE. Aqueous humor dynamics in experimental iridocyclitis. Invest Ophthalmol Vis Sci. 1987;28:477–81.
6. Neri P, Azuara-Blanco A, Forrester JV. Incidence of glaucoma in patients with uveitis. J Glaucoma. 2004;13:461–5.
7. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol. 2003;87:879–84.
8. Cabral DA, Petty RE, Malleson PN, et al. Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol. 1994;21:2370–5.
9. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology. 1997;104:236–44.
10. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86:51–6.

11. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis: a clinical evaluation and comparison. Ophthalmology. 2002;109:1532–7.
12. Kanski JJ, Shun-shin GA. Systemic uveitis syndromes in childhood: an analysis of 340 cases. Ophthalmology. 1984;91:1247–52.
13. Elgin U, Berker N, Batman A. Incidence of secondary glaucoma in behcet disease. J Glaucoma. 2004;13:441–4.
14. Michelson JB, Chisari FV. Behcet's disease. Surv Ophthalmol. 1982;26:190–203.
15. Takahashi T, Ohtani S, Miyata K, et al. A clinical evaluation of uveitis-associated secondary glaucoma. Jpn J Ophthalmol. 2002;46:556–62.
16. Hamanaka T, Takei A, Takemura T, Oritsu M. Pathological study of cases with secondary open angle glaucoma due to sarcoidosis. Am J Ophthalmol. 2002;134:17–26.
17. Forster DJ, Rao NA, Hill RA, et al. Incidence and management of glaucoma in Vogt-Koyanagi-Harada syndrome. Ophthalmology. 1993;100:613–8.
18. Lubin J, Albert D, Weinstein M. Sixty-fi ve years of sympathetic ophthalmia. Ophthalmology. 1980;87:109–21.
19. Epstein DL, Hashimoto JM, Grant WM. Serum obstruction of aqueous outfl ow in enucleated eyes. Am J Ophthalmol. 1978;86:101–5.
20. Barsotti MF, Bartels SP, Freddo TF, Kamm RD. The source of protein in the aqueous humor of the normal monkey eye. Invest Ophthalmol Vis Sci. 1992;33:581–95.
21. Ladas JG, Yu F, Loo R, et al. Relationship between aqueous humor protein level and outflow facility in patients with uveitis. Invest Ophthalmol Vis Sci. 2001;42:2584–8.
22. Rao NA, Wacker WB, Marak GE Jr. Experimental allergic uveitis: clinicopathologic features associated with varying doses of S antigen. Arch Ophthalmol. 1979;97:1954–8.
23. Alvarado JA, Murphy CG. Outflow obstruction in pigmentary and primary open angle glaucoma. Arch Ophthalmol. 1992;110:1769–78.
24. Marak GE Jr. Phacoanaphylactic endophthalmitis. Surv Ophthalmol. 1992;36:325–39.
25. Oprescu M. The etiopathology of phacoantigenic uveitis and phacolytic glaucoma. Oftalmologia. 1992;36:207–13.
26. Rosenbaum JT, Samples JR, Seymour B. Chemotactic activity of lens proteins and the pathogenesis of phacolytic glaucoma. Arch Ophthalmol. 2009;105:1582–4.
27. Flocks M, Littwin CS, Zimmerman LE. Phacolytic glaucoma; a clinicopathologic study of one hundred thirty-eight cases of glaucoma associated with hypermature cataract. AMA Arch Ophthalmol. 1955;54:37–45.
28. Naumann G, Gass JD, Font RL. Histopathology of herpes zoster ophthalmicus. Am J Ophthalmol. 1968;65:533–41.
29. Hedges TR III, Albert DM. The progression of the ocular abnormalities of herpes zoster. Histopathologic observations of nine cases. Ophthalmology. 1982;89:165–77.
30. Liesegang TJ. Classification of herpes simplex virus keratitis and anterior uveitis. Cornea. 1999;18:127–43.
31. Falcon MG, Williams HP. Herpes simplex kerato- uveitis and glaucoma. Trans Ophthalmol Soc U K. 1978;98:101–4.
32. Panek WC, Holland GN, Lee DA, Christensen RE. Glaucoma in patients with uveitis. Br J Ophthalmol. 1990;74:223–7.
33. Thygeson P. Chronic herpetic keratouveitis. Trans Am Ophthalmol Soc. 1967;65:221–6.
34. Cobo LM, Foulks GN, Liesegang TJ. Oral acyclovir in the therapy of acute herpes zoster ophthalmicus. An interim report. Ophthalmology. 1985;92:1574–83.
35. Dinakaran S, Kayarkar V. Trabeculectomy in the management of Posner-Schlossman syndrome. Ophthalmic Surg Lasers. 2002;33:321–2.
36. Spivey BE, Armaly MF. Tonographic findings in glaucomatocyclitic crises. Am J Ophthalmol. 1963;55:47–51.
37. Rodier-Bonifas C, Cornut PL, Billaud G, et al. Cytomegalovirus research using polymerase chain reaction in Posner-Schlossman syndrome. J Fr Ophtalmol. 2011;34:24–9. https://doi.org/10.1016/j.jfo.2010.10.008.
38. Hong C, Song KY. Effect of apraclonidine hydrochloride on the attack of Posner-Schlossman syndrome. Korean J Ophthalmol. 1993;7:28–33.

39. Hung PT, Chang JM. Treatment of glaucomatocyclitic crises. Am J Ophthalmol. 1974;77:169–72.
40. La Hey E, de Vries J, Langerhorst CT, et al. Treatment and prognosis of secondary glaucoma in Fuchs heterochromic cyclitis. Am J Ophthalmol. 1993;116:327–40.
41. Franceschetti A. Heterochromic cyclitis. Am J Ophthalmol. 1955;39:50–8.
42. Huber A. Glaucoma in Fuch's complicated heterochromia. Ophthalmologica. 1961;142:66–115.
43. Liesegang TJ. Clinical features and prognosis in Fuchs' uveitis syndrome. Arch Ophthalmol. 1982;100:1622–6.
44. Velilla S, Dios E, Herreras JM, Calonge M. Fuchs' heterochromic iridocyclitis: a review of 26 cases. Ocul Immunol Inflamm. 2001;9:169–75.
45. Quentin CD, Reiber H. Fuchs heterochromic cyclitis: rubella virus antibodies and genome in aqueous humor. Am J Ophthalmol. 2004;138:46–54.
46. Groot-Mijnes JD, de Visser L, Rothova A, et al. Rubella virus is associated with Fuchs heterochromic iridocyclitis. Am J Ophthalmol. 2006;141:212–4.
47. Birnbaum AD, Tessler HH, Schultz KL, et al. Epidemiologic relationship between Fuchs heterochromic iridocyclitis and the United States rubella vaccination program. Am J Ophthalmol. 2007;144:424–8.
48. Jones NP. Glaucoma in Fuchs' Heterochromic Uveitis: aetiology, management and outcome. Eye (Lond). 1991;5(Pt 6):662–7.
49. Foster CS, Alter G, DeBarge LR, et al. Efficacy and safety of rimexolone 1% ophthalmic suspension vs 1% prednisolone acetate in the treatment of uveitis. Am J Ophthalmol. 1996;122:171–82.
50. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye: I. The demonstration of three levels of response. Investig Ophthalmol. 1965;4:187–97.
51. Armaly MF. The heritable nature of dexamethasone-induced ocular hypertension. Arch Ophthalmol. 1966;75:32–5.
52. Kwok AK, Lam DS, Ng JS, et al. Ocular hypertensive response to topical steroids in children. Ophthalmology. 1997;104:2112–6.
53. Becker B. Intraocular pressure response to topical steroids. Investig Ophthalmol. 1965;4:198–205.
54. Dreyer EB. Inhaled steroid use and glaucoma. N Engl J Med. 1993;329:1822.
55. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA. 1997;277:722–7.
56. Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history, and risk of glaucoma. Ophthalmology. 1999;106:2301–6.
57. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet. 1997;350:979–82.
58. Stone EM, Fingert JH, Alward WL, et al. Identification of a gene that causes primary open-angle glaucoma. Science. 1997;275:668–70.
59. Booth A, Nguyen T, Polansky J. TIGR and stretch in the trabecular meshwork. Invest Ophthalmol Vis Sci. 1999;40:1888–9.
60. Sawaguchi K, Nakamura Y, Nakamura Y, et al. Myocilin gene expression in the trabecular meshwork of rats in a steroid-induced ocular hypertension model. Ophthalmic Res. 2005;37:235–42.

Chapter 9
Medical and Surgical Management of Uveitic Glaucoma

Rajesh Sasikumar and Piergiorgio Neri

Introduction

Inflammation of the uveal tract might lead to high intraocular pressure (IOP) [1]. A series of components may contribute in the pathogenesis of inflammatory glaucoma, such as trabecular meshwork engorgement by immune-cells and proteins [2, 3], inflammation of the trabecular meshwork itself known as "trabeculitis" [4], peripheral anterior and/or posterior synechiae [5], rubeosis iridis and, consequently, neovascular glaucoma [6], and anterior rotation of the lens-iris diaphragm [7]. In addition, it is well known that the use of steroids in order to control uveitis may lead to secondary IOP elevation [8–10].

Uveitic glaucoma may become a severe complication and contribute to severe visual impairment in patients with uveitis. Although several retrospective reports described the prevalence of glaucoma in patients with uveitis [11–14] the incidence of this complication was more recently reported [15].

Uveitic glaucoma represents one of the pitfalls in the management of uveitis.

Uveitic glaucoma occurs in about 20% of patients with uveitis and requires an urgent treatment that might end in surgery to avoid glaucomatous optic nerve damage. The medical literature reported specific types of uveitis associated with very high rates of IOP elevation (see Chap. 8). By definition, high IOP occurs in 100% of patients with Posner-Schlossman syndrome, but not all patients suffer glaucomatous optic neuropathy. On the contrary, glaucomatous optic nerve damage is relatively common in Fuch's uveitis syndrome. Therefore, it is crucial to have a consistent definition of glaucoma in uveitis.

The term glaucoma should be reserved for conditions with a clear evidence of glaucomatous optic damage, while uveitic or steroid-induced ocular hypertension should be used in cases where increased IOP is the only hallmark. The differentiation

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between normal and pathological optic discs represents a concrete challenge in uveitic eyes, where media opacity often makes this evaluation very hard.

Affected segment of the uveal tract may potentially be more or less associated with uveitic glaucoma: uveitis that affects primarily the posterior segment is associated with a lower risk of uveitic glaucoma. Behçet's disease and Vogt-Koyanagi-Harada syndrome are significantly associated to both posterior and anterior uveal tract involvement (a so called panuveitis) and the risk of secondary glaucoma increases. Approximately 6% of all uveitis occurs in children and the most common systemic association is with juvenile idiopathic arthritis. These pediatric uveitis are often treated with high dose of steroids at their onset and this may lead to uveitic glaucoma that should be promptly addressed.

Diagnosis

When a patient presents high IOP in uveitis, it is crucial to distinguish the possible syndromes that might be associated with glaucoma, such as Fuch's uveitis syndrome, Posner-Schlossman syndrome and rubella associated anterior uveitis. In addition, it is important to carefully examine the iridocorneal angle for potential signs of obstruction, such as peripheral anterior synechia, pigment smudging and angle closure, or inflammation hallmarks like Busacca nodules, pigment deposition or angle neovascularisation.

It is also crucial to monitor carefully IOP in uveitis since marked fluctuation is often observed between visits. Goldmann applanation tonometry (GAT) represents the gold standard, even though modern dynamic contour tonometry might be less affected by changes in central corneal thickness (CCT). CCT should be measured accurately in all patients, since GAT may underestimate the IOP level in those with a CCT <510 μm. Visual field testing with standard automated perimetry represents the most reliable functional test for an accurate monitoring of potential change in retinal sensitivity over time: the presence of a visual field abnormality represents still the only endpoint for the diagnosis of glaucoma, albeit optic disc changes alone are considered the hallmark of the so called pre-perimetric glaucoma. The toughest issue in uveitis is differentiating visual field defects that are related to chorioretinal scarring or media opacity from those that may be secondary to uveitic glaucoma. This requires a careful examination of the patient and appraisal of the whole picture.

Optic disc interpretation represents a difficult issue in case of media opacities such as cataract, posterior capsule opacification, pupillary membrane, vitritis and high degree of anterior chamber inflammation. In addition, diffuse retinal nerve fiber loss from widespread retinal disease may also mimic the expansion of the optic disc cup. In the past stereo disc photography represented a reliable method of comparison of optic disc change over time, even though newer imaging devices, such as scanning laser ophthalmoscopy, polarimetry or optical coherence tomography may offer a more accurate analysis in order to detect subtle changes over time. Moreover, it is strongly recommended to measure the vertical disc diameter when assessing the optic disc for glaucomatous damage: in optic discs <1.5 mm vertical diameter any

cupping at all may be pathological, whereas discs >2.0 mm a correspondingly large cup may still be physiological.

Differential Diagnosis

The important differential diagnoses are the hypertensive uveitis entity and the mechanism of inflammatory glaucoma. The uveitis mostly associated with glaucoma are dealt with in Chap. 8.

It is crucial to differentiate IOP elevation in open angle from that of a closed angle, in order to appropriately plan the therapeutic strategy. In anterior uveitis, angle closure may be secondary to relative pupil block: fibrin at the pupillary margin may obstruct aqueous flow into the anterior chamber and generate a vicious circle that may lead to the acute occurrence of high intraocular pressure. IOP elevation is relatively infrequent in this situation, due to the cyclitis and the consequent reduction in aqueous production at the onset of the disease. More commonly acute angle closure in uveitis may be secondary to 360° secluded pupil: posterior synechia at the pupil margin may obstruct the aqueous flow and lead to acute angle closure glaucoma. The key features of this condition are a deep central anterior chamber, dramatic iris bombe, often with peripheral iris-corneal contact, corneal edema and a very high IOP.

In certain situations, the IOP elevates in the presence of a very shallow central anterior chamber, almost with irido-lenticular contact. In this case, the diagnosis is either forward movement of the lens-iris diaphragm or a phacomorphic IOP elevation.

In case of phacomorphic glaucoma, the lens is generally not large enough to cause a very shallow central anterior chamber, therefore the suspect of an anteriorization of the lens-iris diaphragm should always be put forward. The causes of the latter are any condition that leads to expand the volume of the posterior segment. This may happen in case of posterior scleritis and inflammatory ciliochoroidal effusions, VKH, without forgetting that this may happen after extensive panretinal photocoagulation, after vitrectomy or aqueous misdirection after decompressive surgery.

A pre-existing narrow angle may lead to synechial closure, resulting from chronic intermittent irido-trabecular contact in an eye with synechia in the angle secondary to inflammatory nodules or neovascular membrane with iris neovascularization. Therefore, the careful examination of the angle in all uveitis patients suspected of IOP elevation represent a core component of the correct assessment.

Therapy

An appropriate management of active inflammation represents a priority in uveitic glaucoma. A sub-optimal therapy for the uveitis in the hope of avoiding steroid-induced IOP elevation does not offer any advantage: this is likely to result in further

damage to the outflow pathway and to permanent impair of the aqueous flow. Albeit ocular hypotensive medications are always appropriate, in some diseases, such as Posner-Schlossman syndrome and herpetic uveitis, steroids represent the core component of the treatment. Due to the sensitivity of inflammation to topical steroids in these conditions, the IOP usually comes back to normality as soon as the inflammation settles. Conversely, steroid treatment of inflammation in Fuch's uveitis syndrome is mandatorily contraindicated. A balance between adequate control of inflammation and steroid-induced IOP elevation is considered a must, in order to maintain a healthy optic nerve.

Medical Management

Medical approach is the first approach to uveitic glaucoma. No study has specifically addressed the effect of topical glaucoma medication in uveitis.

Non-selective ß-blockers such as timolol are still used as first-line treatment in uveitis glaucoma, in contrast with primary open-angle glaucoma. Among those available, metipranolol is best avoided, since this has been previously reported to induce uveitis in a proportion of cases [16].

Topical carbonic anhydrase inhibitors (CAIs) such as brinzolamide and dorzolamide may exert a minimal action in controlling the IOP in POAG patients but they may surprisingly have a dramatic decrease in some chronic uveitis, and this is presumed to be due to increased sensitivity of the diseased ciliary body to aqueous suppressants.

The prostaglandin agonists are considered the most effective agents in lowering the IOP by increasing uveoscleral outflow through changes in ciliary body matrix. Initial concerns that prostaglandin agents might precipitate or exacerbate uveitis [17–20] and herpetic keratitis [21–23] were raised, although this suspect was never proved [24]. On the other hand, prostaglandins are not safe in patient with previous history of cystoid macular edema (CME) [25–27], aphakia in uveitis, aggressive cases of herpetic keratouveitis, poorly controlled anterior uveitis.

Alpha-adrenergic agonists may efficiently reduce IOP by a combination of aqueous suppression and increased uveoscleral outflow. Unfortunately, these drugs are associated with frequent local side effects and tachyphylaxis when used for prolonged periods: severe allergy to brimonidine and even granulomatous anterior uveitis may also be a prominent feature that limit their use in uveitic patients. These agents also appear to act via prostaglandin release and their efficacy may be reduced if used concomitantly with NSAIDs.

Miotic agents, such as pilocarpine, must be avoided since they lead not only to increased vascular permeability but also may induce formation of posterior synechia.

Systemic CAIs are also required in a significant proportion of patents. It has been reported that patients requiring systemic CAIs in addition to topical therapy fall into 3 broad categories as the following:

1. Group 1: rapid responder. They have a rapid response to systemic CAIs that can often subsequently be managed on topical therapy alone in the long term. Patients in this group may require surgery only in case of advanced glaucomatous nerve damage and/or repeated frequent attacks with acute IOP elevation risk leading to a further visual impairment.
2. Group 2: partially responder. IOP is controlled but only with a heavy regimen of systemic CAIs and maximum quantity of topical agents. Albeit some patients might tolerate this in the long term, this type of treatment does not seem to be sustainable and most patients will opt for surgery.
3. Group 3: they are so called non-responder. Despite maximum medical therapy, the IOP may remain very high, often higher than 30 mmHg. Regardless of the extent of optic nerve damage, surgery is needed as a rescue therapy in order to avoid glaucomatous visual loss.

Acute Pupillary Block

Acute angle closure represents an emergency in uveitis and must always be promptly treated. The correct approach starts with an intensive pupillary dilatation and anti-inflammatory medication that may break posterior synechia and re-establish aqueous flow. It essential to start the treatment immediately with no delay in order to avoid a more radical approach.

The use of intracameral tissue plasminogen activator (TPA) has been described in cases of acute pupil block secondary to fibrinous inflammation [28]. However, acute attack of uveitis with posterior synechia and pupillary seclusion may present a normal or even low IOP because of cyclitis and the need to treat may not be appreciated. If TPA needs to be used in an eye with iridotomy or iridectomy, it is crucial to inject it before performing those, since its injection after either procedure may lead to a significant iris bleeding.

Laser iridotomy may provide temporary relief of pupillary block but this is not a potential curative treatment, since its failure rate is consistently high. Surgical iridectomy with synechiolysis and aggressive control of anterior segment inflammation are nowadays essential for long-term success [30]. Moreover, since secluded pupil rapidly develop peripheral anterior synechia, synechiolysis and surgical iridectomy have to be planned even after laser iridotomy performed as a rescue treatment.

Surgical Management

A high proportion of uveitic glaucoma needs a surgical approach. Compared with primary open-angle glaucoma, IOP in uveitic glaucoma is usually much higher despite medical therapy and most patients are already taking systemic CAIs unsuccessfully. Reluctance to operate may be induced by a higher risk of surgical failure,

possible postoperative hypotony and inflammation, leading to a more conservative management. On the other hand, suboptimal control of IOP in uveitic glaucoma will certainly cause severe visual impairment in a consistent number of patients. Modern surgical techniques may minimize the risks of surgery and may offer a stable IOP control for the majority of the patients.

Several surgical options have been proposed such as cyclophotocoagulation, trabeculectomy and aqueous shunts. The decision to operate is based on the following parameters: current IOP level, history of IOP elevation, severity of optic nerve damage, appearance of the drainage angle and response to medical treatment.

Inflammation control has to be the first step in managing uveitic glaucoma in view of a surgery, and elevated IOP has to be managed medically as best as possible in the interim. In some instances hot surgery is needed: under these circumstances, the use of perioperative systemic or intraocular corticosteroids has to be considered.

Cyclophotocoagulation [29] should not be considered as an option in inflammatory glaucoma: ciliary destructive surgery may be associated with severe exacerbations of uveal inflammation and permanent impairment of a ciliary body that is already suffering from inflammatory disease. This could result in a potential irreversible hypotony which can be as dangerous as chronic uveitic glaucoma. In children treatment with cyclophotocoagulation has proven unsatisfactory in the long term since the ciliary epithelium regenerates and leads to new elevations of the IOP [30].

Trabeculectomy with low-dose mitomycin C (0.2 mg/ml) is the most studied surgical approach for phakic patients with uveitis. The caveat in this surgery is that even in the absence of over drainage, hypotony may occur by low aqueous production, particularly in younger patients which are more prone to hypotony maculopathy. Multiple releasable and/or adjustable sutures are used to ensure tight flap closure and minimal initial drainage, in order to prevent hypotony. Early postoperative period is crucial for a successful long-term outcome: selective suture release is performed to establish adequate flow and a similar control is achieved with fixed scleral flap sutures that might be selectively lasered in the early postoperative period.

Antimetabolites play a primary role in the success of the surgical therapy: 53% of the patients have a complete IOP control after 5 years [31]. The reported success rate in such study was superior than expectancies for trabeculectomy without antiproliferative in uveitic glaucoma [32]: only 30% of eyes achieved a successful IOP control with no need of medications at 5 years after trabeculectomy without antimetabolites. In this second study the success rate increased to 50% in those who received postoperative 5FU injections.

Unfortunately, few studies were published on the long-term control of IOP in mitomycin C-augmented trabeculectomy in patients with uveitis. The use of MMC in uveitic eyes is associated with lower IOP on fewer medications than eyes undergoing trabeculectomy with intraoperative 5FU [33].

Again, it is crucial the stress the role played by the control of inflammation in uveitic glaucoma: in higher-risk cases trabeculectomy surgery may have a poor outcome if the inflammatory component is not optimally suppressed. However, uveitic patients may have a significant risk of later failure provoked by recurrences of uveitis or sub-

sequent cataract surgery. Moreover, nearly 50% of patients develop cataract after trabeculectomy [34]. Cataract may develop for the following reasons: corticosteroid treatment, trabeculectomy surgery itself, uveitis, the initial IOP elevation and aqueous suppressant treatment for IOP elevation. Subsequent cataract surgery may exert a negative influence on trabeculectomy in about one fourth of the patients.

Aqueous shunt implantation may offer a more stable IOP control in patients with high risk of trabeculectomy failure, such as previous failed filter, prior intraocular surgery, aphakia and pseudophakia, young age, black race and patients likely to require cataract surgery.

Aqueous shunts offer a wide range of options: Ahmed glaucoma valve, the Baerveldt glaucoma implant and the Molteno implant are some of the possible devices available in the market. Aqueous shunts are progressively used in the management of patients with refractory glaucoma and in some centers, they have replaced trabeculectomy as the first option in the surgical management of non-uveitic glaucoma. Molteno [35] reported successful IOP control (≤21 mmHg) in 87% of eyes after 5 years and 93% at 10 years. Both the Baerveldt and Ahmed devices may warrant an optimal short-term result. Even though Da Mata reported an excellent 94% of controlled IOP at 1 year after Ahmed glaucoma valve implantation, this time of follow up is too short to be meaningful. On the other hand, it is encouraging that the 10 eyes followed for a further year maintained IOP control. Similar results were obtained by Ceballos, who described successful IOP control with the Baerveldt glaucoma implant in 92% at 2 years [15, 36]. The use of MMC with aqueous shunt implantation is controversial, and no clear benefit has been reported.

Prognosis

The prognosis in most types of uveitic glaucoma often depends on the application of the "zero tolerance" concept for both uveitis and IOP elevation. Sub-optimal treatment of inflammation in order to prevent a possible steroid-induced IOP elevation leads always to severe worsening of uveitis. Cataract should also be aggressively managed as it hampers optic disc assessment preventing adequate management of glaucoma. In conclusion, the prognosis for eyes with uveitic glaucoma should present a much better outcome than historically has been described, if all the factors would be appropriately addressed.

References

1. Ritch R. Pathophysiology of glaucoma in uveitis. Trans Ophthalmol Soc UK. 1981;101:321–4.
2. Gonzales CA, Ladas JG, Davis JL, et al. Relationships between laser flarephotometry values and complications of uveitis. Arch Ophthalmol. 2001;119:1763–9.
3. Ladas JG, Yu F, Loo R, et al. Relationship between aqueous humor protein level and outflow facility in patients with uveitis. Invest Ophthalmol Vis Sci. 2001;42:2584–2588.4.

4. Amano S, Oshika T, Kaji Y, et al. Herpes simplex virus in the trabeculumof an eye with corneal endothelitis. Am J Ophthalmol. 1999;127:721–2.
5. Moorthy RS, Mermoud A, Baervedt G, et al. Glaucoma associated with uveitis. Surv Ophthalmol. 1997;41:361–94.
6. Salmon JF, Ursell PG, Frith P. Neovascular Glaucoma as a complication of retinal vasculitis in Crohn disease. Am J Ophthalmol. 2000;130:528–30.
7. Panek WC, Holland GN, Lee DA, et al. Glaucoma in patients with uveitis. Br J Ophthalmol. 1990;74:223–7.
8. Vannas S, Ojala L. Treatment of uveitis complicated by cortisone-inducedglaucoma; some experiences. Acta Ophthalmol. 1966;44:313–22.
9. Akduman L, Kolker AE, Black DL, et al. Treatment of persistent glau-coma secondary to periocular corticosteroids. Am J Ophthalmol. 1996;122:257.
10. Thoe Schwartzenberg GW, Buys YM. Glaucoma secondary to topical useof steroid cream. Can J Ophthalmol. 1999;34:222–5.
11. Foster CS, Harlikova K, Baltazis S, et al. Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated uveitis. Acta Ophthalmol. 2000;78:576–9.
12. Merayo-Lloves J, Power WJ, Rodriguez A, et al. Secondary glaucoma inpatient with uveitis. Ophthalmologica. 1999;213:300–4.
13. Caprioli J, Samson CM, Foster CS, et al. Uveitis and glaucoma. J Glaucoma. 2000;9:463–7.
14. Takahashi T, Ohtani S, Miyata K, et al. A clinical evaluation of uveitis-associated secondary glaucoma. Jpn J Ophthalmol. 2002;46:556–62.
15. Neri P, Azuara Blanco A, Forrester JV. Incidence of glaucoma in patients with uveitis. J Glaucoma. 2004 Dec;13(6):461–5.
16. Akingbehin T, Villada JR. Metipranolol associated granulomatous anterior uveitis. Br J Ophthalmol. 1991;75:519–23.
17. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86:51–6.
18. Kiuchi Y, Okada K, Ito N, et al. Effect of a single drop of latanoprost on intraocular pressure and blood-aqueous barrier permeability in patients with uveitis. Kobe J Med Sci. 2002;48:153–9.
19. Smith SL, Pruitt CA, Sine CS, et al. Latanoprost 0.005% and anterior segment uveitis. Acta Ophthalmol Scand. 1999;77:668–72.
20. Warwar RE, Bullock JD, Ballal D. Cystoid macular edema and anterior uveitis associated with latanoprost use: experience and incidence in a retrospective review of 94 patients. Ophthalmology. 1998;105:263–8.
21. Kaufman HE, Varnell ED, Toshida H, et al. Effects of topical unoprostone and latanoprost on acute and recurrent herpetic keratitis in the rabbit. Am J Ophthalmol. 2001;131:643–6.
22. Kaufman HE, Varnell ED, Thompson HW. Latanoprost increases the severity and recurrence of herpetic keratitis in the rabbit. Am J Ophthalmol. 1999;127:531–6.
23. Wand M, Gilbert CM, Liesegang TJ. Latanoprost and herpes simplex keratitis. Am J Ophthalmol. 1999;127:602–4.
24. Barton K, Pavesio CE, Towler HMA, Lightman S. Uveitis presenting de novo in the elderly. Eye (Lond). 1994;8:288–91.
25. Ayyala RS, Cruz DA, Margo CE, et al. Cystoid macular edema associated with latanoprost in aphakic and pseudophakic eyes. Am J Ophthalmol. 1998;126:602–4.
26. Callanan D, Fellman RL, Savage JA. Latanoprost-associated cystoid macular edema. Am J Ophthalmol. 1998;126:134–5.
27. Heier JS, Steinert RF, Frederick AR. Cystoid macular edema associated with latanoprost use. Arch Ophthalmol. 1998;116:680–2.
28. Skolnick CA, Fiscella RG, Tessler HH, Goldstein DA. Tissue plasminogen activator to treat impending pupillary block glaucoma in patients with acute fibrinous HLA-B27 positive iridocyclitis. Am J Ophthalmol. 2000;129:363–6.

29. Spencer NA, Hall AJ, Stawell RJ. Nd:YAG laser iridotomy in uveitic glaucoma. Clin Exp Ophthalmol. 2001;29:217–9.
30. Schlote T, Derse M, Zierhut M. Transscleral diode laser cyclophotocoagulation for the treatment of refractory glaucoma secondary to inflammatory eye diseases. Br J Ophthalmol. 2000;84:999–1003.
31. Heinz C, Koch JM, Heiligenhaus A. Transscleral diode laser cyclophotocoagulation as primary surgical treatment for secondary glaucoma in juvenile idiopathic arthritis: high failure rate after short term follow up. Br J Ophthalmol. 2006;90:737–40.
32. Stavrou P, Murray PI. Long-term follow-up of trabeculectomy without antimetabolites in patients with uveitis. Am J Ophthalmol. 1999;128:434–9.
33. Towler HM, Bates AK, Broadway DC, Lightman S. Primary trabeculectomy with 5-fluorouracil for glaucoma secondary to uveitis. Ocul Immunol Inflamm. 1995;3:163–70.
34. Katz GJ, Higginbotham EJ, Lichter PR, et al. Mitomycin C versus 5-fl uorouracil in high-risk glaucoma filtering surgery. Extended follow-up. Ophthalmology. 1995;102:1263–9.
35. Ceballos EM, Beck AD, Lynn MJ. Trabeculectomy with antiproliferative agents in uveitic glaucoma. J Glaucoma. 2002;11:189–96.
36. Molteno AC, Sayawat N, Herbison P. Otago glaucoma surgery outcome study: long-term results of uveitis with secondary glaucoma drained by Molteno implants. Ophthalmology. 2001;108:605–13.

Part VI
Inflammatory Choroidal Neovascular Membranes and Inflammatory Deposits Complicating Uveitis

Chapter 10
Inflammatory Choroidal Vascular Membranes

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Epidemiology

Choroidal neovascularization (CNV) can complicate a wide range of ocular disorders including various inflammatory chorioretinopathies. This chapter will review the pathogenesis, etiology, clinical presentation, multimodal imaging, and treatment of inflammatory CNV.

Inflammatory CNV is a sight threatening complication that results from the process of angiogenesis and abnormal proliferation of choroidal vessels and may be associated with various noninfectious and infectious uveitic entities [1–5]. Inflammatory disorders complicated by CNV typically occur in young patients and the visual prognosis is guarded, despite diverse treatment strategies [6].

Inflammatory causes of CNV represent the third most common cause of CNV after age-related macular degeneration (AMD) and pathologic myopia [1, 7–9]. The reported incidence of inflammatory CNV across all forms of posterior uveitis is low with a two-year incidence of 2.7% [10]. However the rates of inflammatory CNV development vary significantly according to the specific disease. The reported prevalence of inflammatory CNV in punctate inner choroiditis (PIC) ranges from 22–100% and is 22–50% in multifocal choroiditis with panuveitis (MFC/MCP), [10–18] while the reported prevalence in birdshot chorioretinopathy is 1.0–11% [19–21]. In persistent placoid maculopathy (PPM), the reported prevalence of inflammatory CNV is very high, approximately 56–90% [22, 23] while in patients with serpiginous choroidopathy, this complication occurs in 4.7–35% of patients [10, 24–27]. Inflammatory CNV can complicate acute posterior multifocal placoid pigment epitheliopathy (APMPPE) but at a significantly lower rate than PPM and

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serpiginous. With infectious etiologies, the prevalence of inflammatory CNV is less common and has been reported to be 3.8–5% [28–30] with presumed ocular histoplasmosis syndrome (POHS) and less than 1% with toxoplasmosis cases [31].

Pathogenesis

Although inflammatory CNV is known to be a potential complication of uveitis, its pathophysiology, still remains poorly understood [32]. Because of the relatively low incidence of inflammatory CNV and the difficulty in developing an accurate experimental model, the most remarkable pathogenic information has been provided through histopathological studies of CNV secondary to AMD and other disorders. The analysis of the ultrastructural features in surgically excised submacular CNV lesions in choroidal inflammatory conditions has identified the associated presence of macrophages, fibrocytes, myofibroblasts, glial cells, and lymphocytes [33–35]. A two-component model has therefore been proposed to describe CNV. The vascular component of CNV is comprised of vascular endothelial cells, pericytes and precursors of endothelial cells. The extravascular component is comprised of inflammatory cells (macrophages, lymphocytes, granulocytes, and foreign body giant cells), glial cells, retinal pigment epithelial (RPE) cells and fibroblasts [36]. Thus CNV development is a process which involves both inflammation and angiogenesis, and the relevance of each component depends on both the underlying disease and the dynamic stage of CNV development.

Inflammation, typically chronic inflammation, at the level of the Bruch's membrane RPE complex usually sets the stage for the development of inflammatory CNV. Antigen deposition in the area of Bruch's membrane due to the underlying uveitic disorder may lead to a focal inflammatory response followed by a break in Bruch's membrane and resulting in the disruption of homeostasis between inhibitory and stimulatory mediators of angiogenesis. These processes eventually lead to the proliferation of choroidal blood vessels under the RPE and into the subretinal space [37] where the neovascular membrane may leak and bleed leading to serous retinal detachment and fibrotic scarring [7, 38, 39].

Inflammatory CNV typically occurs in a younger demographic and therefore the most common subtype is type 2 neovascularization (NV), unlike that noted in the AMD population [40]. While type 1 NV is located in the sub-RPE space and typically associated with a pigment epithelial detachment (PED), type 2 NV is located in the sub-neurosensory retina compartment and is loosely correlated with the dye based angiographic feature of classic or well defined neovascularization [8, 41, 42]. A greater adherence of the RPE to Bruch's membrane in younger patients may explain the predisposition to develop type 2 NV in inflammatory cases of CNV [41]. Excised inflammatory CNV has been shown to overexpress vascular endothelial growth factor (VEGF) by immunohistochemistry methods [38, 43, 44]. VEGF reduces junctional integrity of the RPE and vascular endothelium and upregulates

leukocyte adhesion molecules to the endothelium, thus facilitating the infiltration of leukocytes into tissues [45–48].

The pathogenesis of CNV involves three stages.

The Initiation Stage

VEGF plays a key role as the inciting stimulus of CNV development. VEGF is produced by a number of potential sources including ganglion cells, endothelial cells, pericytes, Müller cells, photoreceptors, and RPE cells [49, 50]. VEGF-A is the prototypical member of the same gene family which also includes placental growth factor (PlGF), VEGF-B, VEGF-C, VEGF-D, and Parapoxvirus Orf-virus-encoded VEGF-E [51, 52].

In a response to hypoxia, VEGF is produced and triggers growth of endothelial cells from arteries, veins, and lymphatics [53–55]. In addition, VEGF enhances microvascular permeability and promotes monocyte chemotaxis thus acting as a survival factor for endothelial cells.

The Active Stage

This stage is characterized by the progressive enlargement of the CNV complex, which is mainly related to the presence of several inflammatory cells, synergistically acting with aberrant cytokines [43, 56–58]. Vascular endothelium and macrophages produce matrix metalloproteinases which degrade the extracellular matrix promoting CNV infiltration through Bruch's membrane and tissue planes [37, 59]. In this stage, the CNV undergoes maturation and becomes less responsive to VEGF, unlike its properties in the initiation stage. Once the new vessels are formed, the endothelial cells start to secrete other factors to recruit pericytes that promote vessel stabilization, endothelium differentiation, and growth arrest. The most important of these factors is PDGF-B which works through its receptors expressed by pericytes [60–62].

The Involutional Stage

In the final stage, a shift toward anti-angiogenic and anti-proteolytic activities, resulting in the involutional stage of CNV [37]. This stage is characterized by the presence of TGF-β and TIMP-3, produced by the RPE, which are able to influence both the secretion of the extracellular matrix and tissue remodeling which eventually lead to the development of a fibrotic cicatrix and a medium where the CNV no longer needs

VEGF [63]. The RPE cells, directed by TNF-α and other growth factors, de-differentiate and proliferate, and together with the choroidal fibroblasts show a wound repair pattern. The outcomes of these processes are the maturation of established vessels and the formation of scar tissue [64].

Differential Diagnosis

There are many uveitic disorders that can be complicated by inflammatory CNV the most common of which include multifocal choroiditis with panuveitis syndrome (MFC/MCP), punctate inner choroidopathy (PIC), presumed ocular histoplasmosis syndrome (POHS), HLA-A29 birdshot chorioretinopathy, placoid disorders including acute posterior multifocal placoid pigment epitheliopathy (APMPPE), persistent placoid chorioretinopathy (PPM), relentless placoid chorioretinitis, serpiginous chorioretinopathy, and toxoplasmosis chorioretinopathy.

See the Table for a detailed list of etiologies that should be included in the differential diagnosis of inflammatory CNV.

Non-Infectious		Infectious	
Punctate inner choroidopathy (PIC)		Tuberculosis	
Multifocal choroiditis with panuveitis (MFC or MCP)		Presumed ocular histoplasmosis (POHS)	
Vogt-Koyanagi-Harada (VKH)		Syphilitic chorioretinitis	
Placoid Disorders	Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)	Toxoplasmosis	
	Persistent placoid chorioretinopathy	Rubella retinopathy	
	Relentless placoid chorioretinitis	Toxocara	
	Serpiginous choroiditis	West Nile virus	
Sarcoidosis		Fungal	*Aspergillus fumigatus*
Tubulointerstitial nephritis and uveitis			
Eales disease			*Candida albicans*
Birdshot choroiditis			
Sympathetic ophthalmia			*Cryptococcus neoformans*
Idiopathic			

Clinical Presentation and Multimodal Imaging

Inflammatory CNV may harbor common underlying features across various uveitis disorders including the presence of a yellow-white infiltrate associated with retinal edema (subretinal or intraretinal fluid) and subretinal blood [56]. Inflammatory CNV not uncommonly emanates from the edge of a chorioretinal scar or a choroidal granuloma and can be located in the macular, extramacular, or peripapillary regions [65]. The majority of inflammatory CNV cases, however, develop in the extrafoveal

location [1, 13]. Foveal involvement can be detected early by the patient who may complain of metamorphopsia or central scotoma. However, extrafoveal inflammatory CNV may develop in an asymptomatic patient and may be incidentally detected especially if heme or fluid is noted on retinal evaluation [65].

As inflammatory CNV lesions are typically type 2 NV in morphology, a grey green membrane and a pigment ring may be identified on examination or color fundus photography and a classic well defined pattern of leakage may be appreciated with dye based fluorescein angiography (FA) [41, 66]. Spectral domain optical coherence tomography (SD-OCT) may display subretinal hyperreflective material (SHRM) which may represent the type 2 NV lesion or associated inflammatory fibrin or fibrosis [67]. SD-OCT may also illustrate subretinal or intraretinal fluid, which provides a valuable biomarker of response to treatment especially in extra-foveal lesions where visual acuity may still be preserved. More recently, inflammatory CNV has been associated with a unique OCT feature referred to as a pitchfork sign characterized by vertical hyperreflective lines emanating from the type 2 NV [68]. OCT angiography may provide an additional important tool to detect inflammatory CNV and its response to treatment especially if there is no fluid noted with OCT. Cases of type 1 NV associated with inflammatory diseases have been documented and therefore close evaluation with examination and multimodal imaging is essential [69].

Multimodal Imaging and Diagnosis

This section will selectively highlight the individual diseases associated with inflammatory CNV and will briefly describe the associated multimodal imaging features of these disorders, although inflammatory CNV has similar presenting findings with each condition.

Punctate Inner Choroidopathy (PIC) and Multifocal Choroiditis and Panuveitis (MFC/MCP)

PIC and MFC/MCP lesions are commonly bilateral small, round, yellowish-white punctate lesions that evolve into punched-out chorioretinal scars (Fig. 10.1a) [70–73]. Whereas PIC lesions are confined to the posterior pole and associated with minimal vitritis, MFC/MCP lesions are larger and more diffuse and associated with panuveitis. This distinction in distribution explains the varying localization of CNV which is commonly associated with the inflammatory lesions. However, this may explain the difficulty in differentiating CNV from the inflammatory lesions. Therefore, examination for hemorrhage and multimodal imaging is essential. On FA, inflammatory CNV is characterized by early iso- or hyperfluorescence with variable late leakage and staining, [74] whereas MFC lesions tend to be iso- or hypofluorescence with late leakage and staining (Fig. 10.1c) [75–78]. On indocyanine green angiography (ICGA), inflammatory lesions are commonly hypofluorescent

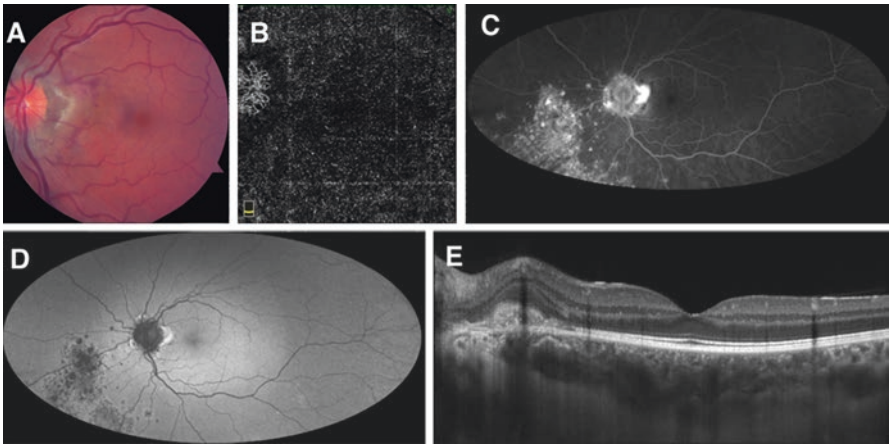

Fig. 10.1 Multifocal choroiditis and panuveitis. Color fundus photograph illustrates subretinal hemorrhage in the temporal juxtapapillary region of the left eye (**a**). Optical coherence tomography angiography (**b**) shows a corresponding choroidal neovascular membrane that leaks with fluorescein angiography (**c**). In the nasal periphery, staining of inflammatory lesions is noted in the late frame of the fluorescein angiogram (**c**). On fundus autofluorescence, inflammatory lesions are centrally hypoautofluorescent with a hyperautofluorescent ring around the central lesion (**d**). Optical coherence tomography B-scan (**e**) illustrates subretinal hyperreflective material (SHRM) that corresponds to the type 2 choroidal neovascular membrane

throughout the study, which may be in contrast to a hyperfluorescent CNV [79, 80]. With OCT, inflammatory and CNV lesions appear similar, with focal hyperreflective pigment epithelial detachments and RPE breaks and eruption of the lesion from the subRPE to the subretinal space (Fig. 10.1e). The choroid may display infiltration with loss of the normal vascular architecture. In the later stages of disease, these areas can lead to outer retinal or chorioretinal atrophy [71, 72, 81–83]. In settings where FA and OCT may be inconclusive, OCT angiography can distinguish CNV from inflammatory lesions, [84, 85] especially when the FA is inconclusive (Fig. 10.1b) [74, 86]. Fundus autofluorescence (FAF) shows hypoautofluorescent spots (although acute lesions may be hyperautofluorescent) with hyperautofluorescent margins that fade as the lesions regress (Fig. 10.1d) [87, 88].

HLA-A29 Birdshot Retinopathy

These patients present with creamy ovoid depigmented choroidal lesions extending to the periphery in all quadrants and giving the characteristic ‘birdshot’ fundus pattern. The lesions eventually become more atrophic with chronicity [89]. Inflammatory CNV typically presents with subretinal hemorrhage and associated intraretinal fluid (Fig. 10.2). Inflammatory lesions may be challenging to detect with FA in the early stages of disease [19] but can display mild late staining especially in the later stages of disease when atrophy has ensued (Fig. 10.2) [90–92]. With ICGA, birdshot

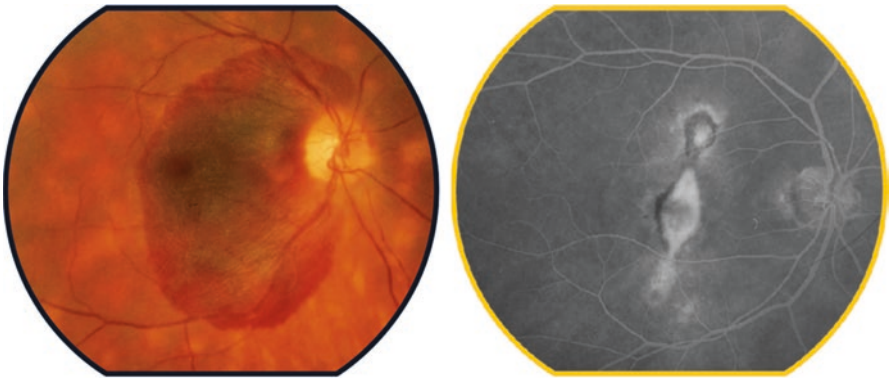

Fig. 10.2 Birdshot chorioretinopathy. Fundus photography (left) illustrates subretinal hemorrhage within the posterior pole of the right eye due to a choroidal neovascular membrane. Note the characteristic oval yellow-white, "birdshot" choroidal lesions extending to the periphery. Late fluorescein angiography (right), from a different patient with birdshot disease, displays late staining of a classic choroidal neovascular membrane that extends through the fovea. (Courtesy of The Retina Atlas. Editors Freund KB, Sarraf D, Mieler WF, Yannuzzi LA. Elsevier 2017 (2nd Edition))

lesions appear as evenly-sized, round-oval, hypofluorescent dark spots in the intermediate and late phases of the angiogram and are often noted to aggregate along the choroidal vessels [90, 93]. Inflammatory CNV associated with HLA A29 disease will typically display early classic or well-defined lacy hyperfluorescence with late leakage and a hot spot with ICGA. In the absence of CNV, OCT demonstrates focal or generalized disruption of the ellipsoid zone and thinning of the inner or outer retina with choroidal thinning especially involving the Sattler's layer [94, 95]. While type 2 NV associated with subretinal hyperreflective material (SHRM) is more typical with OCT analysis, a pigment epithelial detachment caused by type 1 NV may be noted in select cases [67, 96]. OCT angiography can aid in the confirmation of CNV. OCT angiography has also shown a predilection for flow deficits in the deep retinal capillary plexus [97] with choroidal flow voids that co-localize with hypofluorescent ICG lesions [98]. Capillary loops, telangiectatic vessels, increased intercapillary spaces and altered vascular architecture in both the superficial and deep capillary plexuses have also been documented in birdshot chorioretinopathy using OCT angiography [99]. FAF reveals hypoautofluorescence with chronic birdshot lesions circumferentially around the optic nerve and linearly along retinal vessels corresponding to RPE atrophy [100, 101].

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Color fundus photography of APMPPE lesions illustrate multiple**,** bilateral, yellow-white, placoid subretinal lesions in the posterior pole that pigment over time, leaving well-demarcated alternating areas of focal RPE atrophy and proliferation [102].

In the acute stages of disease, hypofluorescence of the choroid is noted with both the early stages of FA and ICGA corresponding to the APMPPE lesions and due to choroidal ischemia [103, 104]. In the late stages of FA, intense staining of the APMPPE lesions is noted. With subacute and resolved lesions, early hypofluorescence is replaced by hyperfluorescent window or transmission defects due to RPE (and choriocapillaris) atrophy that is the legacy of the APMPPE lesions. Less intense late staining is also present [105]. With OCT, acute APMPPE lesions display outer retinal hyperreflectivity extending along Henle's layer and associated with a wider choriocapillaris band due to the associated inner choroidal ischemia [104, 106, 107]. As the lesions evolve, hypertrophy of the RPE may ensue associated with drusenoid deposition. While these RPE alterations may improve, complete ellipsoid zone recovery may not be noted and outer retinal and RPE atrophy may ensue with OCT. Presence of hemorrhage by macular examination or subretinal or intraretinal fluid with OCT are important clues of the presence of concurrent inflammatory CNV. OCT angiography demonstrates hypoperfusion and loss of choriocapillaris flow with acute placoid lesions while healed lesions illustrate projection artifact due to choriocapillaris atvrophy [69, 102, 107, 108]. OCT angiography can provide a very practical and non-invasive tool to monitor choroidal ischemia, progression of disease and response to therapy [69]. FAF demonstrates hyperautofluorescence associated with acute and subacute lesions and hypoautofluorescence corresponding to atrophy associated with chronic lesions [106].

Serpiginous Choroiditis

Color fundus photography of serpiginous lesions illustrates ill-defined, yellow-white patches of choroiditis that originate typically from the peripapillary region and progress centrifugally in a serpentine fashion. With time, chronic lesions develop pigmentary alterations that ultimately lead to fibrosis and atrophy (Fig. 10.3). Recurrent lesions commonly extend from the edges of old chorioretinal scars [27, 109, 110]. With FA, acute lesions are hypofluorescent early, due to inner choroidal ischemia, and stain late, while chronic lesions only stain late (Fig. 10.3) [111–113]. This is in contrast to the early, well-defined, lacy hyperfluorescence of type 2 or classic NV that characteristically originates from the edge of a chorioretinal plaque or scar. ICG and OCT angiography are best at illustrating choriocapillaris non perfusion that is the underlying etiology of placoid diseases such as serpiginous choroiditis [69, 108, 114–118]. OCT is essential in detecting inflammatory CNV in eyes with serpiginous and the associated presence of subretinal fluid or hemorrhage. OCT of the active inflammatory lesions will also display ellipsoid zone disruption associated with outer retinal hyperreflectivity [119, 120]. However, it is important to note that in some cases of serpiginous, vein occlusions, retinal phlebitis and papillitis can occur from primary active disease and present with hemorrhage and fluid as well. FAF demonstrates hypoautofluorescent haloes which are often identified surrounding the edges of a hyperautofluorescent lesions [119, 121].

