CHAPTER 8

Noninfectious Anterior and Intermediate Uveitis

Highlights

- Anterior uveitis, the most common form of uveitis, is usually treated with topical corticosteroids.
- The first episode of mild, nongranulomatous, unilateral anterior uveitis may not require further systemic workup.
- Intermediate uveitis can be associated with systemic diseases, including sarcoidosis and multiple sclerosis.
- Pars planitis, a subtype of idiopathic or undifferentiated intermediate uveitis, is characterized by the presence of snowballs (aggregates of inflammatory cells in the vitreous) and snowbanks (inflammatory exudates on the pars plana).

Anterior Uveitis

Anterior uveitis is the most common type of uveitis, accounting for more than 90% of cases in a community-based practice. Incidence in the United States varies by age, from approximately 7 cases per 100,000 person-years in individuals aged 14 years and younger to approximately 220 cases per 100,000 person-years in adults aged 65 years and older.

Because uveitis may occur secondary to inflammation of the cornea and/or sclera, it is important for the physician to evaluate these structures carefully to rule out primary keratitis or scleritis. Inflammation of the sclera and the cornea is covered in depth in BCSC Section 8, *External Disease and Cornea*. See Chapter 7 in this volume for discussion of scleritis.

Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology.* 2004;111(3): 491–500.

Reeves SW, Sloan FA, Lee PP, Jaffe GJ. Uveitis in the elderly: epidemiological data from the National Long-term Care Survey Medicare Cohort. *Ophthalmology.* 2006;113(2):307–321.

Acute Anterior Uveitis

The classic presentation of acute anterior uveitis is the sudden onset of eye pain, redness, and photophobia that can be associated with decreased vision. In nongranulomatous anterior uveitis, the inflammatory infiltrate is typically composed of lymphocytic and plasma cells; clinically, fine keratic precipitates (KPs) can dust the corneal endothelium. The clinical description of granulomatous anterior uveitis is related to the appearance of the KPs (large, yellow, and "greasy," with inferior cornea distribution). See Chapter 5 for further discussion about KPs and other findings associated with anterior uveitis.

Active anterior uveitis is characterized by inflammatory cells and flare in the anterior chamber, which distinguishes anterior uveitis from non-uveitic entities such as dry eye and conjunctivitis. Severe cases may show a protein coagulum in the aqueous (fibrin) or, less commonly, a hypopyon (Fig 8-1). Occasionally, a fibrin net forms across the pupillary margin (Fig 8-2), potentially producing a seclusion membrane and iris bombé. Iris vessels may be dilated, and on rare occasions, a spontaneous hyphema occurs. Cells may also be present in the anterior vitreous. Fundus lesions are not characteristic, although uveitic macular edema and optic disc edema may occur with high-grade inflammation. Intraocular pressure (IOP) is often low due to increased uveoscleral outflow or decreased aqueous production secondary to ciliary body inflammation. Occasionally, IOP is elevated due to trabeculitis, obstruction of the trabecular meshwork by debris and cells, or pupillary block.

The inflammation usually lasts several days to weeks, up to 3 months. There are 2 patterns of inflammation: One is acute and bilateral. The other is an acute and unilateral attack, with recurrences alternating between the 2 eyes, although the disease is usually not active in both eyes simultaneously. This pattern is typical for *human leukocyte antigen (HLA)-B27–associated anterior uveitis.* Other features of HLA-B27–associated anterior uveitis include high-grade inflammation (ie, significant number of anterior chamber cells [see Chapter 5, Table 5-7]) at presentation, hypopyon, fibrin, and posterior synechiae. The age at onset of HLA-B27–associated anterior uveitis ranges from 20 to 40 years, and men are more likely to be affected than women.