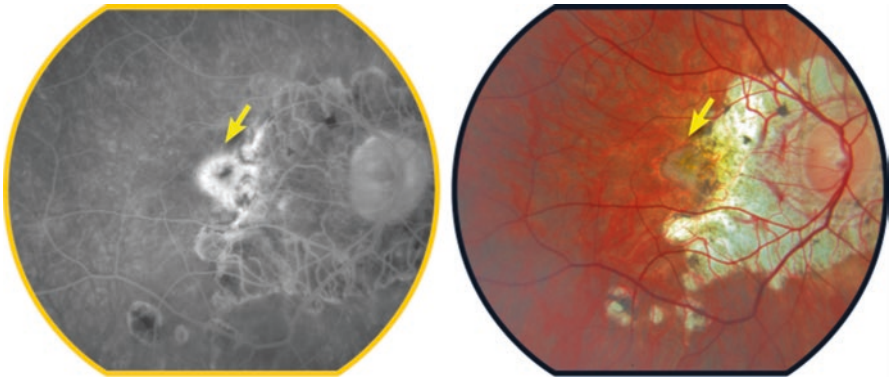

Fig. 10.3 Serpiginous choroiditis. Fluorescein angiography (left) illustrates leakage from a classic choroidal neovascular membrane (arrow) originating from the edge of a chorioretinal scar due to serpiginous choroiditis in the right eye. Fundus photograph (right) demonstrates the choroidal neovascular membrane (arrow) and atrophy noted in the fluorescein images. (Courtesy of The Retina Atlas. Editors Freund KB, Sarraf D, Mieler WF, Yannuzzi LA. Elsevier 2017 (2nd Edition))

Relentless and Persistent Placoid

Persistent and relentless placoid chorioretinitis are entities within the placoid disease spectrum and share similar features to the aforementioned serpiginous choroiditis and APMPPE. In persistent placoid, well delineated, yellow-white plaque-like lesion(s), often large and central, display continued activity and evidence of inner choroidal ischemia over the course of several weeks or months without evidence of resolution, while in relentless placoid, lesions are recurrent and multifocal and expand in size, commonly over months [23, 122, 123]. In both, differentiating inflammatory CNV from inflammatory lesions is clearer as placoid lesions are hypofluorescent early and stain late on FA and are hypofluorescent throughout the ICGA [122]. In contrast, inflammatory CNV displays well defined hyperfluorescence with FA and ICGA consistent with type 2 NV (Fig. 10.4). OCT angiography is especially informative and shows inner choroidal flow deficits that co-localize with the plaque(s) [69]. OCT may illustrate subretinal fluid due to the CNV membrane and hyperreflectivity of the outer retinal layers that can track in Henle's layer corresponding to the plaques [123–125]. FAF demonstrates hyperautofluorescence lesion early in the disease and hypoautofluorescence lesions in the chronic phases of disease consistent with RPE atrophy [126, 127].

Presumed Ocular Histoplasmosis

POHS is defined by the triad of peripapillary atrophy, "punched-out" macular and mid peripheral chorioretinal scars, and the absence of overlying vitritis (Fig. 10.5a). As in other diseases, inflammatory CNV is most commonly located at the edge of a

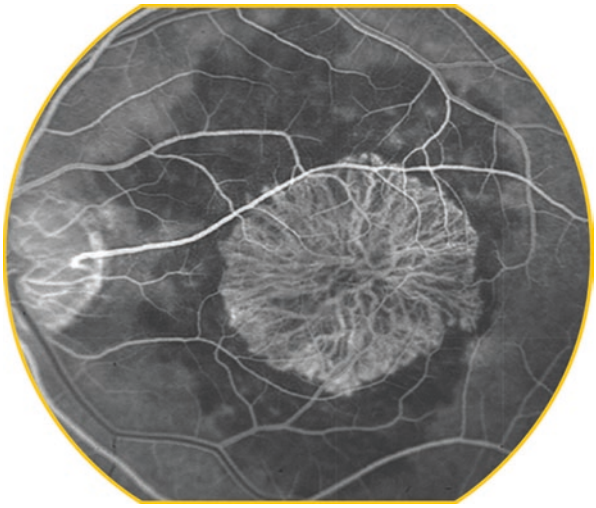

Fig. 10.4 Persistent placoid chorioretinitis. Fluorescein angiography illustrates the characteristic inner choroidal ischemia remarkable in placoid diseases. Note the large overlying classic type 2 choroidal neovascular membrane which is a common complication of persistent placoid chorioretinitis. (Courtesy of The Retina Atlas. Editors Freund KB, Sarraf D, Mieler WF, Yannuzzi LA. Elsevier 2017 (2nd Edition))

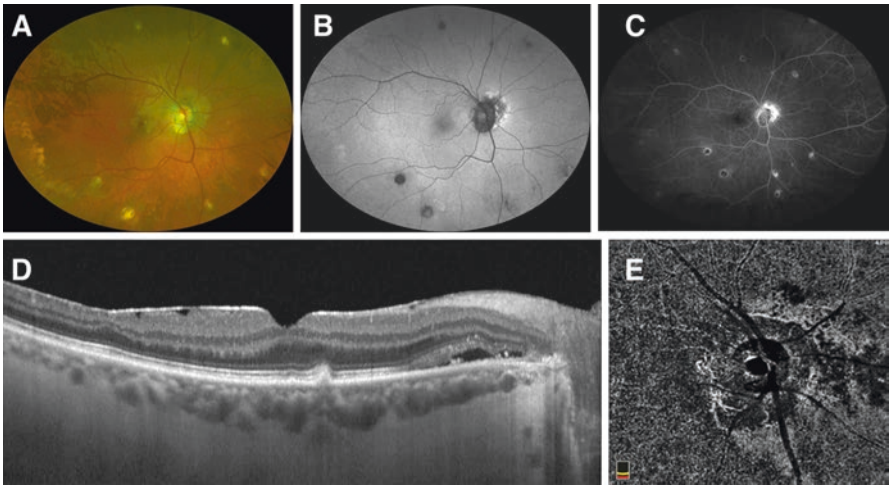

Fig. 10.5 Presumed ocular histoplasmosis. Fundus photographs illustrate focal areas of "punched out" chorioretinal atrophy (**a**) that are hypoautofluorescent on fundus autoflurescence (**b**). These lesions are centrally hypofluorescent with a ring of staining on fluorescein angiography (**c**). Note the presence of peripapillary choroidal neovascularization that is hyperautofluorescent (**b**) with fundus autoflurescence and hyperfluorescent (**c**) with fluorescein angiography. Choroidal neovascular membrane is confirmed by OCT angiography (**e**) as a lacy neovascular network that surrounds the nerve. On optical coherence tomography (**d**) there is peripapillary subretinal fluid

pre-existing scar in the macular or peripapillary region (Fig. 10.5c–e). CNV in this disease, as with the other inflammatory disorders, is of the type 2 variety and typically displays a yellow-green subretinal discoloration and a concentric pigment ring. In advanced cases, a central disciform lesion can be observed [29, 76, 128–130]. With FA, the inflammatory CNV may show early well defined lacy hyperfluorescence (type 2 NV) and late leakage while the peripapillary atrophy and

chorioretinal scars may exhibit a window defect pattern of early transmission hyperfluorescence with progressive late staining [128]. ICGA may enhance identification of the CNV through blood or if the lesion is type 1 NV and under the RPE [128]. OCT demonstrates loss of the outer retinal structures with disruption of the ellipsoid zone and RPE and associated choroidal hyper-transmission corresponding to the histoplasmosis scars, [128] while OCT may display subretinal fluid and/or subretinal hyper reflective material, i.e. SHRM, or more rarely a PED, corresponding to the CNV (Fig. 10.5d) [131]. OCT angiography may enhance identification of the microvascular morphology of the neovascular lesion in POHS, [132] whereas the punched-out chorioretinal lesions may display flow loss in the choriocapillaris and deeper choroidal layers (Fig. 10.5e) [133]. FAF shows hypoautofluorescent lesions that correspond to areas of absent RPE present in chorioretinal scars secondary to ocular histoplasmosis (Fig. 10.5b) [128].

Toxoplasmosis

The "headlight in the fog" description refers to the classic toxoplasmosis presentation of a focal, white-yellow retinochoroiditis associated with media haze due to a dense vitritis. The acute toxoplasmosis lesion typically displays poorly demarcated borders and is often recurrent or reactivated and located adjacent to a pigmented and/or atrophic scar [134, 135]. Furthermore, the focal retinochoroiditis can be associated with perivasculitis, venous sheathing, or segmental arteriolar plaques referred to as the Kyrieleis sign [134, 136]. Inflammatory CNV may complicate toxoplasmosis scars and typically grows along or emanates from the edges of the atrophic chorioretinal scar and can present with sub retinal hemorrhage and intra- or subretinal fluid, best detected with OCT. With FA, the active toxoplasmosis retinochoroiditis stains intensely while the inflammatory CNV may display early well defined, lacy hyperfluorescence with late leakage typical of a type 2 classic NV. On OCT, active toxoplasmosis retinitis exhibits hyperreflectivity within the inner and outer layers of the retina that often progresses to thinning and cavitation with resolution of the acute inflammation [136]. OCT is essential to detect intraretinal and subretinal fluid associated with inflammatory CNV due to toxoplasmosis and is the most important barometer to assess response to treatment with anti-VEGF therapy [137].

Treatment

Given the relative rarity of inflammatory CNV and the lack of randomized controlled clinical trials, widespread consensus for the treatment of inflammatory CNV does not exist. As a result, there are varying approaches but accurate diagnosis and evaluation of the underlying uveitic disorder are the mainstays of management of inflammatory CNV. Two general approaches are available: (1) modifying inflammatory activity and (2) intravitreal anti-VEGF therapy. Laser destruction or surgical

excision of the lesion is no longer considered a primary mode of therapy of inflammatory CNV.

Since the underlying inflammatory activity is a modifiable risk factor for inflammatory CNV, [10] inflammation control is crucial in the prevention of progressive structural and functional damage of the various tissues of the eye. This may include local or systemic regimens of steroid treatment or long-term immunosuppressant therapy [138]. Recommended management approaches include: observation, systemic immunosuppression and/or steroids, and periocular or intraocular steroid therapy. These approaches have been reported to be effective in preserving visual and anatomical function and controlling inflammatory CNV activity [12] [139, 140].

Laser and surgical management have shown variable efficacy in the management of inflammatory CNV. Photodynamic therapy (PDT) with or without the addition of steroids has been reported successfully in some cases [141]. With extrafoveal type 2 inflammatory NV, argon laser photocoagulation or surgical removal of the neovascular membrane has been reported. However, both modalities have shown variable success rates with a high rate of recurrence and potential complications from the procedure or surgery and therefore these approaches are no longer considered standard of care [6, 142–148].

As VEGF plays an essential role in CNV development and has been successful in other neovascular diseases, most importantly AMD, anti-VEGF therapy has been used in combination with anti-inflammatory agents such as immunosuppression or corticosteroids [149–155]. Management with intravitreal anti-VEGF therapy has been shown to be an effective treatment modality with significant visual and anatomic improvement paired with a very low rate of complication [70, 151, 156] in both infectious and non-infectious inflammatory disorders [1]. Patients tend to be successfully treated with a relatively small number of injections unlike other neovascular diseases such as AMD [155].

Corticosteroids have been used for decades and still represent a viable option in the treatment of uveitis due to their strong and rapid anti-inflammatory effects [157]. In addition to the inhibition of pro-inflammatory mediators, steroids also seem to interfere with VEGF production [158] [159]. Steroids inhibit the proliferation of vascular endothelial cells by suppressing the actions of inflammatory cells and the secretion of proangiogenic cytokines. In addition, steroids decrease vascular permeability by stabilizing the basement membrane of the CNV, and this may prevent vascular budding. Immunosuppression is therefore required in order to override the chronic inflammatory drive [8]. By reducing the VEGF stimulus of the growth of new vessels and by decreasing inflammation, which is the primary cause of VEGF release, these drugs still remain an important consideration for the treatment of inflammatory CNV.

Although the majority of uveitis cases are mainly treated by systemic and/or local steroids and anti-VEGF injections, there are circumstances in which steroids may be relatively contraindicated or may not elicit an appropriate response. Steroids are also poorly tolerated and can be complicated by significant side effects including weight gain, emotional disturbance, hypertension, gastritis, glaucoma and cataract [160, 161].

Steroid sparing immunosuppressive agents provide a viable treatment option, especially for long term management, and can inhibit angiogenesis and the development of inflammatory CNV [1]. Various agents have been studied including infliximab, [162, 163] cyclosporin, [139] mycophenolate mofetil [142] and systemic and intravitreal methotrexate [164] and have found success in the treatment of uveitic disorders. However, there are no clear guidelines on the use of these agents, nor on the choice of agents for managing inflammatory CNV.

Prognosis

The natural history of subfoveal inflammatory CNV is associated with a relatively poor visual outcome which is usually attributed to the chronic recurrent course and the lack of a standard therapeutic regimen [10, 65, 165]. However unlike CNV due to AMD, inflammatory CNV is associated with a better prognosis and requires less injections for stabilization. This may be attributed to the type 2 NV pattern, smaller size, association with younger patients with healthier RPE and a good response to the associated angio-static effect of the corticosteroids [166, 167].

References

1. Agarwal A, et al. An update on inflammatory choroidal neovascularization: epidemiology, multimodal imaging, and management. J Ophthalmic Inflamm Infect. 2018;8(1):13.
2. Fine SL, Owens SL, Haller JA, Knox DL, Patz A. Choroidal neovascularization as a late complication of ocular toxoplasmosis. Am J Ophthalmol. 1981;91(3):318–22.
3. Lampariello DA, Primo SA. Ocular toxocariasis: a rare presentation of a posterior pole granuloma with an associated choroidal neovascular membrane. J Am Optom Assoc. 1999;70(4):245–52.
4. Khairallah M, Ben Yahia S, Attia S, Jelliti B, Zaouali S, Ladjimi A. Severe ischemic maculopathy in a patient with West Nile virus infection. Ophthalmic Surg Lasers Imaging. 2006;37(3):240–2.
5. Orth DH, Fishman GA, Segall M, Bhatt A, Yassur Y. Rubella maculopathy. Br J Ophthalmol. 1980;64(3):201–5.
6. Julián K, et al. Intravitreal bevacizumab as first local treatment for uveitis-related choroidal neovascularization: Long-term results. Acta Ophthalmol. 2011;89(2):179–84.
7. Neri P, Lettieri M, Fortuna C, Manoni M, Giovannini A. Inflammatory choroidal neovascularization. Middle East Afr J Ophthalmol. 2009;16(4):245–51.
8. Dhingra N, Kelly S, Majid M, Bailey C, Dick A. Inflammatory choroidal neovascular membrane in posterior uveitis-pathogenesis and treatment. Indian J Ophthalmol. 2010;58(1):3–10.
9. Bansal R, et al. Diagnostic challenges in inflammatory choroidal neovascular membranes. Ocul Immunol Inflamm. 2017;25(4):554–62.
10. Baxter SL, et al. Risk of choroidal neovascularization among the uveitides. Am J Ophthalmol. 2013;156(3):468–77.
11. Brown J, Folk JC, Reddy CV, Kimura AE. Visual prognosis of multifocal choroiditis, punctate inner choroidopathy, and the diffuse subretinal fibrosis syndrome. Ophthalmology. 2013;103(7):1100–5.

12. Flaxel CJ, Owens SL, Mulholland B, Schwartz SD, Gregor ZJ. The use of corticosteroids for choroidal neovascularisation in young patients. Eye. 1998;12(Pt 2):266–72.
13. Wu K, et al. Clinical characteristics of inflammatory choroidal neovascularization in a chinese population. Ocul Immunol Inflamm. 2016;24(3):261–7.
14. Essex RW, et al. Punctate inner choroidopathy: clinical features and outcomes. Arch Ophthalmol. 2010;128(8):982–7.
15. Gerstenblith AT, et al. Punctate inner choroidopathy. a survey analysis of 77 persons. Ophthalmology. 2007;114(6):1201–4.
16. Fung AT, et al. Multifocal choroiditis without panuveitis: clinical characteristics and progression. Retina. 2014;34(1):98–107.
17. Thorne JE, et al. Multifocal choroiditis with panuveitis. incidence of ocular complications and of loss of visual acuity. Ophthalmology. 2006;113(12):2310–6.
18. Kedhar SR, Thorne JE, Wittenberg S, Dunn JP, Jabs DA. Multifocal choroiditis with panuveitis and punctate inner choroidopathy: comparison of clinical characteristics at presentation. Retina. 2007;27(9):1174–9.
19. Thorne JE, Jabs DA, Peters GB, Hair D, Dunn JP, Kempen JH. Birdshot retinochoroidopathy: ocular complications and visual impairment. Am J Ophthalmol. 2005;140(1):45–51.
20. Silpa-Archa S, Cao JH, Boonsopon S, Lee J, Preble JM, Foster CS. Birdshot retinochoroidopathy: differences in clinical characteristics between patients with early and late age of onset. Ocul Immunol Inflamm. 2017;25(5):589–95. Epub 2016 Apr 12.
21. Shantha JG, Ho VY, Patel P, Forooghian F, Yeh S. Choroidal neovascularization associated with birdshot chorioretinopathy. Ophthalmic Surg Lasers Imaging Retina. 2016;47(5):450–7.
22. Kolomeyer AM, Brucker AJ. Persistent placoid maculopathy: a systematic review. Retina. 2018;38(10):1881–95.
23. Golchet PR, Jampol LM, Wilson D, Yannuzzi LA, Ober M, Stroh E. Persistent placoid maculopathy. a new clinical entity. Ophthalmology. 2007;114(8):1530–40.
24. Christmas NJ, Oh KT, Oh DM, Folk JC. Long-term follow-up of patients with serpinginous choroiditis. Retina. 2002;22(5):550–6.
25. Laatikainen L, Erkkilä H. A follow-up study on serpiginous choroiditis. Acta Ophthalmol. 1981;59(5):707–18.
26. Laatikainen L, Erkkila H. Subretinal and disc neovascularisation in serpiginous choroiditis. Br J Ophthalmol. 1982;66(5):326–31.
27. Nazari Khanamiri H, Rao NA. Serpiginous choroiditis and infectious multifocal serpiginoid choroiditis. Surv Ophthalmol. 2013;58(3):203–32.
28. RE GJS. An epidemiologic study of presumed ocular histoplasmosis. Trans Am Acad Ophthalmol Otolaryngol. 1971;5:994–1005.
29. Lou Lewis M, van Newkirk MR, Gass JDM. Follow-up study of presumed ocular histoplasmosis syndrome. Ophthalmology. 1980;87(5):390–9.
30. Oliver A, Ciulla TA, Comer GM. New and classic insights into presumed ocular histoplasmosis syndrome and its treatment. Curr Opin Ophthalmol. 2005;16(3):160–5.
31. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41(1):95–108.
32. Shah RS, Soetikno BT, Lajko M, Fawzi AA. A mouse model for laser-induced choroidal neovascularization. J Vis Exp. 2015;106:e53502.
33. Thomas JW, Grossniklaus HE, Lambert M, Aaberg TM, L'Hernault N. Ultrastructural features of surgically excised idiopathic subfoveal neovascular membranes. Retina. 1993; 13(2):93–8.
34. Saxe SJ, Grossniklaus HE, Lopez PF, Lambert HM, Sternberg P, L'hernault N. Ultrastructural features of surgically excised subretinal neovascular membranes in the ocular histoplasmosis syndrome. Arch Ophthalmol. 1993;111(1):88–95.
35. Grossniklaus HE, Hutchinson AK, Capone A, Woolfson J, Lambert HM. Clinicopathologic features of surgically excised choroidal neovascular membranes. Ophthalmology. 1994;101(6):1099–111.
36. Spaide RF. Perspectives: Rationale for combination therapies for choroidal neovascularization. Am J Ophthalmol. 2006;141(1):149–56.

37. Grossniklaus HE, Green WR. Choroidal neovascularization. Am J Ophthalmol. 2004;141(1):149–56.
38. Shimada H, Yuzawa M, Hirose T, Nakashizuka H, Hattori T, Kazato Y. Pathological findings of multifocal choroiditis with panuveitis and punctate inner choroidopathy. Jpn J Ophthalmol. 2008;52(4):282–8.
39. Tatar O, et al. Effect of bevacizumab on inflammation and proliferation in human choroidal neovascularization. Arch Ophthalmol. 2008;126:782–90.
40. Freund KB, Zweifel SA, Engelbert M. Edirorial: Do we need a new classification for choroidal neovascularization in age-related macular degeneration? Retina. 2010;30(9):1333–49.
41. Gass JDM. Biomicroscopic and histopathologic considerations regarding the feasibility of surgical excision of subfoveal neovascular membranes. Am J Ophthalmol. 1994;118(3):285–98.
42. Lafaut BA, Bartz-Schmidt KU, Vanden Broecke C, Aisenbrey S, De Laey JJ, Heimann K. Clinicopathological correlation in exudative age related macular degeneration: histological differentiation between classic and occult choroidal neovascularisation. Br J Ophthalmol. 2000;84(3):239–43.
43. Perentes Y, Chan CC, Bovey E, Uffer S, Herbort CP. Massive vascular endothelium growth factor (VEGF) expression in Eales' disease. Klin Monatsbl Augenheilkd. 2002;219(4):311–4.
44. Guerin E, et al. SDF1-alpha is associated with VEGFR-2 in human choroidal neovascularisation. Microvasc Res. 2008;75(3):302–7.
45. Caicedo A, Espinosa-Heidmann DG, Piña Y, Hernandez EP, Cousins SW. Blood-derived macrophages infiltrate the retina and activate Muller glial cells under experimental choroidal neovascularization. Exp Eye Res. 2005;81(1):38–47.
46. Chen Y, Hua R. Therapeutic efficacy of conbercept for inflammatory choroidal neovascularization. J Ocul Pharmacol Ther. 2017;34(3):235–6.
47. Espinosa-Heidmann DG, et al. Bone marrow transplantation transfers age-related susceptibility to neovascular remodeling in murine laser-induced choroidal neovascularization. Invest Ophthalmol Vis Sci. 2013;54(12):7439–49.
48. Eilken HM, et al. Pericytes regulate VEGF-induced endothelial sprouting through VEGFR1. Nat Commun. 2017;8(1):1574.
49. Gulati N, Forooghian F, Lieberman R, Jabs DA. Vascular endothelial growth factor inhibition in uveitis: a systematic review. Br J Ophthalmol. 2011;95(2):162–5.
50. Bhutto IA, et al. Pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) in aged human choroid and eyes with age-related macular degeneration. Exp Eye Res. 2006;82(1):99–110.
51. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9(6):669–76.
52. Alitalo K, Tammela T, Petrova TV. Lymphangiogenesis in development and human disease. Nature. 2005;438(7070):946–53.
53. Sheridan CM, Pate S, Hiscott P, Wong D, Pattwell DM, Kent D. Expression of hypoxia-inducible factor-1α and -2α in human choroidal neovascular membranes. Graefes Arch Clin Exp Ophthalmol. 2009;247(10):1361–7.
54. Kwak N, Okamoto N, Wood JM, Campochiaro PA. VEGF is major stimulator in model of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2000;41(10):3158–64.
55. Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res. 2008;27(4):331–71.
56. Pichi F, et al. The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. Prog Retin Eye Res. 2017;59:178–201.
57. Espinosa-Heidmann DG, Suner IJ, Hernandez EP, Monroy D, Csaky KG, Cousins SW. Macrophage depletion diminishes lesion size and severity in experimental choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44(8):3586–92.
58. Sakurai E, Anand A, Ambati BK, Van Rooijen N, Ambati J. Macrophage depletion inhibits experimental choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44(8):3578–85.
59. Steen B, Sejersen S, Berglin L, Seregard S, Kvanta A. Matrix metalloproteinases and metalloproteinase inhibitors in choroidal neovascular membranes. Invest Ophthalmol Vis Sci. 1998;39(11):2194–200.

60. Jain RK. Molecular regulation of vessel maturation. Nat Med. 2003;9(6):685–93.
61. Gaengel K, Genové G, Armulik A, Betsholtz C. Endothelial-mural cell signaling in vascular development and angiogenesis. Arterioscler Thromb Vasc Biol. 2009;29(5):630–8.
62. Thomas M, Augustin HG. The role of the angiopoietins in vascular morphogenesis. Angiogenesis. 2009;12(2):125–37.
63. Sheridan CM, Rice D, Hiscott PS, Wong D, Kent DL. The presence of AC133-positive cells suggests a possible role of endothelial progenitor cells in the formation of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2006;47(4):1642–5.
64. Kent D, Sheridan C. Choroidal neovascularization: a wound healing perspective. Mol Vis. 2003;9:747–55.
65. D'Ambrosio E, Tortorella P, Iannetti L. Management of uveitis-related choroidal neovascularization: from the pathogenesis to the therapy. J Ophthalmol. 2014;2014:450428.
66. Grossniklaus HE, Gass JDM. Clinicopathologic correlations of surgically excised type 1 and type 2 submacular choroidal neovascular membranes. Am J Ophthalmol. 1998;126(1):59–69.
67. Dansingani KK, et al. Subretinal hyperreflective material imaged with optical coherence tomography angiography. Am J Ophthalmol. 2016;169:235–48.
68. Hoang QV, Cunningham ET, Sorenson JA, Freund KB. The 'pitchfork sign': a distinctive optical coherence tomography finding in inflammatory choroidal neovascularization. Retina. 2013;35(3):e23–4.
69. Klufas MA, et al. Optical coherence tomography angiography reveals choriocapillaris flow reduction in placoid chorioretinitis. Ophthalmol Retina. 2016;35(3):e23–4.
70. Mansour AM, Mackensen F, Mahendradas P, Khairallah M, Lai TYY, Bashshur Z. Five-year visual results of intravitreal bevacizumab in refractory inflammatory ocular neovascularization. Clin Ophthalmol. 2012;6:1233–7.
71. Munk MR, et al. Idiopathic multifocal choroiditis/punctate inner choroidopathy with acute photoreceptor loss or dysfunction out of proportion to clinically visible lesions. Retina. 2015;35(2):334–43.
72. Spaide RF, Goldberg N, Freund KB. Redefining multifocal choroiditis and panuveitis and punctate inner choroidopathy through multimodal imaging. Retina. 2013;33(7):1315–24.
73. Tavallali A, Yannuzzi L. Idiopathic multifocal choroiditis. J Ophthalmic Vis Res. 2016;11(4):429–32.
74. Ahnood D, Madhusudhan S, Tsaloumas MD, Waheed NK, Keane PA, Denniston AK. Punctate inner choroidopathy: a review. Surv Ophthalmol. 2017;62(2):113–26.
75. Parnell JR, Jampol LM, Yannuzzi LA, Gass JD, Tittl MK. Differentiation between presumed ocular histoplasmosis syndrome and multifocal choroiditis with panuveitis based on morphology of photographed fundus lesions and fluorescein angiography. Arch Ophthalmol. 2001;119(2):208–12.
76. Watzke RC, Claussen RW. The long-term course of multifocal choroiditis (presumed ocular histoplasmosis). Am J Ophthalmol. 1981;91(6):750–60.
77. Raven ML, Ringeisen AL, Yonekawa Y, Stem MS, Faia LJ, Gottlieb JL. Multi-modal imaging and anatomic classification of the white dot syndromes. Int J Retina Vitreous. 2017;3:12.
78. Shakoor A, Vitale AT. Imaging in the diagnosis and management of multifocal choroiditis and punctate inner choroidopathy. Int Ophthalmol Clin. 2012;3:12.
79. Levy J, Shneck M, Klemperer I, Lifshitz T. Punctate inner choroidopathy: resolution after oral steroid treatment and review of the literature. Can J Ophthalmol. 2005;40(5):605–8.
80. Tiffin PA, Maini R, Roxburgh ST, Ellingford A. Indocyanine green angiography in a case of punctate inner choroidopathy. Br J Ophthalmol. 1996;80(1):90–1.
81. Zhang X, Zuo C, Li M, Chen H, Huang S, Wen F. Spectral-domain optical coherence tomographic findings at each stage of punctate inner choroidopathy. Ophthalmology. 2013;120(12):2678–83.
82. Channa R, et al. Characterization of macular lesions in punctate inner choroidopathy with spectral domain optical coherence tomography. J Ophthalmic Inflamm Infect. 2012;2(3):113–20.

83. Vance SK, Khan S, Klancnik JM, Freund KB. Characteristic spectral-domain optical coherence tomography findings of multifocal choroiditis. Retina. 2011;31(4):717–23.
84. Astroz P, et al. Optical coherence tomography angiography to distinguish choroidal neovascularization from macular inflammatory lesions in multifocal choroiditis. Retina. 2018;38(2):299–309.
85. Klufas MA, O'Hearn T, Sarraf D. Optical coherence tomography angiography and widefield fundus autofluorescence in punctate inner choroidopathy. Retin Cases Brief Rep. 2015;9(4):323–6.
86. Levison AL, Baynes KM, Lowder CY, Kaiser PK, Srivastava SK. Choroidal neovascularisation on optical coherence tomography angiography in punctate inner choroidopathy and multifocal choroiditis. Br J Ophthalmol. 2017;101(5):616–22.
87. Li M, Zhang X, Wen F. The fundus autofluorescence spectrum of punctate inner choroidopathy. J Ophthalmol. 2015;2015:202097.
88. Campos J, Campos A, Mendes S, Neves A, Beselga D, Sousa JC. Punctate inner choroidopathy: a systematic review. Med Hypothesis Discov Innov Ophthalmol. 2014;3(3):76–82.
89. Minos E, et al. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. Orphanet J Rare Dis. 2016;11(1):61.
90. Fardeau C, Herbort CP, Kullmann N, Quentel G, LeHoang P. Indocyanine green angiography in birdshot chorioretinopathy. Ophthalmology. 1999;106(10):1928–34.
91. Levinson RD, Gonzales CR. Birdshot retinochoroidopathy: Immunopathogenesis, evaluation, and treatment. Ophthalmol Clin N Am. 2002;15(3):343–50.
92. Soubrane G, Bokobza R, Coscas G. Late developing lesions in birdshot retinochoroidopathy. Am J Ophthalmol. 1990;109(2):204–10.
93. Papadia M, Herbort CP. Reappraisal of birdshot retinochoroiditis (BRC): a global approach. Graefes Arch Clin Exp Ophthalmol. 2013;251(3):861–9.
94. Birch DG, Williams PD, Callanan D, Wang R, Locke KG, Hood DC. Macular atrophy in birdshot retinochoroidopathy: an optical coherence tomography and multifocal electroretinography analysis. Retina. 2010;30(6):930–7.
95. Keane PA, et al. Characterization of birdshot chorioretinopathy using extramacular enhanced depth optical coherence tomography. JAMA Ophthalmol. 2013;131(3):341–50.
96. Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. Retina. 2013;33(9):1735–62.
97. Phasukkijwatana N, Iafe N, Sarraf D. Optical coherence tomography angiography of A29 birdshot chorioretinopathy complicated by retinal neovascularization. Retin Cases Brief Rep. 2017;11(Suppl 1):S68–72.
98. Pepple KL, Chu Z, Weinstein J, Munk MR, Van Gelder RN, Wang RK. Use of en face swept-source optical coherence tomography angiography in identifying choroidal flow voids in 3 patients with birdshot chorioretinopathy. JAMA Ophthalmol. 2018;136(11):1288–92.
99. Pohlmann D, Macedo S, Stübiger N, Pleyer U, Joussen AM, Winterhalter S. Multimodal imaging in birdshot retinochoroiditis. Ocul Immunol Inflamm. 2017;25(5):621–32.
100. Giuliari G, Hinkle DM, Foster CS. The spectrum of fundus autofluorescence findings in birdshot chorioretinopathy. J Ophthalmol. 2010;2009:567693.
101. Koizumi H, Pozzoni MC, Spaide RF. Fundus autofluorescence in birdshot chorioretinopathy. Ophthalmology. 2008;115(5):e15–20.
102. Heiferman MJ, et al. Acute posterior multifocal placoid pigment epitheliopathy on optical coherence tomography angiography. Retina. 2017;37(11):2084–94.
103. Park D, Schatz H, McDonald HR, Johnson RN. Indocyanine green angiography of acute multif-ocal posterior placoid pigment epitheliopathy. Ophthalmology. 1995;102(12):1877–83.
104. Mrejen S, Sarraf D, Chexal S, Wald K, Freund KB. Choroidal involvement in acute posterior multifocal placoid pigment epitheliopathy. Ophthalmic Surg Lasers Imaging Retina. 2016;47(1):20–6.
105. Jones NP. Acute posterior multifocal placoid pigment epitheliopathy. Br J Ophthalmol. 1995;79(4):384–9.

106. Roberts PK, Nesper PL, Onishi AC, Skondra D, Jampol LM, Fawzi AA. Characterizing photoreceptor changes in acute posterior multifocal placoid pigment epitheliopathy using adaptive optics. Retina. 2018;38(1):39–48.
107. Burke TR, et al. Application of OCT-angiography to characterise the evolution of chorioretinal lesions in acute posterior multifocal placoid pigment epitheliopathy. Eye (Lond). 2017;31(10):1399–408.
108. Dolz-Marco R, Sarraf D, Giovinazzo V, Freund KB. Optical coherence tomography angiography shows inner choroidal ischemia in acute posterior multifocal placoid pigment epitheliopathy. Retin Cases Brief Rep. 2017;11(Suppl 1):S136–43.
109. Lim WK, Buggage RR, Nussenblatt RB. Serpiginous choroiditis. Surv Ophthalmol. 2005;50(3):231–44.
110. Cunningham ET, Gupta A, Zierhut M. The creeping choroiditides – serpiginous and multifocal serpiginoid choroiditis. Ocul Immunol Inflamm. 2014;22(5):345–8.
111. Chisholm IH, Gass JDM, Hutton WL. The late stage of serpiginous (geographic) choroiditis. Am J Ophthalmol. 1976;82(3):343–51.
112. Mansour AM, Jampol LM, Packo KH, Hrisomalos NF. Macular serpiginous choroiditis. Retina. 1988;8(2):125–31.
113. Van Liefferinge T, Sallet G, De Laey JJ. Indocyanine green angiography in cases of inflammatory chorioretinopathy. Bull Soc Belge Ophtalmol. 1995;257:73–81.
114. Giovannini A, Ripa E, Scassellati-Sforzolini B, Ciardella A, Tom D, Yannuzzi L. Indocyanine green angiography in serpiginous choroidopathy. Eur J Ophthalmol. 1996;6(3):299–306.
115. Squirrell DM, Bhola RM, Talbot JF. Indocyanine green angiographic findings in serpiginous choroidopathy: evidence of a widespread choriocapillaris defect of the peripapillary area and posterior pole. Eye (Lond). 2001;15(Pt 3):336–8.
116. Montorio D, et al. Swept-source optical coherence tomography angiography in serpiginous choroiditis. Br J Ophthalmol. 2018;102(7):991–5.
117. El Ameen A, Herbort CP Jr. Serpiginous choroiditis imaged by optical coherence tomography angiography. Retin Cases Br Rep. 2018;12(4):279–85.
118. Pakzad-Vaezi K, Khaksari K, Chu Z, Van Gelder RN, Wang RK, Pepple KL. Swept-source OCT angiography of serpiginous choroiditis. Ophthalmol Retin. 2018;2(7):712–9.
119. Cardillo Piccolino F, Grosso A, Savini E. Fundus autofluorescence in serpiginous choroiditis. Graefes Arch Clin Exp Ophthalmol. 2009;247(2):179–85.
120. Gallagher MJ, Yilmaz T, Cervantes-Castañeda RA, Foster CS. The characteristic features of optical coherence tomography in posterior uveitis. Br J Ophthalmol. 2007;91(12):1680–5.
121. Arantes TEF, Matos K, Garcia CR, Silva TGC, Sabrosa AS, Muccioli C. Fundus autofluorescence and spectral domain optical coherence tomography in recurrent serpiginous choroiditis: case report. Ocul Immunol Inflamm. 2011;19(1):39–41.
122. Jones BE, et al. Relentless placoid chorioretinitis: a new entity or an unusual variant of serpiginous chorioretinitis? Arch Ophthalmol. 2000;118(7):931–8.
123. Kovach JL. Persistent placoid maculopathy imaged with spectral domain OCT and autofluorescence. Ophthalmic Surg Lasers Imaging. 2010;41:S101–3.
124. Amer R, Florescu T. Optical coherence tomography in relentless placoid chorioretinitis. Clin Exp Ophthalmol. 2008;36(4):388–90.
125. Gendy MG, Fawzi AA, Wendel RT, Pieramici DJ, Miller JA, Jampol LM. Multimodal imaging in persistent placoid maculopathy. JAMA Ophthalmol. 2014;132(1):38–49.
126. Yeh S, et al. Fundus autofluorescence imaging of the white dot syndromes. Arch Ophthalmol. 2010;128(1):46–56.
127. Patel M, Vavvas DG. Fundus autofluorescence in ampiginous choroiditis. Ophthalmic Surg Lasers Imaging Retina. 2014;44(4):393–7.
128. Diaz RI, Sigler EJ, Rafieetary MR, Calzada JI. Ocular histoplasmosis syndrome. Surv Ophthalmol. 2015;60(4):279–95.
129. Kleiner RC, Ratner CM, Enger C, Fine SL. Subfoveal neovascularization in the ocular histoplasmosis syndrome. A natural history study. Retina. 1988;8(4):225–9.

130. Schlaegel TF, Weber JC. Follow-up study of presumed histoplasmic choroiditis. Am J Ophthalmol. 1971;71(6):1192–5.
131. Adhi M, Jusufbegovic D, Schaal S. Sequential chorioretinal changes in presumed ocular histoplasmosis syndrome analyzed using spectral domain optical coherence tomography. Ocul Immunol Inflamm. 2017;25(4):545–53.
132. Liu TYA, Zhang AY, Wenick A. Evolution of choroidal neovascularization due to presumed ocular histoplasmosis syndrome on multimodal imaging including optical coherence tomography angiography. Case Rep Ophthalmol Med. 2018;2018:4098419.
133. Wang JC, Laíns I, Sobrin L, Miller JB. Distinguishing white dot syndromes with patterns of choroidal hypoperfusion on optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina. 2017;48(8):638–46.
134. Delair E, Latkany P, Noble AG, Rabiah P, McLeod R, Brézin A. Clinical manifestations of ocular toxoplasmosis. Ocul Immunol Inflamm. 2011;19(2):91–102.
135. Park YH, Nam HW. Clinical features and treatment of ocular toxoplasmosis. Korean J Parasitol. 2013;51(4):393–9.
136. Bonfioli AA, Orefice F. Toxoplasmosis. Semin Perinatol. 2005;20(3):129–41.
137. Ouyang Y, et al. Subretinal fluid in eyes with active ocular toxoplasmosis observed using spectral domain optical coherence tomography. PLoS One. 2015;10(5):e0127683.
138. Leal I, Sousa DC, Costa J, Vaz-Carneiro A. Analysis of the cochrane review: Cortisteroid implants for chronic non-infectious Uveitis. Cochrane database syst rev. 2016;2:CD010469. Acta Medica Port. 2018;31(5):243–6.
139. Dees C, Arnold JJ, Forrester JV, Dick AD. Immunosuppressive treatment of choroidal neovascularization associated with endogenous posterior uveitis. Arch Ophthalmol. 1998;116(11):1456–61.
140. Brueggeman RM, Noffke AS, Jampol LM. Resolution of punctate inner choroidopathy lesions with oral prednisone therapy. Arch Ophthalmol. 2002;120(7):996.
141. Fine SL, et al. Laser treatment for subfoveal neovascular membranes in ocular histoplasmosis syndrome: results of a pilot randomized clinical trial. Arch Ophthalmol. 1993;120(7):996.
142. Hogan A, Behan U, Kilmartin DJ. Outcomes after combination photodynamic therapy and immunosuppression for inflammatory subfoveal choroidal neovascularisation. Br J Ophthalmol. 2005;89(9):1109–11.
143. Giovannini A, Neri P, Mercanti L, Bruè C. Photodynamic treatment versus photodynamic treatment associated with systemic steroids for idiopathic choroidal neovascularisation. Br J Ophthalmol. 2007;91(5):620–3.
144. Leslie T, Lois N, Christopoulou D, Olson JA, Forrester JV. Photodynamic therapy for inflammatory choroidal neovascularisation unresponsive to immunosuppression. Br J Ophthalmol. 2005;89(2):147–50.
145. Nowilaty SR, Bouhaimed M. Photodynamic therapy for subfoveal choroidal neovascularisation in Vogt-Koyanagi-Harada disease. Br J Ophthalmol. 2006;90(8):982–6.
146. Parodi MB, Iacono P, Kontadakis DS, Zucchiatti I, Cascavilla ML, Bandello F. Bevacizumab vs photodynamic therapy for choroidal neovascularization in multifocal choroiditis. Arch Ophthalmol. 2010;128(9):1100–3.
147. Chan WM, Lai TYY, Lau TTY, Lee VYW, Liu DTL, Lam DSC. Combined photodynamic therapy and intravitreal triamcinolone for choroidal neovascularization secondary to punctate inner choroidopathy or of idiopathic origin: one-year results of a prospective series. Retina. 2008;28(1):71–80.
148. Olsen TW, Capone A Jr, Sternberg P Jr, Grossniklaus HE, Martin DF, Aaberg TM Sr. Subfoveal choroidal neovascularization in punctate inner choroidopathy: surgical management and pathologic findings. Ophthalmology. 1996;103(12):2061–9.
149. Tran THC, Fardeau C, Terrada C, Ducos De Lahitte G, Bodaghi B, Lehoang P. Intravitreal bevacizumab for refractory choroidal neovascularization (CNV) secondary to uveitis. Graefes Arch Clin Exp Ophthalmol. 2008;246(12):1685–92.
150. Mansour AM, et al. Three-year visual and anatomic results of administrating intravitreal bevacizumab in inflammatory ocular neovascularization. Can J Ophthalmol. 2012;47(3):269–74.

151. Rouvas A, et al. Intravitreal ranibizumab for the treatment of inflammatory choroidal neovascularization. Retina. 2011;31(5):871–9.
152. Hernández-Martínez P, Dolz-Marco R, Alonso-Plasencia M, Abreu-Gonzalez R. Aflibercept for inflammatory choroidal neovascularization with persistent fluid on intravitreal ranibizumab therapy. Graefes Arch Clin Exp Ophthalmol. 2014;252(8):1337–9.
153. Arevalo JF, et al. Intravitreal bevacizumab for inflammatory choroidal neovascularization: Results from the Pan-American collaborative retina study group at 24 months. Retina. 2011;31(2):353–63.
154. Cerquaglia A, Fardeau C, Cagini C, Fiore T, LeHoang P. Inflammatory choroidal neovascularization: beyond the intravitreal approach. Ocul Immunol Inflamm. 2018;26(7):1047–52.
155. Iannetti L, Paroli MP, Fabiani C, Nardella C, Campanella M, Pivetti-Pezzi P. Effects of intravitreal bevacizumab on inflammatory choroidal neovascular membrane. Eur J Ophthalmol. 2013;23(1):114–8.
156. D'Souza P, Ranjan R, Babu U, Kanakath AV, Saravanan VR. Inflammatory choroidal neovascular membrane: Long-term visual and anatomical outcomes after intravitreal anti-vascular endothelial growth factor therapy. Retina. 2018;38(7):1307–15.
157. Rothova A. Corticosteroids in uveitis. Ophthalmol Clin N Am. 2002;15(3):389–94.
158. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. Exp Eye Res. 2005;80(2):249–58.
159. Oliver A, Ciulla TA. Corticosteroids as antiangiogenic agents. Ophthalmol Clin N Am. 2006;19(3):345–51.
160. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf. 2016;15(4):457–65.
161. Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289–94.
162. Bian ZM, Elner SG, Elner VM. Regulation of VEGF mRNA expression and protein secretion by TGF-β2 in human retinal pigment epithelial cells. Exp Eye Res. 2007;84(5):812–22.
163. Regatieri CV, Dreyfuss JL, Melo GB, Lavinsky D, Farah ME, Nader HB. Dual role of intravitreous infliximab in experimental choroidal neovascularization: Effect on the expression of sulfated glycosaminoglycans. Invest Ophthalmol Vis Sci. 2009;50(11):5487–94.
164. Mateo-Montoya A, Baglivo E, De Smet MD. Intravitreal methotrexate for the treatment of choroidal neovascularization in multifocal choroiditis. Eye (Lond). 2013;27(2):277–8.
165. Pai S, Hebri S, Lootah A. Management of recurrent inflammatory choroidal neovascular membrane secondary to Vogt-Koyanagi-Harada syndrome, using combined intravitreal injection of bevacizumab and triamcinolone acetate. Indian J Ophthalmol. 2012;60(6):551–2.
166. Mansour AM, et al. Long-term visual outcomes of intravitreal bevacizumab in inflammatory ocular neovascularization. Am J Ophthalmol. 2009;148(2):310–6.
167. Winterhalter S, Joussen AM, Pleyer U, Stübiger N. Inflammatory choroidal neovascularisations. Klin Monatsbl Augenheilkd. 2012;229(9):897–904.

Chapter 11
Treatment of Inflammatory Choroidal Neovascular Membranes

Piergiorgio Neri

Introduction

The development of choroidal neovascular membrane (CNV) is a result of angiogenic drive mediated by local inflammation or secondary to degenerative disruption of the retinal pigment epithelium (RPE)—Bruch's membrane complex. It can also be due to a combination of both mechanisms. The pathology of neovascular membranes is similar between the different kinds of membranes, with the exception that CNV membranes in uveitis are more likely to be of type II [1].

The natural course and visual prognosis of inflammatory CNV are generally considered to be more favorable than the CNV resulting from age-related macular degeneration (AMD). It may be due to the classic nature and smaller size of the membrane and younger age of patients as compared to AMD-related CNV [2].

Treatment of CNV has evolved rapidly in recent years. Treatment of CNV has largely been extrapolated from the results of studies of CNV in AMD and myopia. Several techniques have been proposed for the management of inflammatory CNV in the past, such as argon laser photocoagulation, surgical removal, and photodynamic therapy [3]. On the other hand, those techniques were abandoned since years in order to leave the scene to newer, safer and more appropriate ones.

While the underlying inflammation is generally treated with periocular, intravitreal and systemic steroids, their long course may lead to several complications and this represents a clear warning that has to be considered for the optimal control of the disease [4]. The safety and efficacy of systemic immunosuppressive steroid sparing drugs for the treatment of uveitic CNV were reported [5], showing a satisfying control in combination with systemic steroids.

Nowadays, local vascular endothelial growth factor (VEGF) inhibition plays a crucial role in neovascular process and the modern approach to inflammatory CNV

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has intravitreal anti-VEGF agents as a strongly recommended therapy [6]. This method is widely used in the treatment of age-related macular degeneration and pathologic myopia, but no randomized control trial has been published yet for uveitic CNV. Furthermore, no trials are available in uveitis to compare the available anti-VEGF drugs at this time or to compare the intravitreal injection protocol to be applied. Therefore, anti-VEGF agents are empirically used for the treatment of inflammatory CNV and the pro re nata (PRN) technique is empirically used.

Treatment of CNV Associated with Infectious Uveitis

Infectious uveitis is rarely associated with the occurrence of inflammatory CNV, which has to be promptly treated with the combination of anti-VEGF and anti-infective agents. In this section we will describe the most typical forms and their therapy.

Bacteria

Choroidal neovascularization is rarely associated with bacterial infections and the medical literature offers only few case reports.

On the other hand, a series of different conditions might induce a bacterial embolus, such as cardiac infections (endocarditis, aortic valve infection, renal and bone abscess) or intravenous drug abuse and may trigger the neovascular proliferation.

CNV occurring in bacterial infections is generally located at the edge of the primary chorioretinal lesion, or near an old atrophic scar.

Tuberculosis (TB) is the bacterial disease which has been more commonly associated with CNV.

The treatment of such CNV is based on the association of systemic drugs and anti-VEGF agents that should be given in collaboration with the infectivologist. The role played by TB in serpiginous choroiditis is discussed deeper in this chapter afterwards.

Unfortunately, due to the scarce prevalence of all the forms, no trials and few case reports are available in the literature and an empirical therapy has to be promptly initiated.

Viruses

Viruses are unfrequently associated with CNV, albeit RPE, Bruch's membrane and choroid are significantly involved and might induce neoangiogenesis.

Rubella was the very first viral infection associated with CNV, when in 1978 Frank and Purnell described a congenital rubella retinopathy in two patients who

presented a unilateral CNV, lately degenerated to scar tissue. Other reports described the same pattern few years later.

CNV in West Nile virus was more recently described, successfully treated with intravitreal anti-VEGF injections.

Although the medical literature does not present many cases associated with viral retinopathies, RPE impairment might trigger VEGF over production in whatever posterior pole viral uveitis. The empirical approach to these diseases is represented by the systemic therapy coupled with intravitreal anti-VEGF therapy.

Protozoa

Although a series of protozoa have been rarely associated with retinal diseases, such as *Trypanosoma cruzi*, *Trypanosoma evansi*, and *Leishmania*, *Toxoplasma gondii* represents the most relevant one associated with CNV occurrence with an esteemed prevalence in between 0.3% and 19%. In ocular toxoplasmosis, CNV is peculiarly located at the edge of an old chorioretinal scar and rarely may occur in active toxoplasmic retinochoroiditis. Up to date, CNV occurring in ocular toxoplasmosis is empirically treated with intravitreal anti-VEGF.

Fungi

Systemic mycoses may involve any organ, including skin, bronchopulmonary and digestive tract, central nervous system and eyes as well.

Several reports described CNV as a potentially severe complication of fungal infections, such as *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*.

Among fungal infections, *Histoplasma capsulatum* is an endemic fungus in some areas in United States, and represents the most relevant one. The ocular histoplasmosis syndrome presents a typical triad: linear, peripheral chorioretinal scars, peripapillary atrophy and CNV. In the past, when the histoplasmin skin test resulted negative, the term "presumed ocular histoplasmosis syndrome" (POHS) was proposed, speculating on a possible choroidal immune-reaction to the infective agent. The acronym is no longer commonly used and this issue will be discussed afterwards in this chapter.

Helminthes

Parasitic worms can affect humans, involve the eyes and potentially trigger choroidal neoangiogenesis. Among helminthes, *Toxocara canis* may rarely generate CNV, typically occurring near an active or quiescent choroidal granuloma. The empirical

use of intravitreal anti-VEGF drugs may exert a good control of the neoangiogenesis.

Treatment of CNV Associated with Non-infectious Uveitis

Non-infectious posterior and pan-uveitis uveitis are frequently associated with the occurrence of inflammatory CNV, which may represent a severe complication in different subtypes. In this section we will describe the most common forms and their treatment.

Intravitreal Anti-Vascular Endothelial Growth Factor Injections

In CNV secondary to inflammatory diseases, a closed circuit exists between VEGF and inflammatory cells because leukocytes and macrophages can produce VEGF themselves, and this interaction between VEGF and inflammation seem to stimulate growth and maintenance of the CNV [7]. Therefore, many strategies for inhibiting VEGF signaling are under study as potential treatments for inflammatory CNV [6].

Adán et al. [8] showed a significant improvement in visual acuity in 88.8% of eyes with inflammatory CNV and a significant reduction in foveal thickness after bevacizumab injection as primary treatment. Other studies [9–11] have shown that VA can improve in at least 30% of CNV secondary to inflammatory diseases. Kramer [12] reported a retrospective study of ten patients with CNV related to inflammatory diseases, who were treated with a mean of 2.7 intravitreal bevacizumab injections and achieved resolution of subretinal fluid on optical coherence tomography (OCT) in all patients, with improvement in visual acuity in nine of ten eyes. They concluded that intravitreal bevacizumab is an effective treatment for CNV related to inflammatory diseases when inflammation is controlled. Mansour et al. [13] have reported one of the largest series to date on the 24-month visual outcomes of intravitreal bevacizumab in inflammatory ocular neovascularization. However, their series included variable follow-up (minimum of 6 months of follow-up was allowed) and a variety of inflammatory ocular neovascularization, including retinal neovascularization and CNV. Although the majority of their cases were inflammatory CNV cases, only 27 cases had 24 months of follow-up. They concluded that long-term intravitreal anti-VEGF treatment led to significant visual improvement of >2.2 lines and significant foveal flattening in a wide variety of inflammatory ocular diseases without major complications [13].

In patients with MFC and PIC, the natural history has showed that one third can develop CNV, and severe visual loss in these inflammatory diseases is usually because of subfoveal CNV [14]. Previous studies have shown that in CNV secondary to PIC, intravitreal bevacizumab could result in a mean visual improvement of approximately three lines [15, 16]. Arevalo et al. [17] have reported eight cases of

PIC-induced inflammatory CNV, out of which seven had stable or improved vision with intravitreal anti-VEGF injections. Fine et al. [18] reported a case series of six eyes with CNV associated to MFC that were treated with intravitreal anti-VEGF (bevacizumab or ranibizumab) and improved to a VA of 20/30 or better at 6 months.

In a study of 28 eyes, Schadlu et al. [19] reported that 92.8% of eyes treated with intravitreal bevacizumab for CNV secondary to POHS avoided mild visual loss (1.5 ETDRS lines). Adán et al. [8] reported a case of CNV secondary to POHS that required only one injection of bevacizumab with complete resolution within 3 months. Choroidal neovascularization occurs in 15% of VKH patients and is associated with poor visual prognosis. Intravitreal anti-VEGF treatment seems to stabilize visual acuity and reduce subretinal fluid in cases with CNV secondary to VKH, but multiple injections are usually necessary [20].

Intravitreal Anti-VEGF Regimen

Randomized clinical trials (RCT) have demonstrated the efficacy of specific injection regimens for anti-VEGF drugs in the treatment of CNVs secondary to nAMD. These regimens generally include a loading phase of three monthly administrated injections followed by a variable number of retreatments depending on the CNV activity, the visual outcomes and the anti-VEGF drug [21–23]. Separate RCTs have reported the efficacy of a different, more discontinuous, anti-VEGF injection regimen for myopic CNVs. This scheme omits the loading phase and eyes are treated only when the CNV lesion is active, or "pro re nata" (PRN), from the start [24]. There are several independent reports of efficacy of anti-VEGF drugs for inflammatory CNVs [13, 25]. However, the optimal regimen is yet to be determined due to the lack of RCTs and due to the off-label use of some anti-VEGF agents for the treatment of inflammatory CNVs.

In a study by Arevalo et al. [17] where the authors elected to defer reinjections until there was a recurrence, among 23 eyes with inflammatory CNV the mean time between intravitreal bevacizumab injections was 19.8 weeks and 60.8% needed only one injection at 24 months. Heier et al. [26] compared the efficacy of monthly intravitreal ranibizumab with three monthly injections followed by PRN injections for inflammatory CNV and had found comparable efficacy with both treatment protocols. They have also mentioned that patients on PRN protocol received 38% fewer injections than those on monthly injection protocols to achieve a similar outcome. In a retrospective study, Roy et al. [27] found that 80% of patients on PRN basis maintained or gained vision at final follow-up.

In a study recently presented at the Association for Research in Vision and Ophthalmology, Invernizzi et al. [28] found that eyes treated with a PRN approach from the beginning had similar outcomes compared to eyes treated with a loading dose of three monthly injections followed by a PRN regimen, and received a significantly lower number of injections at 12 and 24 months. Eyes with iCNV responded promptly to anti-VEGF treatment with a significant improvement in BCVA in both

groups 3 months after starting treatment. This initial gain of 2–3 LogMAR lines was maintained at 12 and 24 months in both groups. The number of recurrences and consequent retreatments was low in both groups, with most of the eyes in the PRN group receiving fewer than three injections during their entire follow-up. This suggests that the initial three-monthly injections given to the latter group did not reduce the number of recurrences and retreatments during the following 2 years.

Immunosuppression

Several methods have been proposed for the treatment of inflammatory CNV but all of them are focused on the control of the CNV itself without considering this occurrence a possible product of the inflammation tout court. It is not rare to observe the onset of a subfoveal CNV with no signs of active uveitis but it is still unclear why CNV can occur in apparently inactive uveitis. Some years ago, the role of a low grade, subclinical inflammation involving the retina has been speculated. The hypothesized role played by the low-grade inflammation might be reasonably the real trigger of uveitic CNV and is not distant to what happens in the joints for chronic arthritis [29] where hypoxia, oxidative stress and inflammation lead to the occurrence of the intra-articular neovascularization. This hypothesis is supported by the evidence that inflammatory process plays a role in other types of neoangiogenesis, such as in age related macular degeneration (AMD) [30, 31].

The majority of the physicians rely to steroids as the first-line drug for the control of non-infectious ocular inflammation. The supposed additional role of systemic corticosteroids for the control of inflammatory CNV has been previously reported [32]. Before the advent of anti-VEGF, there was an interest in treating inflammatory CNV with steroids. In a study of ten patients who received oral prednisone and eight who received sub-Tenon's triamcinolone, there appeared to be a short-term improvement in visual acuity [33]. However, this effect had vanished by 4 weeks after the treatment started, and visual acuities were worse than baseline at 3 months after treatment initiation. It is likely that steroids act to improve visual acuity by reducing leakage of the inflammatory CNV over the first few weeks, but it is unlikely that they can lead to complete stabilization of the CNV as a solo therapy.

At the same time, since ocular side effects of systemic corticosteroids, such as cataract, ocular hypertension and glaucoma [34] can occur, steroid-sparing drugs should be appropriately associated. Some physicians have attempted to treat inflammatory CNV in the context of non-infectious uveitis with immunosuppression. The largest study before anti-VEGF era [35] treated 17 eyes inflammatory CNV with systemic steroids and cyclosporine, azathioprine, or with both agents. The patients were followed for a median of 15 months during which there was resolution of active CNV in ten eyes, recurrence in three eyes, and persistent leakage in three cases. In addition to this case series, there are a number of pertinent case reports. Nussenblatt and colleagues used the immunosuppressive and anti-angiogenic drug sirolimus to treat subfoveal CNV in the context of quiescent PIC in a 33-year-old female, achieving a return to 20/16 vision with excellent fluorescein

angiographic and OCT results [36]. A case of CNV occurring 16 months after the onset of sympathetic ophthalmia in a 3-year-old boy responded to cyclosporine 5 mg/kg over a period of 3 months.

Albeit the role of immunosuppression in ophthalmology is clearly established [35], several points are still unsolved, particularly which steroid-sparing drug should be considered the most suitable one. Dees et al. [35] reported 14 patients with uveitic CNV successfully treated with systemic immunosuppressants, even though they did not propose a single regimen. Mycophenolate mofetil has reached a considerable role in the treatment of uveitis [35] and its complications [37, 38]. On the other hand, it is important to stress that immunosuppressive agents should be chosen on the basis of the systemic assessment and status of the single patient.

Combination Therapy with Immunosuppression and Intravitreal Injections of Anti-VEGF

Although anti-VEGF are considered the real "*Copernican Revolution*" in ophthalmology and the gold standard for the treatment of the neovascular process secondary to age-related macular degeneration and myopic maculopathy, regulating VEGF represents just the tip of the iceberg for the control of inflammatory CNV. For such reason, the use of systemic steroids is common for non-infectious CNV [39, 40], albeit the possible severe side effects such as cataract [41] and glaucoma [42]. So far, the role of immunosuppression for the treatment of inflammatory CNV still remains not well defined. Some preliminary studies have proved that immunosuppressive agents can exert a positive control on the neovascular process. Cyclosporine A (CSA) [43] and Mycophenolate Mofetil (MMF) [37] have been proposed for the long-term control of inflammatory CNV, although the timing, the choice of drug and the combination with other treatment still remain unclear.

Neri et al. [44] retrospectively analysed patients affected by inflammatory CNV which received immediate versus delayed immunosuppressive agents in addition to the oral steroid and intravitreal anti-VEGF treatment. At 6, 24 and at 36 months of follow up, BCVA showed a statistically significant difference in favor of the group where systemic immunosuppression was started at the time of intravitreal injection treatment for the inflammatory CNV. This concept is furthermore reinforced by looking at the number of inflammatory CNV recurrences in the two groups: the group in which immunosuppression was delayed showed a mean number of recurrences of 2.1, while the group where immunosuppression was started at baseline had 0.4. This may be an additional proof that the concept of zero tolerance to the background choroidal inflammation might exert a much better long-term control of the disease.

On the other hand, Invernizzi et al. [28] observed that patients who received additional systemic immunosuppression experienced more inflammatory CNV activity and needed more injections. This apparently contradictory result could be explained by the fact that their study did not analyze the timing and the reasons why patients were started on immunosuppressive drugs. Clinicians may have decided to

start immunosuppressive treatment in patients that recurred more during the first few months, aiming thereby to reduce the number of injections. Alternatively, the requirement for immunosuppression might indicate more aggressive disease with chronic inflammation that can promote the reactivation of the inflammatory CNV.

Conclusions

CNV still represent a severe complication of uveitis. While the therapy for infectious subtype is mainly based on empirical intravitreal injection of anti-VEGF with or without the specific therapy for the infective agent, the treatment for the CNV associated with non-infectious uveitis deserves a more structured therapy. The modern approach is mainly based on the combination of steroids, prevalently given systemically, systemic immunosuppressive agents and intravitreal anti-VEGF. When treating an inflammatory the physician must also ensure that the ocular inflammation is completely controlled, which may require an increase in medication dosage or addition of another immunosuppressive agent. The few retrospective results available in the literature suggest that inflammatory CNVs respond quickly to anti-VEGF treatment and, unlike AMD-related CNVs, tend to remain quiescent once they have become inactive. This could be because most inflammatory CNV are located between Bruch's membrane and the retinal pigment epithelium (RPE) similar to "classic" lesions in AMD that usually respond faster to anti-VEGF injections. A second hypothesis could be that uveitic eyes, in contrast to nAMD, often have a healthier RPE that can prevent recurrences by reacting and enveloping the inflammatory CNV, similarly to what is commonly observed in myopic CNVs.

The comparison between the two available treatment regimens (PRN versus loading dose) highlights that the loading phase of three injections within the first 3 months of treatment does not confer any advantage in terms of visual outcome or number of recurrences. Further studies are needed to confirm these findings but a PRN anti-VEGF treatment regimen from the beginning seems to be as effective as more intense anti-VEGF management.

References

1. Arnold JJ, Campain A, Barthelmes D, et al. Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. Ophthalmology. 2015;122(6):1212–9.
2. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? Retina. 2010;30(9):1333–49.
3. Wu K, Zhang X, Su Y, et al. Clinical characteristics of inflammatory choroidal neovascularization in a Chinese population. Ocul Immunol Inflamm. 2016;24(3):261–7.
4. Shoughy SS, Jaroudi MO, Tabbara KF. Regression of peripapillary choroidal neovascular membrane in a patient with sarcoidosis after oral steroid therapy. Saudi J Ophthalmol. 2014;28(2):160–2.

5. Nobrega MJ, et al. Anecortave may help choroidal neovascularization regression in serpiginous choroiditis. Can J Ophthalmol. 2007;42(1):151–2.
6. Mansour AM, Arevalo JF, Fardeau C, et al. Three-year visual and anatomic results of administrating intravitreal bevacizumab in inflammatory ocular neovascularization. Can J Ophthalmol. 2012;47(3):269–74.
7. Gillies MC, Campain A, Walton R, et al. Time to initial clinician-reported inactivation of neovascular age-related macular degeneration treated primarily with ranibizumab. Ophthalmology. 2015;122(3):589–94.e1.
8. Adán A, Mateo C, Navarro R, Bitrian E, Casaroli-Marano RP. Intravitreal bevacizumab (avastin) injection as primary treatment of inflammatory choroidal neovascularization. Retina. 2007;27(9):1180–6.
9. Hohberger B, Rudolph M, Bergua A. Choroidal neovascularization associated with punctate inner choroidopathy: combination of intravitreal anti-VEGF and systemic immunosuppressive therapy. Case Rep Ophthalmol. 2015;6(3):385–9.
10. Ganesh S, Ahmed A, Biswas J. Analysis of the clinical profile and management of inflammatory choroidal neovascular membranes in uveitic eyes: a study from a tertiary referral center. Ocul Immunol Inflamm. 2019;27:424–34.
11. Arrevola L, Acero MA, Peral MJ. Two-year outcome of aflibercept for the treatment of choroidal neovascularization in punctate inner choroidopathy. Case Rep Ophthalmol. 2019;10(1):24–31.
12. Kramer M. Photodynamic therapy for inflammatory CNV: do we know enough? Ocul Immunol Inflamm. 2005;13(5):331–3.
13. Mansour AM, Mackensen F, Arevalo JF, Ziemssen F, Mahendradas P, Mehio-Sibai A, Hrisomalos N, Lai TY, Dodwell D, Chan WM, Ness T, Banker AS, Pai SA, Berrocal MH, Tohme R, Heiligenhaus A, Bashshur ZF, Khairallah M, Salem KM, Hrisomalos FN, Wood MH, Heriot W, Adan A, Kumar A, Lim L, Hall A, Becker M. Intravitreal bevacizumab in inflammatory ocular neovascularization. Am J Ophthalmol. 2008;146(3):410–6.
14. Tavallali A, Yannuzzi LA. Idiopathic multifocal choroiditis. J Ophthalmic Vis Res. 2016;11(4):429–32.
15. Tsaousis KT, Nassr M, Kapoor B, Konidaris VE, Tyradellis S, Empeslidis T. Long-term results of intravitreal bevacizumab and dexamethasone for the treatment of punctate inner choroidopathy associated with choroidal neovascularization: a case series. SAGE Open Med Case Rep. 2018;6:2050313X18772478.
16. Chen SN, Chen YL, Yang BC. Long-term outcome of punctate inner choroidopathy or multifocal choroiditis with active choroidal neovascularization managed with intravitreal bevacizumab. Ocul Immunol Inflamm. 2019:1–6. https://doi.org/10.1080/09273948.2019.1588335.
17. Arevalo JF, Adan A, Berrocal MH, Espinoza JV, Maia M, Wu L, Roca JA, Quiroz-Mercado H, Ruiz-Moreno JM, Serrano MA, Pan-American Collaborative Retina Study Group. Intravitreal bevacizumab for inflammatory choroidal neovascularization: results from the Pan-American Collaborative Retina Study Group at 24 months. Retina. 2011;31(2):353–63.
18. Fine HF, Zhitomirsky I, Freund KB, Barile GR, Shirkey BL, Samson CM, Yannuzzi LA. Bevacizumab (avastin) and ranibizumab (lucentis) for choroidal neovascularization in multifocal choroiditis. Retina. 2009;29(1):8–12.
19. Schadlu R, Blinder KJ, Shah GK, Holekamp NM, Thomas MA, Grand MG, Engelbrecht NE, Apte RS, Joseph DP, Prasad AG, Smith BT, Sheybani A. Intravitreal bevacizumab for choroidal neovascularization in ocular histoplasmosis. Am J Ophthalmol. 2008;145(5):875–8.
20. Wu K, Zhang X, Su Y, Ji Y, Zuo C, Li M, Wen F. Clinical characteristics of inflammatory choroidal neovascularization in a Chinese population. Ocul Immunol Inflamm. 2016;24(3):261–7.
21. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO study. Am J Ophthalmol. 2009;148(1):43–58.e1.
22. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. Am J Ophthalmol. 2008;145(2):239–48.e5.
23. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537–48.

24. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology. 2014;121(3):682–92.e2.
25. Spiteri Cornish K, Williams GJ, Gavin MP, Imrie FR. Visual and optical coherence tomography outcomes of intravitreal bevacizumab and ranibizumab in inflammatory choroidal neovascularization secondary to punctate inner choroidopathy. Eur J Ophthalmol. 2011;21(4):440–5.
26. Heier JS, Brown D, Ciulla T, Abraham P, Bankert JM, Chong S, Daniel PE Jr, Kim IK. Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: a phase I clinical trial. Ophthalmology. 2011;118(1):111–8.
27. Roy R, Saurabh K, Bansal A, Kumar A, Majumdar AK, Paul SS. Inflammatory choroidal neovascularization in Indian eyes: etiology, clinical features, and outcomes to anti-vascular endothelial growth factor. Indian J Ophthalmol. 2017;65(4):295–300.
28. Invernizzi A, Pichi F, Symes R, Zagora S, Nguyen V, Erba S, Xhepa A, De Simone L, Cimino L, Gillies MC, McCluskey PJ. Twenty-four month outcomes of inflammatory choroidal neovascularization treated with intravitreal anti vascular endothelial growth factors: a comparison between two treatment regimens. Abstract 3859, ARVO Annual Meeting, Vancouver Convention Centre, Vancouver, BC, Canada.
29. McGarry T, Biniecka M, Veale DJ, Fearon U. Hypoxia, oxidative stress and inflammation. Free Radic Biol Med. 2018;125:15–24.
30. Chen M, Rajapakse D, Fraczek M, Luo C, Forrester JV, Xu H. Retinal pigment epithelial cell multinucleation in the aging eye – a mechanism to repair damage and maintain homoeostasis. Aging Cell. 2016;15(3):436–45.
31. Balne PK, Agrawal R, Au VB, Lee B, Ghosh A, Sethu S, Agrawal M, Narayanan R, Connolly J. Dataset of plasma and aqueous humor cytokine profiles in patients with exudative age related macular degeneration and polypoidal choroidal vasculopathy. Data Brief. 2018;19:1570–3.
32. Flaxel CJ, Owens SL, Mulholland B, Schwartz SD, Gregor ZJ. The use of corticosteroids for choroidal neovascularisation in young patients. Eye (Lond). 1998;12(Pt 2):266–72.
33. Martidis A, et al. Corticosteroids as an antiangiogenic agent for histoplasmosis-related subfoveal choroidal neovascularization. J Ocul Pharmacol Ther. 1999;15(5):425–8.
34. Dibas A, Yorio T. Glucocorticoid therapy and ocular hypertension. Eur J Pharmacol. 2016;787:57–71.
35. Dees C, et al. Immunosuppressive treatment of choroidal neovascularization associated with endogenous posterior uveitis. Arch Ophthalmol. 1998;116(11):1456–61.
36. Nussenblatt RB, et al. The treatment of multifocal choroiditis associated choroidal neovascularization with sirolimus (rapamycin). Acta Ophthalmol Scand. 2007;85(2):230–1.
37. Neri P, Manoni M, Fortuna C, Lettieri M, Mariotti C, Giovannini A. Association of systemic steroids and mycophenolate mofetil as rescue therapy for uveitic choroidal neovascularization unresponsive to the traditional immunosuppressants: interventional case series. Int Ophthalmol. 2010;30(5):583–90.
38. Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A. Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate mofetil. Int Ophthalmol. 2009;29(3):127–33.
39. Vitale AT, Foster CS. Corticosteroids. In: Vitale AT, Foster CS, editors. Diagnosis and treatment of uveitis. Philadelphia: W.B. Saunders Company; 2002. p. 142–58.
40. Ferrante P, Ramsey A, Bunce C, Lightman S. Clinical trial to compare efficacy and side-effects of injection of posterior sub-Tenon triamcinolone versus orbital floor methylprednisolone in the management of posterior uveitis. Clin Exp Ophthalmol. 2004;32:563–8.
41. Llop SM, Papaliodis GN. Cataract surgery complications in uveitis patients: a review article. Semin Ophthalmol. 2018;33(1):64–9.
42. Neri P, Azuara-Blanco A, Forrester JV. Incidence of glaucoma in patients with uveitis. J Glaucoma. 2004;13(6):461–5.
43. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporine-induced resolution of choroidal neovascularization associated with sympathetic ophthalmia. Arch Ophthalmol. 1998;116(2):249–50.
44. Neri P, Arapi I. Inflammatory choroidal neovascularization: how combined anti-VEGF and inflammation suppressive therapy is going to become the treatment of choice. Acta Ophthalmologica, 89(s248).

Part VII
Cystoid Macular Edema Complicating Uveitis

Chapter 12
Pathophysiology of Uveitic Macular Edema

Ilaria Testi, Andres Rousselot, Rupesh Agrawal, and Carlos Pavesio

Macular edema is defined as an abnormal leakage and accumulation of fluid in macular area. Macular edema is one of the main causes of permanent visual loss in uveitis as a consequence of chronic inflammation. The prevalence among uveitis patients is approximately 30%, according to the anatomic site and uveitis entity, associations with systemic diseases, onset and duration of uveitis [1, 2]. In a large cross-sectional study on the impact of uveitic macular edema on visual acuity, 44% of patients with cystoid macular edema (CME) had a visual acuity of 20/60 or less in at least one eye [3].

Macular edema can develop in anterior, intermediate, posterior and panuveitis, caused by different autoimmune and infectious etiologies. The most common uveitis entities complicated by CME include Birdshot retinochoroiditis, intermediate uveitis, acute retinal necrosis, sarcoidosis, Behçet's disease and juvenile idiopathic arthritis, with visual loss caused by macular edema seen mainly in Birdshot retinochoroiditis, intermediate uveitis, sarcoidosis and acute retinal necrosis [3, 4].

When uveitic macular edema is present, visual prognosis depends on duration of the edema and status of retinal layers, on the basis that chronic inflammation and longstanding edema lead inevitably to an irreversible disruption of the retinal neural architecture with subsequent permanent visual loss.

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Extracellular fluid can infiltrate retinal layers, accumulate in cavities commonly referred to as cysts, most often in the outer plexiform layer and inner nuclear layer, or collect in the subretinal space as subretinal fluid.

Macular edema is the consequence of an imbalance between fluid entry, fluid exit and retinal hydraulic conductivity leading to intraretinal and subretinal fluid accumulation [5]. The etiology is multifactorial, resulting from several different mechanisms that all act synergistically, towards an increase of the inner and outer blood-retinal barrier permeability. Synthesis of pro-inflammatory mediators, retinal pigment epithelium (RPE) dysfunction, vascular incompetence, changes in membrane conductance and permeability and osmotic forces play a determinant role in the pathogenesis of uveitic macular edema [1, 5, 6].

Regulation of Fluid and Molecules Transport: The Retinal Barriers

In the normal eye, the volume and composition of the extracellular compartment is controlled by the inner and outer retinal barrier, that regulate the entry of fluids and molecules into the neurosensory retina from the vitreous, retinal vessels and choroid through the RPE to the subretinal space. This process is guaranteed by the integrity of the structures that form the blood-retinal barriers and by the osmotic forces that exist across these barriers.

Inner Retinal Barrier

The inner blood retinal barrier is located in the inner retinal microvasculature and it is formed by tight junctions between endothelial cells (Fig. 12.1). Its main function is the regulation of fluid and molecule transport across retinal capillaries. Changes in both transcellular and paracellular transport across vascular bed can lead to an increase in barrier permeability, contributing to the subsequent alteration in flow.

Inter-Endothelial Cell Transport

Paracellular transport occurs between endothelial cells and is regulated by molecular complexes located in the intercellular spaces, consisting of tight junctions, adherens junctions and gap junctions (Fig. 12.1).

Tight junctions are formed by different types of transmembrane proteins, as occludins, claudins and junctional adhesion molecules (JAM), linked to the actin

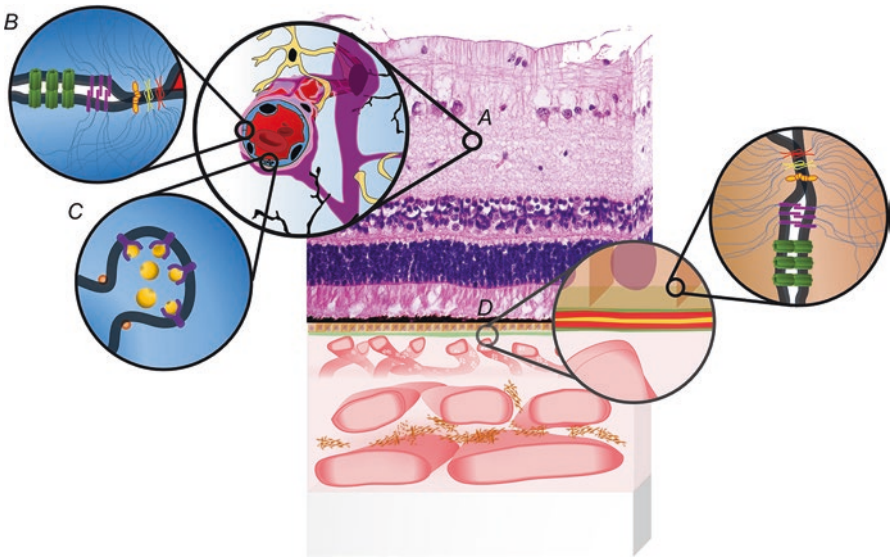

Fig. 12.1 Retinal barriers. (**a**) Inner blood retinal barrier, located in the inner retinal microvasculature, and neurovascular unit; (**b**) paracellular transport, regulated by tight junctions, adherens junctions and gap junctions; (**c**) transcellular transport, regulated by caveolae-mediated transcytosis. (**d**) Outer retinal barrier, consisting of RPE and intercellular junctions

cytoskeleton by cytoplasmic-scaffolding proteins, including members of the membrane-associated guanylate kinase homologue (MAGUK) family as the zonula occludens (ZO), essential in tight junctions formation.

Adherent junctions are constituted by (VE)-cadherins. Being determinant in vascular endothelial growth factor (VEGF)-R interaction, they prove decisive in the retinal barrier development process and subsequently in the regulation of paracellular permeability [5, 7].

Trans-Endothelial Cell Transport

Transcellular transport is regulated by caveolae-mediated transcytosis and consist of the migration of plasma membrane vesicles from one side of the cell to the other (Fig. 12.1). Vesicles contain receptors for albumin, transferrin, insulin, lipoproteins, immunoglobulins, platelet-derived growth factor (PDGF), VEGF and transforming growth factor-beta (TGF-β). Through the regulation of plasma macromolecules entry into the retinal tissue, transcytosis has a determinant role in the maintenance of the retinal protein gradients and subsequent in the modulation of fluid movements [5, 7].

The 'Neuro-Vascular Unit'

The development of inner retinal blood barrier is the result of close association of neurons, glia and pericytes with the vascular endothelium. The so called 'neuro-vascular unit' contributes to its dynamic regulation by the interaction between astrocytes and Muller cells with pericytes and smooth muscle cells, providing an extremely selected and regulated environment for the proper functioning of retinal cells (Fig. 12.1) [5–9].

Pericytes are specialized mural cells located at the luminal surface of retinal capillaries, their coverage on vessels directly contributes to the endothelial barrier function, with the ratio of their density to endothelial cells being 1:1. Pericytes are moreover involved in regulation of tight junctions proteins expression, modulating the inner blood-retinal barrier both in physiologic and pathologic conditions [5, 10].

Retinal glial cells include macroglia, composed of Muller cells and astrocytes, and microglia. Muller cells, as a functional link, play a crucial role in the neuro-vascular unit. Being directly connected with blood vessels, they are responsible for the formation and maintenance of a competent retinal barrier. Muller cells regulate the homeostasis of the extracellular environment through aquaporins and trans-membrane potassium channels and act in the local immune response and surveillance, releasing immunomodulatory mediators. Under condition of stress, the cells can synthesize pro-inflammatory cytokines as well as vast amounts of VEGF, with subsequent increase in vascular permeability [5, 11].

Also microglia cells are involved in retinal immuno surveillance. Directed towards immunosuppression in physiological condition, they can turn to a pro-inflammatory state able to influence Muller cells capability to regulate extracellular homeostasis [5, 6].

Outer Retinal Barrier

The outer blood retinal barrier consists of RPE and intercellular junctions, including tight, adherens and gap junctions, that regulate transport between the choriocapillaris and the retina, preventing the entry of fluids and molecules from the choroid to the subretinal space and, according to osmotic forces, allow flow exit towards the choroid, maintaining the adhesion between photoreceptors and RPE (Fig. 12.1) [5–7].

Role of Inflammation in Pathogenesis of Uveitic Macular Edema

Intraretinal fluid accumulates when there is loss of integrity and dysfunction in the inner and/or outer blood retinal barriers and this can due to inflammatory mediators that act modifying equilibrium of retinal milieu. Macular edema can result from an

increased influx of fluid inside the retina or from an insufficient drainage mechanism. Both components are subject to the influence of inflammation that, through the release and diffusion of pro-inflammatory mediators, has probably the principal initiating role in the development of uveitis related macular edema [1, 4, 6].

Bead based multiplex assays and proteomics analysis allowed the measurement of cytokines and chemokines in aqueous humor of patients with uveitis with and without macular edema. Aqueous analysis revealed high levels of intraocular inflammatory mediators, including VEGF and IL-6 that has been shown to be correlated with the presence of macular edema not only in uveitis but also in other non-inflammatory diseases, like proliferative diabetic retinopathy and branch retinal vein occlusion [2, 12–15].

Increased Permeability of Retinal Barriers

In uveitis patients with macular edema, angiography with fluorescein-conjugated dextrans showed that 4 and 20-kDa molecules crossed the inner blood retinal barrier, whereas no passage was observed in healthy controls [16]. This demonstrates the breakdown of inner blood retinal barrier present in inflammatory conditions such as uveitis.

Role of Glial Cells

Muller cells and microglial activation contributes to vessels' altered permeability through VEGF and pro-inflammatory cytokine production, including IL-6, IL-1, TNFα, INFα, INFβ, INFγ, IL-8. VEGF regulates tight junction proteins adhesion and expression and, through the interaction with its receptor, induces a cascade of intracellular phosphorylations of VE-cadherins and occludins, that together with the production of metalloproteinases stimulated by other inflammatory mediators, results in the degradation of tight junction proteins (Fig. 12.2). The result is a loss of integrity of the blood-retinal barrier with an associated increase of capillary permeability (Fig. 12.3) [1, 2, 4–6].

According to the same mechanisms, the disruption of RPE intercellular junctions favors fluid accumulation in the subretinal space (Fig. 12.3). It has been observed that exudative retinal detachment, suggestive of outer retinal barrier breakdown, is present in about 50% of uveitis related CME [17]. This suggests that inner and outer blood retinal dysfunction can take place together, and that the latter mechanism is probably underestimated.

A further mechanism involved in barriers permeability increase is the diapedesis of the leukocytes through the capillary walls. The process, caused by the up-regulation of intercellular adhesion molecule 1 (ICAM-1), due to elevated levels of VEGF produced by activated glial cells, contributes to retinal barriers dysfunction [5, 18].

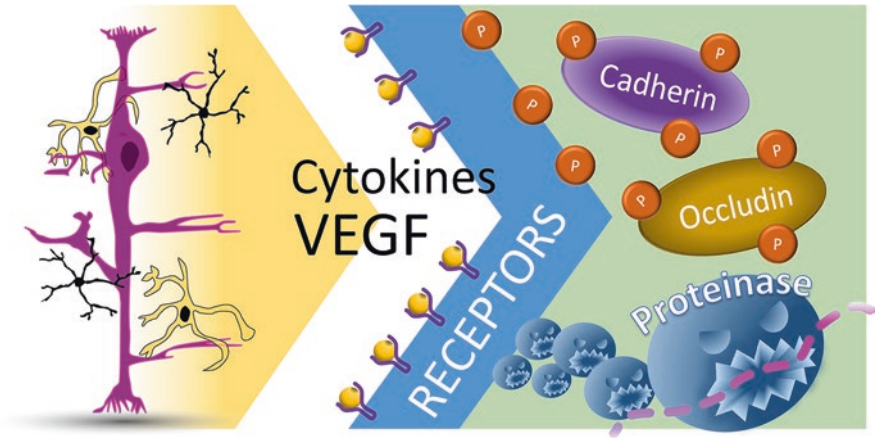

Fig. 12.2 VEGF and cytokines release. Activation of Muller cells and microglial induces the release of VEGF and pro-inflammatory cytokines that, interacting with the receptors, lead to phosphorylation of VE-cadherins and occludins and production of metalloproteinases

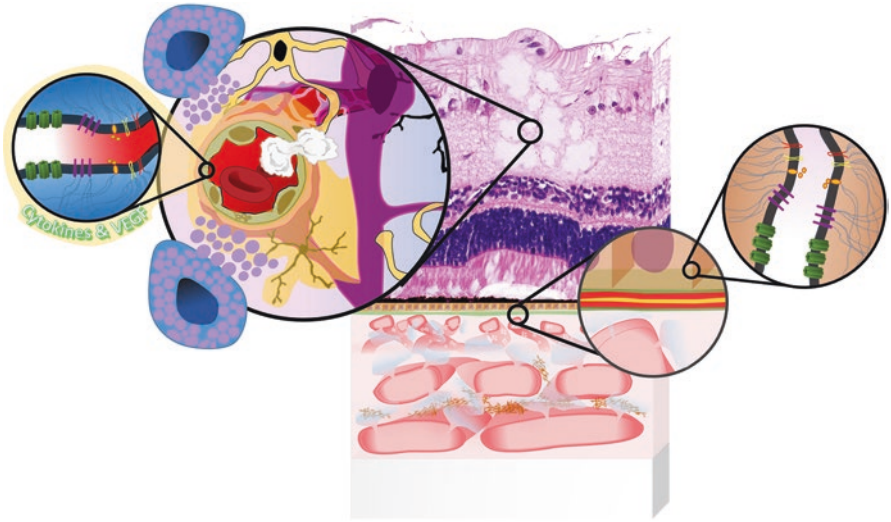

Fig. 12.3 Increased permeability. Degradation of tight junction proteins and disruption of RPE intercellular junctions due to pro-inflammatory mediators induce a loss of integrity of inner and outer retinal barrier with associated increase of permeability and retinal fluid accumulation

The angiographic petaloid pattern of cystoid macular edema is the result of fluid accumulation in the space between Muller cell fibers. Some researches believe that at the beginning the cystic spaces observed at OCT are swollen Muller cells and that the subsequent accumulation of fluid in the outer plexiform layer is a late phenomena due to cell displacement and disruption [19, 20].

Role of Retinal Pigment Epithelium

We have already established that disruption of RPE intercellular junctions can favor the entry of fluid from the choroidal space. Unlike retinal vessel, choroidal capillaris are characterized by extensive attenuation of the endothelium and numerous fenestrae [21]. In physiologic conditions passage of water of fluid through the choriocapillaris is slowed by the tight junctions. Several inflammatory mediators, including cytokines and VEGF, and activation of matrix metalloproteinases can alter the expression of the proteins constituting intercellular junctions [5, 6].

Similarly enhanced permeability of choroidal vessels or increase in their pressure can lead to RPE and outer retinal barrier disruption, due to the induced mechanical stress that can alter RPE conductivity and its performance in fluid drainage [5].

The RPE also secretes pro-inflammatory mediators such as IFNβ, IL-1, IL-6, IL-8, MCP-1 and gain the capability to turn into antigen presenting cell to the immune system, participating itself in the amplification of the inflammatory pathway. The synthesis of cycloxygenases is responsible for the production of prostaglandins, well known predisposing factors for macular edema [1, 6].

Role of Mast Cells

Mast cell degranulation is involved in outer retinal barrier dysfunction and has an essential role in ocular inflammation, being the first activated cells in experimental autoimmune uveitis [22]. Mast cells secrete various pro-inflammatory factors, including cytokines, chemokines, prostaglandins, growth factors and proteases. The production of histamine, that is not only a well known vasodilator, can seriously affect the integrity of retinal barriers through the control of VEGF-regulated genes transcription, including genes of proteins involved in tight junction structure [5, 22].

Reduction of Drainage Systems

In addition to vascular incompetence and RPE dysfunction, changes in membrane conductance and osmotic forces play a determinant role in the pathogenesis of uveitic macular edema.

Role of Muller Cells

Muller cells regulate the homeostasis of the extracellular milieu through aquaporins and transmembrane potassium channels (Kir). Reduction of potassium conductance has been observed in models of uvetis related macular edema constituting the mechanism of cytotoxic edema [23, 24]. In physiologic condition neural activity demands a rapid intake of sodium and calcium into the nervous cell, associated with an

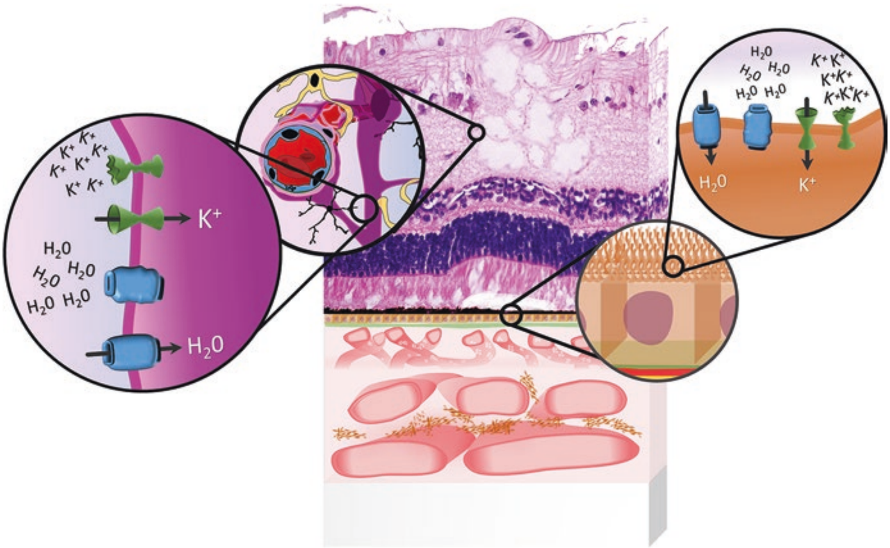

Fig. 12.4 Reduce drainage. Pro-inflammatory mediators leads to an overall decrease in synthesis and/or a mislocation of potassium channels resulting in functional alterations in Muller cell and RPE transmembrane conductivity, leading to cytotoxic macular edema

excretion of potassium in the extracellular space. Muller cell potassium channel Kir 4.1 and Kir 2.1 ensure a rapid transfer of potassium from the extracellular environment into its intracellular space, to avoid accumulation and neuronal hyperexcitability. Kir 4.1 channels work simultaneously with AQP4 in the extrusion of potassium and water into retinal capillaries through an ATP-dependent active transport. The presence of inflammation leads to an overall decrease in synthesis and/or a mislocation of Kir 4.1 channels, resulting in cellular polarization anomalies, intracellular edema and accumulation of subretinal fluid (Fig. 12.4) [1, 4–6]. It has been demonstrated that endogenous and therapeutical corticosteroids control the expression and localization of Kir and AQP4 channels, both in normal and inflamed rat eyes [5, 23].

Cytotoxic and Vasogenic Macular Edema

The functional alterations in Muller cell and RPE transmembrane conductivity lead to the formation of cytotoxic macular edema, characterized by healthy retinal capillary barrier in the absence of any vascular leakage on retinal angiography, despite manifest edema on optical coherence tomography (OCT). The cytotoxic macular edema can occur simultaneously with the vasogenic component of the inflammatory macular edema, resulting from the increase in permeability of the blood retinal barriers, due to secretion and diffusion of pro-inflammatory mediators from the activated glial cells.

Other Factors Involved in Uveitic Macular Edema Pathogenesis

Other factors can be involved in macular thickening due to intraretinal or subretinal fluid accumulation in uveitis patients.

Concurrent Systemic Risk Factors

Patients with high blood pressure, hypercholesterolemia, increased BMI and prolonged heavy smoking have a higher risk of cardiovascular disease due to the well known development of atherosclerotic lesions in the arteries. These conditions can also modify the structure and function of microscopic blood vessels through the activation of a low-grade systemic inflammatory response involving oxidative stress, leukocytes diapedesis and endothelial barrier dysfunction. The consequence is a systemic microvascular leakage that can take part in the development of uveitis related macular edema. In support of this hypothesis, trace microalbuminuria has been detected in uveitis patients with macular edema compared to patient without macular edema [2, 25–27].

Increasing age have been associated with an increased risk of macular edema. The decreased functioning of retinal cells occurring during life, enhanced by intraocular inflammation, can be associated with cellular dysfunction and vascular incompetence, resulting in increase in the entry of fluid through retinal vessels and reduction of drainage through RPE [2, 25, 26].

Ocular Complications of Inflammatory Disease

Intraocular inflammation is a well-known cause of epiretinal membrane (ERM). ERM specifically associated with uveitis differ from the idiopathic ERM in cellular composition and appear characterized by inflammatory cells such as microglia, macrophages and Muller cell extensions, suggesting that the etiology result from a different pathogenic mechanism [4, 28–30].

Pro-inflammatory mediators have been identified in the vitreous of patients with such membranes, including TNFα, activated complements, fibrinogen and other innate immune response factors [31]. Inflammation can hence lead to both the formation and exacerbation of epimacular membrane. Proliferation of the cellular components and contraction of the membrane can result in vitreomacular traction and localized elevation with macular edema.

Other mechanisms involved in the pathogenesis of uveitic macular edema are development of inflammatory choroidal vascularization, severe complication of intraocular inflammation resulting from a pathological process involving the RPE

and Bruch's membrane, papillary edema that diffuses by contiguity to macular area and central chorioretinopathy exacerbated by the chronic use of steroids.

In summary, any retinal stress can initiate an innate immune response, programmed to neutralize the insulting stimulus and restore homeostasis. This leads to activation of immune competent retinal resident cells such as Muller cells, microglia and RPE, associated to the production of pro-inflammatory mediators (VEGF, cytokines, histamine, prostaglandins, chemokines and other permeating factors), resulting in blood retinal barrier breakdown and macular edema. Furthermore the inflammatory activation of glial cell determines changes in synthesis and localization of water and ionic transmembrane channels in Muller and RPE cells, altering the hydraulic conductivity leading to intraretinal and subretinal fluid accumulation. Uveitic macular edema hence is the result of the activation of different inflammatory pathways which can be further evidenced by the effectiveness of treatment with local corticosteroids.

References

1. de Smet MD, Okada AA. Cystoid macular edema in uveitis. Dev Ophthalmol. 2010;47:136–47. Review.
2. Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18(6):487–92. Review.
3. Lardenoye CW, van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. Ophthalmology. 2006;113(8):1446–9.
4. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. Eye (Lond). 2016;30(10):1277–92.
5. Daruich A, Matet A, Moulin A, et al. Mechanism of macular edema: beyond the surface. Prog Retin Eye Res. 2018;63:20–68.
6. de Smet MD. Insights into the physiopathology of inflammatory macular edema. Dev Ophthalmol. 2017;58:168–77.
7. Díaz-Coránguez M, Ramos C, Antonetti DA. The inner blood-retinal barrier: cellular basis and development. Vis Res. 2017;139:123–37.
8. Yao H, Wang T, Deng J, Liu D, Li X, Deng J. The development of blood-retinal barrier during the interaction of astrocytes with vascular wall cells. Neural Regen Res. 2014;9(10):1047–54.
9. van der Wijk AE, IMC V, van Veen HA, et al. Spatial and temporal recruitment of the neurovascular unit during development of the mouse blood-retinal barrier. Tissue Cell. 2018;52:42–50.
10. Park DY, Lee J, Kim J, et al. Plastic roles of pericytes in the blood-retinal barrier. Nat Commun. 2017;8:15296.
11. Reichenbach A, Bringmann A. New functions of Müller cells. Glia. 2013;61(5):651–78.
12. Takase H, Futagami Y, Yoshida T, et al. Cytokine profile in aqueous humor and sera of patients with infectious or noninfectious uveitis. Invest Ophthalmol Vis Sci. 2006;47:1557–61.
13. Curnow SJ, Murray Philip I. Inflammatory mediators of uveitis: cytokines and chemokines. Curr Opin Ophthalmol. 2006;17:532–7.
14. van Kooij B, Rothova A, Rijkers GT, de Groot-Mijnes JD. Distinct cytokine and chemokine profiles in the aqueous of patients with uveitis and cystoid macular edema. Am J Ophthalmol. 2006;142:192–4.
15. Mocan MC, Kadayifcilar S, Eldem B. Elevated intravitreal interleukin-6 levels in patients with proliferative diabetic retinopathy. Can J Ophthalmol. 2006;41:747–52.

16. Atkinson EG, Jones S, Ellis BA, et al. Molecular size of retinal vascular leakage determined by FITC-dextran angiography in patients with posterior uveitis. Eye (Lond). 1991;5(Pt 4):440–6.
17. Grajewski RS, Boelke AC, Adler W, et al. Spectral-domain optical coherence tomography findings of the macula in 500 consecutive patients with uveitis. Eye (Lond). 2016;30(11):1415–23.
18. Crane IJ, Liversidge J. Mechanisms of leukocyte migration across the blood-retina barrier. Semin Immunopathol. 2008;30(2):165–77.
19. Tranos PG, Wickremasinghe SS, Stangos NT, et al. Macular edema. Surv Ophthalmol. 2004;49(5):470–90. Review.
20. Choi JY, Buzney SM, Weiter JJ. Cystoid macular edema: current modes of therapy. Int Ophthalmol Clin. 2005;45(4):143–51.
21. Bernstein MH, Hollenberg MJ. Fine structure of the choriocapillaris and retinal capillaries. Invest Ophthalmol. 1965;4:1016–25.
22. Bousquet E, Zhao M, Thillaye-Goldenberg B, et al. Choroidal mast cells in retinal pathology: a potential target for intervention. Am J Pathol. 2015;185(8):2083–95.
23. Zhao T, Li Y, Weng C, Yin Z. The changes of potassium currents in RCS rat Müller cell during retinal degeneration. Brain Res. 2012;1427:78–87.
24. Eberhardt C, Amann B, Feuchtinger A, et al. Differential expression of inwardly rectifying K+ channels and aquaporins 4 and 5 in autoimmune uveitis indicates misbalance in Müller glial cell-dependent ion and water homeostasis. Glia. 2011;59(5):697–707.
25. Lopes de Faria JM, Jalkh AE, Trempe CL, et al. Diabetic macular edema: risk factors and concomitants. Acta Ophthalmol Scand. 1999;77(2):170–5.
26. van Kooij B, Probst K, Fijnheer R, et al. Risk factors for cystoid macular oedema in patients with uveitis. Eye (Lond). 2008;22(2):256–60. Epub 2006 Oct 6.
27. van Kooij B, Fijnheer R, Roest M, Rothova A. Trace microalbuminuria in inflammatory cystoid macular edema. Am J Ophthalmol. 2004;138:1010–5.
28. Iannetti L, Tortorella P, D'Ambrosio E, et al. Epiretinal membranes in patients with uveitis: morphological and functional analysis with spectral domain optical coherence tomography. Biomed Res Int. 2013;2013:284821.
29. Sheybani A, Harocopos GJ, Rao PK. Immunohistochemical study of epiretinal membranes in patients with uveitis. J Ophthalmic Inflamm Infect. 2012;2(4):243–8.
30. Lehpamer B, Moshier E, Pahk P, et al. Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol. 2014;157(5):1048–55.
31. Harada C, Mitamura Y, Harada T. The role of cytokines and trophic factors in epiretinal membranes: involvement of signal transduction in glial cells. Prog Retin Eye Res. 2006;25(2):149–64.