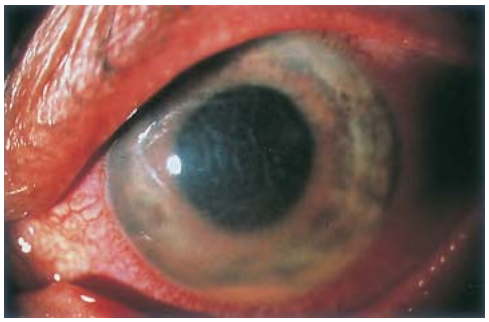

Figure 8-1 Acute HLA-B27–positive anterior uveitis accompanied by marked conjunctival injection, fixed pupil, loss of iris detail from corneal edema, and hypopyon. The patient had eye pain and photophobia. *(Courtesy of David Meisler, MD.)*

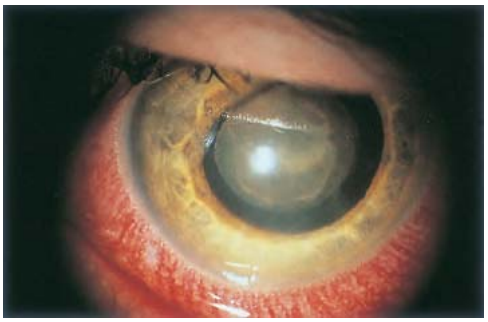

Figure 8-2 Ankylosing spondylitis. Acute unilateral anterior uveitis with severe anterior chamber reaction, central fibrinous exudate contracting anterior to the lens capsule, and posterior synechiae from the 10 o'clock to 12 o'clock position. *(Courtesy of David Meisler, MD.)*

Unilateral anterior uveitis should also raise suspicion for an infectious etiology, especially herpetic anterior uveitis. Sarcoidosis can present as an acute, bilateral or unilateral, granulomatous anterior uveitis. In most cases, the first episode of acute anterior uveitis does not require a systemic workup, although high-grade or bilateral uveitis might warrant targeted testing. See Chapter 5 for further discussion about indications for testing.

For all forms of acute nongranulomatous anterior uveitis, ocular morbidity can be reduced by timely diagnosis, aggressive initial therapy, and patient adherence. Topical corticosteroids are first-line treatment, and administration every 1–2 hours may be necessary. Very severe inflammation may require periocular and/or oral corticosteroids in addition to topical treatment. Periocular corticosteroids should not be used unless infectious etiologies have been thoroughly investigated or infection has been treated before corticosteroid use. Topical cycloplegic agents can relieve pain due to ciliary body spasm, as well as lyse or prevent formation of posterior synechiae. Mydriasis may also be attained with conjunctival cotton pledgets soaked in tropicamide, cyclopentolate, or phenylephrine hydrochloride (Fig 8-3).

Although a protracted course of treatment is typically not required for acute nongranulomatous anterior uveitis, systemic corticosteroid-sparing immunomodulatory therapy (IMT) may be necessary for long-term therapy if the inflammation recurs frequently or becomes chronic, or if complications arise from long-term use of topical or periocular corticosteroids. Antimetabolites are usually the first-line treatment for anterior uveitis without associated systemic inflammatory disease. A tumor necrosis factor (TNF) inhibitor may be considered for second-line treatment of anterior uveitis, particularly in patients who are HLA-B27 positive. Of note, *none* of the TNF inhibitors are approved by the US Food and Drug Administration (FDA) to treat undifferentiated or isolated anterior uveitis; the FDA indications for adalimumab are for noninfectious intermediate, posterior, and panuveitis.

Rosenbaum JT. Evolving "diagnostic" criteria for axial spondyloarthritis in the context of anterior uveitis. *Ocul Immunol Inflamm.* 2016;24(4):445–449.

Van Gelder RN. Diagnostic testing in uveitis. *Focal Points: Clinical Modules for Ophthalmologists.* American Academy of Ophthalmology; 2013, module 4.