Chapter 13
Differential Diagnosis of Uveitic Macular Edema

Ilaria Testi, Andres Rousselot, Rupesh Agrawal, and Carlos Pavesio

Macular edema (ME) can complicate all uveitic phenotypes, both infectious and autoimmune in origin. Typically ME occurs in posterior and intermediate uveitis with a reported incidence of 66% and 65%, respectively, whereas posterior pole involvement in anterior uveitis depends on chronicity and activity of the disease [1, 2]. Both patients with active uveitis and those with minimal features of inflammation may develop recurrent or chronic edema due to the release of pro-inflammatory mediators. The most common uveitis entities complicated by ME include diseases with posterior segment involvement (Birdshot retinochoroiditis, intermediate uveitis, acute retinal necrosis, sarcoidosis and Behçet's disease). Among isolated anterior uveitis, juvenile idiopathic arthritis can be complicated by significant damage to the posterior pole due to long term chronic active inflammation [2, 3].

Visual loss caused by ME mainly affects patients with Birdshot retinochoroiditis, intermediate uveitis, sarcoidosis and acute retinal necrosis [3]. Visual prognosis depends on the intensity of the uveitis and integrity of anatomical structures, since it is recognised that chronic inflammation and longstanding edema lead to an irreversible disruption of retinal neural architecture with subsequent permanent visual

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loss. It is therefore necessary to identify the underlying cause of macular edema, distinguishing among infectious and noninfectious uveitis and, within etiological categories, to recognize specific clinical entities, so that an appropriate therapy can be established and the risk of functional visual loss prevented.

Different factors can be involved in intraretinal or subretinal fluid accumulation in uveitis patients. Inflammation can lead to the formation of epiretinal membrane, involvement of the RPE and inner choroid can result in the development of choroidal neovascularization or inflammatory macular edema can occur in patients after cataract surgery. The correct identification of the anatomical site primarily responsible for the edema will allow proper targeting therapy and will hopefully reduce long-term visual loss. Use of multimodal imaging techniques including optical coherence tomography (OCT), fluorescein and ICG angiography (FA and ICG) and other tools, is therefore necessary for a proper therapeutic management.

Macular Edema in Anterior Uveitis

Anterior uveitis is less frequently complicated by macular edema when compared to the other phenotypes that directly involve the posterior segment. According to SUN (Standardization of uveitis nomenclature) Working Group anatomic classification, anterior uveitis is defined as an intraocular inflammatory disease having anterior chamber as primary site of inflammation, including iritis, iridocyclitis and anterior cyclitis. Structural complications like macular edema do not change the anatomic classification as macular region and posterior segment are not the primary site of inflammatory process and thus are not considered in the classification of uveitis [4].

Acute anterior uveitis (AAU) is the most common form of uveitis and includes a heterogenous group of diseases. Human leucocyte antigen B27 (HLA-B27) associated uveitis is the most frequently recognized form of AAU [5, 6]. Several systemic inflammatory disorders known as seronegative spondyloarthropathies show a link with HLA-B27, with the strongest association seen in ankylosing spondylitis, where HLA-B27 is present in >90% of Caucasian patients affected by the disease [6, 7]. The other inflammatory HLA-B27 related diseases include psoriatic arthritis, reactive arthritis and inflammatory bowel diseases. Since HLA-B27 associated AAU affects mainly young adults in their productive years, it is important to recognize and treat promptly the potential vision threating complications like ME. HLA-B27 uveitis is characterized by acute recurrent inflammatory attacks, inducing the release of pro-inflammatory mediators in the vitreous cavity that might lead to the accumulation of fluid in the intraretinal space. The rate of ocular complications varies among the studies, depending on geographical area and study population, study design and duration of follow up. Posterior segment can be involved in 15–20% of cases, manifesting as disc edema, ME, retinal vasculitis and vitritis [8, 9]. Studies reported an incidence of ME uniformly distributed between 4% and 32%, with the highest rate corresponding to 38%, and males are reported to be involved more frequently [8, 10–12].

The incidence of ME is significantly lower in viral induced AU. Posterior segment complications are rarely described in anterior uveitis caused by *Herpes Simplex* virus, *Varicella Zoster* virus or *Cytomegalovirus* [10, 13–15]. In Fuchs heterochromic uveitis, a chronic iridocyclitis predominantly associated with *Rubella* or herpes virus infection, macular edema is typically absent. The absence of ME despite prolonged inflammatory involvement in longstanding uveitis with vitreous infiltration should be considered as contributory criteria for the diagnosis of Fuchs uveitis [15–17].

ME occurs less frequently in children with uveitis than in adults, probably due to a stronger vitreoretinal posterior pole adherence that might prevent fluid accumulation [18]. The most common anterior uveitis entity in childhood is associated with juvenile idiopathic arthritis (JIA). The disease is characterized by an asymptomatic insidious course with an ongoing chronic low grade ocular inflammation potentially resulting in vision threating complications as band keratopathy, ME, glaucoma and cataracts [19]. Incidence of ME in JIA has been reported to be around 3%, but it might be underestimated since high percentage of ME is detected with OCT that is difficult to use in children due to the limited cooperation [19–21]. Moreover the presentation is often asymptomatic and a detailed history is difficult to obtain. ME in JIA is not common at presentation like in other pediatric entities such as intermediate uveitis and usually develops during the course of disease, mostly in advanced, poorly controlled disease. Data reported that 50% of ocular complications develop 10 years after the onset of the disease [20]. Some risk factors have been identified for the development of ME. Male gender has been associated with a more severe disease at the diagnosis and recognized as an independent risk factor for the onset of ME. Young age at onset (3 years old or younger), uveitis as first manifestation or short interval between arthritis and uveitis are associated with an increased risk of ocular complications [19, 20, 22].

Macular Edema in Intermediate Uveitis

Intermediate uveitis (IU) and pars planitis, defined as a subset of uveitis where vitreous is the major site of inflammation, are characterized by a long disease course with frequent complications, often requiring systemic treatment [4]. IU is associated with systemic diseases in 9–31% of cases, most frequently with sarcoidosis and multiple sclerosis. Infectious conditions like Lyme's disease, tuberculosis and syphilis, intraocular lymphoma or other pediatric non-infectious diseases as TINU (tubulointerstitial nephritis and uveitis syndrome) can also manifest as IU [23].

IU and pars planitis are frequently complicated by ME. The incidence varies from 12% to 51%, depending on duration and severity of the disease, with the presence of pars plana exudate associated with severe vitreous disease and increased incidence of ME [23, 24]. Children with IU under the age of 16 are less likely to develop ME compared to adults, where it occurs more frequently with increasing age at the onset of uveitis. ME is more common in pars planitis compared to IU

associated with systemic diagnosis, with a lower reported incidence in patients with sarcoidosis [24]. ME is the most common cause of visual impairment and thus plays a crucial role in the management of the disease with regards to the decision of starting treatment. While cases of IU with mild inflammation can be manage with observation, in the event of complications such as ME, a prompt therapeutic intervention is required to avoid chronic changes in retinal layers and subsequent irreversible visual loss [10, 24].

Macular Edema in Retinal Vasculitis

Retinal vasculitis (RV) is a sight threatening inflammation involving retinal vessels, characterized by perivascular sheathing resulted from exudation of inflammatory cells around the affected vessel, with or without cotton wool spots and intraretinal hemorrhages depending on etiology and disease behaviour.

RV may occur as an idiopathic condition or represent an ocular manifestation of an underlying bacterial, viral or parasitic infection as tuberculosis, syphilis, Lyme's disease, toxoplasmosis and viral retinitis, or occur in association with systemic inflammatory disorders including Behçet's disease, sarcoidosis, multiple sclerosis and collagen vascular diseases. Some isolated ocular conditions can involve retinal vessels like Birdshot retinochoroiditis or idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN). Also, malignancy and ocular lymphoma can be associated with retinal vasculitis.

RV is a clinical finding in 6–15% of patients with uveitis and increase twice the risk of ME compared to eyes without vasculitis. The vascular damage caused by inflammation of the vessel wall can result in the disruption of the blood retinal barrier, seen as perivascular whitish infiltrates on fundus examination or as vascular leakage on fluorescein angiography, leading to intraretinal fluid accumulation and development of ME [25].

The differential diagnosis of primary or secondary ocular disorders complicated by ME in the presence of retinal vasculitis is based on a detailed history taking and review of systems, ocular examination, including ancillary tests as fluorescein angiography, and diagnostic workup with laboratory and imaging tests.

It is mandatory to identify the type of retinal vessels involved—arteries, veins or both. Phlebitis is typically associated with Behçet's disease, sarcoidosis, tuberculosis, multiple sclerosis, pars planitis and Birdshot retinochoroiditis, while retinal arteritis is more commonly seen in acute retinal necrosis, IRVAN or systemic collagen vascular diseases [26].

Characteristic clinical features may help in the diagnosis. Vascular involvement can be focal, diffuse or segmental. Nodular or segmental periphlebitis is strongly associated with sarcoidosis, especially in the presence of candlewax drippings, while diffuse occlusive periphlebitis with perivascular choroiditis patches is suggestive of ocular tuberculosis [27, 28].

Vascular changes in uveitis related vasculitis are characterized by perivascular infiltration of lymphocytes resulting in a perivasculitis rather than a true vasculitis of the vessel. Histopathologic studies in patients with sarcoidosis associated vasculitis correlate with ophthalmic clinical features observed on fundus examination. Reports showed that a nodular proliferation of epithelioid cells around blood retinal vessels correspond to the perivascular exudates and candle wax drippings seen on fundus examination [29]. ME can occur in up to 72% of cases of sarcoidosis, constituting the most important complication significantly associated with poor visual prognosis in patients with posterior involvement [30]. ME is usually not observed as initial manifestation of the disease, occurring most of the time as a long-term complication in the presence of chronic inflammation. Pathologic examination confirmed a segmental perivascular lymphocytic infiltration involving retinal veins also in multiple sclerosis (MS). The periphlebitis complicate up to 20% of MS patients with blood-retinal-barrier disruption and intraretinal fluid accumulation. Cystoid macular edema and in particular microcystic macular edema, defined as cystic lacunar areas of hyporeflectivity with clear boundaries, predominantly involves the inner nuclear layer of the retina, has been observed on OCT in MS. The explanation could be the breakdown of the blood retinal barrier in a part of the nervous system that lacks myelin. Microcystic intraretinal fluid more commonly occurs in association with a prior episode of optic neuritis and correlates with greater disease severity and lower visual acuity with thinner retinal nerve fiber layer resulting in poor visual prognosis [31–33].

Retinal vasculitis can manifest in association with cotton wool spots that represent microinfarct of the retinal fiber layer due to occlusive vasculopathy. Collagen vascular diseases, such as systemic lupus erythematosus (SLE), polyarteritis nodosa, Granulomatosis with Polyangiitis, Churg-Strauss syndrome and cryoglobulinemia, induce precapillary retinal arteriolar occlusion, resulting in formation of cotton wool spots and intraretinal fluid accumulation due to intraocular release of vascular growth factors and permeability mediators. Histopathologic studies in eyes of patients with SLE revealed fibrinoid change with thrombus formation without a true inflammation of vessels wall, and similar changes occur also in central nervous system disease. Thus retinal involvement in collagen vascular diseases often occurs without significant intraocular inflammation and that can help in distinguishing these kinds of disorders from other retinal vasculitis associated with active vascular sheathing and perivascular inflammatory infiltrates [26, 34]. These forms are best called vasculopathy rather than vasculitis.

Transient retinal infiltrates, in the absence of an underlying infectious etiology, can be pathognomonic of Behçet's disease. Ocular involvement in Behçet's disease is characterized by bilateral recurrent attacks of occlusive retinal vasculitis that can lead to cystoid macular edema in up to 60% of cases, constituting the most common cause of vision impairment during follow-up [26, 35]. ME can result from the inflammatory involvement or be the consequence of branch retinal vein occlusion, a common complication of Behcet retinal vasculitis. It has been reported that 42% of patients with Behçet's disease has a permanent visual loss due to ME. When promptly treated with anti-inflammatory and/or immunosuppressive therapy, the

disease can be associated with a good visual prognosis, unless the coexistence of other macular complications, including macular ischemia, serous retinal detachment, macular atrophy, epiretinal membrane or subretinal neovascularization. Different disorders other than Behçet's disease such as tuberculosis, Eales disease, SLE and less frequently sarcoidosis and multiple sclerosis can manifest as ischemic retinal vasculitis, leading to intraretinal fluid accumulation, due to hypoxic induction of vascular growth factors expression, and subsequent macular ischemia, resulting in irreversible damage and permanent visual impairment.

Categorization between infectious or noninfectious uveitis is mandatory for an appropriate therapeutical management of ME in the presence of retinal vasculitis. A detailed history and physical examination combined with clinical features, guide the ophthalmologist in the diagnostic workup. If there are no signs and symptoms suggestive of associated systemic disease, an infectious etiology should be ruled out by complete blood count, erythrocyte sedimentation rate and/or C-reactive protein and, according to suggestive clinical features, syphilis, Lyme's disease, toxoplasmosis serology, tuberculin skin test (PPD skin test) and/or gamma interferon release assay (IGRA) for tuberculosis and human immunodeficiency virus serology (different serology can be requested on the basis of clinical suspicion). An appropriate investigation to rule out a coexistent systemic vasculitis includes serum angiotensin converting enzyme, rheumatoid factor, antinuclear antibody, anti-ds DNA, antineutrophil cytoplasmic antibody, antiphospholipid antibodies (lupus anticoagulants and anticardiolipin antibodies), extractable nuclear antigens, complement, protein electrophoresis and cryoglobulins. Human leukocyte antigen (HLA) testing is truly only helpful in identifying Birdshot retinochoroiditis (HLA-A29), where an association of virtually 100% is present [36]. Imaging studies as chest X-ray, CT scan, brain magnetic resonance (MR), gallium scan or sacroiliac X ray or MR should be requested based on the review of systems and clinical examination of the patients. Figure 13.1 lists the common diagnostic tests useful for the evaluation of patients with retinal vasculitis.

In the absence of any clinical and diagnostic findings retinal vasculitis is considered idiopathic. Malignancy should always be considered in case of refractory uveitis that initially improved with the treatment, even if ME is not a characteristic finding of intraocular lymphoma and is usually related to prior interventions [37].

Macular Edema in Posterior Uveitis

Posterior uveitis include a subset of inflammatory disorders involving retina and choroid as primary site of the disease. These entities, both autoimmune and infectious, manifest with suggestive clinical and angiographic features that can help in the differential diagnosis.

Two different mechanisms are involved in the pathogenesis of macular edema: the inflammatory process with the release of mediators leading to the breakdown of

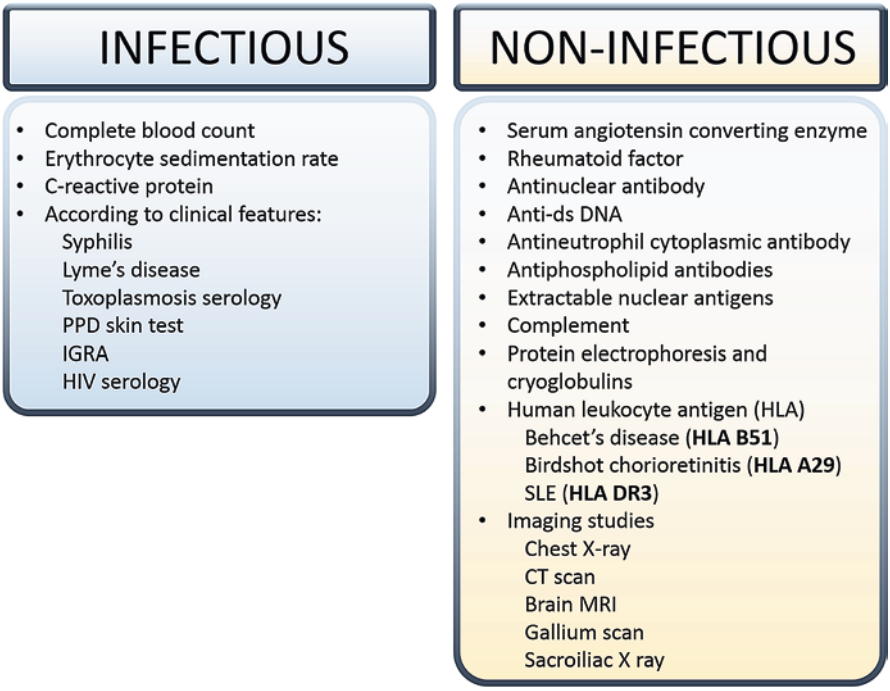

Fig. 13.1 Common diagnostic tests for the evaluation of patients with retinal vasculitis

the blood retinal barrier and the disruption of retinal layers derived from direct tissue damage.

Among infectious disease tuberculosis, syphilis, Lyme disease, toxoplasmosis and acute retinal necrosis can be associated with the development of ME. Toxoplasmosis is the most common infectious posterior uveitis manifesting as a focus of necrotizing retinochoroiditis, often adjacent to a variably pigmented retinochoroidal scar, with variable inflammatory involvement of vitreous and retinal vessels, producing the classic 'headlight in the fog' sign in the presence of severe vitritis. Macular localization is usually associated with serous retinal detachment and ME and can be complicated by choroidal neovascularization, resulting in intraretinal and subretinal fluid accumulation [38, 39]. The diagnosis is essentially clinical and supported by serological confirmation. Both syphilis and Lyme's disease can present with posterior involvement as neuroretinitis, chorioretinitis or retinal vasculitis, complicated by ME or serous detachment. Characteristic clinical patterns of syphilis are the presence of small superficial preretinal infiltrates migrating across retinal surface over the course of the disease and placoid chorioretinitis, while borreliosis can manifest as a peripheral multifocal choroiditis characterized by multiple, small, round, punched-out lesions associated with intraocular inflammation. Tuberculous associated uveitis can involve any tissue of the eye, most commonly manifesting as choroiditis. It can be associated with significant ocular morbidity

with ME occurring in up to 30% of cases. ME has also been described as the only possible ocular manifestation in both syphilis and tuberculosis [40–43]. Interpretation of serological tests for Lyme's disease and immunological tests for tuberculosis (IGRA or PPD skin test) is difficult and require some caution. The disease must be diagnosed by the correlation of laboratory data to clinical findings in the context of a strong clinical suspicion with a suggestive patient history and consistent ocular features.

Cystoid macular edema is a well-known complication of acute retinal necrosis, characterized by progressive peripheral foci of retinal necrosis associated with severe vitritis and occlusive vasculitis. Different mechanisms are involved in the pathogenesis of macular edema: in the acute phase of the disease it can be secondary to the release of pro-inflammatory mediators in the vitreous cavity, while later in the course peripheral retinal ischemia and vitreomacular traction can play a role in intraretinal fluid accumulation [44]. In HIV infected patients with viral retinitis receiving highly active antiretroviral therapy (HAART) the immune reconstitution inflammatory syndrome (IRIS) can be associated with inflammatory complications such as macular edema or epiretinal membrane formation. IRIS more commonly occurs in CMV retinitis and is characterized by various degree of tissue destructive inflammation due to immune recovery after initiation of HAART, which is due to the presence of CMV antigens in the eye and CD4 lymphocytes reconstitution. Before the introduction of antiretroviral therapy, CMV retinitis was characterized by mild or absent intraocular inflammation with macular edema rarely reported due to low lymphocytes count and immunosuppressed state. Intraocular inflammation, manifesting as vitritis and macular edema, appeared after the introduction of HAART and requires a prompt anti-inflammatory approach to avoid bad visual prognosis not due to the retinitis itself but to the immunorecovery [45].

Among infectious uveitis, other emerging diseases as Dengue fever and West Nile has been associated with maculopathy and chorioretinopathy, respectively, complicated by macular edema [46, 47].

Autoimmune systemic diseases manifesting as choroiditis like sarcoidosis or Vogt Koyanagi Harada syndrome and noninfectious isolated ocular conditions such as Birdshot retinochoroiditis can be complicated by intraretinal and subretinal fluid accumulation. Birdshot is classically characterized by creamy choroidal lesions, giving the typical fundus appearance, associated with mild vitritis and retinal vasculitis. The development of macular edema is common and reported in up to 84% of cases [48, 49]. The International Workshop that established the set of diagnostic criteria for Birdshot retinochoroiditis included the presence of cystoid macular edema in the supportive diagnostic findings. The diagnosis is hence based on the required clinical features supported by a strong association with HLA-A29, after the exclusion of systemic diseases and other uveitis entities [50].

Other mechanisms can be involved in intraretinal fluid accumulation in posterior uveitis. Inflammatory choroiditis can lead to the development of choroidal neovascular membrane that rarely leads to intraretinal cystic changes but is more commonly associated with subretinal fluid accumulation. Retinitis and chorioretinitis

can be complicated by epiretinal membrane formation resulting in ME through vitreomacular traction.

In summary, ME can occur as a complication of all uveitis phenotypes, including anterior uveitis. Different mechanisms related to intraocular inflammation can be involved in its pathogenesis, including pro-inflammatory mediators release resulting in breakdown of blood retinal barrier, epiretinal membrane formation or development of inflammatory CNV. Conditions other than uveitis entities such as diabetes, surgery, vascular occlusion or drugs intake must always be considered for a correct therapeutical management (Fig. 13.2). ME is one of the most common causes of visual impairment in patients with uveitis. Identify the underlying cause, distinguishing among infectious and noninfectious uveitis and, within etiological categories, recognize specific clinical entities is mandatory for instituting an appropriate therapy and preventing risk of visual loss.

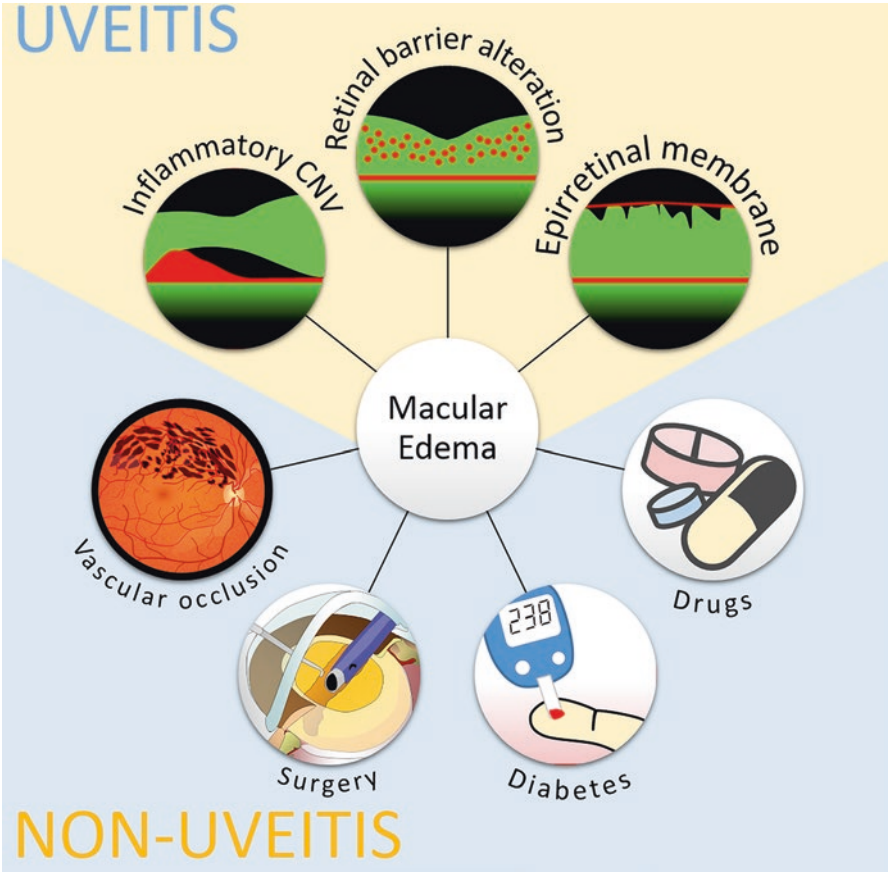

Fig. 13.2 Factors that might be involved in retinal fluid accumulation in patients with uveitis and conditions other than uveitis entities to be considered for a correct therapeutical management of patients with macular edema

References

1. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80:332–6.
2. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. Eye (Lond). 2016;30(10):1277–92.
3. Lardenoye CW, van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. Ophthalmology. 2006;113(8):1446–9.
4. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol. 2005;140(3):509–16.
5. Wakefield D, Yates W, Amjadi S, McCluskey P. HLA-B27 anterior uveitis: immunology and immunopathology. Ocul Immunol Inflamm. 2016;24(4):450–9.
6. Kopplin LJ, Mount G, Suhler EB. Review for disease of the year: epidemiology of HLA-B27 associated ocular disorders. Ocul Immunol Inflamm. 2016;24(4):470–5.
7. Khan MA. Update on spondyloarthropathies. Ann Intern Med. 2002;136:896–907.
8. Rodriguez A, Akova YA, Pedroza-Seres M, Foster CS. Posterior segment ocular manifestations in patients with HLA-B27-associated uveitis. Ophthalmology. 1994;101:1267–74.
9. D'Ambrosio EM, La Cava M, Tortorella P, Gharbiya M, Campanella M, Iannetti L. Clinical features and complications of the HLA-B27-associated acute anterior uveitis: a metaanalysis. Semin Ophthalmol. 2017;32(6):689–701.
10. Agarwal A, Pichi F, Invernizzi A, Gupta V. Disease of the year: differential diagnosis of uveitic macular edema. Ocul Immunol Inflamm. 2018;1:1–17.
11. Sungur G, Yakin M, Uzman S, Balta O, Orman G, Ornek F. Clinical features and prognosis of uveitis in a Turkish patient population with ankylosing spondylitis: incidence and management of ocular complications. Ocul Immunol Inflamm. 2018;23:1–9.
12. Majumdar AK, Kumar A, Roy R, Dutta Majumder P. Clinical profile of HLA B-27-associated uveitis patients in a tertiary care eye hospital in Eastern India. Ocul Immunol Inflamm. 2018;16:1–4.
13. Tugal-Tutkun I, Otük-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: a retrospective study of 111 cases. Int Ophthalmol. 2010;30(5):559–65.
14. Miserocchi E, Waheed NK, Dios E, et al. Visual outcome in herpes simplex virus and varicella zoster virus uveitis. A clinical evaluation and comparison. Ophthalmology. 2002;109:1532–7.
15. Chee S-P, Bacsal K, Jap A, S-Y S-T, Cheng CL, Tan BH. Clinical features of cytomegalovirus anterior uveitis in immunocompetent patients. Am J Ophthalmol. 2008;145(5):834–40.
16. Bouchenaki N, Herbort CP. Fuchs' uveitis: failure to associate vitritis and disc hyperfluorescence with the disease is the major factor for misdiagnosis and diagnosis delay. Middle East Afr J Ophthalmol. 2009;16:239–44.
17. Al-Mansour YS, Al-Rajhi AA, Al-Dhibi H, Abu El-Asrar AM. Clinical features and prognostic factors in Fuchs' uveitis. Int Ophthalmol. 2010;30(5):501–9.
18. De Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol. 2003;87:879–84.
19. Abu Samra K, Maghsoudlou A, Roohipoor R, Valdes-Navarro M, Lee S, Foster CS. Current treatment modalities of JIA-associated uveitis and its complications: literature review. Ocul Immunol Inflamm. 2016;24(4):431–9.
20. Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. Ocul Immunol Inflamm. 2013;21(6):478–85.
21. Ducos de Lahitte G, Terrada C, Tran TH, et al. Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. Br J Ophthalmol. 2008;92(1):64–9.
22. Kalinina Ayuso V, Ten Cate HA, van der Does P, Rothova A, de Boer JH. Male gender as a risk factor for complications in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol. 2010;149(6):994–999.e5.

23. Babu BM, Rathinam SR. Intermediate uveitis. Indian J Ophthalmol. 2010;58:21–7.
24. Niederer RL, Sharief L, Bar A, Lightman SL, Tomkins-Netzer O. Predictors of long-term visual outcome in intermediate uveitis. Ophthalmology. 2017;124(3):393–8.
25. Sharief L, Lightman S, Blum-Hareuveni T, Bar A, Tomkins-Netzer O. Clinical outcome of retinal Vasculitis and predictors for prognosis of ischemic retinal Vasculitis. Am J Ophthalmol. 2017;177:206–12.
26. Abu El-Asrar AM, Herbort CP, Tabbara KF. Differential diagnosis of retinal vasculitis. Middle East Afr J Ophthalmol. 2009;16(4):202–18.
27. Herbort CP, Rao NA, Mochizuki M, members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop on Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm. 2009;17(3):160–9.
28. Agrawal R, Kee AR, Ang L, et al. Tuberculosis or sarcoidosis: opposite ends of the same disease spectrum? Tuberculosis (Edinb). 2016;98:21–6.
29. Gass JD, Olson CL. Sarcoidosis with optic nerve and retinal involvement. Arch Ophthalmol. 1976;94(6):945–50.
30. Rothova A. Ocular involvement in sarcoidosis. Br J Ophthalmol. 2000;84:110–6.
31. Gelfand JM, Nolan R, Schwartz DM, Graves J, Green AJ. Microcystic macular edema in multiple sclerosis is associated with disease severity. Brain. 2012;135(Pt 6):1786–93.
32. Saidha S, Sotirchos ES, Oh J, Syc SB, et al. Relationships between retinal axonal and neuronal measures and global central nervous system pathology in multiple sclerosis. JAMA Neurol. 2013;70(1):34–43.
33. Brar M, Yuson R, Kozak I, et al. Correlation between morphologic features on spectral-domain optical coherence tomography and angiographic leakage patterns in macular edema. Retina. 2010;30:383–9.
34. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis. 2012;2012:290898.
35. Zierhut M, Abu El-Asrar AM, Bodaghi B, Tugal-Tutkun I. Therapy of ocular Behçet disease. Ocul Immunol Inflamm. 2014;22(1):64–76.
36. Herbort CP, Pavésio C, LeHoang P, et al. Why birdshot retinochoroiditis should rather be called 'HLA-A29 uveitis'? Br J Ophthalmol. 2017;101(7):851–5.
37. Carreras E, Salomão DR, Nadal J, et al. Macular edema is a rare finding in untreated vitreoretinal lymphoma: small case series and review of the literature. Int J Retina Vitreous. 2017;3:15.
38. Ouyang Y, Li F, Shao Q, et al. Subretinal fluid in eyes with active ocular toxoplasmosis observed using spectral domain optical coherence tomography. PLoS One. 2015;10(5):e0127683.
39. Ouyang Y, Pleyer U, Shao Q, et al. Evaluation of cystoid change phenotypes in ocular toxoplasmosis using optical coherence tomography. PLoS One. 2014;9(2):e86626.
40. Davis JL. Ocular syphilis. Curr Opin Ophthalmol. 2014;25(6):513–8.
41. Gunasekeran DV, Gupta B, Cardoso J, Pavesio CE, Agrawal R. Visual morbidity and ocular complications in presumed intraocular tuberculosis: an analysis of 354 cases from a non-endemic population. Ocul Immunol Inflamm. 2018;26(6):865–9.
42. Torres RM, Calonge M. Macular edema as the only ocular finding of tuberculosis. Am J Ophthalmol. 2004;138(6):1048–9.
43. Martin NF, Fitzgerald CR. Cystoid macular edema as the primary sign of neurosyphilis. Am J Ophthalmol. 1979;88(1):28–31.
44. Ortega-Evangelio L, Navarrete-Sanchis J, Williams BK, Tomás-Torrent JM. Aflibercept in the management of acute retinal necrosis syndrome-related macular edema. Eur J Ophthalmol. 2018;28(2):259–61.
45. Urban B, Bakunowicz-Łazarczyk A, Michalczuk M. Immune recovery uveitis: pathogenesis, clinical symptoms, and treatment. Mediat Inflamm. 2014;2014:971417.
46. Aggarwal K, Agarwal A, Katoch D, Sharma M, Gupta V. Optical coherence tomography angiography features of acute macular neuroretinopathy in dengue fever. Indian J Ophthalmol. 2017;65(11):1235–8.

47. Afshar AR, Hariprasad SM, Jampol LM, Sheth VS. Use of intravitreous bevacizumab to treat macular edema in West Nile virus chorioretinitis. Arch Ophthalmol. 2012;130(3):396–8.
48. Minos E, Barry RJ, Southworth S, et al. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. Orphanet J Rare Dis. 2016;11(1):61.
49. Rothova A, Berendschot TT, Probst K, van Kooij B, Baarsma GS. Birdshot chorioretinopathy: long term manifestations and visual prognosis. Ophthalmology. 2004;111(5):954–9.
50. Levinson RD, Brezin A, Rothova A, Accorinti M, Holland GN. Research criteria for the diagnosis of birdshot chorioretinopathy: results of an international consensus conference. Am J Ophthalmol. 2006;141(1):185–7.

Chapter 14
Multimodal Imaging of Uveitic Macular Edema

Ilaria Testi, Andres Rousselot, Rupesh Agrawal, and Carlos Pavesio

Macular edema (ME) has been shown to be the leading cause of visual loss in patients with uveitis, occurring in up to 30% of cases [1, 2]. Early detection and prompt treatment is crucial to prevent chronic macular changes and poor visual prognosis.

Clinical assessment of ME is subjective, highly variable and qualitative, revealing alterations in foveal reflex or gross macular thickening, not detecting mild or localized intraretinal fluid accumulation and not providing any information on changes in retinal morphology. An objective and quantitative measure of ME is important in determining progression of the disease or its response to treatment, both in clinical practice and research. Fluorescein angiography (FA) is considered a highly effective test for evaluating uveitis activity in terms of vasculitis and ME, documenting leakage of retinal vessels and in macular area, but its invasiveness and semi-quantitative evaluation has led it to be replaced by non invasive techniques like optical coherence tomography (OCT). Fundus autofluorescence (FAF) represents an important adjunctive, non-invasive, tool to assess morphologic features of the macula, while, among functional tests, microperimetry is becoming a more common

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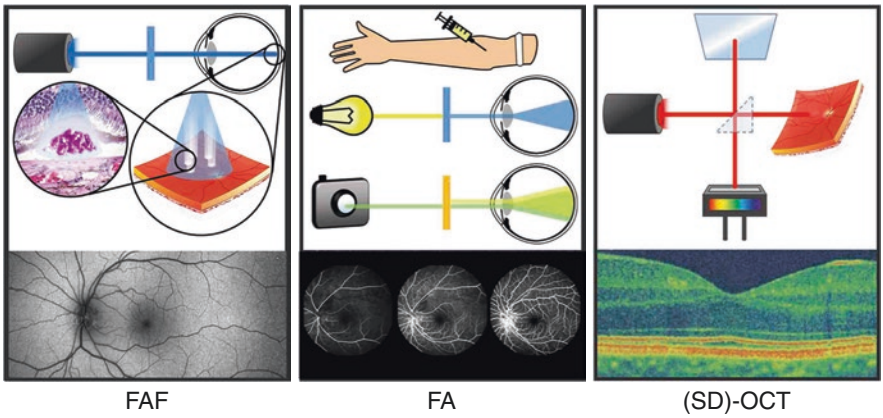

Fig. 14.1 Multimodal retinal imaging approach for morphological and functional characterization of macular edema (fundus autofluorescence (FAF), fluorescein angiography (FA), (spectral domain-)optical coherence tomography (SD-OCT))

tool for measuring retinal sensitivity and photoreceptor function. Thus, ME is best managed using a multimodal retinal imaging approach that allows a morphological and functional characterization of the disease (Fig. 14.1).

Optical Coherence Tomography in Uveitic Macular Edema

Spectral-domain optical coherence tomography (SD-OCT) has become the standard diagnostic tool to detect and monitor macular changes in various retinal diseases, including uveitis. The technique is a non-invasive, objective tool that provides real time high-resolution cross-sectional imaging of the retina, yielding highly reproducible measurements thanks to mapping software and eye tracking technology. OCT provides precise quantitative measuring of retinal thickness and individual layers together with information concerning retinal morphology, structure and reflectivity. In addition to its non invasiveness and quantitative evaluation, quick imaging acquisition and safety profile have made OCT become the gold standard technique in the diagnosis and management of ME.

In patients with ME, OCT images usually show retinal thickening together with the presence of low intraretinal reflectivity corresponding to areas of fluid accumulation. Regarding retinal morphological changes occurring in macular edema, Markomichelakis et al. demonstrated that there are no differences in OCT patterns of fluid accumulation between uveitic and diabetic ME, although the initial process leading to that complication is different in both these diseases [3, 4]. The authors identified three different pattern of uveitic ME (Fig. 14.2):

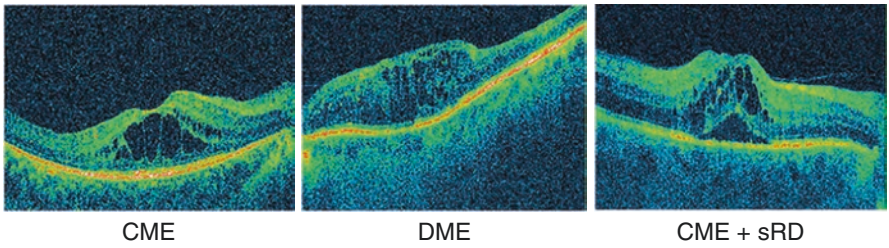

Fig. 14.2 OCT images of uveitic macular edema patterns: cystoid macular edema (CME), diffuse macular edema (DME), CME with serous retinal detachment (CME + sRD)

- cystoid macular edema (CME), characterized by clearly defined low-reflective intraretinal cystoid spaces, separated by high-signal elements bridging the retinal tissue;
- diffuse macular edema (DME), defined as diffuse increased macular thickness with disturbance of the layered retinal structure and spongy appearance of the retina;
- with or without serous retinal detachment (RD), defined as separation of the neuroretina from the retinal pigment epithelium (RPE)/choriocapillaris band due to subretinal fluid accumulation, that typically appears low reflective and forms an angle of 20–30° between the two layers.

Distribution of different patterns of ME was as follow: DME in 60.7%, CME in 39.3% and RD in 20.2% of cases, with RD coexisted with either DME or CME in 6% and 14% of cases, respectively. Higher frequency of CME compared to diffuse type was described by Iannetti et al. in two different series of 71 eyes of 55 patients underwent SD-OCT and previously in 43 eyes of 39 patients underwent time-domain OCT, mainly in patients with long-standing uveitis. This could be explained by the changes occurring with chronic intraretinal fluid accumulation related to the duration of ME. It has been demonstrated by histopathologic studies that the retinal thickening and spongy appearance observed in DME corresponds to the swelling of Muller cells in the outer plexiform layer. Chronic inflammation and persistent edema lead to necrosis of Muller cells and subsequently to formation of intraretinal cystoid spaces observed in CME [3, 5, 6].

Fluid is predominantly located in the outer retinal layers, although cystoid spaces are also formed toward the inner retina. No differences were found in macular thickness and patterns of ME between uveitis phenotypes and between patients with idiopathic uveitis and uveitis secondary to other diseases. Thus, qualitative and quantitative characterization of ME seem not to be related to different types of uveitis [3, 6].

Subfoveal serous RD is a common features of uveitic ME, found most frequently in patients with uveitis compared to diabetics, due to disruption and deterioration of RPE caused by inflammation [7]. RD develops typically in the early stages of the

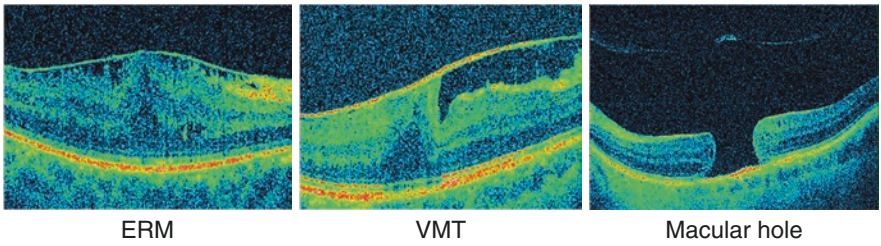

Fig. 14.3 OCT images of vitreoretinal interface abnormalities in patients with uveitis: epiretinal membrane (ERM), vitreomacular traction (VMT) and lamellar/full-thickness macular holes

disease and respond well to the anti-inflammatory treatment [8]. No significant differences in distribution of serous RD were found between cystoid and diffuse macular edema [3, 5].

Vitreoretinal interface abnormalities are commonly seen in patients with uveitis as a complication of active inflammation. OCT provides precise morphological information on the inner retinal and vitreoretinal interface changes, including epiretinal membrane formation (ERM), vitreomacular traction (VMT) and lamellar/full-thickness macular holes (Fig. 14.3). On OCT, ERM appears as a hyper-reflective band adhering to the retinal layer. OCT has a high sensitivity in detecting ERM compared to fundus biomicroscopy, revealing the presence of epiretinal membrane in up to 40% of patients with uveitis, and, when ERM is detected ophthalmoscopically, often reveals a concomitant VRT, defined as partial vitreous detachment with persistent vitreous attachment to the fovea, with high-reflective and thickened appearance of the posterior hyaloid, located posteriorly to the hyporeflective vitreous and corresponding to the bridging fibrocellular proliferative tissue. The high frequency of vitreoretinal interface abnormalities in uveitis patients confirms the hypothesis that a tractional mechanism may act as a co-factor in the macular edema formation. Presence of ERM has been found to be independent from anatomic site of inflammation, different patterns of macular edema and macular thickness [3, 6, 9].

OCT provides not only parameters such as retinal thickness, patterns of ME and fluid localization or morphological changes of retinal layers, but also adds information on new reflectivity aspects. In recent years hyperreflective spots (HRS) have been investigated in patients with ME related to diabetic retinopathy, retinal vein occlusion and age-related maculopathy. HRS are defined as punctiform, round or oval, small, hyper-reflective white foci located both in the inner retina and in the outer retina (Fig. 14.4). Various authors hypothesized different etiology of diabetic related HRS, including extravasated lipoproteins or hard exudates [10]. HRS described in uveitic macular edema are smaller than those occurring in diabetic maculopathy or retinal vein occlusion, maybe due to a different mechanism of origin. Considering the clear inflammatory origin of uveitis and the absence of hard exudates in the disease, it has been hypothesized that uveitis related HRS correspond to inflammatory cells (microglial and leukocytes). Histopathologic studies performed on murine autoimmune induced uveitis confirmed this hypothesis [11,

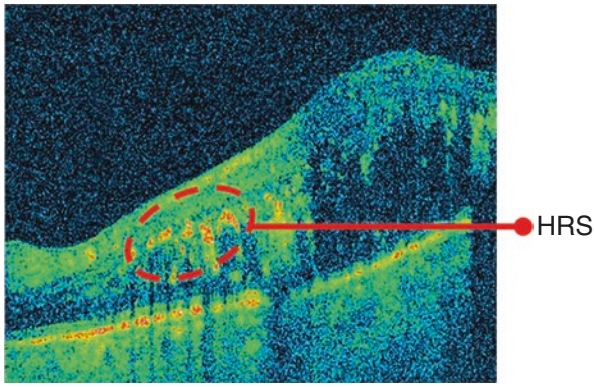

Fig. 14.4 Hyperreflective spots (HRS) in the inner and outer retina

12]. Diapedesis of leukocytes and activation of microglia are involved in the physiopathogenesis of uveitic ME, releasing pro-inflammatory mediators that increase vascular and epithelial permeability, resulting in intraretinal fluid accumulation. When the inflammatory process resolves, the infiltration of cells into the retina decreases. HRS were observed in the outer retinal layers in almost half of the patients at baseline and the number of foci diminished during follow-up after the treatment with the resolution of the edema, remaining more frequently located in the inner retinal layers [11]. These findings could be explained by the fact that at baseline, when the inflammatory process is active and ME is present, activated microglia migrate from the inner retina toward the outer layers, site where HRS are more frequently observed on OCT during active disease. Resting microglia is located in the inner retinal layers and this finding correlates with the location of HRS observed after the resolution of the inflammation. Hence macular thickness was found to be associated with both the number and the distribution of the foci [11].

Correlation between OCT findings and visual prognosis is still controversial in uveitic ME.

While for diabetic ME, foveal thickness correlates with the visual acuity, for uveitic ME, it is still debated whether such a relation exists [3, 4, 6, 13]. Several studies have tried to correlate macular thickness and other variables such pattern of ME with visual prognosis in the uveitic population. Some authors found that the presence of CME was significantly associated to a worse visual prognosis compared to DME, with a greater mean foveal thickness in patient with CME that negatively correlate with visual acuity [3, 6, 14]. Tran et al. confirmed the correlation between foveal thickness and visual function only in patients with CME, characterized by a mean macular thickness of 404 μm, whereas this relation was absent in patients with DME and a lower mean central thickness (303 μm). The authors also found that DME was associated with a poorer visual prognosis compared to patients with CME, characterized more frequently by visual recovery [13].

Also the correlation between serous RD and visual acuity is controversial. While some authors correlated the presence of RD with a worse visual prognosis, in other studies RD was not found to have a significant impact on visual acuity, similar to

subretinal fluid observed in central serous chorioretinopathy that does not adversely affect visual prognosis [3, 6, 13]. Authors demonstrated that visual acuity is worse during the presence of RD but the visual outcome at 3 and 6 months of follow-up was similar in patients with and without RD, since it seems to respond well to conventional treatment [8, 14].

The Multicenter Uveitis Steroid Treatment (MUST) trial demonstrated that a 20% change in central retinal thickness correlated with clinically important changes in visual acuity, in particular for each 100 μm lower retinal thickness, the visual acuity was 5.3 letters higher after 6 months of follow-up [15].

Payne et al. demonstrated that a logarithmic transformation of OCT retinal thickness provides a better correlation with logMAR visual acuity, with each 0.1 unit increase in log retinal thickness corresponding to a 0.082 unit worsening in baseline visual acuity [16].

It has been show that other OCT structural features might serve as prognostic factors for visual acuity. Integrity of the high-reflective band of the external limiting membrane and IS/OS line or ellipsoid zone is strongly associated with a better visual outcome [6, 17]. The presence of ERM was not found correlated with visual acuity [3, 6, 14]. Authors failed to demonstrate an association between the number and localisation of HRS with visual prognosis [11].

Sivaprasad et al. evaluated the anti-inflammatory therapeutic effect on the different patterns of uveitic ME and found that DME, external CME and serous RD responded well to treatment. Cysts located in the inner retina were more refractory to treatment compared to cysts in the outer retina layers that tend to disappear faster. Overall all type of CME and inner CME were significantly associated with final visual acuity [18]. Assessment of macular edema patterns by OCT could hence give valuable information on final prognosis.

Fluorescein Angiography in Uveitic Macular Edema

Prior to the advent of modern tools as OCT, fluorescein angiography (FA) was an essential technique for detecting ME. However, it only provides a descriptive and subjective assessment of angiographic findings as macular leakage and pooling of the dye in the presence of ME, without measurements of central retinal thickness or information regarding retinal morphology and reflectivity. Moreover being an invasive technique, intravenous injection of the dye can be complicated by adverse reactions, from nausea to anaphylactic shock, and it is even contraindicated in some situations as renal failure, severe cardiovascular disease or pregnancy.

The Angiography Scoring for Uveitis Working Group (ASUWOG) graded macular edema from 1 to 4 based on FA images at 10 min (Fig. 14.5) [19]. Grade 1 corresponds to faint hyperfluorescence, grade 2 to incomplete ring of leakage, grade 3 to complete ring of leakage and grade 4 to pooling of dye in cystic spaces.

Several authors have tried to associate OCT patterns with FA findings in patients with uveitic macular edema and evaluate the discrepancies between the two tech-

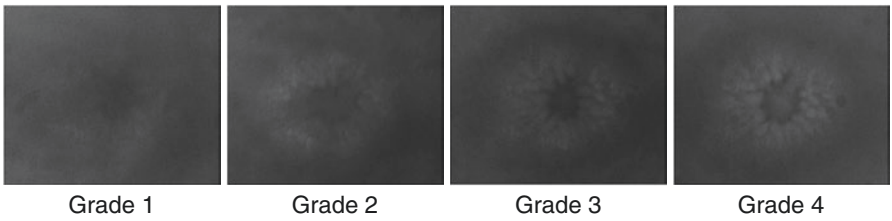

Fig. 14.5 The Angiography Scoring for Uveitis Working Group (ASUWOG): grade 1, faint hyperfluorescence; grade 2, incomplete ring of leakage; grade 3, complete ring of leakage; grade 4, pooling of dye in cystic spaces

niques. Kempen et al. found a moderate agreement in the diagnosis of macular thickening (MT) and macular leakage (ML) (k = 0.44), with ML present in 40% of cases without MT and MT present in 34% of cases free of ML. Biomicroscopic examination failed to detect 40% and 45% of cases of MT and ML, respectively, and diagnosed ME in 17% and 17% of the cases free of MT and ML, respectively [20]. These findings could be explained by the fact that OCT and FA measure two related pathologic characteristics that are different from each other. Leakage from blood vessels in macular area is not always associated with an increase in macular thickness like in cases of macular atrophy or at the beginning of the inflammatory process when the thickening has not yet occurred or in case of epiretinal membrane. On the other hand macular thickness can be increased due to causes other than leakage as dysfunction of RPE or in eyes with inactive uveitis. Tran et al. found similar results in 86% of eyes that underwent both OCT and FA. Serous RD was detected in 6% of cases by OCT without a correlated hyperfluorescence on FA, that appeared in 7% of cases free from intraretinal fluid accumulation on OCT [13]. A lower grade of agreement (54%) was found by Ossewaarde-van Norel et al. [21] Consistencies was common in active uveitis, while discrepancies were frequently observed in the presence of mild degree of ME. ML was noted in 50% of cases of Birdshot retinochoroiditis without MT, maybe due to the lower macular thickness found in these patients compared to other uveitis entities; while MT in eyes free from ML was frequently observed in intermediate uveitis compared to other phenotypes. The authors found a high correlation between cystoid appearance on OCT and the corresponding findings on FA [21].

Although OCT is superior in providing gradable images and is a non invasive, lower cost, reproducible technique, FA is especially useful in cases of ME that require an evaluation of the overall activity of uveitis (vasculitis, neovascularization or optic disk leakage). However when OCT failed to detect ME and clinical findings of ML are evident, FA is likely to provide additional information; vice versa when ML is absent on FA but signs of macular involvement are clinically important an OCT follow up is requested. Thus FA and OCT are complementary techniques, providing different information on ME, and the results of both investigations may influence the therapeutic decision, unless, given the positivity of the first test, the second one does not provide further information to start the treatment.

Fundus Autofluorescence in Uveitic Macular Edema

Fundus autofluorescence (FAF) is a noninvasive technique useful for the evaluation of ME. FAF maps retinal distribution of lipofuscin, a fluorescent pigment that accumulates in the RPE as a metabolic product of incomplete degradation of photoreceptor outer segment and represent an indicator of retinal oxidative damage, containing peroxidation products of proteins and lipids.

In eye with ME, an increase in FAF has been documented. This finding might be explained by accumulation of lipofuscin due to RPE cell destruction, displacement of macular pigment by cystoid macular spaces (referred as 'pseudo autofluorescence', since usually macular pigment blocks FAF signal from the RPE) or presence of retinoids (autofluorescent proteins that accumulate in the extracellular fluid during the active inflammatory process) [10, 14, 22]. Roesel et al. demonstrated that an increase in FAF is correlated with a worse visual acuity [22].

Near infrared autofluorescence (NIR-AF), a technique that visualize melanin distribution in the RPE and choroid, has been studied in patients with diabetic ME. It has been found that a reduced NIR- FAF in ME could be due to the block of signal from the RPE and choroid in the presence of retinal fluid, however it has not yet been studied in patients with uveitis [10].

OCT Angiography in Uveitic Macular Edema

OCT angiography (OCTA) in uveitis can provide important information on uveitis activity other that leakage from vessels detected by conventional FA. OCTA, visualizing microvascular morphology and capillary perfusion, identifies areas of flow void as manifestation of ischemia or inflammation and detects choroidal neovascularization that can complicate inflammatory disorders. OCTA is able to detect patterns associated with ME, that typically appears as roundish hypointense intraretinal spaces, varying in dimension and location depending on the depth of scan section [23, 24]. Kim et al. analyzed 16 eyes with uveitic macular edema and correlated the presence of the cysts in the inner retina layers with lower vessels density in the deep capillary plexus [25]. These findings were later on confirmed in diabetic retinopathy by Spaide et al., that identified ischemia of the deep capillary plexus as a driving mechanism in the onset of ME [26].

Microperimetry in Uveitic Macular Edema

Microperimetry provides a quantitative measure of functional vision in term of retinal sensitivity, together with fixation evaluation, allowing the possibility of correlating loss of retinal sensitivity to area of ME. Roesel et al. found a negative correlation

between microperimetry measurements and logMAR visual acuity, while no association emerged between fixation abnormality and poor visual prognosis, increased foveal thickness and retinal sensitivity [27].

Ultrasound in Uveitic Macular Edema

Ultrasound is limited in detecting ME, however it could be useful in detecting the cause of ME in patients with posterior scleritis revealing an increase in chorioscleral thickness together with a T-sign.

In conclusion SD-OCT is considered the gold standard to detect and manage macular edema. An integrated multimodal imaging approach may provide additional details and information on disease activity and pathophysiology, allowing a better morphological and functional characterization of ME.

Results of different investigations may influence the therapeutic decision.

References

1. De Smet MD, Okada AA. Cystoid macular edema in uveitis. Dev Ophthalmol. 2010;47:136–47. Review.
2. Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18(6):487–92. Review.
3. Markomichelakis NN, Halkiadakis I, Pantelia E, et al. Patterns of macular edema in patients with uveitis: qualitative and quantitative assessment using optical coherence tomography. Ophthalmology. 2004;111(5):946–53.
4. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol. 1999;127(6):688–93.
5. Iannetti L, Accorinti M, Liverani M, Caggiano C, Abdulaziz R, Pivetti-Pezzi P. Optical coherence tomography for classification and clinical evaluation of macular edema in patients with uveitis. Ocul Immunol Inflamm. 2008;16:155–60.
6. Iannetti L, Spinucci G, Abbouda A, De Geronimo D, Tortorella P, Accorinti M. Spectral-domain optical coherence tomography in uveitic macular edema: morphological features and prognostic factors. Ophthalmologica. 2012;228(1):13–8.
7. Catier A, Tadayoni R, Paques M, et al. Characterization of macular edema from various etiologies by optical coherence tomography. Am J Ophthalmol. 2005;140(2):200–6.
8. Ossewaarde-van Norel J, Berg EM, Sijssens KM, Rothova A. Subfoveal serous retinal detachment in patients with uveitic macular edema. Arch Ophthalmol. 2011;129(2):158–62.
9. Onal S, Tugal-Tutkun I, Neri P, P Herbort C. Optical coherence tomography imaging in uveitis. Int Ophthalmol. 2014;34(2):401–35.
10. Midena E, Bini S. Multimodal retinal imaging of diabetic macular edema: toward new paradigms of pathophysiology. Graefes Arch Clin Exp Ophthalmol. 2016;254(9):1661–8.
11. Berasategui B, Fonollosa A, Artaraz J, et al. Behavior of hyperreflective foci in non-infectious uveitic macular edema, a 12-month follow-up prospective study. BMC Ophthalmol. 2018;18(1):179.
12. Chu CJ, Herrmann P, Carvalho LS, et al. Assessment and in vivo scoring of murine experimental autoimmune uveoretinitis using optical coherence tomography. PLoS One. 2013;14(8):e63002.

13. Tran TH, de Smet MD, Bodaghi B, Fardeau C, Cassoux N, Lehoang P. Uveitic macular oedema: correlation between optical coherence tomography patterns with visual acuity and fluorescein angiography. Br J Ophthalmol. 2008;92(7):922–7.
14. Ossewaarde-van Norel A, Rothova A. Imaging methods for inflammatory macular edema. Int Ophthalmol Clin. 2012;52(4):55–66.
15. Sugar EA, Jabs DA, Altaweel MM, et al. Identifying a clinically meaningful threshold for change in uveitic macular edema evaluated by optical coherence tomography. Am J Ophthalmol. 2011;152(6):1044–1052.e1045.
16. Payne JF, Bruce BB, Lee LB, Yeh S. Logarithmic transformation of spectral-domain optical coherence tomography data in uveitis-associated macular edema. Invest Ophthalmol Vis Sci. 2011;52(12):8939–43.
17. Cohen LM, Goldstein DA, Fawzi AA. Structure-function relationships in uveitic cystoid macular edema: using en face optical coherence tomography to predict vision. Ocul Immunol Inflamm. 2016;24(3):274–81.
18. Sivaprasad S, Ikeji F, Xing W, Lightman S. Tomographic assessment of therapeutic response to uveitic macular oedema. Clin Exp Ophthalmol. 2007;35(8):719–23.
19. Tugal-Tutkun I, Herbort CP, Khairallah M, The Angiography Scoring for Uveitis Working Group (ASUWOG). Scoring of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation (dual fluorescein and ICG angiographic scoring system for uveitis). Int Ophthalmol. 2010;30:539–52.
20. Kempen JH, Sugar EA, Jaffe GJ, et al. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group. Fluorescein angiography versus optical coherence tomography for diagnosis of uveitic macular edema. Ophthalmology. 2013;120(9):1852–9.
21. Ossewaarde-van Norel J, Camfferman LP, Rothova A. Discrepancies between fluorescein angiography and optical coherence tomography in macular edema in uveitis. Am J Ophthalmol. 2012;154(2):233–9.
22. Roesel M, Henschel A, Heinz C, Dietzel M, Spital G, Heiligenhaus A. Fundus autofluorescence and spectral domain optical coherence tomography in uveitic macular edema. Graefes Arch Clin Exp Ophthalmol. 2009;247(12):1685–9.
23. Pichi F, Sarraf D, Arepalli S, et al. The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. Prog Retin Eye Res. 2017;59:178–201.
24. Pichi F, Sarraf D, Morara M, Mazumdar S, Neri P, Gupta V. Pearls and pitfalls of optical coherence tomography angiography in the multimodal evaluation of uveitis. J Ophthalmic Inflamm Infect. 2017;7(1):20.
25. Kim AY, Rodger DC, Shahidzadeh A, et al. Quantifying retinal microvascular changes in uveitis using spectral-domain optical coherence tomography angiography. Am J Ophthalmol. 2016;171:101–12.
26. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015;133(1):45–50.
27. Roesel M, Heimes B, Heinz C, Henschel A, Spital G, Heiligenhaus A. Comparison of retinal thickness and fundus-related microperimetry with visual acuity in uveitic macular oedema. Acta Ophthalmol. 2011;89(6):533–7.

Chapter 15
Treatment of Uveitic Macular Edema

Ilaria Testi, Andres Rousselot, Rupesh Agrawal, and Carlos Pavesio

Aim of therapy in uveitis is to control intraocular inflammation, reduce recurrences of the disease and prevent the development of sight-threatening complications including macular edema (ME). Since ME is the leading cause of permanent vision loss in uveitis, early detection and prompt treatment is essential to prevent chronic macular changes resulting in poor visual prognosis [1, 2].

Release of pro-inflammatory mediators such as interferon gamma, interleukin 6, tumor necrosis factor alfa (TNF alfa) and vascular endothelial grown factor (VEGF) play a crucial role in retinal vascular hyperpermeability and retinal pigment epithelium dysfunction, leading to accumulation of intraretinal fluid in macular area [1, 2]. Thus numerous therapeutic approaches targeting different inflammatory pathways have demonstrated efficacy in the treatment of uveitic ME.

Due to potent antiinflammatory response, the mainstay for the management of uveitic ME is corticosteroid therapy [3–5]. Treatment strategies differs according to the etiology of the uveitis and the type of ocular involvement of the disease: in unilateral involvement local approach is a reasonable alternative and is usually preferred over systemic therapy, which is still indicated as first line treatment for

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bilateral cases, but also the presence of an active systemic disease will favour the systemic approach [3–5]. Given the well-known side effects with chronic use of high-dose immunomodulatory drugs, intravitreal route of drug administration is a valid alternative in selected cases, considering that it achieves the highest concentration of therapy where it is most wanted, and at the same time minimizing systemic complications. Since intravitreal injections of corticosteroids, including short and long acting corticosteroid implants, are not free from ocular adverse events, alternative drugs as anti VEGF, methotrexate, sirolimus or adalimumab have all been tested, leading to resolution of ME with varying degrees of success.

Systemic Therapy

Corticosteroids

In bilateral ME, systemic corticosteroids are considered the standard first line treatment [3–5]. Relatively high initial dose of oral prednisone or equivalent started at 1 mg/kg/day is generally required to achieve anatomical recovery of the edema and restoration of visual acuity. When resolution of ME and control of inflammation is achieved, steroids are tapered slowly; alternatively non-corticosteroid immunomodulatory agents may be introduced for the management of noninfectious uveitis to control persistent or severe inflammation and prevent the relapse of ME [6].

Given the presence of retinal barriers, high dose of oral steroids or systemic immunosuppressive agents are often needed to reach therapeutic levels in the intraocular compartment, leading to development of potential systemic adverse events associated with chronic high dosage. Local administration of corticosteroids as intravitreal injection becomes thus a safe and effective approach for the management of ME especially for patients with unilateral disease, cases refractory to systemic treatment or in case of contraindications to oral steroids.

The Multicenter Uveitis Steroid Treatment (MUST) randomized trial compared the efficacy of systemic anti-inflammatory therapy (prednisone or corticosteroid sparing agents if required) and intravitreal fluocinolone acetonide implant in patients with noninfectious uveitis [7–9]. At the primary 2-year time point, ME improved faster with local therapy compared to systemic treatment, but longer follow-up revealed that the proportion of ME in patients treated with systemic therapy continued to decrease through 54 months while it remained steady in the implant arm, reaching a similar proportion in the groups from the 36 months of follow up onward, without a significant difference in visual acuity between the two groups [7, 8]. Extended follow-up of the cohort through 7 years demonstrated that ME outcomes did not differ between the groups, even if visual acuity was better in patients treated with systemic therapy [9]. This study concludes that both approaches are successful in treating ME but intravitreal therapy is able to reach control of inflammatory ME faster, even though in the longer follow up, systemic therapy seemed to do better.

Since the prevention of irreversible macular damage caused by chronic disease activity is essential to preserve a good visual acuity, a treatment that acts earlier could be considered useful. However, the superiority of the implant in a faster control of inflammation did not result in a better long-term visual prognosis, probably because the severe recurrences in the implant group may cause more damage to the macula than the low-grade inflammation occurring during the slow tapering of steroids or under chronic systemic treatment.

Different studies have demonstrated that despite control of inflammation with systemic immunomodulatory agents, uveitic ME may persist in about 50% of cases [7, 10]. In such refractory cases local management with adjunctive intravitreal therapy is essential for the resolution of ME.

Immunosuppressive Agents

Conventional immunosuppressive therapy include antimetabolites such as Azathioprine, Methotrexate and Mycophenolate mofetil, calcineurin inhibitors such as Cyclosporine and Tacrolimus, or alkylating agents like Cyclophosphamide and Chlorambucil.

Immunosuppressive agents are usually introduced in the management of noninfectious uveitis to control persistent or severe inflammation and prevent the onset of structural complications as ME [6]. Failure of systemic corticosteroids, contraindications to steroids and need for corticosteroid-sparing agents to maintain the remission are other indications to start the treatment [6]. Development of bilateral ME during the ongoing immunosuppressive treatment influences the decision to adjust systemic therapy, conversely few studies recognized development of ME as an independent indicator for initiating immunosuppressive therapy [6].

Considering systemic side effects of immunosuppressive drugs including risk of malignancy and infections, use of immunomodulatory agents in the management of noninfectious uveitis is increasingly spreading, especially in refractory disease or as first-line treatment in case of severe intraocular inflammation.

Immunomodulatory Agents

Efficacy of monoclonal anti-tumor necrosis factor (TNF) antibodies has been shown in severe noninfectious uveitis complicated by long-standing refractory ME [11]. TNF-alfa is one of the mediators involved in the inflammatory pathways, leading to vascular hyper-permeability and intraretinal fluid accumulation through activation of T cells and macrophages. High level of TNF-α has been found in eyes with uveitis [12, 13].

Several studies reported efficacy of anti TNF alfa agents in the treatment of refractory uveitis with a reduction of central retinal thickness (CRT) on optical

coherence tomography (OCT) [14–19]. Etanercept may produce ocular inflammation and it does not seem to be effective in controlling uveitis and thus is not recommended in patients with uveitis. Infliximab has shown a rapid anti-inflammatory activity, especially in Behçet's disease, providing within few days a complete control of inflammation in 89% of patients with resolution of ME and improvement in BCVA [20]. Adalimumab has been associated with regression of ME in 70% of refractory uveitis together with an improvement in BCVA [15]. Lejoyeux et al. compared efficacy of Infliximab (IFX) and Adalimumab (ADA) in 25 patients with refractory inflammatory ME [21]. Both the treatments were comparable in terms of effectiveness at 6 and 24 months with about half of patients responding to anti TNF alfa therapy. At 6 months, 50% of patients treated with ADA and 61% of patients treated with IFX showed a response, registered as a decrease in median central foveal thickness from baseline of 61 and 66 μm, respectively at 6 and 24 months, in the ADA group versus 92 and 52 μm in the IFX group [21]. From the study emerged that the use of ADA as a second-line anti-TNF-α treatment after IFX was not effective, while the administration of IFX as a second-line of anti-TNF-α resulted effective in patients in whom ADA was switched to IFX.

Anti-TNF-α agents represent an effective treatment for long-standing uveitic ME. A contentious issue is about starting the treatment earlier as first-line therapy in patients with severe sight threatening disease to prevent the visual loss due to structural changes occurring in chronic disease and derived from long-standing accumulation of intraretinal fluid [22, 23].

Interferon (IFN) treatment has been successfully used in the management of uveitis refractory to standard care, especially in Behçet's disease [24, 25]. IFN is an intracellular cytokine with a wide range of activities, including immunomodulation of both innate and adaptive responses. Fardeau et al. in the BIRDERFERON study evaluated changes in central foveal thickness (CFT) on OCT in a group of patients with bilateral posterior autoimmune uveitis complicated by ME and treated with subcutaneous IFN-α2a, in comparison to patients treated with systemic corticosteroids or no treatment [24]. From the study, it was concluded that IFN-α and systemic steroids, compared to no treatment, were associated with significant improvement both in anatomical features and in visual acuity; the treatment groups showed a similar anti-edematous effect on inflammatory ME [24]. Action is usually very quick and patients show response to therapy within 2 weeks [26].

Use of IFN-α is limited by development of adverse effects as depression, leukopenia, thrombocytopenia and appearance of auto-antibodies. Few cases of granulomatous uveitis and Vogt Koyanagi Harada disease have been reported in patients treated with IFN-α [24].

Local Therapy

Local therapy is now considered a valuable and effective approach in the management of ME especially in unilateral diseases and in uveitis where ME persists despite control of inflammation with systemic treatment [4, 27]. Local steroid

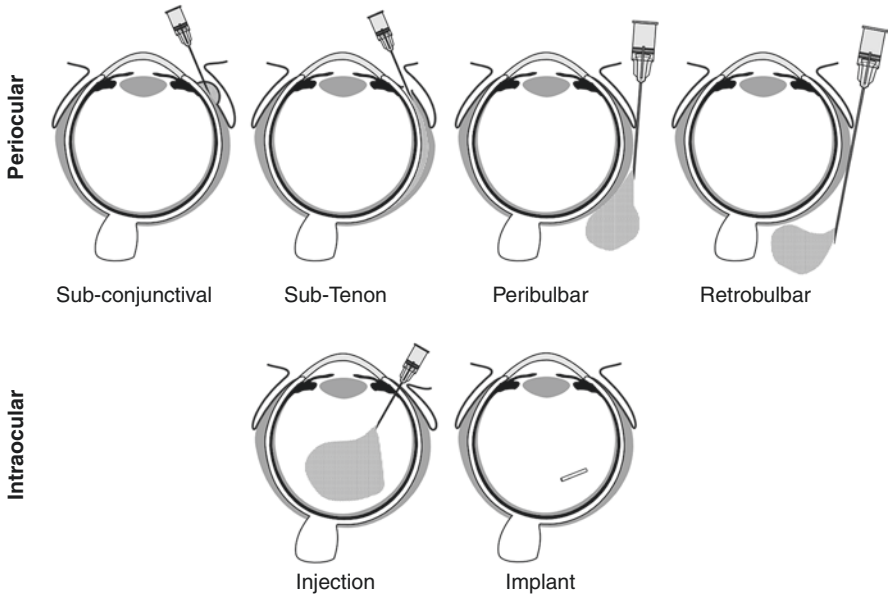

Fig. 15.1 Routes of ocular drug delivery: periocular (sub-conjunctival, sub-Tenon, peribulbar, retrobulbar) and intravitreal (injections and long-term devices)

treatment includes periocular and intravitreal injections and long-term intraocular and periocular devices (Fig. 15.1). Furthermore the development of local side effects such as cataract and raised intraocular pressure has encouraged the intravitreal use of alternative drugs as anti-VEGF or methotrexate with varying degrees of success.

Periocular and Intravitreal Corticosteroids

Corticosteroids commonly administer locally include triamcinolone acetonide, dexamethasone and fluocinolone acetonide. Triamcinolone acetonide can be injected as suspension through periocular or intravitreal administration route. When administered as intravitreal injection in a non vitrectomized eye at a dose of 4 mg, the effective concentration in vitreous cavity is maintained over a 3 month period. Dexamethasone is three times more potent than triamcinolone but, being a small molecule with a very short half-life, is administered through a sustained-release implant (0.7 mg), which is suggested to act over a period of 6 months. Fluocinolone acetonide is delivered in different doses by sustained-release devices, surgically placed or injected in vitreous cavity, able to release the drug over a period of 3 years.

Intravitreal triamcinolone acetonide and the dexamethasone sustained-release implant are the most widely used for the treatment of ME.

Recently Thorne et al. for the MUST Trial Research Group has conducted the POINT (PeriOcular versus INTravitreal corticosteroids) study, a randomized

comparative trial between periocular triamcinolone acetonide (PTA), intravitreal triamcinolone acetonide (ITA) and intravitreal dexamethasone implant (IDI), evaluating the efficacy and safety of steroids injections in the treatment of ME in 192 patients with active or inactive noninfectious uveitis [28]. From the study, it was inferred the superiority of both intravitreal therapies compared to periocular treatment and the comparability of IDI and ITA at 8 weeks [28]. The main outcomes evaluated were change in central subfield thickness (CST) as measured by OCT at 8 weeks, change in best corrected visual acuity (BCVA) over a 24 month follow-up and safety profile evaluated as risk of intraocular pressure (IOP) elevation. CST improved at 8 weeks in all treatment groups with a decrease in macular thickness of 23% in the PTA arm, 39% in ITA and 46% in IDI [28]. Evaluating the proportion of baseline (ProBL) CST at 8 weeks (CST at 8 weeks/CST at baseline) both ITA and IDI were superior to PTA and IDI was not inferior to ITA [28]. Patients treated with intravitreal injections had higher proportion of eyes with resolution of ME in the absence of significant differences between ITA and IDI group [28]. Overall, BCVA improved in all the groups, with a greater increment in the intravitreal treatment groups compared to the periocular one (4–7 letter at 4–8 weeks and 5 letters at 24 weeks) [28]. No significant difference in BCVA improvement was found among the intravitreal groups. Risk of having a IOP >24 mmHg or increased >10 mmHg from baseline was higher and comparable in the IDI and ITA groups, while risk of IOP elevation >30 mmHg was rare and did not differ among the arms [28]. From the study thus emerged that the efficacy in management of ME and improvement of visual acuity is comparable between intravitreal treatments and superior to the periocular approach, regardless of the type of corticosteroids administered and with modestly greater rates of mild increase in IOP.

Arcinue et al. compared efficacy and safety of the surgically placed implant of fluocinolone acetonide (FAI) compared to IDI in patients with non-infectious uveitis [29]. Both implants were effective in decreasing the baseline CRT [29]. Even if IDI group obtained the largest decrease in mean CRT at 1 month, with a progressive increase in mean CRT until the 12 month, but still inferior compared to baseline, and FAI arm showed a continuous decrease in CRT over the 12 month period, the comparison between the two groups was not statistically significant [29]. Regarding safety profile, eyes treated with FAI had a statistically higher rate of IOP elevation needed glaucoma medications, surgery or laser, and were 4.7 times more at risk of development cataract and undergoing surgery; all these findings were consistent with data from previous studies [29–31].

Although characterized by a shorter duration of action and subsequently by the need of repeat implantations, IDI is preferable comparable to FAI, considering the lower rates of intraocular complications with a comparable efficacy in term of control of inflammation and decrease in mean CRT. Furthermore IDI appears less invasive, technically easier to implant and less expensive than FAI.

Intravitreal corticosteroids can unmask an unknown infectious underlying process or may result in worsening of intraocular inflammation when injected in eyes with infectious uveitis. Recently the efficacy and safety of intravitreal corticosteroid injections for the treatment of refractory ME has been demonstrated also in

infectious uveitis [32]. Fonollosa et al. reported a case series of eye with ME secondary to infectious ocular disease, in which previous treatments including oral steroids, anti-VEGF injections and vitrectomy were ineffective in the control of ME. In all the cases intravitreal injection of steroids (IDI) was effective in resolution of ME and improve of visual acuity, without reactivation of the infectious inflammatory process [32]. The risk of reactivation of underlying disease or worsening of inflammation can be avoided by administering concomitant appropriate antimicrobial treatment when steroids are injected or being sure that the patient had received a complete course of therapy before injecting.

Intravitreal AntiVascular Endothelial Growth Factor

The use of antivascular endothelial growth factor (anti VEGF) is a fairly new paradigm in the treatment of uveitic ME. Being a regulator of angiogenesis and vascular permeability, the release of VEGF plays a crucial role in development of inflammatory ME, resulting in retinal vessel hyperpermeability. Higher concentration of VEGF has been found in patients with uveitis and ME [33, 34]. Anti-VEGF drugs thus, inhibiting one of the inflammatory pathways involved in intraretinal fluid accumulation, have acquired a therapeutical role in the treatment of uveitic ME.

Given the limited anti-inflammatory effect, in eyes with ME and active inflammation anti VEGF should be used in addition to anti-inflammatory therapy. These agents can be useful in patients with infectious uveitis, where immunomodulatory therapy, both systemic and local, would potentially be associated with the risk of worsening of inflammation if administered without a proper antimicrobial treatment, and in patients with contraindications for local corticosteroids, like steroid-responders who are already known to develop IOP elevation.

To this day, there are no clinical trials comparing the efficacy of the available anti-VEGF agents (ranibizumab, bevacizumab and aflibercept) in the treatment of uveitic ME. Several studies have confirmed the efficacy of anti-VEGF in decrease CRT and improvement of visual acuity in eyes with persistent ME and remission of inflammation [35–38]. Recently Lasave et al. compared the efficacy of intravitreal bevacizumab (IVB) versus ITA in the management of persistent noninfectious uveitic cystoid macular edema in eye with well-controlled inflammation [35]. From the study emerged that repeated IVB improve inflammatory ME and BCVA as effectively as ITA at 24 months of follow-up [35]. Given the short duration, patients treated with IVB needed at least two or more injections to achieve resolution of ME, while the group treated with ITA did not required more than two [35]. Improvement of CRT has thus been transient after IVB with the need of repeated injections to achieve control of ME [35]. Intraocular complications such elevation in IOP was significantly higher in the group treated with ITA compared to IVB [35].

Considering the ocular side effects commonly seen in intravitreal corticosteroid administration, anti VEGF therapy can be useful in the treatment of chronic and persistent ME in eyes with well-controlled uveitis. Alternately in eyes with active

inflammatory disease in the presence of contraindications for local steroid therapy, intravitreal anti-VEGF should be associated with anti-inflammatory therapy. Considering the short-lasting effect, multiple injections are often needed to achieve resolution of ME.

Intravitreal Methotrexate

Intravitreal administration of Methotrexate (MTX) can be alternate treatment option in patients with active ocular inflammation and/or ME difficult to treat with conventional therapy. The well-known side effects of systemic corticosteroids and immunosuppressive therapy together with intraocular complications of the commonly used local steroid treatments have made intravitreal MTX an alternative therapy for uveitis and uveitic ME. Intravitreal MTX was first used in the treatment of intraocular lymphoma [39]. Given its anti-inflammatory effects mediated by adenosine and resulting in inhibition of neutrophils, macrophage and T cell activity, efficacy of intravitreal MTX was evaluated and confirmed also in the treatment of noninfectious uveitis. Taylor et al. studied the efficacy of intravitreal MTX in 15 steroid-responders with unilateral active noninfectious uveitis and/or ME [40]. Main outcomes evaluated were BCVA, ocular inflammation, time to relapse, level of systemic therapy and CRT. From the study, it emerged that local administration of MTX is effective in improving VA with a gain of at least ten letters at 3 month follow-up in 87% of patients [40]. CRT improved from a mean baseline of 425 to 275 μm at 6 months [40]. In three patients MTX allowed reduction of immunosuppressive therapy [40]. Relapse were observed at a median time of 4 months, but repeat injections have been proven to have similar efficacy (gain of 17 letters by month 2 after reinjection) [40]. Corneal epitheliopathy is a well-known side effect of MTX, mostly treated and resolved symptomatically with topical therapy [40]. Even though this study indicates that intravitreal MTX represents a valid anti-inflammatory treatment option in the management of patients with unilateral noninfectious uveitis and ME with good results and safety profile, proper trials are needed to confirm this impression.

Intravitreal Sirolimus

Sirolimus (Rapamycin) is an immunosuppressant targeting T cell proliferation through the inhibition of pro-inflammatory mediators such interleukins 2, 4 and 15. The SAVE (Sirolimus as a Therapeutic Approach UVEitis) study first evaluated and confirmed the efficacy of local administration of Sirolimus in control of intraocular inflammation in noninfectious uveitis [41]. Improvement in central macular thickness (CMT) was noted at 3 month follow-up compared to baseline, but benefits could not be observed at 6 months, suggesting the need for repeat injections [41]. At

1 year follow-up reduction in intraocular inflammation was reported in 70% of patients, with no statistically improvement in mean VA or CRT [41]. From the SAVE-2 study, it has emerged that intravitreal Sirolimus can lead to reduction of ME and low dose (440 μg) Sirolimus administered monthly is more efficacious than high dose (880 μg) administered every 2 months due to variation in effect duration [42]. Results from SAKURA Study-1 demonstrated improvement in intraocular inflammation at 5 months together with preservation of VA and reduction in corticosteroids in patients received repeated intravitreal injections of low dose Sirolimus [43]. Majority of the patients had an improvement in CRT >50 μm at 5 month follow-up, with better results in patients without epiretinal membrane or posterior hyaloid membrane traction [43].

Intravitreal Anti-tumor Necrosis Factor (TNF)

Limited studies are available on the outcome following intravitreal use of anti-tumor necrosis factor in the management of uveitic ME. Markomichelakis et al. evaluated efficacy of a single intravitreal injection of Infliximab in Behçet's disease with unilateral involvement [44]. The study reported a significant improvement in BCVA and intraocular inflammation, but, despite decrease in CMT, ME persisted in 80% of eyes affected [44]. No adverse effects were noted in the study contrary to the potential immunogenic and retinotoxic effects reported in literature [45, 46]. Furthermore, intravenous administration of Infliximab appeared to have a faster action compared to intravitreal injection [44]. Hamam et al. evaluated the short-term efficacy of intravitreal Adalimumab in active noninfectious uveitis, observing a complete resolution of ME in five out of eight eyes, together with control of inflammation and improve of VA [47].

Large-scale and long-term trials are required to determine the role of intravitreal administration of anti TNF in inflammatory ocular diseases to assess its efficacy and safety.

Vitrectomy

Pars plana vitrectomy has been explored as a surgical treatment option in patients with persistent inflammation and ME [48]. Beneficial effects may be explained by the removal of inflammatory mediators that accumulates in vitreous cavity and improving in oxygenation of hypoxic retina with subsequent reduction in VEGF production [48]. Furthermore intraocular inflammation can often lead to fibrosis of the vitreoretinal surface, resulting in the formation of epiretinal membrane (ERM) with vitreomacular traction and development of ME [48]. The presence of ERM has been associated with higher risk of medical treatment failure as well as with reduced efficacy of intravitreal therapy [49, 50]. Lehpamer et al. evaluated the effects of

ERM on the response of ME to systemic and local treatment [49]. From the study, it emerged that the presence of severe ERM with wrinkling results in a limited response to treatment in terms of both CRT and VA, while ERM without wrinkling does not affect the outcome [49]. Other studies confirmed the limited efficacy of intravitreal injections on eye with ERM, revealing a worse visual acuity at a 3 month follow-up compared to eyes without ERM underwent the same treatment [50]. It has also been observed that patients with posterior vitreous detachment (PVD) seem to respond better to the local therapy [50]. Munk et al. showed a greater and faster decrease in CRT in patient with PVD compared to those with vitreomacular adhesion or posterior vitreous attachment [50]. This can be explained by mechanical traction, that might prevent the decreasing in retinal thickness, and different configuration of vitreoretinal surface, that may result in variable drug concentration and absorption. The removal of pathologic vitreoretinal adhesion thus can help in the management of ME refractory to standard care.

References

1. de Smet MD, Okada AA. Cystoid macular edema in uveitis. Dev Ophthalmol. 2010;47:136–47. Review.
2. Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18(6):487–92. Review.
3. de Smet MD, Julian K. The role of steroids in the management of uveitic macular edema. Eur J Ophthalmol. 2011;21(Suppl 6):S51–5.
4. Shah KK, Majumder PD, Biswas J. Intravitreal therapeutic agents in noninfectious uveitic macular edema. Indian J Ophthalmol. 2018;66(8):1060–73.
5. Goldhardt R, Rosen BS. Uveitic macular edema: treatment update. Curr Ophthalmol Rep. 2016;4(1):30–7.
6. Dick AD, Rosenbaum JT, Al-Dhibi HA. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: Fundamentals Of Care for UveitiS (FOCUS) initiative. Ophthalmology. 2018;125(5):757–73.
7. Tomkins-Netzer O, Lightman S, Drye L, et al. Outcome of treatment of uveitic macular edema: the multicenter uveitis steroid treatment trial 2-year results. Ophthalmology. 2015;122(11):2351–9.
8. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group, Kempen JH, Altaweel MM, et al. Benefits of systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, and panuveitis: fifty-four-month results of the Multicenter Uveitis Steroid Treatment (MUST) trial and follow-up study. Ophthalmology. 2015;122(10):1967–75.
9. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group, Kempen JH, Altaweel MM, et al. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA. 2017;317(19):1993–2005.
10. Kempen JH, Altaweel MM, Holbrook JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the Multicenter Uveitis Steroid Treatment trial. Ophthalmology. 2011;118:1916–26.

11. Schaap-Fogler M, Amer R, Friling R, Priel E, Kramer M. Anti-TNF-α agents for refractory cystoid macular edema associated with noninfectious uveitis. Graefes Arch Clin Exp Ophthalmol. 2014;252(4):633–40.
12. Santos Lacomba M, Marcos Martín C, Gallardo Galaera JM, et al. Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. Ophthalmic Res. 2001;33:251–5.
13. Pérez-Guijo V, Santos-Lacomba M, Sánchez-Hernández M, Castro-Villegas Mdel C, Gallardo-Galera JM, Collantes-Estévez E. Tumour necrosis factor-alpha levels in aqueous humour and serum from patients with uveitis: the involvement of HLA-B27. Curr Med Res Opin. 2004;20(2):155–7.
14. Murphy CC, Greiner K, Plskova J, Duncan L, Frost A, Isaacs JD, Rebello P, Waldmann H, Hale G, Forrester JV, Dick AD. Neutralizing tumor necrosis factor activity leads to remission in patients with refractory noninfectious posterior uveitis. Arch Ophthalmol. 2004;122(6):845–51.
15. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119(8):1575–81.
16. Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch Clin Exp Ophthalmol. 2012;250(5):713–20.
17. Androudi S, Tsironi E, Kalogeropoulos C, Theodoridou A, Brazitikos P. Intravitreal adalimumab for refractory uveitis-related macular edema. Ophthalmology. 2010;117(8):1612–6.
18. Markomichelakis NN, Theodossiadis PG, Pantelia E, Papaefthimiou S, Theodossiadis GP, Sfikakis PP. Infliximab for chronic cystoid macular edema associated with uveitis. Am J Ophthalmol. 2004;138(4):648–50.
19. Farvardin M, Afarid M, Mehryar M, Hosseini H. Intravitreal infliximab for the treatment of sight-threatening chronic noninfectious uveitis. Retina. 2010;30(9):1530–5.
20. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum. 2011;41:61–7.
21. Lejoyeux R, Diwo E, Vallet H, et al. Infliximab and adalimumab in uveitic macular edema. Ocul Immunol Inflamm. 2018;26(7):991–6.
22. Lee RWJ, Dick AD. Treat early and embrace the evidence in favour of anti-TNF-a therapy for Behcet's uveitis. Br J Ophthalmol. 2010;94(3):269–70.
23. Olivieri I, Padula A, Leccese P, D'Angelo S, Giasi V. Long-lasting remission of severe Behçet's disease after the end of infliximab therapy. J Rheumatol. 2009;36(4):85.
24. Fardeau C, Simon A, Rodde B, et al. Interferon-alpha2a and systemic corticosteroid in monotherapy in chronic uveitis: results of the randomized controlled BIRDFERON study. Am J Ophthalmol. 2017;177:182–94.
25. Kötter I, Günaydin I, Zierhut M, Stübiger N. The use of interferon alpha in Behçet disease: review of the literature. Semin Arthritis Rheum. 2004r;33(5):320–35.
26. Deuter CM, Kotter I, Gunaydin I, et al. Efficacy and tolerability of interferon alpha treatment in patients with chronic cystoid macular oedema due to non-infectious uveitis. Br J Ophthalmol. 2009;93(7):906–13.
27. Tan HY, Agarwal A, Lee CS, et al. Management of noninfectious posterior uveitis with intravitreal drug therapy. Clin Ophthalmol. 2016;10:1983–2020.
28. Multicenter Uveitis Steroid Treatment Trial Research Group; Writing Committee, Thorne JE, Sugar EA, Holbrook JT, et al. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: the PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) trial. Ophathalmology. 2018 Sep 20. pii: S0161-6420(18)31133-3.
29. Arcinue CA, Cerón OM, Foster CS. A comparison between the fluocinolone acetonide (Retisert) and dexamethasone (Ozurdex) intravitreal implants in uveitis. J Ocul Pharmacol Ther. 2013;29(5):501–7.

30. Taban M, Lowder CY, Kaiser PK. Outcome of fluocinolone acetonide implant (Retisert) reimplantation for chronic noninfectious posterior uveitis. Retina. 2008;28:1280–8.
31. Jaffe GJ, Martin D, Callanan D, et al. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four week results of a multicenter randomized clinical study. Ophthalmology. 2006;113:1020–7.
32. Fonollosa A, Llorenç V, Artaraz J, et al. Safety and efficacy of intravitreal dexamethasone implants in the management of macular edema secondary to infectious uveitis. Retina. 2016;36(9):1778–85.
33. Weiss K, Steinbrugger I, Weger M, et al. Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab. Eye. 2009;23(9):1812–8.
34. Jeon S, Lee WK, Jung Y. Changes in the intraocular cytokine levels after intravitreal bevacizumab in uveitic macular edema. Ocul Immunol Inflamm. 2012;20:360–4.
35. Lasave AF, Schlaen A, Zeballos DG, et al. Twenty-four months follow-up of intravitreal bevacizumab injection versus intravitreal triamcinolone acetonide injection for the management of persistent non-infectious uveitic cystoid macular edema. Ocul Immunol Inflamm. 2017;20:1–9.
36. Cervantes-Castañeda RA, Giuliari GP, Gallagher MJ, et al. Intravitreal bevacizumab in refractory uveitic macular edema: one-year follow-up. Eur J Ophthalmol. 2009;19(4):622–9.
37. Mackensen F, Heinz C, Becker MD, Heiligenhaus A. Intravitreal bevacizumab (avastin) as a treatment for refractory macular edema in patients with uveitis: a pilot study. Retina. 2008;28(1):41–5.
38. Soheilian M, Rabbanikhah Z, Ramezani A, Kiavash V, Yaseri M, Peyman GA. Intravitreal bevacizumab versus triamcinolone acetonide for refractory uveitic cystoid macular edema: a randomized pilot study. J Ocul Pharmacol Ther. 2010;26(2):199–206.
39. Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008;92(3):383–8.
40. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology. 2009;116(4):797–801.
41. Ibrahim MA, Sepah YJ, Watters A, et al. One-year outcomes of the SAVE study: sirolimus as a therapeutic approach for UVEitis. Transl Vis Sci Technol. 2015;4(2):4.
42. Nguyen QD, Sadiq MA, Soliman MK, Agarwal A, Do DV, Sepah YJ. The effect of different dosing schedules of intravitreal sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, in the treatment of non-infectious uveitis (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2016;114:T3.
43. Nguyen QD, Merrill PT, Clark WL, et al. Intravitreal sirolimus for noninfectious uveitis: a phase III Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA). Ophthalmology. 2016;123(11):2413–23.
44. Markomichelakis N, Delicha E, Masselos S, Sfikakis PP. Intravitreal infliximab for sight-threatening relapsing uveitis in Behçet disease: a pilot study in 15 patients. Am J Ophthalmol. 2012;154(3):534–541.e1.
45. Giganti M, Beer PM, Lemanski N, Hartman C, Schartman J, Falk N. Adverse events after intravitreal infliximab (Remicade). Retina. 2010;30(1):71–80.
46. Elezoglou A, Kafasi N, Kaklamanis PH, et al. Infliximab treatment-induced formation of autoantibodies is common in Behçet's disease. Clin Exp Rheumatol. 2007;25(4 Suppl 45):S65–9.
47. Hamam RN, Barikian AW, Antonios RS, et al. Intravitreal adalimumab in active noninfectious uveitis: a pilot study. Ocul Immunol Inflamm. 2016;24(3):319–26.
48. Darsová D, Pochop P, Štěpánková J, Dotřelová D. Long-term results of pars plana vitrectomy as an anti-inflammatory therapy of pediatric intermediate uveitis resistant to standard medical treatment. Eur J Ophthalmol. 2018;28(1):98–102.
49. Lehpamer B, Moshier E, Pahk P, et al. Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol. 2014;157(5):1048–55.
50. Munk MR, Ram R, Rademaker A, et al. Influence of the vitreomacular interface on the efficacy of intravitreal therapy for uveitis-associated cystoid macular oedema. Acta Ophthalmol. 2015;93(7):e561–7.

Chapter 16
Epiretinal Membranes and Subretinal Fibrosis

Blanca C. Flores-Sánchez and Lyndon da Cruz

Epiretinal Membranes

Background

An epiretinal membrane (ERM) consists of a fibrocellular collection on the internal surface of the retina with the potential to contract [1]. In general, ERMs can be classified as idiopathic, when the only associated process is a posterior vitreous detachment; or secondary to other pathological processes of the vitreoretinal interface including trauma, surgery, retinal breaks or inflammation [2]. These processes ultimately lead to thickening and separation of the posterior hyaloid as well as disruption of inner retinal layers, allowing for fibrocellular proliferation [1].

Clinically, these membranes range from very thin, subclinical structures (sometimes known as 'cellophane') which do not affect visual function, to extensive, thick, contractile structures causing retinal puckering (wrinkling) or traction detachment with significant clinical symptoms [1, 3]. Intraocular inflammation facilitates the accumulation of inflammatory factors, which regulate the migration of glial cells and fibroblasts to the vitreous gel, thus contributing to the pathogenesis of ERM formation [4]. Epiretinal membranes commonly arise on the macular area in cases of chronic uveitis or uveitic macular oedema, potentially causing distortion and visual loss [5].

Pars plana vitrectomy (PPV) with membrane peeling effectively removes idiopathic ERMs. Successful ERM peeling yields relatively high visual improvement rates (up to 90%) with low recurrence rates (between 1–16%) [6]. However, a

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concomitant underlying chronic inflammatory condition could affect these results, making it more plausible for the membrane to recur. Also, visual acuity improvement is poorer after removal of ERM associated with uveitis, and visual outcomes will depend on the status of the overall preserved anatomy of the macula and on any associated pathology in other sectors of the eye [7].

Epidemiology

The advent of Optical Coherence Tomography (OCT) and its introduction into clinical practice allows for better visualization of the vitreomacular interface and intraretinal structures. This in turn, aids in the detection of ERM more accurately and to characterize any associated vitreoretinal traction. The prevalence of macular ERM is higher in OCT studies of patients with uveitis, ranging from 40% to 77% in at least one eye [8–10]. It is more prevalent in patients with intermediate and posterior or panuveitis due to more direct involvement of the vitreoretinal junction and subsequent development of retinal oedema [11]. Following the Standardization of Uveitis Nomenclature subtypes, the prevalence of ERM is as follows: anterior uveitis 28.1%; intermediate uveitis 57%; and posterior or panuveitis 43.4% [12]. These findings contrast with the lower prevalence of idiopathic ERMs, ranging from 1% to 28.9% depending on the ethnic group and specific predisposing factors [13].

Significant risk factors for the development of ERM in patients with uveitis include the following: older age, male sex, long course of inflammation and history of cataract extraction. Additionally, history of PPV or ocular procedures (e.g. retinal laser and intravitreal injections) can independently cause unilateral ERM in uveitis cases [12].

Older age has been reported as a consistent risk factor for idiopathic ERMs as well, with increased prevalence in populations over 60 years, and peaking at 70–79 [12, 13]. Cataract surgery contributes to posterior vitreous detachment by accelerating vitreous liquefaction, hence increasing the risk of ERM formation (incidence of 9.1% at 5 years after cataract surgery) [14]. In uveitic patients that undergo cataract extraction, ERM formation ranges from 4.47% to 56% [15].

Pathophysiology

Inflammatory ERMs differ in composition from idiopathic ERMs, which suggests that they may develop under different pathogenic processes. The latter are formed by extracellular matrix components, including collagen and fibronectin, as well as different types of cells, such as glial cells (Müller and astrocytes), hyalocytes, retinal pigment epithelial (RPE) cells and fibroblasts [16]. Sheybani and colleagues characterized the histological components of ERM in two patients with uveitis [17]. They found elevated cytokines and chronic inflammatory cells in abundance,

predominantly T lymphocytes and histiocytes, but also plasma cells and scarce eosinophils. RPE cells were absent from these tissue samples. Macrophages are abundant in ERM samples excised from cases of Pars Planitis; it is not clear yet where they derive from but they are considered to be a key regulator of cellular behavior during the inflammatory response leading to gliosis formation [4].

Snead and colleagues classified ERM into three histological types according to their cellular components: simple, tissue repair and neovascular membrane [18]. The cellularity of the tissue repair membranes included glial cells, RPE cells and inflammatory cells (macrophages and lymphocytes). Some of the biological mediators involved in its formation are Transforming Growth Factor (TGF)-β, Interleukin (IL)-6, and Platelet Derived Growth Factor (PDGF). Uveitic ERM would fall into this category, since they are thought to arise from a cytokine-driven repair process: activated cytokines in uveitis induce gliosis formation in the retina [17]. Cytokine IL-6 activates reactive gliosis endogenously in glial cells and it is up regulated in retinal degenerative processes [19]. These findings are consistent with the high levels of IL-6 and IL-10 found in the ERM specimens studied by Sheybani and colleagues. Glial cells stimulate ERM formation during an inflammatory stimulus by supporting the adherence of contractile fibroblast-like cells [20]. However, compared to idiopathic ERM, uveitic ERMs appear not to involve differentiation of RPE cells.

The central retina lies within a region of increased blood flow and it is vulnerable to the effects of blood-retinal barrier breakdown. This accounts for the associated macular and disc oedema frequently seen in cases of posterior inflammation. Progression of ERM in uveitis results from the continuous exposure of the vitreoretinal interface to inflammatory molecules and serum derived proteins, which regulate the underlying cellular infiltration and deposition [4].

Clinical Features

Visual disturbance secondary to ERM depends on the associated structural abnormalities of the underlying retina, including crinkling and thickening of outer and inner layers [21]. Therefore, not all patients with uveitis-related ERM are symptomatic even if the membrane is centrally located. When it becomes dense enough to induce contraction, macular dysfunction develops resulting in metamorphopsia (80% of cases) and drop in near central vision; but also micropsias and monocular diplopia in rare instances [5].

Clinically, ERMs can be visualized on the inner surface of the macula as fibrocellular proliferations with different grades of translucency. In the earliest stage an ERM is seen as a “cellophane light reflex” without associated retinal distortion. In more advanced stages, the iridescent light reflex becomes irregular and shrinkage of the membrane occurs, causing retinal folds and tortuosity of the underlying vessels. A macular pucker consists of a dense grey membrane that obscures the underlying retinal details and produces gross retinal distortion and wrinkling [21]. These

membranes can be centrally or eccentrically located depending on the specific disease. Longer duration of the inflammatory process is associated with clinically thicker ERMs [22].

A retrospective study found presenting visual acuities <20/200 in 38% of patients with uveitis and macular oedema with associated ERM and secondary retinal wrinkling, compared to 16% in those without ERM [10]. In the group of patients with ERM, a similar proportion continued to have visual acuity of <20/200 at 3 and 6 months follow-up (37% and 39% respectively) after receiving corticosteroid treatment. The presence of ERM was also significantly linked to less reduction of central subfoveal thickness at 6 months in this same study, suggesting a poorer response to treatment.

Anatomical OCT features that correlate with poorer visual outcomes in patients with uveitic ERM include foveal involvement, disruption of ellipsoid zone, and focal attachment to the inner surface with significant distortion of the retinal contour. In contrast, patients with thin central membranes present with better vision [23]. It is not yet clear the way in which central retinal thickness correlates with visual acuity in uveitic ERM, as some studies have found an association between increased subfoveal thickness and decrease in vision, and others have failed to prove it [22].

Cystoid macular oedema (CMO) is the most frequent cause of visual loss in patients with an altered blood-retinal barrier and it can complicate any type of uveitis [24]. Its treatment can be challenging in refractory cases and it is therefore important to assess structural macular changes carefully to recognize contributing factors that can influence response to treatment. The presence of an ERM and incomplete vitreous detachment are considered as risk factors for uveitic macular oedema treatment failure and poor visual prognosis [25, 26].

Investigations

In the past, many studies relied on color fundus photos to identify and characterize ERM. Nowadays, high resolution OCT provides a more sensitive tool for ERM detection and follow-up, especially under media opacity conditions that preclude adequate examination of the posterior segment. Approximately 38% of ERMs can be missed from color fundus photos even with clear media [12]. Similarly, Milani and colleagues reported a false negative rate of 36.8% when attempting detection of cellophane membranes or macular puckers through biomicroscopy, which were then positively identified through OCT [27].

Based on OCT imaging, an ERM has been defined as a continuous, hyperreflective signal at the level of the internal limiting membrane (l) with or without evidence of contraction, including wrinkling, flattening or anatomical distortion of the retinal surface [12, 22]. On OCT scans, between 30–50% of uveitic ERMs present with a focal pattern of attachment; this could be due to a tendency of global inflammatory ERMs to start contracting and lead to focal retinal distortion [5, 23, 28]. Over time,

uveitic ERMs tend to proliferate, becoming denser and more centrally located. Maitra and colleagues noted a propensity of parafoveal uveitic ERMs to involve the fovea and to increase its central thickness after 1 year from baseline [5].

Fundus Autofluorescence is an alternative imaging modality available for the study of disease processes in patients with uveitis. It relies on the visualization of the main natural retinoid fluorophores contained in lipofuscin, which is an incomplete breakdown molecule of phagocytosed photoreceptor outer segments [29]. In vivo qualitative assessment of lipofuscin patterns has improved the understanding of mechanisms behind some degenerative diseases. Abnormal accumulation of lipofuscin causes the RPE to lose its phagocytic ability, resulting in photoreceptor damage [30]. The main autofluorescence patterns are: increased autofluorescence, which results from RPE dysfunction; and decreased autofluorescence, which results from photoreceptor loss [31]. Uveitic CMO causes an increase in the macular autofluorescence pattern that is thought to arise from protein accumulation in the extracellular fluid and pigment displacement rather than from lipofuscin accumulation. Presence of a concomitant ERM accentuates hyper-autofluorescence in uveitic macular oedema [9]. In cases of ERM without macular oedema, a reduced foveal autofluorescence can be correlated with outer retinal deformation and ellipsoid zone disruption, which denotes an altered RPE/photoreceptor complex [32]. If severe macular dragging happens after contraction of an ERM, autofluorescence imaging will show hyper-autofluorescent lines in the areas where the retinal vessels were originally located before displacement [33].