HLA-B27–related diseases

HLA-B27 is a major histocompatibility complex (MHC) class I antigen present in approximately 8% of the general population in the United States. In some populations, approximately 40%–50% of patients with acute anterior uveitis are HLA-B27 positive. Although

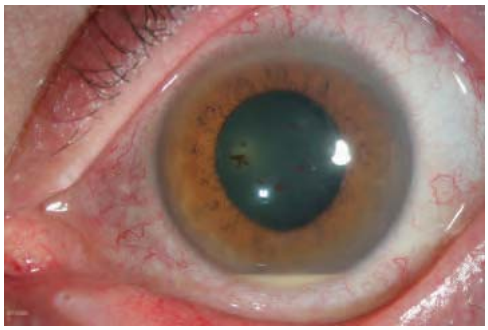

Figure 8-3 Acute nongranulomatous anterior uveitis. Hypopyon and anterior capsule ring of pigment after lysis of posterior synechiae by treatment with dilating agents. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

patients with recurrent acute nongranulomatous anterior uveitis should be tested for HLA-B27, the presence of HLA-B27 does not necessarily indicate that the uveitis is HLA-B27 associated. The clinical characteristics of the uveitis should be consistent with those of HLA-B27–associated uveitis. Thus, for example, a patient with multifocal choroidal lesions who is HLA-B27 positive does *not* have HLA-B27–associated uveitis, because choroidal lesions are not a characteristic of this entity. See Chapter 4 for additional discussion of HLA disease associations.

Several autoimmune diseases known collectively as *seronegative spondyloarthritis* are strongly associated with both acute nongranulomatous anterior uveitis and HLA-B27. Patients with these diseases, by definition, do not test positive for rheumatoid factor (RF). Seronegative spondyloarthritis includes

- ankylosing spondylitis (AS)
- reactive arthritis
- inflammatory bowel disease–related arthritis (or enteropathic arthritis)
- psoriatic arthritis

These entities are sometimes clinically indistinguishable, and all may be associated with spondylitis and sacroiliitis. Women are more likely than men to experience atypical forms of spondyloarthritis.

Up to 90% of patients with AS test positive for HLA-B27, although most HLA-B27–positive individuals do not develop the disease. The chance that an HLA-B27–positive patient will develop spondyloarthritis or eye disease is 1 in 4. Family members may also have AS or anterior uveitis.

Ankylosing spondylitis AS ranges in severity from asymptomatic to crippling. Symptoms of this disorder include lower back pain and morning stiffness that improves with movement. AS typically affects young men between 20 and 40 years of age. Patients with anterior uveitis may lack symptoms of inflammatory arthritis, or they may not report lower back pain and stiffness unless specifically asked about these symptoms. Sacroiliac imaging studies can be used to screen for evidence of joint inflammation. Patients with anterior uveitis who have possible symptoms of inflammatory arthritis or enthesitis may be referred to a rheumatologist for further evaluation. Pulmonary apical fibrosis and cardiovascular disease (aortic valvular insufficiency) can also occur in AS.

Early diagnosis of AS is important because nonpharmacologic interventions such as exercise, physical therapy, and smoking cessation may help slow disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line systemic treatment for AS. Sulfasalazine may be used for joint disease not controlled with NSAIDs and may reduce the frequency of uveitis recurrences. However, TNF inhibitors are gaining favor as second-line treatment because of their rapid therapeutic effect, overall efficacy, and side effect profile.

Ahn SM, Kim M, Kim YJ, Lee Y, Kim YG. Risk of Acute Anterior Uveitis in Ankylosing Spondylitis According to the Type of Tumor Necrosis Factor-Alpha Inhibitor and History of Uveitis: A Nationwide Population-Based Study. *J Clin Med.* 2022;11(3):631. doi:10.3390/jcm11030631

Chung YM, Liao HT, Lin KC, et al. Prevalence of spondyloarthritis in 504 Chinese patients with HLA-B27-associated acute anterior uveitis. *Scand J Rheumatol.* 2009;38(2):84–90.

Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). *Ann Rheum Dis.* 2015;74(11):1990–1995.

Reactive arthritis Reactive arthritis (formerly, Reiter syndrome) consists of the classic diagnostic triad of nonspecific urethritis, polyarthritis, and conjunctival inflammation, sometimes accompanied by nongranulomatous anterior uveitis. The HLA-B27 allele is found in approximately 50%–75% of patients with reactive arthritis. The condition constitutes less than 2% of all types of spondyloarthritis and occurs most frequently in young adult men, although 10% of patients are female.

Episodes of diarrhea or dysentery without urethritis can trigger reactive arthritis. *Ureaplasma urealyticum,* as well as *Chlamydia, Shigella, Salmonella,* and *Yersinia* species have all been implicated as triggering infections, although pathogens cannot be isolated from affected joints. Arthritis begins within 30 days of infection in 80% of patients. The knees, ankles, feet, and wrists are affected asymmetrically and in an oligoarticular (4 or fewer joints) distribution. Sacroiliitis is present in as many as 70% of patients.

In addition to the classic triad, 2 other conditions are considered major diagnostic criteria:

- keratoderma blennorrhagicum: a scaly, erythematous, irritating disorder of the palms and soles of the feet (Fig 8-4)
- circinate balanitis: a persistent, scaly, erythematous, circumferential rash of the distal penis

Extraarticular findings such as nail bed pitting, oral ulcers, conjunctivitis, uveitis, and constitutional symptoms help establish a diagnosis of reactive arthritis. Most cases resolve after a short episode. Occasionally, the disease becomes chronic.

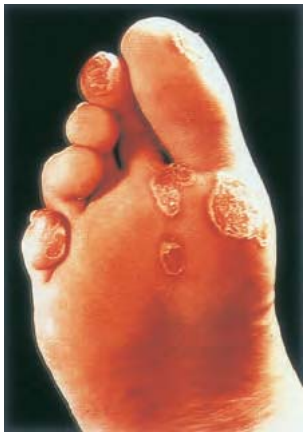

Figure 8-4 Reactive arthritis with pedal discoid keratoderma blennorrhagicum. *(Courtesy of John D. Sheppard Jr, MD.)*

Eye involvement occurs in approximately 20% of cases. Conjunctivitis, the most common ocular finding associated with this disease, is usually mucopurulent and papillary. Punctate and subepithelial keratitis may also occur, occasionally leaving permanent corneal scars. Acute nongranulomatous anterior uveitis occurs in up to 10% of affected patients and may become bilateral and chronic.

Inflammatory bowel disease–related arthritis Acute nongranulomatous anterior uveitis develops in up to 12% of patients with ulcerative colitis and 2.4% of patients with Crohn disease. Occasionally, bowel disease is asymptomatic and follows the onset of uveitis. Twenty percent of patients with inflammatory bowel disease (IBD) have sacroiliitis; of these, 60% are HLA-B27 positive. Patients with both acute anterior uveitis and IBD are more likely to be HLA-B27 positive and have sacroiliitis. Patients with IBD may also develop sclerouveitis, but they are usually HLA-B27 negative and do not develop sacroiliitis, although they can have rheumatoid arthritis–like symptoms. HLA-B27–negative patients with IBD are also more likely to develop intermediate uveitis.

Psoriatic arthritis The diagnosis of psoriatic arthritis is based on the presence of typical cutaneous changes (Fig 8-5), distal interphalangeal joint inflammation (Fig 8-6), and ungual involvement. Twenty percent of patients have sacroiliitis, and IBD occurs more frequently than would be expected by chance. Up to 25% of patients develop anterior uveitis, which tends to be insidious and bilateral; it is also more likely to be chronic compared with the uveitis associated with other types of spondyloarthritis, and the risk is highest in patients with psoriatic spondylitis. Uveitis may be more severe in HLA-B27–positive patients. Treatment consists of cycloplegic and mydriatic agents and corticosteroids, which are usually given topically. In severe cases, periocular or systemic corticosteroids may be required, and chronic cases may need systemic IMT.