OCT-Angiography (OCT-A) technology detects blood flow within the superficial, intermediate and deep capillary networks of the retinal layers without the injection of dye [34]. During an acute episode of cystoid uveitic oedema, OCT-A reveals a decrease in capillary density and complexity in vascular plexus [35]. However, OCT-A has a limited role in the assessment of vitreoretinal interface disorders due to the absence of vessels in this region. An ERM potentially causes vascular displacements in the macular capillary architecture when in exerts tractional forces on its surface. This phenomenon can be captured by OCT-A and represented by an increase in the macular vessel density in superficial and deep capillaries when ERM produces disruption of foveal architecture [33].

Management

One of the main goals in uveitis treatment is the adequate control of inflammation in order to avoid or limit the onset of complications. However, in many instances this is not possible and the development of complications, such as a central ERM, poses a visual threat to patients with chronic uveitis [36]. Membranes without traction can be monitored since no anatomical abnormality is found and vision is usually preserved [37]. Surgical removal of ERMs secondary to uveitis may be required in center-involving cases with focal attachment that are associated with deformation of retinal layers, persistent CMO and visual impairment [5].

PPV is required before peeling of ERMs in uveitis as with all ERMs. PPV may however have many additional benefits in uveitis including clearance of inflammatory mediators and removal of vitreous opacities that obscure the fundus and impair vision. PPV is also used in the repair of retinal detachment and diagnostically, for vitreous, retinal and choroidal biopsies. The excision of tissue samples can aid in the recognition of infectious pathogens or malignant cells [38]. Vitrectomy can achieve visual improvement in 56–68% of eyes and can stabilize vision in 20–24% of patients with chronic uveitis [7, 39].

In cases of uveitic ERM, surgical removal has been documented to be a safe procedure and to offer the possibility of visual improvement. Tanawade and colleagues reported visual improvement in 31.25%, visual stabilization in 31.25% and visual worsening in 37.5% of patients at 6 months following PPV and peeling of uveitic ERMs [38]. The main reasons for reduced postoperative vision were preexisting severe macular damage and unoperated lens opacities. Other series have reported visual improvement of ≥2 and ≥3 Snellen lines in 71% and 82% respectively during the first 3 months after ERM surgery [36, 40].

In cases of idiopathic ERM, concomitant removal of ILM has been deemed beneficial by reducing recurrence rates significantly, but with similar visual outcomes compared to ERM peeling alone [41]. Margherio and colleagues reported an overall recurrence rate for inflammatory ERM of 20%, mostly seen in thicker and vascularized membranes. According to these results, they hypothesized that the type of uveitis and incomplete peeling could affect recurrence rates [42]. ILM peeling would theoretically eliminate the scaffold for fibrocellular proliferation and contraction of myofibroblasts to avoid future formation of membranes [43]. The role of ILM peel in uveitic ERM surgery is not yet clear. Some authors have reported effective resolution of concomitant macular oedema after combined ILM and ERM peel, which is a common association in cases of uveitic ERM [38, 44].

Careful preoperative evaluation is warranted before surgical removal of uveitic ERM, given the variability of postoperative visual outcomes. One of the most important predictors of visual recovery after uveitic ERM peeling is the integrity of the ellipsoid zone. It has been demonstrated that ellipsoid zone disruption correlates negatively with visual acuity and, therefore, a well-documented preoperative anatomical disturbance may indicate poor visual recovery [22].

In a longitudinal study, Nazari et al. found that ERM involving the fovea in patients with inactive uveitis showed a benign course with visual stability after a 2-year period follow-up, despite an increase in thickness and corresponding anatomical changes. These findings suggest that surgical removal should only be attempted after careful clinical evaluation once adequate medical therapy has been established [45]. Monitoring of ERM thickness could serve as a way of predicting which patients will develop visual deterioration, since longer duration of ERM correlates with increased thickness, and thicker ERMs correlate with decreased visual acuity [23].

Specific Uveitis Syndromes and ERM

Intermediate Uveitis presents as an isolated low-grade inflammatory entity (Pars Planitis) in 70% of cases, and the rest are associated with systemic conditions. The most common one is Sarcoidosis, followed by Multiple Sclerosis and Behçet's disease. Bilateral ocular involvement occurs in 81% of cases of intermediate uveitis and it usually follows a chronic course. Frequently, clinical signs at presentation involve the anterior and posterior segments and include mild to moderate anterior uveitis, vitreous haze and cells, retinal vasculitis, and papillitis. Common complications include the development of CMO, cataract and ERM; all of these are associated with worse visual acuity [46].

Pars Planitis affects children and adolescents most commonly, and typical findings include band keratopathy, peripheral corneal endotheliopathy, posterior synechiae, snowballs and snowbanks [47]. ERM formation rates range between 37–40% during biomicroscopic evaluation of the posterior segment, with 6.5% of them considered as severe [38, 48, 49]. It is directly related to disease duration, with a mean interval between onset of Pars Planitis and ERM formation of 6.5–7.9 years [49]. As mentioned previously, it is now possible to detect ERM formation more accurately with the availability of high definition OCT scans, which could facilitate a lower threshold for the diagnosis of vitreomacular interface pathology. Dev and colleagues reported a mean visual acuity of 20/40 in five of seven patients at mean follow-up of 23 months, with reduced or resolved vitritis after surgical removal of ERM [36].

The prevalence of *Sarcoid* with ocular involvement ranges from 13% to 79% in patients with systemic disease, presenting within 1 year after onset. There are two peaks of incidence at 20–30 years and at 50–60 years of age. Posterior segment complications include CMO in up to 76% of cases and a prevalence of ERM formation of 6% [38, 50, 51]. In a retrospective study, Kiryu and colleagues reported a recurrence rate of 27% after PPV and visual improvement of ≥2 Snellen lines in 82% of patients at 12 months, but this improvement was only preserved in 45% at final follow-up due to cataract development and membrane regrowth [40].

Behçet's disease is a chronic relapsing condition with sight threatening ocular manifestations in 70% of cases. It is characterized predominantly by episodes of panuveitis, with several vitreoretinal complications [52]. Central retinal involvement occurs in 24% of eyes at presentation, and it predisposes to permanent visual loss by causing refractory CMO, macular ischaemia secondary to occlusive vasculitis, macular inflammatory infiltrates, macular or optic nerve atrophy, and vitreoretinal interface disease [53]. Prevalence of ERM formation ranges between 10–30% in different series, and it is related to a higher number of acute inflammatory attacks [54–56].

Other Causes of Retinal Vasculitis

Eales disease is a vaso-occlusive idiopathic disorder affecting young males. It comprises four clinical stages: inflammatory, obliterative, ischaemic and proliferative. ERM formation evolves during the proliferative stage, secondary to differentiation of RPE, glial and chronic inflammatory cell populations. ERMs are fibrovascular in nature, and they are likely triggered by ischaemic stimulus secondary to obliteration of small peripheral veins [57]. Goel and colleagues reported macular involvement in 58.2% of patients with Eales disease when evaluated with OCT scans, which was more common in cases of active vasculitis and was significantly associated with poorer visual acuity. The most common abnormality was macular oedema, followed by ERM formation (prevalence of 11.4%) [58]. Saxena and colleagues reported a case of a diffuse posterior ERM secondary to Eales disease that caused severe vitreopapillary and vitreomacular traction, followed by retinal infolding and retinoschisis [59].

Birdshot retinochoroidopathy characteristically presents with scattered spots of inflammation at the level of the RPE and choriocapillaris that eventually lead to depigmented fundus lesions. It is associated with varying degrees of vitritis, retinal phlebitis, exudative vasculopathy, and optic disc swelling. It strongly correlates with a positive Human Leukocyte Antigen A29 and it affects Caucasians predominantly [60]. In a retrospective review of 35 patients, the most common ocular complications were development of cataract, CMO and glaucoma during a mean follow-up of 81.2 months; ERM formation was reported in only in 10.7% of them [61]. However, in another study based on OCT scans, 92% of patients with long-standing disease (>6 years duration) developed ERM; these proliferations were thin and did not cause central visual impairment [62].

The natural history of *Toxoplasmos*is involves recurrent activations of the primary lesion with prominent vitritis and retinochoroiditis in the second to fourth decades of life. Central involvement is a common feature with optic and macular oedema; a bilateral presentation occurs in one third of patients. In congenital cases, prevalence of macular and bilateral involvement is considerably higher (46–55% and 51–85% respectively) [63]. Posterior segment complications include rhegmatogenous and serous retinal detachments, vascular occlusions, retinal neovascularization, macular hole and ERM formation [64]. Miranda and colleagues reported a combination of features in preoperative macular OCT scans of 14 patients with toxoplasmosis scheduled for combined ILM and ERM removal. These included center-involving ERM, CMO and vitreomacular traction [65]. ERM peeling achieved anatomical CMO improvement and reduced central retinal thickness in all patients, with a mean change in visual acuity from 20/200 at baseline to 20/60 at a mean follow-up of 6 months. ERM recurrence was noted in one patient at 5 months postoperatively.

Subretinal Fibrosis

Fibrosis is the end result of a chronic, often immune-associated response at sites of tissue repair [66]. It is defined as the replacement of normal tissue by an overgrowth of scar tissue, secondary to an altered remodeling of the extracellular matrix network [67]. Fibrosis can develop in any area of the subretinal space, but it becomes vision-threatening when it forms below the fovea. It can complicate any chronic retinal disease, including central serous chorioretinopathy, chronic retinal detachment, vitreoproliferative entities and, importantly, uveitis [68–71].

Clinically, fibrosis can be visualized as a well demarcated white-yellow lesion with a solid, opaque appearance; overtime fibrosis can become densely pigmented or can be associated with other anatomical changes such as retinal haemorrhages, oedema or fluid during active phases of the underlying disease [72]. The presence of a retinal fibrotic scar can be confirmed by angiographic fluorescein blockage with late faint staining on the edges of the lesion [69]. OCT scans will show a thick hyperreflective area with distinct borders below the neurosensory retina, with or without atrophy of outer retinal layers and posterior shadowing. Additionally, there could be extensive degenerative intraretinal spaces in chronic cases [73]. Indocyanine green angiography is of limited use in imaging areas of subretinal fibrosis.

The two main mechanisms that can lead to subretinal fibrosis formation in uveitis patients are choroidal neovascularization (CNV) and chronic multifocal or diffuse ocular inflammation. In both processes, the triggering stimulus is retinochoroidal disruption induced by various factors including infections, autoimmune responses, trauma, toxins and radiation (Table 16.1) [68].

Table 16.1 Uveitis entities that complicate with subretinal fibrosis

I. Non-infectious
Vogt-Koyanagi-Harada disease
Subretinal fibrosis and uveitis syndrome
Punctate Inner Choroiditis
Multifocal choroiditis with panuveitis
Serpiginous choroiditis
Birdshot chorioretinopathy
Sarcoidosis
II. Infectious
Toxoplasma retinochoroiditis
Toxocariasis
Presumed Ocular Histoplasmosis Syndrome
Viral retinitis
Onchocerciasis

Choroidal Neovascularization

Pathologic myopia and intraocular inflammation are the leading causes of CNV in patients younger than 50 years, while age-related macular degeneration (AMD) is the main cause in those older than 50 [74–76]. Development of CNV poses a risk of severe vision loss and poor prognosis in uveitis patients; it complicates 2% of inflammatory processes involving the posterior segment (outer retina/RPE/choroidal complex) and, very rarely, anterior or intermediate uveitis (0.06%) [77, 78]. A patient is more likely to develop CNV during active periods of anterior segment inflammation or preretinal neovascularization, as well as if there is a positive history of contralateral CNV [78].

Gass classified CNV into two main types: sub-RPE neovascularization (Type 1) and subretinal neovascularization (Type 2). The latter is considered as an inflammation-related proliferation that occurs secondary to acquired focal defects of Bruch's membrane, giving way to new vessels into the subretinal space [79]. Macrophages, fibrocytic-like cells and RPE cells actively proliferate in reaction to the presence of neovascular sprouts below the sensory retina, and they are clinically visible as a dark plaque or atrophic scar at the edge of the lesion [77, 79].

Formation of CNV and subsequent subretinal fibrosis are considered as part of the ocular wound repair process. After acute injury of the RPE/Bruch's membrane complex, the affected tissue releases cytokines such as PDGF, TGF-α and TGF-β during an early phase, and these induce angiogenesis to enhance tissue repair by improving oxygenation and recruiting inflammatory cells such as macrophages, endothelial cells and myofibroblasts [80]. The response then usually progresses to a late phase, characterised by involution of the vascular and cellular components [81]. During this late phase, a scarring reaction (fibrosis) results if the wound repair process is not properly balanced and the stimulus persists, leading to excessive remodeling of the extracellular matrix and inducing macrophages further to initiate fibrogenesis [82]. Fibronectin and collagen type I and IV are the most common extracellular matrix components found in subretinal fibrosis tissue samples. As subretinal fibrosis matures, it potentially destroys local photoreceptors, RPE cells and choroidal vessels, which leads to retinal degeneration and permanent visual loss [83]. Green and colleagues reported that photoreceptor destruction increases with greater diameter and thickness of disciform scars in patients with AMD [84].

Uveitic CNV frequently recurs and poses a risk of poorer visual outcomes whenever delayed diagnosis precludes timely management. Topographically, inflammatory CNV appears predominantly beneath or near the fovea, or surrounding the optic nerve. Patients complain of metamorphopsia and visual impairment when the location is central, but in extrafoveal locations they may be asymptomatic. Clinically, uveitic CNV is usually of the Gass Type 2 form and presents as a grayish lesion with low levels of associated exudation or haemorrhage, frequently at the edge of other lesions such as an existing chorioretinal scar or granuloma [85]. Additional subtle clinical signs that suggest the presence of CNV but that can be frequently missed during examination include a hypopigmented halo, a hyperpigmented scar or a small single subretinal haemorrhage [86]. Other circumstances that could make

clinical diagnosis difficult include the presence of media opacity such as cataract or vitritis, as well as extensive retinal scarring obscuring fine details.

Since most patients with uveitis develop an inflammatory Type 2 CNV membrane, fluorescein angiography shows a "classic" lesion with a delineated area of early hyperfluorescence where neovascularization lies that increases in late stages due to active leakage. OCT scans show subretinal hyperreflective material above the RPE level [73]. In a retrospective series of 30 eyes of 28 patients, Roy and colleagues reported a prevalence of Type 2 CNV membranes in 84.1% detected by OCT scans, with the remaining being Type 1 [87]. Regarding the location of uveitic CNV, 76.7% presented in the fovea, and only 10% and 13% presented in a juxtafoveal and parapapillary location, respectively.

The therapeutic regimen for inflammatory CNV includes a combination of specific systemic medications for adequate control of inflammation with either photodynamic therapy (for extrafoveal CNV) or intravitreal bevacizumab or ranibizumab (for foveal lesions) with high success rates and visual recovery [85].

Chronic Granulomatous Inflammatory Process

Vogt-Koyanagi-Harada (VKH) disease and Subretinal fibrosis and uveitis syndrome are the two most representative uveitis entities that are known to evolve into severe and extensive subretinal fibrosis. In VKH, subretinal fibrosis has been described as a long-term complication in patients during the chronic phase of the disease and after multiple recurrences. Clinical exacerbations during this phase respond poorly to systemic therapy and are characterized by prolonged episodes of inflammation, which explains why complications present as a hallmark of this chronic phase [88]. Histopathologic studies of an end-stage case of VKH showed that scar tissue was formed by retinal gliosis and marked RPE hypertrophy as well as an important infiltration of T-lymphocytes in the choroid, consistent with a cell-mediated immune response [89].

Prevalence of subretinal fibrosis in VKH varies according to the ethnic group involved; it has been reported between 7–40% with a predilection of Hispanic patients, but only in 2% of patients with Eastern and South Asian descent [69, 90, 91]. Subretinal fibrosis in VKH tends to occur bilaterally and to involve the posterior pole more commonly (in a subfoveal, extrafoveal or peripapillary locations). It is considered a poor prognostic visual sign and, therefore, prompt and adequate treatment of active inflammation is crucial to avoid fibrotic scars [69, 91].

Zhao and colleagues reported a series of seven eyes with VKH and subretinal fibrosis in the posterior pole that caused refractory macular detachment even after successful control of the acute inflammatory process [92]. These patients underwent removal of subretinal fibrosis with retinectomy and silicone oil tamponade. Cases with macular or parapapillary involvement showed favorable visual outcomes, with 60% of them presenting with a final visual acuity of ≥20/200. The authors recommend being cautious when attempting removal of subretinal fibrosis encircling the optic nerve, due to the possibility of massive subretinal haemorrhage and blindness.

Subretinal fibrosis and uveitis syndrome is a poorly defined condition that is invoked in cases of progressive and rapid visual deterioration in the context of multiple foci of granulomatous infiltration of the RPE and choroid [93–96]. Many alternative terms have been used to describe the full spectrum of this disease including 'Progressive subretinal fibrosis with uveitis syndrome', 'Multifocal choroiditis associated with progressive subretinal fibrosis' and 'Diffuse subretinal fibrosis syndrome'. It usually affects young adults without systemic illnesses, but there are a few cases of onset during childhood and in the elderly (the youngest patient being 3 years and the oldest 76 years) [94, 97–100].

The early stage of subretinal fibrosis and uveitis syndrome is characterized by active multifocal choroiditis with scattered hypopigmented lesions in the posterior pole and mid periphery, similar to the presentation in the white dot syndromes [101]. The main difference is that, ultimately, this process leads to massive subretinal fibrotic plaques that eventually expand and fuse to replace the outer retina and choroidal layers particularly in the macula [94, 98, 102]. According to histopathological examinations, the fibrotic reaction is induced by an intense antigenic stimulus that leads to an antibody mediated inflammatory process. Palestine reported the presence of monoclonal antibodies against Müller cells, deposition of complement and immunoglobulins, and a predominant infiltration of B-cell and plasma cells [103]. Electron microscopy results have suggested that this fibrotic tissue derives from the lineage of RPE and glial cells [104].

Subretinal fibrosis and uveitis syndrome represents a singular type of inflammatory reaction and not an aetiological definition [103]. Although it has been described as a variant of Sympathetic Ophthalmia (since some patients present after trauma or surgery with a clinical picture of granulomatous panuveitis showing retinal exudation, diffuse pigmentary changes, papillitis and Dalen Fuchs nodules), it is not generally thought to be associated with this condition. Other possible aetiologies, including infectious and masquerade syndromes, have been ruled out by histopathology [93, 105].

Given the aggressive course of this granulomatous inflammation, management should involve early use of high-dose systemic steroids and potent immunomodulators. Some of the proposed regimens reported in literature include use of cyclophosphamide, cyclosporine, azathioprine or methotrexate [97]. In cases of refractory response to treatment, the use of anti-Tumor Necrosis Factor-α has been attempted with good control of the inflammation [106]. However, despite adequate treatment the disease may still produce blindness.

Conclusions

Epiretinal membranes and subretinal fibrosis commonly develop in response to inflammatory diseases affecting the posterior segment of the eye. Often, they cause major anatomical and functional damage that can lead to profound visual loss. The severity of their clinical presentations usually correlates with the intensity and

duration of the inflammatory stimulus. Typically, they are seen in association with other complications such as macular oedema and choroidal neovascularization. For this reason, their management can be complex and different strategies are needed in order to reduce the risk of blindness. To attain better visual outcomes, it is critical to treat the underlying pathological process promptly and adequately, since disease chronicity and recurrences limit the efficacy of all therapeutic options.

References

1. Clarkson JG, Green WR, Massof D. A histopathologic review of 168 cases of preretinal membrane. Am J Ophthalmol. 1977;84(1):1–17. https://doi.org/10.1016/0002-9394(77)90317-8.
2. Pilli S, Lim P, Zawadzki RJ, Choi SS, Werner JS, Park SS. Fourier-domain optical coherence tomography of eyes with idiopathic epiretinal membrane: correlation between macular morphology and visual function. Eye. 2011;25(6):775–83. https://doi.org/10.1038/eye.2011.55.
3. Hiscott P, Hagan S, Heathcote L, Sheridan CM, Groenewald CP, Grierson I, et al. Pathobiology of epiretinal and subretinal membranes: possible roles for the matricellular proteins thrombospondin 1 and osteonectin (SPARC). Eye. 2002;16(4):393–403. https://doi.org/10.1038/sj.eye.6700196.
4. Gilbert C, Hiscott P, Unger W, Grierson I, McLeod D. Inflammation and the formation of epiretinal membranes. Eye. 1988;2(1):S140–56. https://doi.org/10.1038/eye.1988.140.
5. Maitra P, Kumar DA, Agarwal A. Epiretinal membrane profile on spectral domain optical coherence tomography in patients with uveitis. Indian J Ophthalmol. 2019;67(3):376–81. https://doi.org/10.4103/ijo.IJO_650_18.
6. Chang WC, Lin C, Lee CH, Sung TL, Tung TH, Liu JH. Vitrectomy with or without internal limiting membrane peeling for idiopathic epiretinal membrane: a meta-analysis. PLoS One. 2017;12(6):1–18. https://doi.org/10.1371/journal.pone.0179105.
7. Verbraeken H. Therapeutic pars plana vitrectomy for chronic uveitis: a retrospective study of the long-term results. Graefes Arch Clin Exp Ophthalmol. 1996;234(5):288–93. https://doi.org/10.1007/BF00220702.
8. Markomichelakis NN, Halkiadakis I, Pantelia E, Peponis V, Patelis A, Theodossiadis P, Theodossiadis G. Patterns of macular edema in patients with uveitis: qualitative and quantitative assessment using optical coherence tomography. Ophthalmology. 2004;111(5):946–53. https://doi.org/10.1016/j.ophtha.2003.08.037.
9. Roesel M, Henschel A, Heinz C, Dietzel M, Spital G, Heiligenhaus A. Fundus autofluorescence and spectral domain optical coherence tomography in uveitic macular edema. Graefes Arch Clin Exp Ophthalmol. 2009;247(12):1685–9. https://doi.org/10.1007/s00417-009-1149-8.
10. Lehpamer B, Moshier E, Pahk P, Goldberg N, Ackert J, Godbold J, Jabs DA. Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol. 2014;157(5):1048–55. https://doi.org/10.1016/j.ajo.2014.01.020. Epub 2014 Jan 30.
11. Multicenter Uveitis Steroid Treatment Trial Research Group, Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol. 2010;149(4):550–561.e10. https://doi.org/10.1016/j.ajo.2009.11.019.
12. Nicholson BP, Zhou M, Rostamizadeh M, Mehta P, Agrón E, Wong W, et al. Epidemiology of epiretinal membrane in a large cohort of patients with uveitis. Ophthalmology. 2014;121(12):2393–8. https://doi.org/10.1016/j.ophtha.2014.06.015.
13. Bu SC, Kuijer R, Li XR, Hooymans JMM, Los LI. Idiopathic epiretinal membrane. Retina. 2014;34(12):2317–35. https://doi.org/10.1097/IAE.0000000000000349.

14. Fraser-Bell S, Guzowski M, Rochtchina E, Wang JJ, Mitchell P. Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study. Ophthalmology. 2003;110(1):34–40.
15. Llop SM, Papaliodis GN. Cataract surgery complications in uveitis patients: a review article. Semin Ophthalmol. 2018;33(1):64–9. https://doi.org/10.1080/08820538.2017.1353815.
16. Joshi M, Agrawal S, Christoforidis JB. Inflammatory mechanisms of idiopathic epiretinal membrane formation. Mediat Inflamm. 2013;2013:192582. https://doi.org/10.1155/2013/192582.
17. Sheybani A, Harocopos GJ, Rao PK. Immunohistochemical study of epiretinal membranes in patients with uveitis. J Ophthalmic Inflamm Infect. 2012;2(4):243–8. https://doi.org/10.1007/s12348-012-0074-x.
18. Snead DRJ, James S, Snead MP. Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation. Eye. 2008;22(10):1310–7. https://doi.org/10.1038/eye.2008.36.
19. Xue W, Cojocaru RI, Dudley VJ, Brooks M, Swaroop A, Sarthy VP. Ciliary neurotrophic factor induces genes associated with inflammation and gliosis in the retina: a gene profiling study of flow-sorted, Müller cells. PLoS One. 2011;6(5):e20326. https://doi.org/10.1371/journal.pone.0020326.
20. Hiscott PS, Grierson I, Trombetta CJ, Rahi AH, Marshall J, McLeod D. Retinal and epiretinal glia-an immunohistochemical study. Br J Ophthalmol. 1984;68:698–707.
21. Gass JDM. Macular dysfunction caused by vitreous and vitreoretinal interface abnormalities. In: Gass' atlas of macular diseases, vol. 2. 5th ed. Philadelphia: Saunders; 2012. p. 672–6.
22. Iannetti L, Tortorella P, D'Ambrosio E, Spena R, Zito R, Gharbiya M. Epiretinal membranes in patients with uveitis: morphological and functional analysis with spectral domain optical coherence tomography. Biomed Res Int. 2013;2013:284821. https://doi.org/10.1155/2013/284821.
23. Nazari H, Dustin L, Heussen FM, Sadda S, Rao NA. Morphometric spectral-domain optical coherence tomography features of epiretinal membrane correlate with visual acuity in patients with uveitis. Am J Ophthalmol. 2012;154(1):78–86.e1. https://doi.org/10.1016/j.ajo.2012.01.032.
24. Rothova A, Suttorp-van Schulten MSA, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80(4):332–6. https://doi.org/10.1136/bjo.80.4.332.
25. Markomichelakis NN, Halkiadakis I, Pantelia E, Georgalas E, Chrysanthi K, Theodossiadis, et al. Course of macular edema in uveitis under medical treatment. Ocul Immunol Inflamm. 2007;15(2):71–9. https://doi.org/10.1080/09273940701244509.
26. Rothova A. Inflammatory cystoid macular edema. Curr Opin Ophthalmol. 2007;18(6):487–92. https://doi.org/10.1097/ICU.0b013e3282f03d2e.
27. Milani P, Raimondi G, Morale D, Scialdone A. Biomicroscopy versus optical coherence tomography screening of epiretinal membranes in patients undergoing cataract surgery. Retina. 2012;32(5):897–904. https://doi.org/10.1097/IAE.0b013e31822a8fec.
28. Mori K, Gehlbach PL, Sano A, Deguchi T, Yoneya S. Comparison of epiretinal membranes of differing pathogenesis using optical coherence tomography. Retina. 2004;24(1):57–62. https://doi.org/10.1097/00006982-200402000-00009.
29. Holz FG. Autofluorescence imaging of the macula. Ophthalmologe. 2001;98(1):10–8.
30. Meleth AD, Sen HN. Use of fundus autofluorescence in the diagnosis and management of uveitis. Int Ophthalmol Clin. 2012;52(4):45–54. https://doi.org/10.1097/IIO.0b013e3182662ee9.
31. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: review and perspectives. Retina. 2008;28(3):385–409. https://doi.org/10.1097/IAE.0b013e318164a907.
32. Brito PN, Gomes NL, Vieira MP, Faria PA, Rocha-Sousa A, Fernandes AV, Falcão-Reis F. Possible role for fundus autofluorescence as a predictive factor for visual acuity recovery after epiretinal membrane surgery. Retina. 2013;34(2):273–80. https://doi.org/10.1097/iae.0b013e3182999a02.

33. Nelis P, Alten F, Clemens CR, Heiduschka P, Eter N. Quantification of changes in foveal capillary architecture caused by idiopathic epiretinal membrane using OCT angiography. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1319–24. https://doi.org/10.1007/s00417-017-3640-y.
34. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1–55. https://doi.org/10.1016/j.preteyeres.2017.11.003.
35. Invernizzi A, Cozzi M, Staurenghi G. Optical coherence tomography and optical coherence tomography angiography in uveitis: a review. Clin Exp Ophthalmol. 2019;47:357–71. https://doi.org/10.1111/ceo.13470.
36. Dev S, Mieler WF, Pulido JS, Mittra RA. Visual outcomes after pars plana vitrectomy for epiretinal membranes associated with pars planitis. Ophthalmology. 1999;106(6):1086–90. https://doi.org/10.1016/S0161-6420(99)90247-6.
37. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, Sadda SR, Sebag J, Spaide RF, Stalmans P. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120(12):2611–9. https://doi.org/10.1016/j.ophtha.2013.07.042.
38. Tanawade RG, Tsierkezou L, Bindra MS, Patton NA, Jones NP. Visual outcomes of pars plana vitrectomy with epiretinal membrane peel in patients with uveitis. Retina. 2015;35(4):736–41. https://doi.org/10.1097/IAE.0000000000000378.
39. Henry CR, Becker MD, Yang Y, Davis JL. Pars plana vitrectomy for the treatment of uveitis. Am J Ophthalmol. 2018;190:142–9. https://doi.org/10.1016/j.ajo.2018.03.031.
40. Kiryu J, Kita M, Tanabe T, Yamashiro K, Ieki Y, Miura S, et al. Pars plana vitrectomy for epiretinal membrane associated with sarcoidosis. Jpn J Ophthalmol. 2003;47(5):479–83. https://doi.org/10.1016/S0021-5155(03)00128-X.
41. Schechet SA, DeVience E, Thompson JT. The effect of internal limiting membrane peeling on idiopathic epiretinal membrane surgery, with a review of literature. Retina. 2017;37(5):873–80. https://doi.org/10.1097/IAE.0000000000001263.
42. Margherio RR, Cox MS, Trese MT, Murphy PL, Johnson J, Minor LA. Removal of epimacular membranes. Ophthalmology. 1985;92(8):1075–83. https://doi.org/10.1016/S0161-6420(85)33902-7.
43. Park DW, Dugel PU, Garda J, Sipperley JO, Thach A, Sneed SR, Blaisdell J. Macular pucker removal with and without internal limiting membrane peeling: pilot study. Ophthalmology. 2003;110(1):62–4.
44. Llorenç V, Keller J, Pelegrín L, Adán A. Pars plana vitrectomy for vitreo-retinal complications of birdshot chorioretinopathy. Ocul Immunol Inflamm. 2011;19(5):346–52. https://doi.org/10.3109/09273948.2011.590265.
45. Nazari H, Rao N. Longitudinal morphometric analysis of epiretinal membrane in patients with uveitis. Ocul Immunol Inflamm. 2013;21(1):2–7. https://doi.org/10.3109/09273948.2012.714044.
46. Sancho L, Kramer M, Koriat A, Eiger-Moscovich M, Sharon Y, Amer R. Complications in intermediate uveitis: prevalence, time of onset, and effects on vision in short-term and long-term follow-up. Ocul Immunol Inflamm. 2019;27:447–55. https://doi.org/10.1080/09273948.2017.1420203.
47. Ozdal PC, Berker N, Tugal-Tutkun I. Pars planitis: epidemiology, clinical characteristics, management and visual prognosis. J Ophthalmic Vis Res. 2015;10(4):469–80. https://doi.org/10.4103/2008-322X.176897.
48. Raja SC, Jabs DA, Dunn JP, Fekrat S, Machan CH, Marsh MJ, Bressler NM. Pars planitis: clinical features and class II HLA associations. Ophthalmology. 1999;106(3):594–9.
49. Donaldson MJ, Pulido JS, Herman DC, Diehl N, Hodge D. Pars planitis: a 20-year study of incidence, clinical features, and outcomes. Am J Ophthalmol. 2007;144(6):812–7.
50. Rothova A. Ocular involvement in sarcoidosis. Br J Ophthalmol. 2000;84(1):110–6.

51. Pasadhika S, Rosenbaum JT. Ocular sarcoidosis. Clin Chest Med. 2015;36(4):669–83. https://doi.org/10.1016/j.ccm.2015.08.009.
52. Mesquida M, Pelegrín L, Llorenç V, Espinosa G, Ríos J, Dick AD, Adán A. Pars plana vitrectomy for vitreoretinal complications of Behçet uveitis. Eur J Ophthalmol. 2013;23(1):119–28. https://doi.org/10.5301/ejo.5000194.
53. Kahloun R, Ben Yahia S, Mbarek S, Attia S, Zaouali S, Khairallah M. Macular involvement in patients with Behçet's uveitis. J Ophthalmic Inflamm Infect. 2012;2(3):121–4. https://doi.org/10.1007/s12348-012-0075-9.
54. Öztürk HE, Eşki Yücel Ö, Süllü Y. Vitreomacular interface disorders in Behçet's uveitis. Turk J Ophthalmol. 2017;47(5):261–6. https://doi.org/10.4274/tjo.77632.
55. Amer R, Alsughayyar W, Almeida D. Pattern and causes of visual loss in Behçet's uveitis: short-term and long-term outcomes. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1423–32. https://doi.org/10.1007/s00417-017-3667-0.
56. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet disease: an analysis of 880 patients. Am J Ophthalmol. 2004;138(3):373–80. https://doi.org/10.1016/j.ajo.2004.03.022.
57. Majji AB, Vemuganti GK, Shah VA, Singh S, Das T, Jalali S. A comparative study of epiretinal membranes associated with Eales' disease: a clinicopathologic evaluation. Eye. 2006;20(1):46–54. https://doi.org/10.1038/sj.eye.6701788.
58. Goel N, Kumar V, Arora S, Jain P, Ghosh B. Spectral domain optical coherence tomography evaluation of macular changes in Eales disease. Int J Ophthalmol. 2018;66(3):433–8. https://doi.org/10.4103/ijo.IJO_845_17.
59. Saxena S, Jain A, Akduman L. Vitreopapillary and vitreomacular traction in proliferative Eales' disease. BMJ Case Rep. 2012;2012:2–4. https://doi.org/10.1136/bcr-2012-007231.
60. Herbort CP, Pavesio C, LeHoang P, Bodaghi B, Fardeau C, Kestelyn P, et al. Why birdshot retinochoroiditis should rather be called 'HLA-A29 uveitis'? Br J Ophthalmol. 2017;101(7):851–5. https://doi.org/10.1136/bjophthalmol-2016-309764.
61. Kiss S, Ahmed M, Letko E, Foster CS. Long-term follow-up of patients with birdshot retinochoroidopathy treated with corticosteroid-sparing systemic immunomodulatory therapy. Ophthalmology. 2005;112(6):1066–1071.e2. https://doi.org/10.1016/j.ophtha.2004.12.036.
62. Papadia M, Jeannin B, Herbort CP. OCT findings in birdshot chorioretinitis: a glimpse into retinal disease evolution. Ophthalmic Surg Lasers Imaging. 2012;43(6):S25–31. https://doi.org/10.3928/15428877-20120816-01.
63. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41(1):95–108. https://doi.org/10.1111/j.1442-9071.2012.02838.x.
64. Holland GN. Ocular toxoplasmosis: a global reassessment. Part II: Disease manifestations and management. Am J Ophthalmol. 2004;137(1):1–17. https://doi.org/10.1016/j.ajo.2003.10.032.
65. Miranda AF, De Andrade GC, Novais EA, Maia A, Nascimento H, Muccioli C, Belfort R. Outcomes after pars plana vitrectomy for epiretinal membranes associated with toxoplasmosis. Retina. 2016;36(9):1713–7. https://doi.org/10.1097/IAE.0000000000000973.
66. Stramer BM, Mori R, Martin P. The inflammation – fibrosis link? A Jekyll and Hyde role for blood cells during wound repair. J Invest Dermatol. 2007;127(5):1009–17. https://doi.org/10.1038/sj.jid.5700811.
67. Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008;214(2):199–210. https://doi.org/10.1002/path.2277.
68. Jo YJ, Sonoda KH, Oshima Y, Takeda A, Kohno RI, Yamada J, et al. Establishment of a new animal model of focal subretinal fibrosis that resembles disciform lesion in advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(9):6089–95. https://doi.org/10.1167/iovs.10-5189.
69. Kuo IC, Rechdouni A, Rao NA, Johnston RH. Subretinal fibrosis in patients with Vogt-Koyanagi-Harada disease. Ophthalmology. 2000;107(9):1721–8.

70. Wallyn RH, Hilton GF. Subretinal fibrosis in retinal detachment. Arch Ophthalmol. 1979;97(11):2128–9.
71. Sharma T, Badrinath SS, Gopal L, Ravishankar K, Shanmugam MP, Bhende P, Bhende M, Shetty NS, Deshpande DA, Mukesh BN. Subretinal fibrosis and nonrhegmatogenous retinal detachment associated with multifocal central serous chorioretinopathy. Retina. 1988;18(1):23–9.
72. Daniel E, Toth CA, Grunwald JE, Jaffe GJ, Martin DF, Fine SL, et al. Comparison of Age-related Macular Degeneration Treatments Trials Research Group Risk of scar in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2014;121(3):656–66. https://doi.org/10.1016/j.ophtha.2013.10.019. Epub 2013 Dec 4.
73. Goldman DR, Waheed NK, Duker JS. Atlas of retinal OCT. 1st ed. Edinburgh: Elsevier; 2018. p. 32–3, 36.
74. Agarwal A, Invernizzi A, Singh RB, Foulsham W, Aggarwal K, Handa S, et al. An update on inflammatory choroidal neovascularization: epidemiology, multimodal imaging, and management. J Ophthalmic Inflamm Infect. 2018;8(1):13. https://doi.org/10.1186/s12348-018-0155-6.
75. Rishi P, Gupta A, Rishi E, Shah BJ. Choroidal neovascularization in 36 eyes of children and adolescents. Eye. 2013;27(10):1158–68. https://doi.org/10.1038/eye.2013.155.
76. Miller DG, Singerman LJ. Vision loss in younger patients: a review of choroidal neovascularization. Optom Vis Sci. 2006;83(5):316–25.
77. Dhingra N, Kelly S, Majid MA, Bailey CB, Dick AD. Inflammatory choroidal neovascular membrane in posterior uveitis-pathogenesis and treatment. Indian J Ophthalmol. 2010;58(1):3–10. https://doi.org/10.4103/0301-4738.58467.
78. Baxter SL, Pistilli M, Pujari SS, Liesegang TL, Suhler EB, et al. Risk of choroidal neovascularization among the uveitides. Am J Ophthalmol. 2013;156(3):468–477.e2. https://doi.org/10.1016/j.ajo.2013.04.040.
79. Gass JDM. Biomicroscopic and histopathologic considerations regarding the feasibility of surgical excision of subfoveal neovascular membranes. Am J Ophthalmol. 1994;118(3):285–98. https://doi.org/10.1016/S0002-9394(14)72951-4.
80. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. J Dermatol Sci. 2013;72(3):206–17. https://doi.org/10.1016/j.jdermsci.2013.07.008.
81. Kent D, Sheridan C. Review choroidal neovascularization: a wound healing perspective. Mol Vis. 2003;9:747–55.
82. Wynn TA, Barron L. Macrophages: master regulators of inflammation and fibrosis. Semin Liver Dis. 2010;30(3):245–57. https://doi.org/10.1055/s-0030-1255354.
83. Ishikawa K, Kannan R, Hinton DR. Molecular mechanisms of subretinal fibrosis in age-related macular degeneration. Exp Eye Res. 2016;142:19–25. https://doi.org/10.1016/j.exer.2015.03.009.
84. Green WR, Enger C. Age-related macular degeneration histopathologic studies: the 1992 Lorenz E. Zimmerman lecture. Ophthalmology. 1993;100(10):1519–35. https://doi.org/10.1016/S0161-6420(93)31466-1.
85. DAmbrosio E, Tortorella P, Iannetti L. Management of uveitis-related choroidal neovascularization: from the pathogenesis to the therapy. J Ophthalmol. 2014;2014:450428. https://doi.org/10.1155/2014/450428.
86. Bansal R, Bansal P, Gupta A, Gupta V, Dogra MR, Singh R, Katoch D. Diagnostic challenges in inflammatory choroidal neovascular membranes. Ocul Immunol Inflamm. 2017;25(4):554–62. https://doi.org/10.3109/09273948.2016.1160128.
87. Roy R, Saurabh K, Bansal A, Kumar A, Majumdar AK, Paul SS. Inflammatory choroidal neovascularization in Indian eyes: etiology, clinical features, and outcomes to anti-vascular endothelial growth factor. Indian J Ophthalmol. 2017;65(4):295–300. https://doi.org/10.4103/ijo.IJO_262_16.
88. Keefe GADO, Rao NA. Vogt-Koyanagi-Harada disease. Surv Ophthalmol. 2016;62(1):1–25. https://doi.org/10.1016/j.survophthal.2016.05.002.

89. Chan CC, Palestine AG, Kuwabara T, Nussenblatt RB. Immunopathologic study of Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol. 1988;105(6):607–11. https://doi.org/10.1016/0002-9394(88)90052-9.
90. Zhao C, Dong F, Gao F, Liu X, Pei M, Jia S, Zhang M. Longitudinal observation of subretinal fibrosis in Vogt-Koyanagi-Harada disease. BMC Ophthalmol. 2018;18(1):6. https://doi.org/10.1186/s12886-018-0670-0.
91. Lertsumitkul S, Whitcup SM, Nussenblatt RB, Chan CC. Subretinal fibrosis and choroidal neovascularization in Vogt-Koyanagi-Harada syndrome. Graefes Arch Clin Exp Ophthalmol. 1999;237(12):1039–45.
92. Zhao C, Zhang M, Gao F, Dong F, Zhao C. Surgical treatment of subretinal fibrosis caused macular detachment in Vogt-Koyanagi-Harada disease: a pioneer study surgical treatment of subretinal fibrosis caused macular detachment in Vogt-Koyanagi-Harada disease: a pioneer study. Ocul Immunol Inflamm. 2018;26(1):154–9. https://doi.org/10.1080/09273948.2016.1201519.
93. Wang RC, Zamir E, Dugel PU, Sipperley JO, Thirkill CE, et al. Progressive subretinal fibrosis and blindness associated with multifocal granulomatous chorioretinitis: a variant of sympathetic ophthalmia. Ophthalmology. 2002;109(8):1527–31.
94. Gass JDM, Margo CE, Levy MH. Progressive subretinal fibrosis and blindness in patients with multifocal granulomatous chorioretinitis. Am J Ophthalmol. 1996;122(1):76–85. https://doi.org/10.1016/S0002-9394(14)71966-X.
95. Lim WK, Chee SP, Sng I, Nussenblatt RB, Chan CC. Immunopathology of progressive subretinal fibrosis: a variant of sympathetic ophthalmia. Am J Ophthalmol. 2004;138(3):475–7.
96. Gandorfer A, Ulbig MW, Kampik A. Diffuse subretinal fibrosis syndrome. Retina. 2000;20(5):561–3.
97. Steeples LR, Ashworth J, Jones N. Multifocal chorioretinitis with progressive subretinal fibrosis in a young child. BMJ Case Rep. 2015;2015. pii: bcr2015212526. https://doi.org/10.1136/bcr-2015-212526.
98. Cantrill HL, Folk JC. Multifocal choroiditis associated with progressive subretinal fibrosis. Am J Ophthalmol. 1986;101(2):170–80. https://doi.org/10.1016/0002-9394(86)90590-8.
99. Onoda S, Shibuya K, Miyasaka H, et al. Multifocal choroiditis with subretinal fibrosis. Nihon Ganka Gakkai Zasshi. 1997;101:711–7.
100. Stolowy ND, Donnadieu BP, Comet ACM, Nadeau S, Beylerian MAS, Denis D, Matonti FJ. Diffuse subretinal fibrosis syndrome: a rare entity. Eur J Ophthalmol. 2018;28(6):NP1–6. https://doi.org/10.1177/1120672118777418.
101. Kaiser PK, Gragoudas ES. The subretinal fibrosis and uveitis syndrome. Int Ophthalmol Clin. 1996;36(1):145–52.
102. Croxatto JO, Rao NA, McLean IW, Marak GE. Atypical histopathologic features in sympathetic ophthalmia. A study of a hundred cases. Int Ophthalmol. 1982;4(3):129–35. https://doi.org/10.1007/bf00161902.
103. Palestine AG, Nussenblatt RB, Parver LM, Knox DL. Progressive subretinal fibrosis and uveitis. Br J Ophthalmol. 1984;68(9):667–73.
104. Kim MK, Chan CC, Belfort R Jr, Farah M, Burnier MP, Nussenblatt RB, et al. Histopathologic and immunohistopathologic features of subretinal fibrosis and uveitis syndrome. Am J Ophthalmol. 1987;104(1):15–23.
105. Babu K, Jidesh MV, Sudheer B. Progressive subretinal fibrosis mimicking retinal necrosis with poor visual prognosis in sympathetic ophthalmia: a rare finding. Indian J Ophthalmol. 2018;66(12):1877–9. https://doi.org/10.4103/ijo.IJO_268_18.
106. Adán A, Sanmartí R, Burés A, Casaroli-Marano RP. Successful treatment with infliximab in a patient with Diffuse Subretinal Fibrosis syndrome. Am J Ophthalmol. 2007;143(3):533–4.

Part VIII
Retinal Detachment Secondary to Uveitis

Chapter 17
Retinal Detachment in Uveitis

Arjun B. Sood and Sumit Sharma

Introduction

Uveitis is responsible for an estimated 10% of blindness in the developed world and up to 25% in the developing world [1, 2]. The etiology for severe visual impairment and blindness in uveitis is multifactorial, including cataract, glaucoma, cystoid macular edema, macular scarring, optic neuropathy, ischemia and retinal detachment [3, 4]. Retinal detachment (RD) in uveitis is uncommon but can be difficult to manage when present and often leads to poor visual outcomes. RD most frequently occurs after periods of active intraocular inflammation and in eyes with infectious uveitis. In this chapter, we focus on uveitic conditions predisposing to retinal detachment along with preoperative management and surgical considerations.

Epidemiology

Retinal detachment can be classified as rhegmatogenous from retinal tear, tractional from inflammatory or neovascular membranes, exudative from serous fluid accumulation, or combined mechanism. The first step in managing retinal detachment in uveitis is to establish the correct diagnosis, as treatment options vary based on the underlying etiology. Rhegmatogenous retinal detachment (RRD) is the most common form with a reported prevalence of 3.1% in patients with uveitis [5, 6]. Intraocular inflammation associated with infectious and non-infectious conditions can predispose to retinal detachment, including cytomegalovirus (CMV), acute retinal necrosis, ocular toxoplasmosis (OT), syphilitic uveitis, pars planitis, sympathetic ophthalmia and Vogt-Koyanagi-Harada (VKH) syndrome.

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Uveitic Conditions at Risk for Retinal Detachment

Cytomegalovirus Retinitis

CMV is a double-stranded DNA virus in the herpes virus family. It is an opportunistic infection and is a leading cause of blindness among patients with acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) [7]. Ocular CMV most commonly manifests as posterior uveitis with yellow-white patches of retinal necrosis, hemorrhages and sheathing **(Add photo of CMV and RD in CMV)** [8]. Vision loss in CMV retinitis is secondary to macular retinitis, optic atrophy or retinal detachment arising from breaks within atrophic or necrotic retina [9].

The incidence of retinal detachment in AIDS patients with CMV retinitis was approximately 50% per patient per year, or 33% per eye per year, in the pre-highly active anti-retroviral therapy (HAART) era [10]. Risk factors for retinal detachment in CMV retinitis include bilateral disease, increasing lesion size, active retinitis near the vitreous base, intraocular surgery for ganciclovir implant or vitreous biopsy, and extent of peripheral retinitis [9–12]. For example, retinitis involving more than 25% of the retina has a fivefold greater risk of retinal detachment compared to an eye with 10% of retinal involvement [10].

Since the introduction of HAART, the rate of retinal detachment has declined by approximately 60% with an incidence of 1.0–8.7/100 eye years [9]. This may be related to improved control of viral replication and halting the progression of retinitis. Although the incidence is declining, the overall prevalence of RD may increase as patients with AIDS and CMV retinitis are living longer in the HAART era.

Management of CMV associated retinal detachment presents a unique challenge for the vitreoretinal surgeon given the atrophic and necrotic retina present and inflammatory changes to the vitreous and posterior hyaloid. Repair is complex and usually involves combination scleral buckle and pars plana vitrectomy with intraocular tamponade (silicone oil or long-acting gas). Mathur et al. reported a 78% anatomic success rate following RD repair, while functional vision (acuity greater than 3/60) was achieved in 56% of patients [13]. Management and treatment of CMV associated RRD is similar to management of RRD after acute retinal necrosis, which will be discussed next.

Acute Retinal Necrosis

Acute retinal necrosis (ARN) was first described by Urayama in 1971 as an occlusive panuveitis with necrotizing retinitis [14]. In 1982, Culbertson and colleagues provided the first evidence that members of the herpes virus family were the causative organisms [15]. Since then, ARN has been managed with local and systemic anti-viral therapy [16, 17]. Unfortunately, visual prognosis remains poor despite prompt diagnosis and treatment. Retinal detachment is one of the most common causes of vision loss in ARN and occurs in 50–75% of patients [18, 19].

In 2017, Butler et al. reported outcomes of 36 patients (41 eyes) with ARN managed at a uveitis referral center [16]. Patients received induction with systemic antiviral therapy (either intravenous or oral) and 61% also received intravitreal antivirals. They found 24 eyes (59%) developed at least 1 RD; 6 eyes (15%) at least 2 RDs and 1 eye (2%) developed 3 RDs. The amount of retinitis at presentation was significantly correlated with developing retinal detachment with a nearly 12 times higher rate of detachment for eyes with more than 25% retinitis. Detachment was also correlated with poor visual prognosis, as only 4% of eyes that experienced at least 1 RD achieved 20/40 or better vision, compared to 53% of eyes that never had retinal detachment [16].

Due to the high prevalence of ARN associated retinal detachment and subsequent vision loss, measures to prevent RD have been investigated. Prophylactic laser photocoagulation has been reported by several groups [20–24]. Lau et al. reported outcomes of 27 patients (17 lasered, 10 not lasered) and found RD incidence of 35% in laser group compared to 80% in not lasered group [23]. Meghpara et al. reported on 25 patients (6 lasered, 19 not lasered) and found RD incidence of 0% in the laser group, compared to 26% in the not lasered group [24]. Both studies were limited due to selection bias, since many patients in the non-lasered group had significant media opacity precluding laser indicating a more severe inflammatory response. Many other studies have noted a lack of benefit for prophylactic laser and it is not something we recommend in the management of ARN [20–22].

Early or prophylactic vitrectomy to prevent RD has also been investigated by several groups [25–29]. The rationale is that vitrectomy can relieve vitreous traction, remove inflammatory mediators, and allow placement of long-acting tamponade (gas or silicone oil) to prevent RD [19]. Iwahashi-Shima et al. reported the largest series of ARN patients treated with early vitrectomy versus medical management. The authors did not describe methods for determining the course of treatment. At final follow-up, 58% of eyes in the early vitrectomy group were attached, compared to 75% in the observation group [26]. Hillenkamp et al. reported a 90% RD rate in medically managed patients compared to 40% in eyes treated with early PPV. Unfortunately, final visual outcomes were similar between the two groups [25]. There were two other studies that also reported benefit from early PPV in reducing retinal detachment rates. However, both of these studies did not show corresponding visual improvement and baseline characteristics were also not equal between the two groups [27, 28]. Further investigation is necessary, but at this time there is no evidence for routine early vitrectomy to prevent RD in the management of ARN.

Ocular Toxoplasmosis

Ocular toxoplasmosis is an infectious uveitis caused by the protozoan parasite *Toxoplasma gondii* [30]. Ocular involvement can either be acquired or congenital. In immunocompetent individuals, OT usually presents as a unilateral retinochoroiditis adjacent to an old scar. In the immunocompromised population, in particular

HIV/AIDS or the very elderly, the necrotizing retinitis can be more aggressive and often mimics viral retinal necrosis [31]. Vision loss in OT is most frequently due to macular or optic nerve involvement; however, retinal detachment remains an important cause of ocular morbidity [32].

Bosch-Driessen et al. reported on 150 consecutive patients with ocular toxoplasmosis and found that 9 patients (6%) developed retinal detachment: six rhegmatogenous, two tractional and one unknown (inoperable total RD) [33]. Severe vitritis and active inflammation were factors associated with RD development. The authors hypothesized vitreous inflammation leads to liquefaction and inflammatory membranes that cause traction on the retina resulting in RRD and/or tractional retinal detachments (TRD) [33]. Interestingly, three of nine patients with RD in this series had undergone diagnostic vitrectomy prior to developing RD, indicating surgical intervention may contribute to RD development as opposed to being protective.

Surgical procedures for toxoplasmosis associated RD include pars plana vitrectomy, scleral buckle, or combination, along with gas or silicone oil (SO) tamponade [33–35]. Moreira et al. published surgical outcomes on 22 patients with OT associated RD from Brazil [35]. In this study, 23% of patients had pre-existing PVR. The most common procedure was combination SB, PPV and SO (ten patients). Primary retinal reattachment was achieved in 15/22 patients (68.2%). Final anatomic re-attachment was achieved in 90.9% of patients with an average of 1.5 surgeries (range 1–3). Despite high anatomic re-attachment rates, the functional outcomes and visual prognosis remain poor with 50% of patients having final best corrected visual acuity 20/400 or less [35].

Ocular Syphilis

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum* and is most commonly spread via sexual transmission [36]. Upon inoculation, the organism can spread to the central nervous system and eye within hours to days. Ocular involvement can occur at any stage of infection and involve any part of the eye, with the most common presentation being syphilitic uveitis (SU) [37, 38]. Most patients who are diagnosed with syphilitic uveitis and receive prompt treatment have good visual prognosis, even returning to normal baseline vision. However, severe visual impairment and vision loss can occur with delay in diagnosis and treatment [39].

Rhegmatogenous and tractional detachment are rare complications seen in ocular syphilis [39]. A total of 16 eyes (12 patients) with RRD or TRD have been reported in the literature [40–43]. Usually, RRD or TRD occurs months after treatment and likely is related to inflammatory changes that potentiate vitreous liquefaction, contraction and separation. The Jarisch-Herxheimer reaction may also contribute whereby lipoproteins from *T. pallidum* stimulate macrophages to produce cytokines that exacerbate intraocular inflammation [44]. Therefore, systemic and local steroids have been utilized by some ophthalmologists to limit the inflammatory response, but evidence is lacking [45].

Haug et al. reviewed 11 cases of syphilitic RD in the literature and found that retinal breaks usually occur in areas of prior retinitis and PVR was present in 45% of eyes. Surgical repair varied with the most successful treatment combination being scleral buckle, vitrectomy and silicone oil tamponade [41].

Pars Planitis

Pars planitis is an idiopathic intermediate uveitis that presents with inflammation of the peripheral retina, ciliary body and anterior vitreous. Chronic inflammation causes snowbank formation and exudation at the pars plana [46]. Conventional treatment involves local or systemic corticosteroids followed by immunosuppressive therapy. Transconjunctival cryotherapy applied to the pars plana has also been reported as an effective treatment in reducing vitritis [47]. Chronic and persistent inflammation can lead to fibrosis and tractional membranes overlying the peripheral retina. As a result, retinoschisis has been reported in up to 19% of patients, while retinal detachment has been reported in up to 10% of cases [48–50]. Management of these complications should primarily be directed towards controlling inflammation. Surgery is generally not indicated unless the macula is involved [51].

Endophthalmitis

Endophthalmitis is a severe intraocular infection that occurs when microorganisms are introduced directly into the eye from trauma or intraocular procedures (exogenous), or from hematogenous spread (endogenous) [52]. Acute management of endophthalmitis involves intravitreal anti-microbials, vitreous sampling and systemic antibiotics for endogenous causes. Despite prompt therapy, endophthalmitis is frequently associated with a poor visual prognosis and retinal detachment [53].

The frequency of RD in post-cataract endophthalmitis from the Endophthalmitis Vitrectomy Study was 8% [54]. Lingappan et al. reported on a large series of patients with endogenous fungal endophthalmitis and found approximately 25% of patients developed retinal detachment [55]. Surgical management with pars plana vitrectomy is the most common modality for RD repair. Unfortunately, re-attachment rates are lower for RD associated with endophthalmitis and range from 41–78% [54, 56].

Persistent Exudative Detachment

Exudative retinal detachments (ERD) develop when fluid accumulates in the subretinal space from breakdown of the blood-retinal-barrier [57]. Inflammatory and infectious uveitic conditions can commonly present with exudative detachment,

including Vogt-Koyanagi-Harada (VKH) disease, sympathetic ophthalmia (SO), posterior scleritis, syphilitic uveitis and tuberculosis [58]. The initial treatment for non-infectious ERD involves systemic steroids and immunosuppressive therapy, while infectious causes can be managed with the corresponding antibiotics/antivirals. Surgical drainage is uncommon for exudative detachments but can be considered for chronic subretinal fluid involving the macula [58, 59].

Clinical Examination, Preoperative Management and Surgical Considerations

Diagnosis of retinal detachment in uveitis can be challenging as visualization of the posterior segment may be limited due to active inflammation. Multimodal imaging with optic coherence tomography (OCT), B-scan ultrasound, and ultrawide field fundus imaging are useful modalities to help distinguishing RRD from TRD or exudative detachment [60]. In some circumstances a diagnostic vitrectomy is indicated [61].

Once rhegmatogenous retinal detachment is confirmed, prompt surgical intervention is generally indicated. Ideally, surgery should be performed on eyes that are inactive, but this is not always possible. Therefore, every effort should be made to reduce inflammation prior to pursuing surgical intervention [62]. In non-infectious uveitis, oral prednisone can be administered several days before surgery or high dose intravenous steroids can be given intraoperatively. Intravitreal or subtenons steroids can also help optimize control of inflammation [63]. We will often give these prior to surgery to help quiet the eye. Intravitreal triamcinolone starts to work almost immediately and can be given even a few days prior to surgery. In contrast, the dexamethasone implant (Ozurdex®, Allergan, Irvine, CA) takes 7–10 days to start releasing steroid and should be given at least 1 week prior to surgery. For infectious uveitis, systemic or local anti-microbials should be utilized perioperatively depending on the cause. Silicone oil presents unique challenges in the post-operative period as doses of medications given intravitreally will need to be modified depending on if they are water or lipid soluble to avoid toxicity.

Surgical approaches to repair retinal detachment can be affected by the presence of associated co-morbidities. Corneal opacities and diffuse keratic precipitates may limit the view to the posterior segment during surgery. Concomitant scleritis or scleral thinning may be a contraindication to scleral buckle placement [64]. Pupillary membranes and posterior synechiae can limit intraoperative viewing and can be managed with lysis and pupillary expansion [63]. Cataract can impede view of posterior segment and lensectomy may be required [65]. Finally, the most important factor to in repairing retinal detachment is the presence of proliferative vitreoretinopathy and the propensity to develop PVR following surgery [6].

Conclusion

Retinal detachments in uveitis are infrequently encountered but can present a unique challenge for the vitreoretinal surgeon. A stepwise approach should be undertaken in managing these patients, first by identifying the etiology for detachment followed by adequately controlling inflammation prior to surgery. Surgical repair should then be tailored to each individual situation. With modern day surgical techniques, good outcomes are possible for retinal detachments associated with ocular inflammatory disease.

References

1. Rao NA. Uveitis in developing countries. Indian J Ophthalmol. 2013;61(6):253–4.
2. Williams GJ, Brannan S, Forrester JV, Gavin MP, Paterson-Brown SP, Purdie AT, et al. The prevalence of sight-threatening uveitis in Scotland. Br J Ophthalmol. 2007;91(1):33–6.
3. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. JAMA Ophthalmol. 2016;134(11):1237–45.
4. Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SR, Joshi L, et al. Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology. 2014;121(12):2387–92.
5. De Hoog J, Ten Berge JC, Groen F, Rothova A. Rhegmatogenous retinal detachment in uveitis. J Ophthalmic Inflamm Infect. 2017;7(1):22.
6. Kerkhoff FT, Lamberts QJ, van den Biesen PR, Rothova A. Rhegmatogenous retinal detachment and uveitis. Ophthalmology. 2003;110(2):427–31.
7. Carmichael A. Cytomegalovirus and the eye. Eye (Lond). 2012;26(2):237–40.
8. Port AD, Orlin A, Kiss S, Patel S, D'Amico DJ, Gupta MP. Cytomegalovirus retinitis: a review. J Ocul Pharmacol Ther. 2017;33(4):224–34.
9. Kempen JH, Jabs DA, Dunn JP, West SK, Tonascia J. Retinal detachment risk in cytomegalovirus retinitis related to the acquired immunodeficiency syndrome. Arch Ophthalmol. 2001;119(1):33–40.
10. Freeman WR, Friedberg DN, Berry C, Quiceno JI, Behette M, Fullerton SC, et al. Risk factors for development of rhegmatogenous retinal detachment in patients with cytomegalovirus retinitis. Am J Ophthalmol. 1993;116(6):713–20.
11. Yen M, Chen J, Ausayakhun S, Kunavisarut P, Vichitvejpaisal P, Ausayakhun S, et al. Retinal detachment associated with AIDS-related cytomegalovirus retinitis: risk factors in a resource-limited setting. Am J Ophthalmol. 2015;159(1):185–92.
12. Martin DF, Ferris FL, Brothers RJ, et al. Retinal detachment in eyes treated with a ganciclovir implant [Letter]. Arch Ophthalmol. 1995;113:1355.
13. Mathur G, Ratra D, Bhuibhar SS, Roy R. Clinical outcomes of retinal detachment surgery following cytomegalovirus retinitis in patients on highly active anti-retroviral therapy for acquired immune deficiency syndrome. Ocul Immunol Inflamm. 2015;23(5):400–4.
14. Urayama A, Sasaki T, Nishiyama Y, et al. Unilateral acute uveitis with periarteritis and detachment. Jpn J Ophthalmol. 1971;25:607–19.
15. Culbertson WW, Blumenkranz MS, Haines H, Gass DM, Mitchell KB, Norton EW. The acute retinal necrosis syndrome. Part 2: Histopathology and etiology. Ophthalmology. 1982;89(12):1317–25.

16. Butler NJ, Moradi A, Salek SS, Burkholder BM, Leung TG, Dunn JP, et al. Acute retinal necrosis: presenting characteristics and clinical outcomes in a cohort of polymerase chain reaction-positive patients. Am J Ophthalmol. 2017;179:179–89.
17. Fisher JP, Lewis ML, Blumenkranz M, Culbertson WW, Flynn HW Jr, Clarkson JG, et al. The acute retinal necrosis syndrome. Part 1: Clinical manifestations. Ophthalmology. 1982;89(12):1309–16.
18. Shantha JG, Weissman HM, Debiec MR, Albini TA, Yeh S. Advances in the management of acute retinal necrosis. Int Ophthalmol Clin. 2015;55(3):1–13.
19. Schoenberger SD, Kim SJ, Thorne JE, Mruthyunjaya P, Yeh S, Bakri SJ, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(3):382–92.
20. Tibbetts MD, Shah CP, Young LH, Duker JS, Maguire JI, Morley MG. Treatment of acute retinal necrosis. Ophthalmology. 2010;117(4):818–24.
21. Sternberg P Jr, Han DP, Yeo JH, Barr CC, Lewis H, Williams GA, et al. Photocoagulation to prevent retinal detachment in acute retinal necrosis. Ophthalmology. 1988;95(10):1389–93.
22. Sims JL, Yeoh J, Stawell RJ. Acute retinal necrosis: a case series with clinical features and treatment outcomes. Clin Exp Ophthalmol. 2009;37(5):473–7.
23. Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. Ophthalmology. 2007;114(4):756–62.
24. Meghpara B, Sulkowski G, Kesen MR, Tessler HH, Goldstein DA. Long-term follow-up of acute retinal necrosis. Retina. 2010;30(5):795–800.
25. Hillenkamp J, Nolle B, Bruns C, Rautenberg P, Fickenscher H, Roider J. Acute retinal necrosis: clinical features, early vitrectomy, and outcomes. Ophthalmology. 2009;116(10):1971–5.e2.
26. Iwahashi-Shima C, Azumi A, Ohguro N, Okada AA, Kaburaki T, Goto H, et al. Acute retinal necrosis: factors associated with anatomic and visual outcomes. Jpn J Ophthalmol. 2013;57(1):98–103.
27. Ishida T, Sugamoto Y, Sugita S, Mochizuki M. Prophylactic vitrectomy for acute retinal necrosis. Jpn J Ophthalmol. 2009;53(5):486–9.
28. Luo YH, Duan XC, Chen BH, Tang LS, Guo XJ. Efficacy and necessity of prophylactic vitrectomy for acute retinal necrosis syndrome. Int J Ophthalmol. 2012;5(4):482–7.
29. Huang JM, Callanan P, Callanan D, Wang RC. Rate of retinal detachment after early prophylactic vitrectomy for acute retinal necrosis. Ocul Immunol Inflamm. 2018;26(2):204–7.
30. Englander M, Young LH. Ocular toxoplasmosis: advances in detection and treatment. Int Ophthalmol Clin. 2011;51(4):13–23.
31. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41(1):95–108.
32. Bosch-Driessen LE, Berendschot TT, Ongkosuwito JV, Rothova A. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. Ophthalmology. 2002;109(5):869–78.
33. Bosch-Driessen LH, Karimi S, Stilma JS, Rothova A. Retinal detachment in ocular toxoplasmosis. Ophthalmology. 2000;107(1):36–40.
34. Faridi A, Yeh S, Suhler EB, Smith JR, Flaxel CJ. Retinal detachment associated with ocular toxoplasmosis. Retina. 2015;35(2):358–63.
35. Moreira FV, Iwanusk AM, Amaral ARD, Nobrega MJ, Novelli FJ. Surgical outcomes of rhegmatogenous retinal detachment associated with ocular toxoplasmosis. Arq Bras Oftalmol. 2018;81(4):281–5.
36. Hook EW 3rd. Syphilis. Lancet. 2017;389(10078):1550–1557.
37. Lukehart SA, Hook EW 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. Ann Intern Med. 1988;109(11):855–62.
38. Ghanem KG. Review: Neurosyphilis: a historical perspective and review. CNS Neurosci Ther. 2010;16(5):e157–68.
39. Centers for Disease Control and Prevention (CDC). A cluster of Ocular Syphilis Cases – Seattle, Washington, and San Francisco, California, 2014–2015. MMWR. 2015;64(40);1150–1.
40. Queiroz RP, Diniz AV, Vasconcelos-Santos DV. Fulminant proliferative vitreoretinopathy in syphilitic uveitis. J Ophthalmic Inflamm Infect. 2016;6(1):6.

41. Haug SJ, Takakura A, Jumper JM, Heiden D, McDonald HR, Johnson RN, et al. Rhegmatogenous retinal detachment in patients with acute syphilitic panuveitis. Ocul Immunol Inflamm. 2016;24(1):69–76.
42. Passo MS, Rosenbaum JT. Ocular syphilis in patients with human immunodeficiency virus infection. Am J Ophthalmol. 1988;106(1):1–6.
43. Pournaras JA, Laffitte E, Guex-Crosier Y. Bilateral giant retinal tear and retinal detachment in a young emmetropic man after Jarish-Herxheimer reaction in ocular syphilis. Klin Monatsbl Augenheilkd. 2006;223(5):447–9.
44. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. Am J Trop Med Hyg. 2017;96(1):46–52.
45. Furtado JM, Arantes TE, Nascimento H, Vasconcelos-Santos DV, Nogueira N, de Pinho Queiroz R, et al. Clinical manifestations and ophthalmic outcomes of ocular syphilis at a time of re-emergence of the systemic infection. Sci Rep. 2018;8(1):12071.
46. Babu BM, Rathinam SR. Intermediate uveitis. Indian J Ophthalmol. 2010;58(1):21–7.
47. Sohn EH, Chaon BC, Jabs DA, Folk JC. Peripheral cryoablation for treatment of active pars planitis: long-term outcomes of a retrospective study. Am J Ophthalmol. 2016;162:35–42.e2.
48. Malalis JF, Bhat P, Shapiro M, Goldstein DA. Retinoschisis in pars planitis. Ocul Immunol Inflamm. 2017;25(3):344–8.
49. Malinowski SM, Pulido JS, Folk JC. Long-term visual outcome and complications associated with pars planitis. Ophthalmology. 1993;100(6):818–24; discussion 25.
50. Romero R, Peralta J, Sendagorta E, Abelairas J. Pars planitis in children: epidemiologic, clinical, and therapeutic characteristics. J Pediatr Ophthalmol Strabismus. 2007;44(5):288–93.
51. Jalil A, Dhawahir-Scala FE, Jones NP. Nonprogressive tractional inferior retinal elevation in intermediate uveitis. Ocul Immunol Inflamm. 2010;18(1):60–3.
52. Durand ML. Bacterial and fungal endophthalmitis. Clin Microbiol Rev. 2017;30(3):597–613.
53. Nelsen PT, Marcus DA, Bovino JA. Retinal detachment following endophthalmitis. Ophthalmology. 1985;92(8):1112–7.
54. Doft BM, Kelsey SF, Wisniewski SR. Retinal detachment in the endophthalmitis vitrectomy study. Arch Ophthalmol. 2000;118(12):1661–5.
55. Lingappan A, Wykoff CC, Albini TA, Miller D, Pathengay A, Davis JL, et al. Endogenous fungal endophthalmitis: causative organisms, management strategies, and visual acuity outcomes. Am J Ophthalmol. 2012;153(1):162–6.e1.
56. Chee YE, Eliott D. The role of vitrectomy in the management of fungal endophthalmitis. Semin Ophthalmol. 2017;32(1):29–35.
57. Marmor MF. Control of subretinal fluid: experimental and clinical studies. Eye (Lond). 1990;4(Pt 2):340–4.
58. Amer R, Nalci H, Yalcindag N. Exudative retinal detachment. Surv Ophthalmol. 2017;62(6):723–69.
59. Galor A, Lowder CY, Kaiser PK, Perez VL, Sears JE. Surgical drainage of chronic serous retinal detachment associated with uveitis. Retina. 2008;28(2):282–8.
60. Gupta V, Al-Dhibi HA, Arevalo JF. Retinal imaging in uveitis. Saudi J Ophthalmol. 2014;28(2):95–103.
61. Zhao XY, Xia S, Chen YX. Role of diagnostic pars plana vitrectomy in determining the etiology of uveitis initially unknown. Retina. 2018; https://doi.org/10.1097/IAE.0000000000002372.
62. Shin YU, Shin JY, Ma DJ, Cho H, Yu HG. Preoperative inflammatory control and surgical outcome of vitrectomy in intermediate uveitis. J Ophthalmol. 2017;2017:5946240.
63. Agrawal R, Murthy S, Ganesh SK, Phaik CS, Sangwan V, Biswas J. Cataract surgery in uveitis. Int J Inflamm. 2012;2012:548453.
64. Tabandeh H, Flaxel C, Sullivan PM, Leaver PK, Flynn HW Jr, Schiffman J. Scleral rupture during retinal detachment surgery: risk factors, management options, and outcomes. Ophthalmology. 2000;107(5):848–52.
65. Murthy SI, Pappuru RR, Latha KM, Kamat S, Sangwan VS. Surgical management in patient with uveitis. Indian J Ophthalmol. 2013;61(6):284–90.

Chapter 18
Surgical Considerations in the Uveitic Patient

Parisa Emami and Sunil K. Srivastava

Vitreoretinal procedures in uveitis are performed to achieve various goals including:

- Diagnostic procedures
- Therapeutic procedures
- Procedures to manage uveitis complications

Diagnostic Procedures

In-office procedures to obtain intraocular fluid have long been used in the diagnosis of intraocular infections and inflammation [1]. Samples of aqueous humor and vitreous humor can be used for bacterial and fungal cultures, polymerase chain reaction (PCR) to evaluate the presence of viral or parasitic particles and cytokine analysis, i.e. aqueous humor IL-10:IL-6 ratio for the screening of patients with suspicion of vitreoretinal lymphoma [2]. Vitreous specimen can also be obtained through pars plana vitrectomy. In this section we mainly discuss the surgical approach of obtaining specimens.

Vitreous Biopsy

Compared to vitreous aspiration, vitrectomy yields more volume that can be used in various diagnostic tests. Moreover, vitrectomy enables better visualization of the retina by clearing the vitreous opacities and provides safer removal of vitreous by

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controlling the amount of vitreous traction [3]. Diagnostic vitrectomy is indicated when the clinical picture is atypical or the condition does not respond to treatment as expected by the clinician.

One of the main indications for diagnostic vitrectomy is when there is a suspicion for intraocular lymphoma. Various forms of intraocular lymphoma include vitreoretinal, choroidal or iridial [4]. Vitreoretinal lymphoma can be primary (primary vitreoretinal lymphoma, PVRL) or secondary to systemic lymphoma [5]. It has been reported that approximately 15–25% of patients with central nervous system lymphoma have or will eventually develop intraocular involvement [4]. PVRL, on the other hands, primarily involves the vitreous and retina and is a subtype of non-Hodgkin lymphoma [6]. The most common type of PVRL, seen in 95% of cases, is diffuse large B-cell lymphoma, which is a high-grade tumor. Other rare types include T-cell-rich B-cell lymphoma and T-cell lymphoma [4, 7, 8]. 65–90% of these patients have or will develop central nervous system involvement which results in significant morbidity and mortality [4].

Diagnosis of PVRL can be challenging and delayed as it usually presents with floaters or non-specific uveitis, hence, it is considered a masquerade syndrome. On average, there is a 1–2 year delay between onset of symptoms and the diagnosis of PVRL [9, 10]. Several studies suggest that vitreous cytokine assays to evaluate IL-10:IL-6 ratio (greater than 1.0) can be helpful in the diagnosis of B-cell PVRL [3, 11]. These methods, however, has a sensitivity of ~90% and do not yield enough tissue for cell analysis [11].

Prior to performing a diagnostic vitrectomy, it is important to have a complete plan in place, in terms of type of the specimen, specific tests to be ordered and run on the limited sample, transport arrangements and laboratory receiving the sample. It is important that the pathologist is made aware that the sample is being evaluated for possible PVRL. Systemic corticosteroids need to be stopped a few weeks prior to vitrectomy to minimize false negative results [4].

During vitrectomy, undiluted and diluted samples need to be collected for cytopathology and flow cytometry. Our technique involves a three-port vitrectomy system with valved trocars should be used. While the infusion is turned off, 1–2 ml of undiluted vitreous is aspirated with a 3 ml-syringe connected to the vitreous cutter and manual aspiration. Air infusion can also be used in this step to minimize significant hypotony. The undiluted sample can be sent to the lab fresh, however, the sample needs to be quickly processed to avoid its degradation. In our institution, we place the undiluted specimen into cytology fixative (CytoLyt) immediately after the sample is obtained and prior to transport to the lab. Following this step, saline infusion is turned on and a second diluted sample is collected in a syringe. This sample can be further diluted with RPMI medium 1640 (Sigma–Aldrich, St. Louis, MO). Vitrectomy cassette can also be sent for analysis as the third sample. Specimens need to be delivered and processed quickly, especially those samples not placed in fixatives (Fig. 18.1) [3, 9, 12].

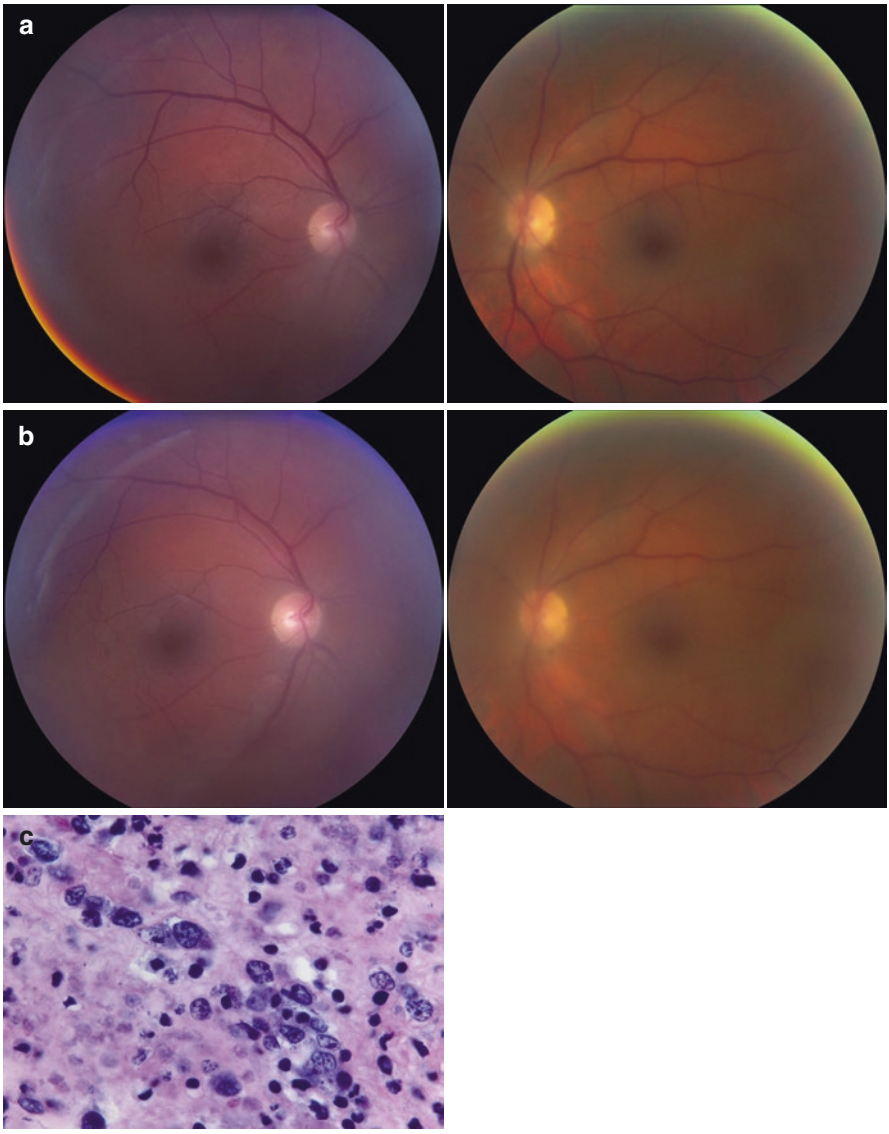

Fig. 18.1 49-year-old man, with 2-year history of idiopathic intermediate uveitis presented with decreased vision and worsening floaters in both eyes for 2 months. Fundus exam on initial visit (**a**) showed vitritis and vitreous haze in both eyes (right eye > left eye). He was treated with systemic and periocular steroid with minimal improvement in symptoms or exam findings (**b**). With high suspicion for vitreoretinal lymphoma, diagnostic vitrectomy was performed and cytology confirmed the diagnosis of large B-cell lymphoma (**c**)

Subretinal Biopsy

If yellow-white subretinal lesions are seen, diagnostic vitrectomy may be combined with aspiration of subretinal material or full-thickness chorioretinal biopsy (Case 2). This method yields higher lymphoma cells especially is there is only minimal vitreous cells on exam. Different methods can be used to aspirate the subretinal deposit. After performing a core vitrectomy and obtaining vitreous specimen, endodiathermy is used to mark the area of interest and to prevent bleeding. A 25-G vitrectomy cutter is used to make a small retinotomy. Then cutter is connected to a 3 ml syringe and subretinal material is aspirated manually. A soft-tip cannula can also be used for aspiration. The contents of the syringe will then flushed in the cytology solution (CytoLyt) container (Fig. 18.2) [13–15].

Therapeutic Procedures

Peri- and intraocular-ocular routes have been used to administer various therapeutic agents in patients with infectious and non-infectious uveitis. In infectious uveitis intravitreal injection of antibiotic, antiviral, antifungal or anti-parasitic medications can be therapeutic and decrease the need for systemic treatment. Intravitreal and subtenon injection of steroid is helpful in treatment of non-infectious inflammatory uveitis. While all these injections can be done in the office and without need for sedation, the relatively short duration of action of these medications is a limiting factor. In the search for long acting, sustained-release treatments, two different surgically placed intraocular implants have been developed and approved by the FDA.

1. *Ganciclovir (Vitrasert®, Bausch and Lomb)*, the first FDA-approved intraocular implant (approved in 1996), is a non-biodegradable implant used in the long-term treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. The pellet contains 4.5 mg of ganciclovir as the active ingredient. The implant has a release rate of 1 mcg/h and lasts 5–8 months [16]. The procedure is performed under local or general anesthesia and in the operating room. The implant is inserted is in the inferotemporal quadrant through a 4–5 mm circumferential sclerotomy located ~4 mm posterior to the limbus and is sutured to the sclera [17]. Clinical trials have shown in patients with AIDS, eyes receiving intravitreal ganciclovir implant had a slower rate of CMV retinitis progression compared to patients who received systemic (intravenous) ganciclovir [18, 19]. The implant has recently been discontinued.
2. *Fluocinolone acetonide (FA) implant (Retisert®, Bausch and Lomb)* is approved by the FDA for inflammatory uveitis (Fig. 18.3). Receiving FDA approval in 2005, retisert is the first intravitreal device used in non-infectious uveitis [20]. It has a release rate of 0.3–0.4 mcg/day and lasts approximately 3 years [20].

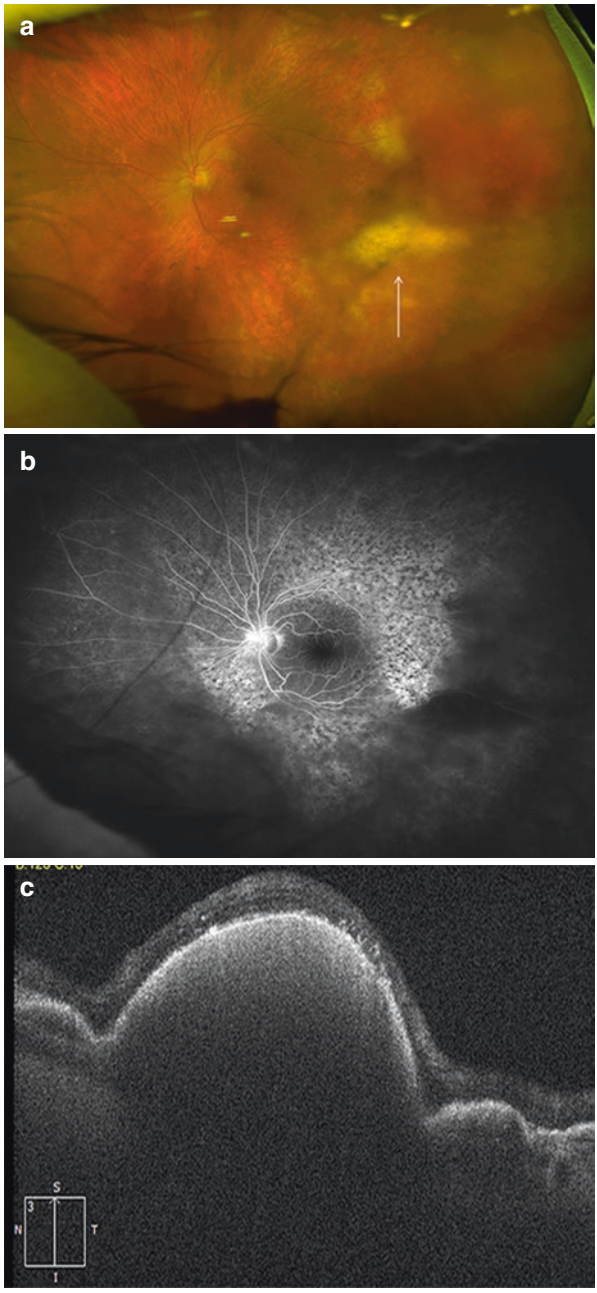

Fig. 18.2 77 year-old female with longstanding history of rheumatoid arthritis and immunosuppression presented with blurry vision and floaters in the left eye. Fundus examination (**a**) showed vitreous haze and yellow subretinal lesion temporally (arrow). Fluorescein angiography (**b**) showed the characteristic "leopard-spot" appearance. Optical coherence tomography (**c**) through the lesion showed presence of subretinal deposits. Patient underwent diagnostic vitrectomy and aspiration of subretinal material. Cytology confirmed the diagnosis of large B cell lymphoma

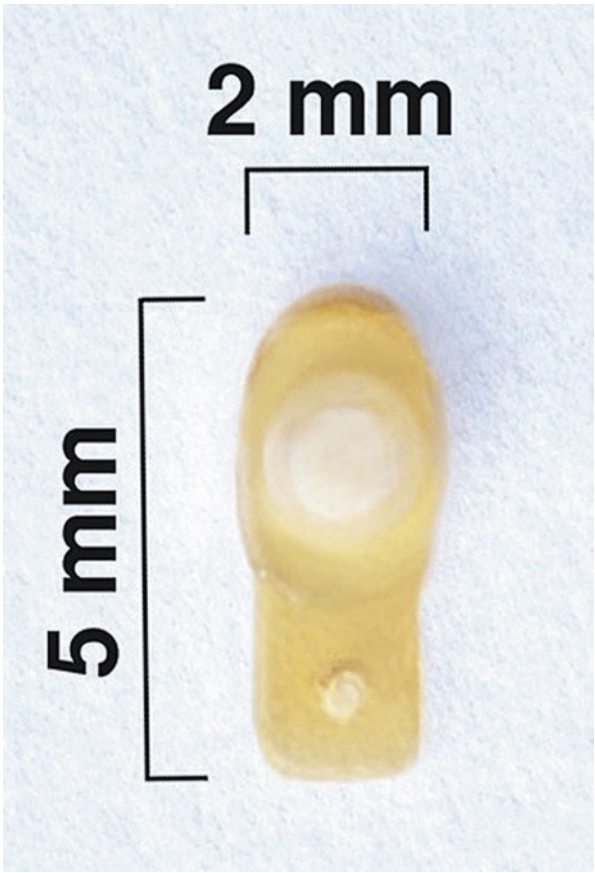

Fig. 18.3 Magnified image of a Retisert implant. The implant contains 0.59 mg of fluocinolone acetonide and lasts approximately 2.5–3 years

The procedure is performed under local (retro- or peri-bulbar block) or general anesthesia. A conjunctival peritomy is performed. The implant is usually inserted in the inferior quadrant unless there is a localized pathology or snow bank over the area. Prior to the insertion of the implant, a double-armed 8-0-prolene suture is passed through the implant hole and is secured with a single throw knot. A 3.5 mm circumferential sclerotomy is then made approximately 4 mm posterior to the limbus. Any prolapsed vitreous need to be excise thoroughly to decrease risk of wound gaping, infection and vitreous traction. The implant is then inserted into the eye. The arms of the prolene suture are then passed through the sclera to secure the implant to the wall of the eye. Multiple interrupted 9-0 prolene sutures are then used to close the sclera and the knots are rotated and buried. The conjunctiva is then thoroughly closed. Indirect ophthalmoscope or direct viewing system should be used to verify the presence and location of the implant in the eye. In the previously vitrectomized eyes, an infusion line needs to be placed prior to the procedure to maintain intraocular pressure and prevent hypotony [21, 22].

In the cases of re-implantation of the implant, an infusion line is inserted prior to the procedure (usually superotemporally to avoid the previous implant). Limited peritomy is performed and the original implant is dissected by cutting and removing the 9-0 prolene sutures. The scleral wound is then gaped open and the implant sutures are grasped with a toothed forceps. The old implant is then removed from the eye and the new implant is inserted through the original incision. If there is thinning of the sclera over the original implant site, a different site will be chosen for the new implant [23].

The efficacy of Retisert implant has been studied extensively. In a study comparing two different doses of FA implant, it was shown that recurrence of uveitis and need for adjunctive surgery significantly decreases in patients who received FA implant [21]. One of the major trials evaluating FA implant was the Multicenter Uveitis Steroid Treatment (MUST) trial [24, 25]. This study compared the effectiveness of systemic immunosuppression with FA implants in patients with intermediate, posterior or panuveitis. The 2-year follow up data showed a superior uveitis control (i.e. Vitreous haze and macular edema) in eyes treated with FA implant. Both groups demonstrated a comparable improvement in visual acuity. Moreover, quality of life scores were found to be higher in the FA implant group. On the other hands, patients in the implant group experienced a higher rate of ocular side effects, including cataract (seen in nearly all phakic eyes after 3 years), increased intraocular pressure and glaucoma, hypotony, choroidal detachment, endophthalmitis, etc. In the 7-year follow-up study of these patients, however, it was found that patients receiving systemic immunosuppression had a better visual outcome compared to the FA implant group [26].

Management of Complications

Uveitis can result in various anterior (cataract, posterior synechiae, glaucoma, hypotony, etc.) and posterior segment (vitreous opacities, epiretinal membrane, retinal detachment, etc.) complications. In this section we will discuss the management of posterior segment complications of uveitis.

Retinal Detachment

Rhegmatogenous retinal detachment is not a common finding in uveitis patients. In fact, it has been reported that rhegmatogenous detachment only involves in 3–7% of eyes with uveitis. A higher incidence was seen in patients with active panuveitis and infectious uveitis [27, 28]. The risk is specifically higher in patients with acute retinal necrosis, reaching 20–73% [29]. Patients with uveitis, especially with intermediate and posterior uveitis, often develop multiple pinpoint retinal breaks due to

peripheral vitreoretinal traction. Assessment of the location of the detachment is helpful in searching for retinal breaks, as is careful examination with a three-mirror lens. Retinal detachments with small breaks in these patients are often inferior and low-lying and may demonstrate multiple demarcation lines. The presence of shifting fluid is an indication that the detachment isn't rhegmatogenous, but this can be misleading if the fluid in a rhegmatogenous case is longstanding and viscous, in which case it can show shifting characteristics.

Detachment of the retina is also seen in eyes with CMV retinitis that have significant peripheral necrosis. In eyes with extensive peripheral pathology and necrosis, insertion of scleral buckle and silicone oil tamponade can be helpful. Control of inflammation at the time of and after surgery is of utmost importance. Uncontrolled inflammation can result in membrane formation and tractional detachment secondary to formation of proliferative vitreoretinopathy [3].

Other type of retinal detachment commonly seen in uveitis is serous retinal detachment. Presence of serous subretinal fluid usually denotes choroidal involvement and inflammation (e.g. in posterior scleritis or Vogt–Koyanagi–Harada disease). This type of detachment is usually transient and is almost always managed medically and by systemic or localized immunosuppression. However, chronic recalcitrant cases can result in retinal pigment epithelial derangement and needs to be treated surgically [30].

Timing of Surgery for Uveitic RD

The presence of intraocular inflammation complicates the management of retinal detachment and introduces several additional variables into our treatment decisions. It's been suggested that an eye should be quiet for at least 3 months prior to cataract surgery. However, we can't wait 3 months if there's a retinal detachment. Patients with uveitis and RRD have active inflammation 46% of the time. If there's significant active inflammation preoperatively, a serious attempt to control the inflammation with systemic and periocular corticosteroids should be made. This puts the surgeon in a difficult position: surgery may need to be delayed for a few weeks to avoid operating on an inflamed eye, but this risks progression of the retinal detachment. Both choices increase the risk of PVR and the risk of a poor visual outcome.

Pre- and Post-Operative Management

In cases where surgery is therapeutically indicated but there is persistent or only recently controlled inflammation, additional oral or periocular steroids are usually indicated, typically starting 1 or 2 weeks prior to surgery. A trial of 1–2 weeks of prednisone 1 mg/kg orally can be helpful to assess whether the fluid improves, with improvement suggesting a serous component to the detachment. This is also useful in getting the uveitis quieter in preparation for surgery. This can be continued

postoperatively for a few days, then tapered. It is important to treat any active infection with the appropriate IV or oral therapy.

A long-acting intravitreal steroid depot such as triamcinolone acetonide can be injected into the vitreous cavity or the sub-Tenon's space at the time of surgery. Of course, the risk of steroid-induced ocular hypertension must be weighed against the risk of increased postoperative inflammation. The same regimen can be applied to patients with chronic inflammation who are on chronic immunosuppressive therapy with no current active inflammation.

There are no systemic immunosuppressants that become fully effective within a few weeks, which means that the initial management of postoperative inflammation involves corticosteroids. Maximal use of oral, periocular, intravitreal and topical steroids may be required, as inflammatory mediators will increase the likelihood of PVR. Local steroid use such as the dexamethasone implant hasn't been shown to improve the prognosis of PVR; however, PVR will be accelerated by the presence of inflammatory cytokines. If the patient's uveitis wasn't adequately controlled preoperatively, it's important to initiate a long-term plan for uveitic control. This is especially important if additional surgeries are likely. In patients with infectious uveitis such as toxoplasmosis or cytomegalovirus control of the infection is a high priority, but the post-infection inflammation may persist for weeks after the infection has resolved. However, corticosteroids can lead to recurrent infection, which will further complicate the management of the inflammation. In these patients, it is essential to use sufficient antimicrobial agents throughout the postoperative course.

Surgical Techniques: Pars Plana Vitrectomy

Although vitrectomy and laser, combined with scleral buckling, will usually be the preferred surgical procedure, ancillary issues may complicate the overall surgical plan. Corneal and lenticular opacities often make visualization difficult. Concomitant cataract extraction is indicated if the cataract precludes adequate visualization for vitrectomy and/or subsequent care (see also Chap. 5). A cataract that significantly reduces vision in a quiet eye should be addressed as long as its removal will likely result in improved vision. The choice of placing an intraocular lens versus performing a lensectomy warrants careful consideration. If the eye is relatively quiet, a simultaneous lens implant is often the preferred choice, as lensectomy precludes the future use of an intravitreal dexamethasone implant. However, visualization is paramount, and a lensectomy alone is an acceptable choice, especially in an eye with residual active inflammation.

The basic steps of PPV remain the same in patients with uveitis.

The standard three-port approach is used for PPV. With the introduction of 23 G, 25 G and 27 G transconjunctival Microincision Vitrectomy systems, surgical techniques have become much safer. Once the hyaloid separation is induced, adequate vitrectomy must be performed with vitreous base dissection to ensure the release of all tractional forces. For pinpoint breaks in the retina that can't be visualized

intraoperatively, or through which subretinal fluid cannot be drained due to the small size of the retinal break, the fluid should be drained through a drainage retinotomy. Endolaser should be applied around the retinotomy site, as well as in the area of the retinal detachment to cover any tiny breaks that may be missed in the periphery. It is important to avoid high-intensity laser burns, as it can easily lead to breakdown iatrogenic retinal holes.

In patients with viral retinitis-related retinal detachments, there may be a need for membrane peeling when severe inflammatory vitreal and retinal membranes are present. Peeling of inflammatory membranes with microsurgical picks, forceps, and scissors or relaxing retinectomy have been employed to relieve traction retinal detachments involving the fovea or peripheral traction resulting in combined rhegmatogenous/traction retinal detachments.

Procedures such as retinotomies and retinectomies are required in a significant proportion of patients. These procedures help to counter the traction caused by retinal shortening and prevent recurrence of the detachment. Usually, once fluid-air exchange is performed, it is best to do a meticulous endolaser photocoagulation around all the breaks and to check for any missed breaks, especially at the edges of retinal or chorioretinal lesions.

Peeling and segmentation of cyclitic membranes with a blade, intraocular forceps, and/or scissors during scleral depression of the ciliary body has been advocated as a treatment for hypotony in eyes with cyclitic membranes.

Surgical Techniques: Scleral Buckling

Tractional components of retinal detachment, especially inferiorly in patients with pars planitis, need to be addressed by both scleral buckling and vitrectomy.

Before the advent of PPV, scleral buckling procedures were performed for the management of retinal detachment associated with uveitis. However, scleral buckle alone is insufficient in achieving anatomical attachment in these patients due to various factors including the existence of multiple breaks (which may be posterior, or difficult to identify due to vitreous inflammation), abnormal vitreous forces, retinal contracture, epiretinal membranes, and other issues. Therefore, various surgeons compared the techniques of primary scleral buckling versus PPV with cryotherapy/laser therapy and internal tamponade. The final reattachment rate was 87.5% in the primary scleral buckle group and 100% in the non-buckle group in a series by Blumenkranz et al. The authors reported higher retinal reoperation and complication rates in the primary buckle group. Subsequently, there has been an increasing trend towards combining scleral buckling along with PPV in order to achieve higher retinal reattachment rates. Scleral buckling is performed to augment the support to the anterior proliferation. At times, surgeons may apply an encircling band to support the anterior vitreous.

Various authors prefer to perform PPV without the use of scleral buckling procedure in patients with retinal detachment resulting from uveitis. The advantages of avoiding scleral buckling include reduction of the intraoperative time and patient

morbidity. Some patients with uveitis also have an associated scleritis. The scleral thinning makes scleral buckle placement difficult, if not impossible. As a result, the surgeon is often forced to alter the surgical plan to accommodate areas of scleral thinning that limit the placement of trocars.

Tamponade

For the purpose of internal tamponade, various reports describe the use of either long-acting gas (C3F8) or silicone oil (1000 or 5000 cSt). In their series, Almeida et al. used silicone oil in 11 eyes out of 12 and used gas tamponade in 1 eye. None of the eyes developed re-detachment. Canzano published a series of six eyes (five patients) where PPV was performed for CMV-related retinal detachment where the authors used gas tamponade alone. They observed re-detachment in one eye at 7 months after initial repair and successfully reattached it without using silicone oil.

The choice of retinal tamponade depends on the degree and severity of the contracture and proliferative retinopathy. In some patients, intraocular gas may be a good choice if the eye can be repaired in a single operation and there is no preoperative PVR.

Considering that postoperative PVR develops in 37% of uveitis patients, compared to 9% of non-uveitis patients, most surgeons prefer the use of silicone oil for achieving tamponade. However, silicone oil requires a second surgery for removal and will interfere with the function of a fluocinolone implant, if present. The use of intravitreal dexamethasone may also be suboptimal; it may not release drug properly if it remains initially within the silicone oil bubble rather than within the liquid vitreous. Intravitreal triamcinolone is difficult to use with silicone oil since it can obscure the postoperative view. In addition, the concern about the oil interface acting as a matrix for inflammatory membranes is an unanswered question. In patients with postviral retinal detachments, silicone oil is the preferred tamponade. When silicone oil is being used in the management of retinal detachment, one can use 5000 cSt oil for longer tamponade in eyes with severe proliferation and contraction, high risk of hypotony, and need for a long-acting tamponade.

Vitreous Opacities

Significant vitreous opacities and debris are sometimes seen in patients with intermediate and panuveitis. These opacities can interfere with vision and also block the view to the retina at the time of exam or during imaging studies Vitrectomy is these patients can improve posterior visualization as well as patient's vision. Some authors have also advocated vitrectomy not only to clear the opacities, but also to improve macular edema and ocular inflammation. Several studies report on the effect of vitrectomy on the course of inflammation, however, data are inconclusive and sometimes contradicting [31–34].

Epiretinal Membrane

Chronic inflammation can result in epiretinal membrane (ERM) formation. ERM causes surface wrinkling on the retina and worsening of cystoid macular edema. Surgical decision-making should be tailored based on symptoms, degree of functional limitations and presence or absence of active inflammation [35].