Anterior uveitis in patients with psoriasis without arthritis has distinct clinical features. The mean age at onset is older than in idiopathic or HLA-B27–associated uveitis,

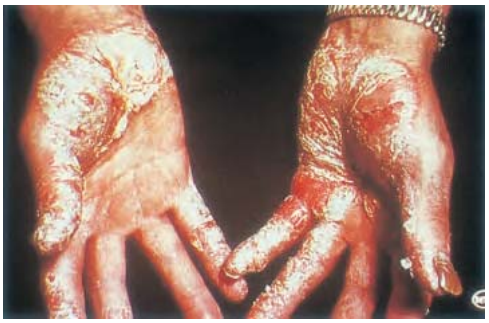

Figure 8-5 Psoriatic arthritis with classic erythematous, hyperkeratotic rash. *(Courtesy of John D. Sheppard Jr, MD.)*

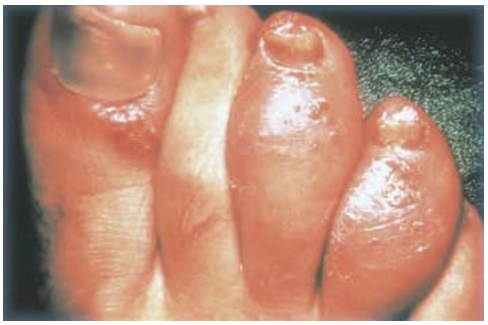

Figure 8-6 Psoriatic arthritis. The patient has "sausage" digits resulting from tissue swelling and distal interphalangeal joint inflammation. *(Courtesy of John D. Sheppard Jr, MD.)*

and the uveitis may be bilateral and of longer duration. Posterior segment involvement can be present.

Egeberg A, Khalid U, Gislason GH, Mallbris L, Skov L, Hansen PR. Association of psoriatic disease with uveitis: a Danish nationwide cohort study. *JAMA Dermatol.* 2015;151(11): 1200–1205.

Köse B, Uzlu D, Erdöl H. Psoriasis and uveitis. *Int Ophthalmol.* 2022;42(7):2303–2310. doi:10.1007/s10792-022-02225-5

Sampaio-Barros PD, Pereira IA, Hernández-Cuevas C, et al; RESPONDIA Group. An analysis of 372 patients with anterior uveitis in a large Ibero-American cohort of spondyloarthritis: the RESPONDIA Group. *Clin Exp Rheumatol.* 2013;31(4):484–489.

Tubulointerstitial nephritis and uveitis syndrome

Tubulointerstitial nephritis and uveitis (TINU) syndrome was originally described as anterior uveitis and renal inflammation occurring predominantly in adolescent girls and women up to their early 30s. It is now recognized that TINU has a variety of ophthalmic manifestations and occurs across a wide age range, with a median age at onset of 15 years. The associated anterior uveitis is typically acute, bilateral and nongranulomatous; it may be recurrent. Ocular symptoms and findings are more severe in patients with recurrent disease, with development of fibrin, posterior synechiae, larger KPs, and in rare cases, hypopyon. Posterior segment involvement may include vitritis, multifocal chorioretinal lesions or scars (Fig 8-7), and retinal vascular leakage, as well as optic disc and macular edema.