References

1. Manku H, McCluskey P. Diagnostic vitreous biopsy in patients with uveitis: a useful investigation? Clin Exp Ophthalmol. 2005;33(6):604–10.
2. Cassoux N, Giron A, Bodaghi B, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2007;48(7):3253–9.
3. Nussenblatt R. Role of surgery in the patient with uveitis. In: Nussenblatt R, Whitcup S, editors. Uveitis fundamentals and clinical practice. 4th ed. China: Elsevier Inc.; 2010. p. 114–31.
4. Chan C, Rubenstein J, Coupland S, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16(11):1589–99.
5. Salomão D, Pulido J, Johnston P, Canal-Fontcuberta I, Feldman AL. Vitreoretinal presentation of secondary large B-cell lymphoma in patients with systemic lymphoma. JAMA Ophthalmol. 2013;131(9):1151–8.
6. Lavine J, Singh A, Sharma S, Baynes K, Lowder C, Srivastava S. Ultra-widefield multimodal imaging of primary vitreoretinal lymphoma. Retina. 2018; https://doi.org/10.1097/IAE.0000000000002260.
7. Cummings T, Stenzel T, Klintworth G, Jaffe GJ. Primary intraocular T-cell-rich large B-cell lymphoma. Arch Pathol Lab Med. 2005;129(8):1050–3.
8. Coupland S, Anastassiou G, Bornfeld N, Hummel M, Stein H. Primary intraocular lymphoma of T-cell type: report of a case and review of the literature. Graefes Arch Clin Exp Ophthalmol. 2005;243(3):189–97.
9. Pulido J, Johnston P, Nowakowski G, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: a review. Int J Retina Vitreous. 2018;4:18.
10. Whitcup S, de Smet M, Rubin B, et al. Intraocular lymphoma. Clinical and histopathologic diagnosis. Ophthalmology. 1993;100(9):1399–406.
11. Kimura K, Usui Y, Goto H, Group JILS. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. Jpn J Ophthalmol. 2012;56(4):383–9.
12. Levasseur S, Wittenberg L, White V. Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. JAMA Ophthalmol. 2013;131(1):50–5.
13. Sen J, Groenewald C, Hiscott P, Smith P, Damato B. Transretinal choroidal tumor biopsy with a 25-gauge vitrector. Ophthalmology. 2006;113(6):1028–31.
14. Levy-Clarke G, Byrnes G, Buggage R, et al. Primary intraocular lymphoma diagnosed by fine needle aspiration biopsy of a subretinal lesion. Retina. 2001;21(3):281–4.
15. Sarafzadeh S, Corrêa Z, Dhamija A, Augsburger J, Trichopoulos N. Intraocular lymphoma diagnosed by fine-needle aspiration biopsy. Acta Ophthalmol. 2010;88(6):705–10.
16. Christoforidis J, Chang S, Jiang A, Wang J, Cebulla C. Intravitreal devices for the treatment of vitreous inflammation. Mediat Inflamm. 2012;2012:126463.
17. Sanborn G, Anand R, Torti R, et al. Sustained-release ganciclovir therapy for treatment of cytomegalovirus retinitis. Use of an intravitreal device. Arch Ophthalmol. 1992;110(2):188–95.

18. Martin D, Parks D, Mellow S, et al. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant. A randomized controlled clinical trial. Arch Ophthalmol. 1994;112(12):1531–9.
19. Musch D, Martin D, Gordon J, Davis M, Kuppermann B. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med. 1997;337(2):63–90.
20. Wang J, Jiang A, Joshi M, Christoforidis J. Drug delivery implants in the treatment of vitreous inflammation. Mediat Inflamm. 2013;2013:780634.
21. Jaffe G, Martin D, Callanan D, et al. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. Ophthalmology. 2006;113(6):1020–7.
22. Jaffe G, McCallum R, Branchaud B, Skalak C, Butuner Z, Ashton P. Long term follow-up results of a pilot trial of a fluocinolone acetonide implant to treat posterior uveitis. Ophthalmology. 2005;112:1192–8.
23. Jaffe G. Reimplantation of a fluocinolone acetonide sustained drug delivery implant for chronic uveitis. Am J Ophthalmol. 2008;145(4):667–75.
24. Tomkins-Netzer O, Lightman S, Drye L, et al. Outcome of treatment of uveitic macular edema: the multicenter uveitis steroid treatment trial 2-year results. Ophthalmology. 2015;122(11):2351–9.
25. Kempen J, Altaweel M, Holbrook J, Jabs D, Sugar E. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol. 2010;149:550–61.
26. Kempen J, Altaweel M, Holbrook J, et al. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. JAMA. 2017;317(19):1993–2005.
27. Kunavisarut P, Srisomboon T, Patikulsila D, et al. Risk factors for development of rhegmatogenous retinal detachment in patients with uveitis. Ocul Immunol Inflamm. 2018;8:1–5.
28. Kerkhoff F, Lamberts Q, van den Biesen P, Rothova A. Rhegmatogenous retinal detachment and uveitis. Ophthalmology. 2003;110:427–31.
29. Schoenberger S, Kim S, Thorne J, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(3):362–92.
30. Galor A, Lowder C, Kaiser P, Perez V, Sears J. Surgical drainage of chronic serous retinal detachment associated with uveitis. Retina. 2008;28(2):282–8.
31. Stavrou P, Baltatzis S, Letko E. Pars plana vitrectomy in patients with intermediate uveitis. Ocul Immunol Inflamm. 2001;9:141–51.
32. Nolle B, Eckardt C. Vitrectomy in multifocal chorioretinitis. Ger J Ophthalmol. 1993;2:14–9.
33. Gutfleisch M, Spital G, Mingels A, et al. Pars plana vitrectomy with intravitreal triamcinolone: effect on uveitic cystoid macular oedema and treatment limitations. Br J Ophthalmol. 2007;91(3):345–8.
34. Kaplan H. Surgical treatment of intermediate uveitis. In: Boke W, Manthey K, Nussenblatt R, editors. Intermediate uveitis. Basel: Karger; 1992. p. 185–9.
35. Jones N. Complications of uveitis and their management. In: Jones N, editor. Uveitis. London: JP Medical Ltd.; 2013.

Part IX
Invasive Technique for Diagnosis of Complications in Uveitis

Chapter 19
The Role of Endoscopy in Uveitic Eyes

Nicolas A. Yannuzzi, Yale Fisher, and Thomas Albini

Overview

The first description of the endoscope as an instrument in pars plana vitrectomy was made by Thorpe for the removal of an intraocular foreign body [1]. Since its initial description, the endoscope has gone through multiple iterations resulting in smaller gauge and higher resolution instrumentation. It has been reported as useful in a variety of roles including endocyclophotocoagulation for glaucoma, cyclitic membrane peeling in chronic hypotony secondary to proliferative vitreoretinopathy or uveitis, intraocular foreign body removal, retained lens fragments, secondary intraocular lens implantation, endophthalmitis, and pediatric retinal surgery [2, 3]. The endoscope as a standalone instrument or combined with conventional wide field viewing systems may bypass compromised media and anterior segment opacities and allow for closer inspection of anterior structures including the ciliary body, posterior iris, pars plana, and anterior vitreous base [4].

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Currently Available Systems

Each endoscope has a xenon light source, a camera, and an endolaser in a single instrument. The first endoscope introduced was a 19-G 10,000 pixel resolution probe with an integrated endolaser (Endo Optiks, Little Silver, NJ, USA) [5]. More recent models provide increased resolution of 10,000–17,000 pixels and smaller gauge options. Currently models are available in 19, 20, and 23 G systems. The gauge size determines the imaging resolution and the field of view. The 19-G has 17,000 pixels and 140°, the 20 G, 10,000 pixels and 110°, and the 23 G, 6000 pixels and 90°, and there is also a 23 G high resolution probe with 10,000 pixels. Recently a 25-G, 6000 pixel model (Fiber Tech Co., Ltd) was introduced [6]. Currently, the most widely used endoscopes are the E2 or E4 fiber-optic systems (Endo Optiks, Little Silver, NJ, USA) though other systems are available by PolyDiagnost (Germany) and Fiber Tech (Tokyo, Japan) [7].

Principles of Endoscopy

To incorporate the endoscope into vitrectomy surgery, it may be safer to start using it in cases with clear media as a backup for a conventional microscope wide field viewing system. Prior to entering the globe, the endoscope should be adjusted for light and focus settings using the surgical drape as a guide [4]. To aid in orientation once inside the globe, the endoscope may be oriented with the corneal apex at the top of the display prior to insertion through the sclerotomy [4]. Next, the lens can be oriented at the top of the screen at the 12 o'clock position with the iris lens diaphragm on a horizontal plane [8]. Once inside the vitreous space, the optic nerve head and macular region facilitate alignment and orientation. Movement of the probe without axial rotation of the endoscope is critical to maintain orientation especially in the periphery (Figs. 19.1 and 19.2). Since the endoscopic screen view is limited, the surgeon must often vary location of the probe to improve or access additional viewing areas.

The learning curve for endoscopy requires transition to monocular viewing. While common in many other medical fields utilizing small gauge endoscopes, ophthalmic surgeons may find the adjustment initially difficult. For the most part, fused fiber scopes are common in ophthalmic endoscopy. These devices permit greater depth of field than glass scopes. Magnification of images is inversely related to the distance from the tissue. Illumination is adjusted by a foot pedal or gain adjustment control located on the main unit. The 23-G endoscope is compatible with standard microcannula systems and can be used when ultrahigh resolution and a brighter light source are not crucial (as can be achieved with the larger endoscopes which require a dedicated sclerotomy).

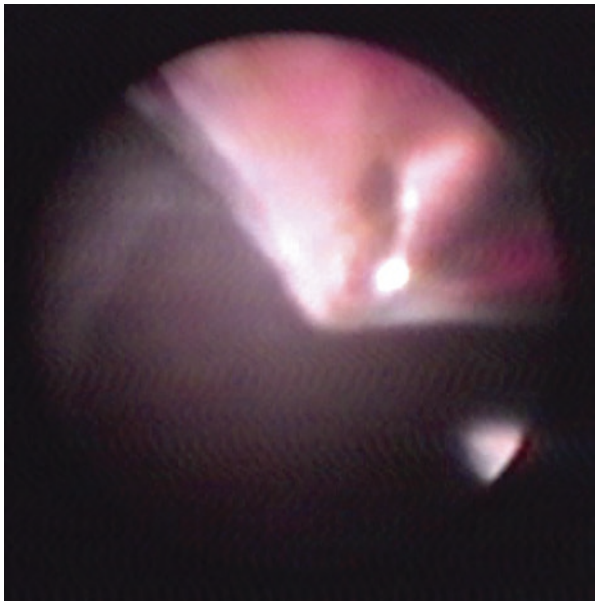

Fig. 19.1 Endoscopic view of trochar placement revealing tented retina around trochar

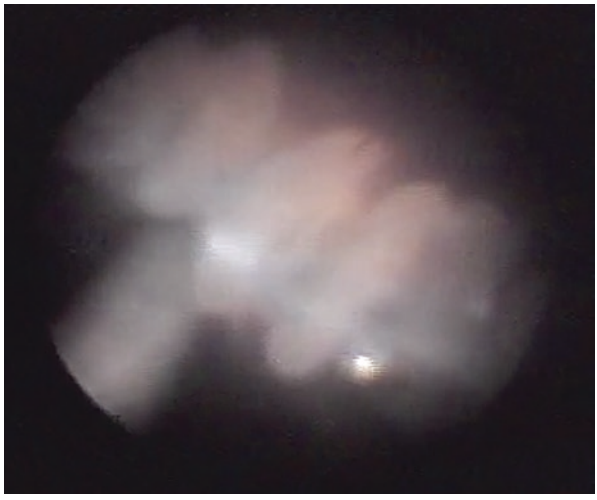

Fig. 19.2 Endoscopic view of trochar and clear view of ciliary body, prior to ciliary body laser

Diagnostic Evaluation and Therapeutic Intervention in Eyes with Severe Media Opacity

Endoscopy may be useful in preoperative evaluation of keratoprosthesis surgery to assess visual potential [9]. An interventional case series by Farias et al. showed that in ten patients with a history of corneal blindness and opaque corneas, after

intraoperative endoscopic evaluation, only three were considered to be adequate candidates for keratoprosthesis while the remainder were found to have significant optic nerve or retinal disease that would have severely limited visual potential. Systematic exploration with the endoscope may provide useful prognostic information not readily apparent by ultrasound such as the presence of maculopathy, retinal hemorrhage, retinal ischemia, proliferative vitreoretinopathy, optic nerve pallor, and macular hole and also may provide a view through media that make ultrasound impossible such as silicone oil [10].

Therapeutically, many vitreoretinal cases in inflamed eyes may have a limited view of the posterior segment. In cases of endophthalmitis, poor visualization through anterior segment media opacity may preclude the ability to perform a thorough vitrectomy and may risk damage to intraocular structures. The endoscope has been described as a viable alternative to conventional viewing in these cases, especially in cases with severe media opacity such as eyes affected by *B. cereus* endophthalmitis [11] and in a variety of other virulent causative organisms [12, 13]. As many of these cases may be post-traumatic, the endoscope may also permit enhanced visualization of foreign bodies and lens fragments and facilitate a more complete vitrectomy.

Aside from endophthalmitis cases, the endoscope may be useful in bypassing corneal dystrophies, corneal ulcers, posterior synechiae, or visually significant cataract or feathering after pneumatic retinopexy [14]. In these scenarios, the endoscopy may avoid the need for additional interventions to bypass media opacity such as temporary keratoprosthesis, iris expansion devices, lensectomy, or combined phacoemulsification which all may lengthen operative time.

Assistance During Routine Surgery When Visualization Is Lost

Although there have been no comparative studies of endoscopic versus conventional vitrectomy, endoscopy has been reported to have successful outcomes in every stage of uncomplicated rhegmatogenous retinal detachment repair in a large series of 127 eyes [15]. It may become particularly useful if the view in a conventional wide field case is compromised (Fig. 19.3). Poor visualization may occur secondary to corneal decompensation or during the air fluid exchange, especially in cases of lens fogging. The endoscope is a useful tool to bypass anterior segment opacities and can be used successfully during drainage of subretinal fluid (Fig. 19.4) [16]. This may be accomplished through a posterior drainage retinotomy. However, the endoscope may be particularly advantageous while draining through peripheral breaks while torting the eye to let the break assume a gravity dependent location [17].

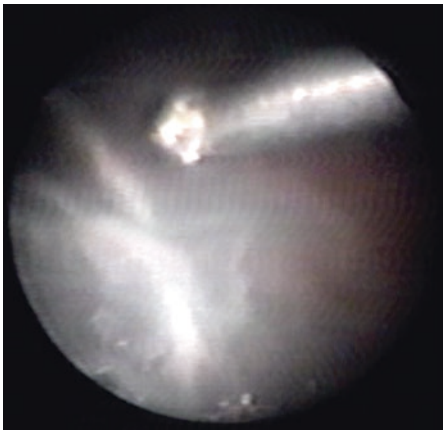

Fig. 19.3 Endoscopic view of detached retina and 20-G cutter in a recurrent retinal detachment and opacified cornea

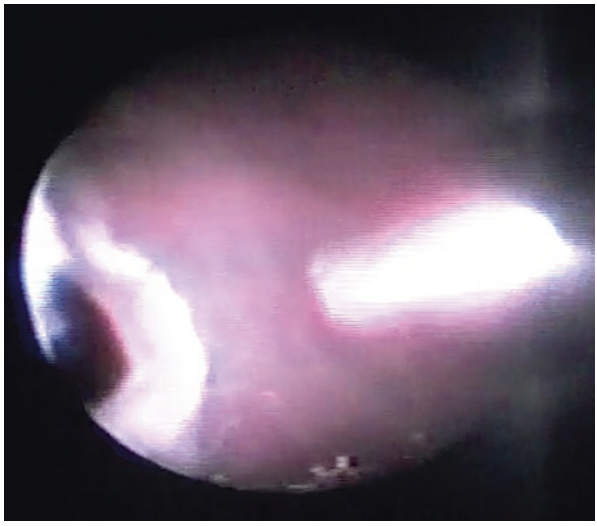

Fig. 19.4 Endoscopic view of cannula approaching retinotomy prior to draining subretinal fluid

Exploration for Microorganisms Sequestered in Anterior Vitreous Cavity

In fungal endophthalmitis, organisms may be sequestered in the anterior vitreous cavity (Fig. 19.5). Endoscopy may be used intraoperatively to explore this area as well as other potential nidi for infection such as the retroirideal space, especially in eyes with significant corneal opacities where visualization of these compartments may be compromised with conventional viewing systems [18].

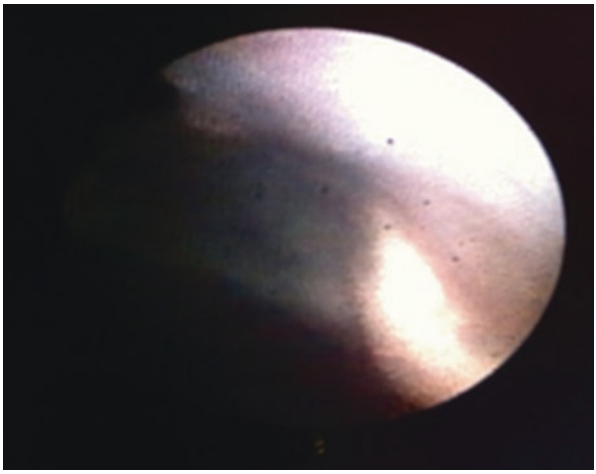

Fig. 19.5 Curvularia fungal endophthalmitis. Fungal mass seen behind iris with 23 G endoscope. This mass could not be observed through the pupil. (Patient reported in: Rachitskaya AV, Reddy AK, Miller D, Davis J, Flynn HW Jr., Smiddy W, Lara W, Lin S, Dubovy S, Albini TA. Prolonged Curvularia endophthalmitis due to organism sequestration. JAMA Ophthalmol. 2014;132(9):1123–6)

Anterior Membrane Dissection in Proliferative Vitreoretinopathy and Chronic Hypotony

Retinal detachments complicated by anterior proliferative vitreoretinopathy as found in recurrent rhegmatogenous retinal detachments, chronic uveitis, and endophthalmitis may have membranes enveloping the ciliary body causing chronic hypotony and phthisis bulbi. These membranes may be difficult to visualize, access, and treat. Endoscopy-assisted vitrectomy has been described as a useful adjunct in these cases with favorable globe-salvage outcomes [19]. The endoscope may enhance visualization and magnification and allow for more clear dissection of these membranes and relief of anterior loop traction than a conventional transpupillary approach with scleral depression [20]. Avoidance of scleral depression may allow the anatomy to be seen in its resting position permitting the surgeon to better appreciate key tractional forces.

Considerations

Though useful in many scenarios, the endoscope has significant limitations including smaller field of view and lack of stereopsis. The surgeon must use monocular clues, changes in focus, and variations in illumination to judge depth. In cases where loss of stereopsis limits the ability to accomplish surgical goals, a temporary keratoprosthesis is always a viable alternative [21]. Another option is hybrid endoscopic vitrectomy where an endoscope is combined with a traditional microscopic wide angle viewing system. This may also be done with a three

dimensional heads-up display where the endoscopic view is reported on the same monitor as the wide field microscopic view [22]. Despite these considerations, endoscopy remains a useful adjunctive technique in several clinical scenarios which may be encountered in the uveitic retinal detachment. For those interested in pursuing ophthalmic endoscopy, additional information, techniques and animated programs and videos are available on a free educational website, ophthalmicedge.org.

References

1. Thorpe H. Ocular endoscope: instrument for removal of intravitreous nonmagnetic foreign bodies. Trans Am Acad Ophthalmol Otolaryngol. 1934;39:422.
2. Marra KV, Yonekawa Y, Papakostas TD, Arroyo JG. Indications and techniques of endoscope assisted vitrectomy. J Ophthalmic Vis Res. 2013;8(3):282–90.
3. Wong SC, Lee TC, Heier JS. 23-Gauge endoscopic vitrectomy. Dev Ophthalmol. 2014;54:108–19.
4. Dang S, Heier JS, Goldberg RA. Practical applications of endoscopic vitrectomy for the vitreoretinal surgeon. Retin Physician. 2017;14:47–8.
5. Boscher C, Kuhn F. Endoscopic evaluation and dissection of the anterior vitreous base. Ophthalmic Res. 2015;53(2):90–9.
6. Kita M, Fujii Y, Hama S. Twenty five-gauge endoscopic vitrectomy for proliferative vitreoretinopathy with severe corneal opacity. Jpn J Ophthalmol. 2018;62(3):302–6.
7. Yu YZ, Zou YP, Zou XL. Endoscopy-assisted vitrectomy in the anterior vitreous. Int J Ophthalmol. 2018;11(3):506–11.
8. Wong SC, Lee TC, Heier JS, Ho AC. Endoscopic vitrectomy. Curr Opin Ophthalmol. 2014;25(3):195–206.
9. Farias CC, Ozturk HE, Albini TA, et al. Use of intraocular video endoscopic examination in the preoperative evaluation of keratoprosthesis surgery to assess visual potential. Am J Ophthalmol. 2014;158(1):80–86.e2.
10. Reddy Pappuru RR, Tyagi M, Paulose RM, et al. Role of diagnostic endoscopy in posterior segment evaluation for definitive prognostication in eyes with corneal opacification. Am J Ophthalmol. 2017;176:9–14.
11. Pan Q, Liu Y, Wang R, et al. Treatment of Bacillus cereus endophthalmitis with endoscopy-assisted vitrectomy. Medicine (Baltimore). 2017;96(50):e8701.
12. De Smet MD, Carlborg EA. Managing severe endophthalmitis with the use of an endoscope. Retina. 2005;25(8):976–80.
13. Ren H, Jiang R, Xu G, et al. Endoscopy-assisted vitrectomy for treatment of severe endophthalmitis with retinal detachment. Graefes Arch Clin Exp Ophthalmol. 2013;251(7):1797–800.
14. de Smet MD, Mura M. Minimally invasive surgery-endoscopic retinal detachment repair in patients with media opacities. Eye (Lond). 2008;22(5):662–5.
15. Yokoyama S, Kojima T, Mori T, et al. Clinical outcomes of endoscope-assisted vitrectomy for treatment of rhegmatogenous retinal detachment. Clin Ophthalmol. 2017;11:2003–10.
16. Sonoda Y, Yamakiri K, Sonoda S, et al. Endoscopy-guided subretinal fluid drainage in vitrectomy for retinal detachment. Ophthalmologica. 2006;220(2):83–6.
17. Hattori T, Sonoda KH, Kinoshita S. Two useful techniques of pars plana vitrectomy using endoscope. Eye (Lond). 2006;20(12):1466–8.
18. Rachitskaya AV, Reddy AK, Miller D, et al. Prolonged Curvularia endophthalmitis due to organism sequestration. JAMA Ophthalmol. 2014;132(9):1123–6.

19. Lee GD, Goldberg RA, Heier JS. Endoscopy-assisted vitrectomy and membrane dissection of anterior proliferative vitreoretinoapthy for chronic hypotony after previous retinal detachment repair. Retina. 2016;36(6):1058–63.
20. Boscher C, Kuhn F. An endoscopic overview of the anterior vitreous base in retinal detachment and anterior proliferative vitreoretinopathy. Acta Ophthalmol. 2014;92(4):e298–304.
21. Kuhn F, Witherspoon CD, Morris RE. Endoscopic surgery vs temporary keratoprosthesis vitrectomy. Arch Ophthalmol. 1991;109(6):768.
22. Kita M, Mori Y, Hama S. Hybrid wide-angle viewing-endoscopic vitrectomy using a 3D visualization system. Clin Ophthalmol. 2018;12:313–7.

Chapter 20
Retinal and Choroidal Biopsies

Rehan M. Hussain, Thomas A. Albini, and Harry W. Flynn Jr.

Indications for Retinal and Chorioretinal Biopsy

The initial evaluation of patients with uveitis involves obtaining a detailed history in combination with slit-lamp examination of the anterior and posterior segment, and fundus examination. Ancillary tests that may aid in diagnosis include fluorescein angiography, indocyanine green angiography, optical coherence tomography, echography, radiologic and serologic tests [1]. Empiric therapy with close observation is often employed when the diagnosis cannot be certain after exhausting these diagnostic tools.

When these approaches fail and an infectious or neoplastic process is suspected but the diagnosis remains unclear, posterior segment biopsy techniques can be considered [2]. Diagnostic uncertainty has been reported in up to 33% of uveitis patients [3]. For suspected infectious diseases such as herpetic or toxoplasmosis retinitis, serologic testing may have utility in ruling out disease if there is a negative result; though given the high percentage of the general population with positive antibody titers, a positive result is not sufficiently diagnostic [4]. There has been an increased need for posterior segment biopsy techniques due to an increased incidence of patients with iatrogenic immunosuppression and increased use of intravitreal steroids, which may confuse the diagnosis of inflammatory disease [5]. Furthermore, infectious and malignant processes may be manifested primarily or only in the eye, in which case the diagnostic yield from systemic testing is limited. Choroidal biopsy may be indicated when there is suspicion of a malignant process such as posterior uveal melanoma and the diagnosis is not clear from patient history or examination.

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Perioperative Planning

It is paramount to consult with an ocular pathologist prior to obtaining a biopsy specimen in order to ensure rapid transport and appropriate handling and preparation of the tissue, which will maximize the diagnostic yield of the surgery [2]. The pathologist should be aware of and experienced with the clinical diagnosis being considered and involved in surgical plan, especially as regards the handling of the specimen. The tools available to the pathologist include light microscopy (LM) and electron microscopy (EM), immunohistochemistry, and polymerase chain reaction (PCR). Cultures for suspected infection are sent to the laboratory at the time of surgery, and on appropriate mediums for aerobic, anaerobic, fungal and mycobacterial infection. Polymerase chain reaction (PCR) can be sent at the same for analysis of viral and/or toxoplasmosis genome.

Vitreous Biopsy for Chorioretinitis

In selected cases of vitritis, retinitis or choroiditis, a vitreous biopsy can provide a diagnosis, especially if marked vitritis is present. Immunohistochemistry classically will show a predominance of CD4+ cells in non-infectious uveitis, neutrophils in infectious uveitis, and light chain restriction in lymphoma. Cultures and antibody testing may be positive in infectious uveitis only. Cytokine analysis will show elevated IL-1, IL-2, and IL-6 in non-infectious uveitis, elevated IL-6 in infectious uveitis, and elevated IL-10 in lymphoma [6–8].

PCR may show microbial or viral products in infectious uveitis or monoclonal gene rearrangement in primary vitreoretinal lymphoma. PCR is useful for the identification of the causative pathogen in delayed endophthalmitis and in one study had a higher rate of positive identification of the causative organism (92%) than microscopy (0%) or diagnostic culture (24%) [9]. PCR also has been shown to be a valuable tool in the diagnosis of viral chorioretinitis, whether obtained from the aqueous or vitreous [10]. Sensitivities exceed 90% for varicella-zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV), with specificities in excess of 95% for these organisms [11]. False positive rates have been reported as low as 0% [12]. The diagnostic yield of vitreous biopsy alone for uveitis cases with high suspicion of malignancy or infection ranges from 39% to 61.5% [13, 14].

Vitrectomy can also be therapeutic by debulking infectious material and reducing the load of inflammatory cells and debris.

Transvitreal Retinal and Choroidal Biopsy

Transvitreal retinal biopsy may be necessary for atypical uveitis with primary retinal pathology (such as in select cases of *Mycobacterium tuberculosis*, syphilis, or viral retinitis, toxoplasmosis or lymphoma), especially if there is limited vitreous

spillover of inflammation. In Peyman's series of patients who had chorioretinal resection for suspected intraocular tumor, the complication rate was 80%, though most complications were self-limited, and two thirds of patients retained their eye postoperatively with useful vision [15]. In Peyman's later series of 14 transvitreal internal retinal biopsies, in which a smaller amount of tissue was removed, there were no significant complications [16].

The ideal biopsy specimen includes the junction of involved and uninvolved retina. For retinitis, the advancing edge of the lesion has the most active replicating organisms, whereas the center of the lesion is more likely to be necrotic. If possible, biopsy sites are preferred to be peripheral, nasal, superior (to allow more effective tamponade), avascular, rectangular, and sufficiently large to yield a diagnosis (at least 2 × 2 mm, ideally 3 × 5 mm). The more tissue given the more likely the pathologist has enough to work with to make a diagnosis [2, 17, 18]. Multiple biopsies at the same surgery can avoid sample bias and decrease the chances that the biopsied tissue is totally fibrosed or degenerated without revealing the disease process (Figs. 20.1, 20.2, and 20.3).

The surgical technique of transvitreal chorioretinal biopsy involves the following steps [2, 19]:

- Pars plana vitrectomy (PPV) to remove core and cortical vitreous
  - Chandelier light is optional to allow bimanual technique for biopsy
  - Lifting the posterior hyaloid may lower the risk of proliferative vitreoretinopathy (PVR) but must be done cautiously in areas of active retinitis or atrophic retina
- Endodiathermy or endolaser to delineate the biopsy site and improve hemostasis
- Excise retina and/or choroid with vertical scissors, leaving a small anchoring attachment
  - Can use a cannula to inject balanced saline solution and create a subretinal bleb if the retina is attached
  - For choroidal biopsy, scissors penetrate choroid until white sclera is visible
  - Alternatively, the vitreous cutter can be used for endoresection [19]
- Remove tissue with forceps, soft tip cannula or large bore blunt cannula, grasping as little tissue as possible to avoid crushing the specimen
- Elevate intraocular pressure to reduce incidence of hemorrhage (especially with choroidal biopsy)
- Laser around normal retina (do not laser biopsy edges involved by inflammation)
- Fluid-air-exchange
- Long acting gas tamponade or silicone oil—silicone oil is advantageous in cases of widespread viral retinitis with many retinal breaks [20]
- Mark edges of specimen (if orientation is pertinent to the pathologist)
- Divide specimen into thirds if possible

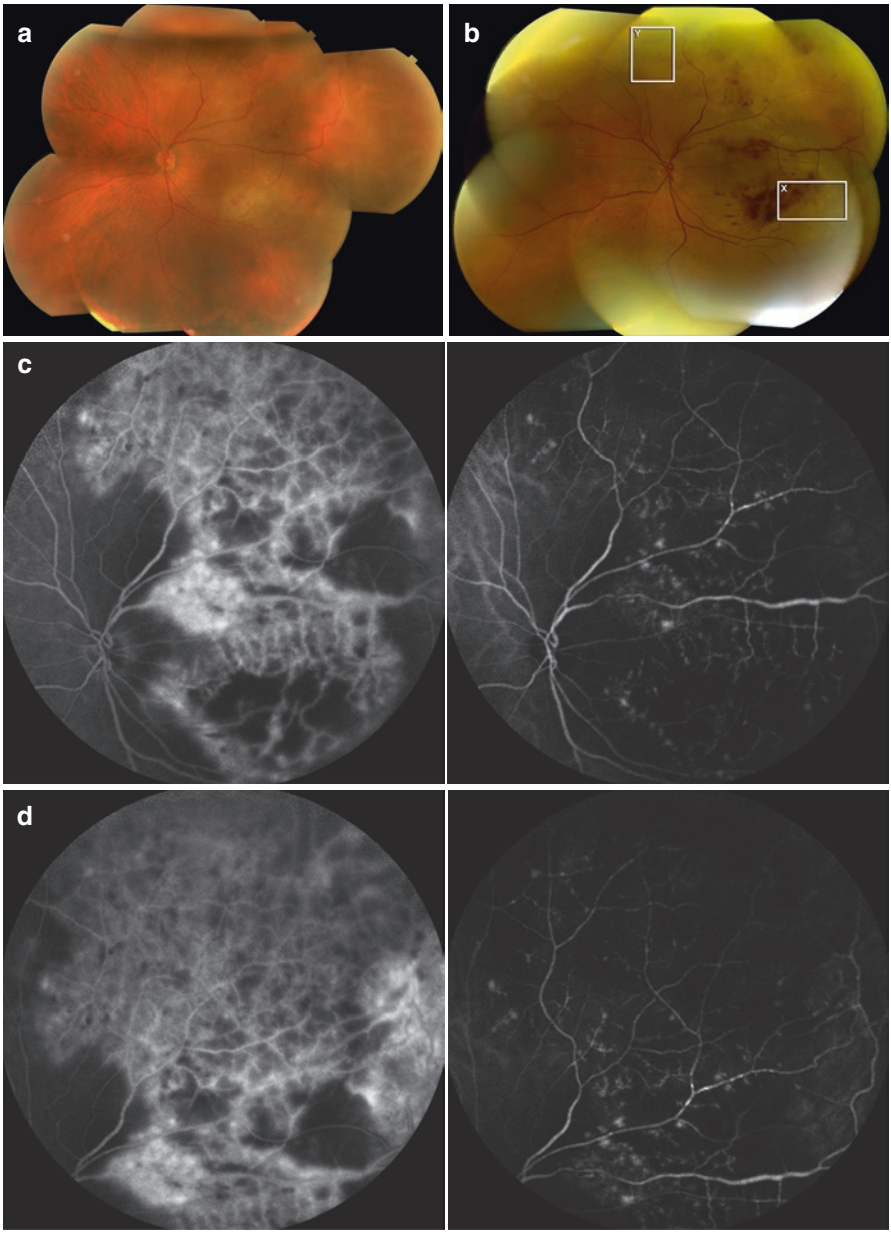

Fig. 20.1 Montage fundus photography of the left eye in a 66-year-old female with intraretinal lymphoma. Photography taken 5 days following diagnostic vitrectomy of the left eye demonstrates an area of retinal whitening and hemorrhage in the inferotemporal macula (**a**). Photography taken 19 days following diagnostic vitrectomy and 2 days prior to retinal biopsy demonstrates progression of retinal involvement (**b**). Overlay indicates approximate locations of biopsy sites, labeled X and Y. Simultaneous fluorescein angiography (left) and indocyanine green angiography (right) obtained 19 days following diagnostic vitrectomy demonstrates areas of retinal vasculitis and lack of retinal and choroidal perfusion in the areas of biopsy site X (**c**) and biopsy site Y (**d**)

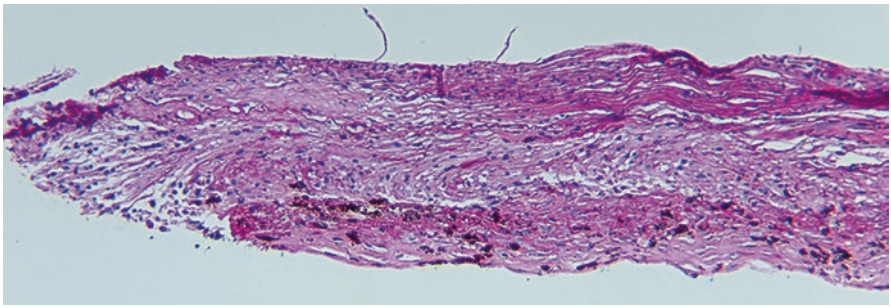

Fig. 20.2 Histology of tissue obtained from retinal biopsy X (hematoxylin and eosin stain, 20×). The tissue exhibits extensive fibrosis. Neither normal retinal histology nor prominent lymphocytic infiltration is present

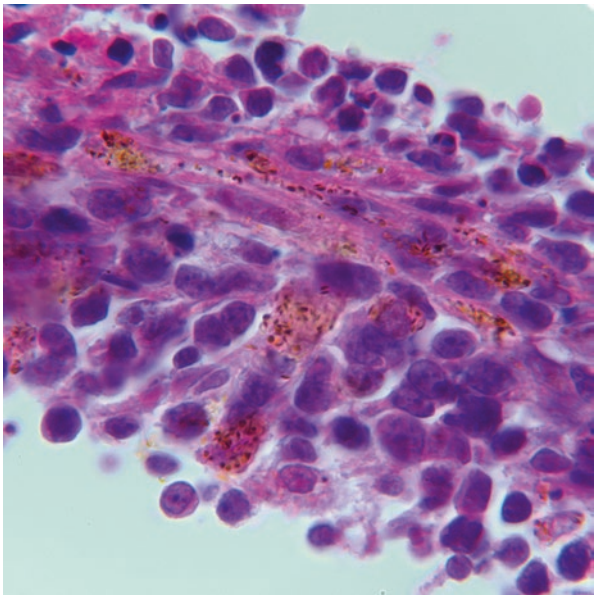

Fig. 20.3 Histology of tissue obtained from retinal biopsy Y (hematoxylin and eosin stain, 100×). Numerous large lymphocytes with multiple nucleoli, large nuclei, abundant cytoplasm, and mitotic figures were observed obscuring the retinal architecture

- First portion placed in formaldehyde (for light microscopy) or glutaraldehyde fixative (for electron microscopy)
- Second portion is frozen for immunopathological and molecular characterization
- Third portion is for microbiology cultures

In patients with retinal detachment secondary to infectious retinitis, endoretinal biopsy can be performed at time of retinal detachment repair with PPV [17, 21]. The separation of the retina from the underlying RPE and choroid reduces the risk of inadvertent choroidal hemorrhage during the biopsy. Rutzen et al. published a retrospective series of 24 transvitreal retinal biopsies and 9 chorioretinal/choroidal biopsies from 1984 to 1993 in Los Angeles, during the height of the AIDS epidemic. The

biopsies were all taken during retinal detachment repair surgery in eyes with symptoms suggestive of viral retinitis. The clinical diagnosis was confirmed by EM, immunohistochemical staining, in situ DNA hybridization, and/or PCR in 10 of the 19 eyes (53%). Virus was identified in 7/10 cases of suspected cytomegalovirus retinitis, in 1/7 cases of acute retinal necrosis (ARN), and in 2/2 cases of progressive outer retinal necrosis (PORN). The remaining five biopsies disclosed *Candida* organisms (n = 1), subretinal fibrosis (n = 1), and chronic inflammation (n = 3). Of nine chorioretinal/choroidal biopsies, some of the various diagnosis included lymphoma (n = 2), subretinal neovascularization (n = 1), uveal melanocytic proliferation (n = 1), Toxoplasmosis (n = 1), viral retinitis (n = 1), and unspecified chronic inflammation (n = 3) [21].

Cole et al. described a series of nine eyes with combined retinal and choroidal biopsy through a 20 G PPV approach with 20 G vertical cutting intraocular scissors (as outlined in the steps above). The specimens were placed in formaldehyde for LM and EM studies, with an occasional frozen section for immunopathology. Six of nine (67%) eyes were referred for panuveitis of undetermined etiology, one with scleritis with choroidal mass (11%), one with uveitis and vasculitis with subretinal deposits (11%), and one with uveitis and choroidal mass (11%). Positive histologic diagnosis was confirmed in 5/9 (55%) of the chorioretinal biopsies: one case of tuberculosis, two cases of toxoplasma gondii, and two cases B cell lymphoma. Two of those cases required the use of PCR to determine the diagnosis of toxoplasmosis and tuberculosis. The four remaining biopsies revealed chronic inflammation without evidence of malignancy or infection. Three cases had complications (33%), which included two vitreous hemorrhages that self-resolved and one retinal detachment that was successfully repaired with one operation [2].

Though not a commonly employed technique, Damato et al. described removal choroidal melanomas piecemeal with the vitreous cutter, followed by adjunctive ruthenium plaque brachytherapy in select cases. The most common complications were retinal detachment in 16/52 eyes (31%) and cataract progression in 25/52 eyes (48%). None of the patients developed local recurrence but one died of metastatic disease [19]. More recent studies of the PPV approach to diagnose indeterminate choroidal tumors yielded a definitive diagnosis in 57–100% of cases, with lower rates of vitreous hemorrhage and retinal detachment comparatively, especially in those studies utilizing 23- and 25-G surgery [22–25].

Transscleral Choroidal Biopsy

The technique for transscleral chorioretinal biopsy was pioneered by Peyman and Foulds in the early 1980s. This approach involves creating a focal peritomy and isolating the extraocular muscles of the involved quadrant with silk sutures [26]. A PPV should be considered to reduce risk of retina bulging into the biopsy site, which could cause retinal incarceration or tear [27]. Laser or cryotherapy barrier is applied around the planned biopsy site, which is marked. A 6 × 6 mm nearly full thickness

scleral flap is dissected 5–6 mm posterior to the limbus, with a posterior hinge. Diathermy or cautery is applied to outer margin of inner choroidal bed. The choroid is incised with a sharp blade, then 0.12 forceps are inserted to complete dissection with the aid of Vannas scissors. The tissue is ideally delivered in one piece and placed in fixative. Any prolapsed vitreous should be removed with scissors, and the wound closed with 9-0 nylon or 7-0 vicryl suture. A fluid-gas exchange is then performed.

Foulds reported a series of 34 transscleral biopsies of the choroid and retina for the diagnosis of choroidal melanoma, ARN, chronic uveitis, and progressive retinal pigment epitheliopathy. The only reported adverse event was a retinal break with associated vitreous hemorrhage and resultant PVR [28]. This complication may have been avoided if vitrectomy was performed prior to the transscleral biopsy.

Johnston and colleagues performed a review of 14 retinal and choroidal biopsies performed in 13 patients with uveitis suspected to be of infectious or malignant origin. One patient had consecutive biopsies performed in the same eye. Four biopsies were performed with a transscleral approach and ten were performed by PPV. The pathologic diagnosis differed from the initial suspected diagnosis in 5/13 (39%) of cases and guided specific appropriate treatment in 7/13 (54%) cases. In the six remaining cases, the biopsy did not provide a definitive diagnosis but was able to exclude malignancy. The only intraoperative complication was one retinal break, while postoperative complications that may have been related to the procedure included one localized retinal detachment, two cataracts, and one phthisical eye [29].

Fine-Needle Choroidal Biopsy

In suspected cases of posterior uveal melanoma, fine-needle choroidal biopsy can be considered if there is diagnostic uncertainty. More recently, the sample can be sent for gene expression profiling, which is an accurate prognostic indicator in predicting the risk of metastasis [30]. The transvitreal fine-needle aspiration biopsy approach is generally safe; there is a theoretical risk of tumor dissemination along the needle track though it has never been reported with smaller than 25 G needle size (Fig. 20.4). Other possible complications include subretinal and vitreous hemorrhage [31, 32].

Complications of Intraocular Biopsy

The risks of retinal and choroidal biopsy vary depending on the surgical approach, but generally include the following:

- Proliferative vitreoretinopathy
- Traction and/or rhegmatogenous retinal detachment

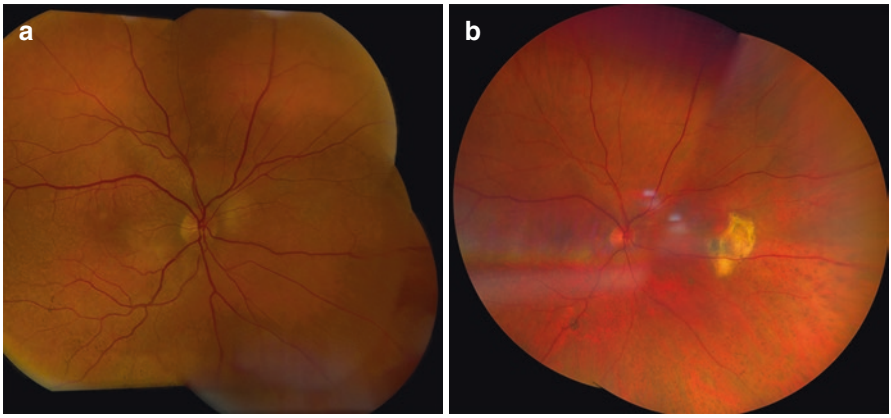

Fig. 20.4 Fundus photography of the right eye of 50 year old male with presumed uveal lymphoid hyperplasia who underwent transvitreal fine needle biopsy of the nasal choroid in an area with highest choroidal thickening as demonstrated on ultrasonography. (**a**) Shows the fundus prior to the procedure with six subtle subretinal infiltrates. (**b**) Fundus photograph taken 1 month after the biopsy with a scar in the area of biopsy

- Elevated or low intraocular pressure
- Cataract progression
- Peripheral retinal tears and retinal detachment
- Choroidal or vitreous hemorrhage
- Endophthalmitis
- Exacerbation of the underlying inflammatory disease

In deciding in whether to perform a chorioretinal biopsy, it is imperative to consider the risks, benefits, and alternatives to performing an invasive surgical intervention. Other less invasive options should be pursued first.

References

1. Nussenblatt RB, Davis JL, Palestine AG. Chorioretinal biopsy for diagnostic purposes in cases of intraocular inflammatory disease. Dev Ophthalmol. 1992;23:133–8.
2. Cole CJ, Kwan AS, Laidlaw DA, Aylward GW. A new technique of combined retinal and choroidal biopsy. Br J Ophthalmol. 2008;92(10):1357–60.
3. Henderly DE, Genstler AJ, Smith RE, Rao NA. Changing patterns of uveitis. Am J Ophthalmol. 1987;103(2):131–6.
4. Park SS, D'Amico DJ, Foster CS. The role of invasive diagnostic testing in inflammatory eye diseases. Int Ophthalmol Clin. 1994;34(3):229–38.
5. Vertes D, Snyers B, De Potter P. Cytomegalovirus retinitis after low-dose intravitreous triamcinolone acetonide in an immunocompetent patient: a warning for the widespread use of intravitreous corticosteroids. Int Ophthalmol. 2010;30(5):595–7.

6. Pochat-Cotilloux C, Bienvenu J, Nguyen AM, Ohanessian R, Ghesquieres H, Seve P, et al. Use of a threshold of interleukin-10 and Il-10/Il-6 ratio in ocular samples for the screening of vitreoretinal lymphoma. Retina. 2018;38(4):773–81.
7. Groen-Hakan F, Eurelings L, ten Berge JC, van Laar J, Ramakers CRB, Dik WA, et al. Diagnostic value of serum-soluble interleukin 2 receptor levels vs angiotensin-converting enzyme in patients with sarcoidosis-associated uveitis. JAMA Ophthalmol. 2017;135(12):1352–8.
8. Fabiani C, Sota J, Tosi GM, Franceschini R, Frediani B, Galeazzi M, et al. The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases. Clin Rheumatol. 2017;36(10):2307–18.
9. Lohmann CP, Linde HJ, Reischl U. Improved detection of microorganisms by polymerase chain reaction in delayed endophthalmitis after cataract surgery. Ophthalmology. 2000;107(6):1047–51; discussion 51–2.
10. Harper TW, Miller D, Schiffman JC, Davis JL. Polymerase chain reaction analysis of aqueous and vitreous specimens in the diagnosis of posterior segment infectious uveitis. Am J Ophthalmol. 2009;147(1):140–7.e2.
11. Van Gelder RN. CME review: polymerase chain reaction diagnostics for posterior segment disease. Retina. 2003;23(4):445–52.
12. McCann JD, Margolis TP, Wong MG, Kuppermann BD, Luckie AP, Schwartz DM, et al. A sensitive and specific polymerase chain reaction-based assay for the diagnosis of cytomegalovirus retinitis. Am J Ophthalmol. 1995;120(2):219–26.
13. Davis JL, Miller DM, Ruiz P. Diagnostic testing of vitrectomy specimens. Am J Ophthalmol. 2005;140(5):822–9.
14. Mruthyunjaya P, Jumper JM, McCallum R, Patel DJ, Cox TA, Jaffe GJ. Diagnostic yield of vitrectomy in eyes with suspected posterior segment infection or malignancy. Ophthalmology. 2002;109(6):1123–9.
15. Peyman GA, Raichand M, Schulman J. Diagnosis and therapeutic surgery of the uvea—Part I: Surgical technique. Ophthalmic Surg. 1986;17(12):822–9.
16. Peyman GA. Internal retinal biopsy: surgical technique and results. Int Ophthalmol. 1990;14(2):101–4.
17. Freeman WR, Wiley CA, Gross JG, Thomas EL, Rao NA, Liggett PE. Endoretinal biopsy in immunosuppressed and healthy patients with retinitis. Indications, utility, and techniques. Ophthalmology. 1989;96(10):1559–65.
18. Westerfeld C, Mukai S. Retinal and choroidal biopsy. Int Ophthalmol Clin. 2009;49(1):145–54.
19. Damato B, Groenewald C, McGalliard J, Wong D. Endoresection of choroidal melanoma. Br J Ophthalmol. 1998;82(3):213–8.
20. Almeida DR, Chin EK, Tarantola RM, Tegins EO, Lopez CA, Boldt HC, et al. Long-term outcomes in patients undergoing vitrectomy for retinal detachment due to viral retinitis. Clin Ophthalmol. 2015;9:1307–14.
21. Rutzen AR, Ortega-Larrocea G, Dugel PU, Chong LP, Lopez PF, Smith RE, et al. Clinicopathologic study of retinal and choroidal biopsies in intraocular inflammation. Am J Ophthalmol. 1995;119(5):597–611.
22. Kvanta A, Seregard S, Kopp ED, All-Ericsson C, Landau I, Berglin L. Choroidal biopsies for intraocular tumors of indeterminate origin. Am J Ophthalmol. 2005;140(6):1002–6.
23. Bechrakis NE, Foerster MH, Bornfeld N. Biopsy in indeterminate intraocular tumors. Ophthalmology. 2002;109(2):235–42.
24. Seregard S, All-Ericsson C, Hjelmqvist L, Berglin L, Kvanta A. Diagnostic incisional biopsies in clinically indeterminate choroidal tumours. Eye (Lond). 2013;27(2):115–8.
25. Sen J, Groenewald C, Hiscott PS, Smith PA, Damato BE. Transretinal choroidal tumor biopsy with a 25-gauge vitrector. Ophthalmology. 2006;113(6):1028–31.
26. Martin DF, Chan CC, de Smet MD, Palestine AG, Davis JL, Whitcup SM, et al. The role of chorioretinal biopsy in the management of posterior uveitis. Ophthalmology. 1993;100(5):705–14.

27. Peyman GA, Raichand M. Full-thickness eye wall resection of choroidal neoplasms. Ophthalmology. 1979;86(6):1024–36.
28. Foulds WS. The uses and limitations of intraocular biopsy. Eye (Lond). 1992;6(Pt 1):11–27.
29. Johnston RL, Tufail A, Lightman S, Luthert PJ, Pavesio CE, Cooling RJ, et al. Retinal and choroidal biopsies are helpful in unclear uveitis of suspected infectious or malignant origin. Ophthalmology. 2004;111(3):522–8.
30. Harbour JW. A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile. Methods Mol Biol. 2014;1102:427–40.
31. Augsburger JJ, Shields JA. Fine needle aspiration biopsy of solid intraocular tumors: indications, instrumentation and techniques. Ophthalmic Surg. 1984;15(1):34–40.
32. Shields JA, Shields CL, Ehya H, Eagle RC Jr, De Potter P. Fine-needle aspiration biopsy of suspected intraocular tumors. The 1992 Urwick Lecture. Ophthalmology. 1993;100(11):1677–84.

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