In many cases, systemic symptoms precede the development of uveitis. However, patients may be asymptomatic or develop systemic symptoms and tubulointerstitial nephritis

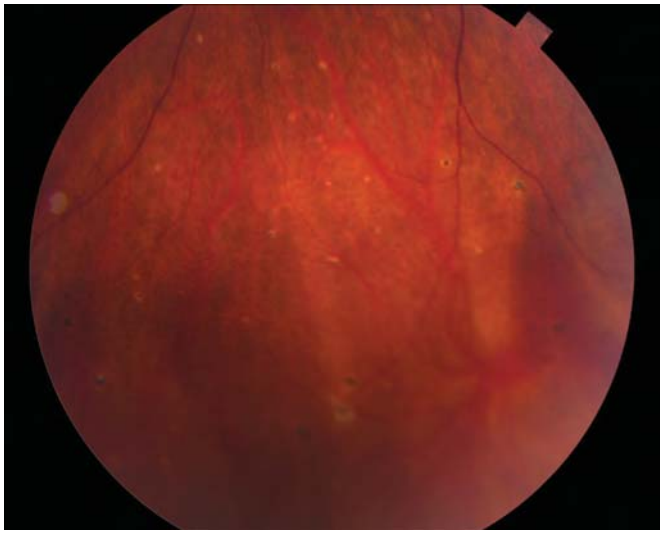

Figure 8-7 Tubulointerstitial nephritis–associated uveitis with chorioretinal scars in the peripheral retina. *(Courtesy of Debra A. Goldstein, MD.)*

after the onset of uveitis. The following findings are required for a clinical diagnosis of TINU syndrome:

- abnormal serum creatinine level or decreased creatinine clearance
- abnormal urinalysis findings, with increased β_2-microglobulin level, proteinuria, presence of eosinophils, pyuria or hematuria, urinary white cell casts, and normoglycemic glycosuria
- associated systemic illness, consisting of fever, weight loss, anorexia, fatigue, arthralgias, and myalgias; there may also be abnormal liver function, eosinophilia, and an elevated erythrocyte sedimentation rate

The etiology remains unclear. The syndrome has been reported to be strongly associated with HLA-DRB1*01:02. The predominance of activated $CD4^+$ (helper) T lymphocytes in the kidney interstitium suggests a role for cellular immunity. Renal biopsies have shown severe interstitial fibrosis. Seroreactivity against retinal and renal antigens has been demonstrated. Infection and drug reaction are among the potential triggers. Flares of renal disease do not occur simultaneously with ocular flares.

Initially, TINU syndrome is very responsive to treatment with high-dose oral corticosteroids. The renal disease tends to resolve over time, but ocular inflammation can be chronic and require systemic IMT.

Ali A, Rosenbaum JT. TINU (tubulointerstitial nephritis uveitis) can be associated with chorioretinal scars. *Ocul Immunol Inflamm.* 2014;22(3):213–217.

Koreishi AF, Zhou M, Goldstein DA. Tubulointerstitial nephritis and uveitis syndrome: characterization of clinical features. *Ocul Immunol Inflamm.* 2021;29(7–8):1312–1317.

Okafor LO, Hewins P, Murray PI, Denniston AK. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a systematic review of its epidemiology, demographics, and risk factors. *Orphanet J Rare Dis.* 2017;12(1):128.

Pakzad-Vaezi K, Pepple KL. Tubulointerstitial nephritis and uveitis. *Curr Opin Ophthalmol.* 2017;28(6):629–635.

Glaucomatocyclitic crisis

Glaucomatocyclitic crisis (also known as *Posner-Schlossman syndrome*) usually manifests as a recurrent unilateral, acute, mild nongranulomatous anterior uveitis associated with markedly elevated IOP. Symptoms are vague: discomfort, blurred vision, and halos. In addition to elevated IOP, signs include corneal edema, small KPs, low-grade anterior chamber inflammation, and a slightly dilated pupil. Episodes last from several hours to several days, and recurrences are common over many years. An increase in KPs is often noted with recurrences.

Recent studies suggest ocular cytomegalovirus (CMV) infection as a possible cause of glaucomatocyclitic crisis, with specific genotypes of CMV associated with anterior uveitis versus retinitis. Corneal endotheliitis, linear KPs, and male preponderance are more common in CMV-associated glaucomatocyclitic crisis. Polymerase chain reaction testing can be performed on aqueous humor to confirm the presence of CMV DNA; there may be a role for antiviral therapy in such cases. See BCSC Section 10, *Glaucoma,* for additional discussion.

Traditionally, treatment for acute inflammation has been topical corticosteroids and antiglaucoma medications, including systemic carbonic anhydrase inhibitors, if necessary. Long-term surveillance may be required in addition to careful IOP monitoring.

Chee SP, Jap A. Presumed Fuchs heterochromic iridocyclitis and Posner-Schlossman syndrome: comparison of cytomegalovirus-positive and negative eyes. *Am J Ophthalmol.* 2008;146(6):883–889.

Oka N, Suzuki T, Inoue T, Kobayashi T, Ohashi Y. Polymorphisms in cytomegalovirus genotype in immunocompetent patients with corneal endotheliitis or iridocyclitis. *J Med Virol.* 2015;87(8):1441–1445.

Lens-associated uveitis

Although the exact mechanism is unknown, an immune reaction to lens material may result in ocular inflammatory disease, including acute nongranulomatous anterior uveitis (Table 8-1).

Phacoantigenic uveitis Phacoantigenic uveitis (also called *phacoantigenic glaucoma*) was previously termed *phacoanaphylactic uveitis,* which was a misnomer because none of the mediators of anaphylaxis (ie, immunoglobulin E, mast cells, and basophils) are present in the eye. Phacoantigenic uveitis is an ocular inflammation that occurs after disruption of the lens capsule (traumatic or surgical) in patients previously sensitized to lens protein, for example, as a result of cataract extraction in the fellow eye; this inflammation may occur within 24 hours of capsular rupture.

Clinically, patients exhibit an anterior uveitis that may be granulomatous or nongranulomatous (Fig 8-8). Small or large KPs are usually present. Anterior chamber reaction varies from mild (eg, postoperative inflammation involving a small amount of retained lens cortex) to severe (eg, traumatic lens capsule disruption); hypopyon may be present. Posterior synechiae are common, and IOP is often elevated. Inflammation in the anterior vitreous cavity is common, but fundus lesions do not occur.

Histologically, a zonal granulomatous inflammation is present at the site of lens injury. Neutrophils are clustered around the lens material with surrounding lymphocytes, plasma cells, epithelioid cells, and occasional giant cells.

Table 8-1 Lens-Induced Uveitis

	Etiology	Clinical Features	Treatment
Phacoantigenic uveitis	Disrupted lens capsule (as a result of surgery, trauma)	Red eye, anterior chamber cells and flare, keratic precipitates, posterior synechiae, elevated IOP	Topical or systemic corticosteroids Removal of lens material
Phacolytic uveitis	Leakage of lens protein through intact capsule	Elevated IOP, anterior chamber cell and flare, refractile bodies, mature/hypermature cataract	Reduction of IOP Cataract surgery

IOP = intraocular pressure.

Treatment consists of topical and in severe cases, systemic corticosteroids, as well as cycloplegic and mydriatic agents. Surgical removal of all lens material is usually curative. When small amounts of lens material remain, corticosteroid therapy alone may be sufficient to allow resorption of the inciting material. It is important to differentiate this inflammatory process from postoperative infectious endophthalmitis. Visual outcomes can deteriorate rapidly in patients with infectious endophthalmitis if the infection is not treated quickly and aggressively.

Phacolytic uveitis Phacolytic uveitis (or *phacolytic glaucoma*) is due to leakage of lens protein through microscopic openings in the intact lens capsule of a mature or hypermature cataract (Fig 8-9). Macrophages engorged with lens proteins clog the trabecular meshwork and cause an acute increase in IOP. Refractile bodies (lipid-laden macrophages) can be seen in the aqueous, but KPs and synechiae are often absent. Therapy includes IOP reduction, often through use of osmotic agents and topical medications, followed quickly by cataract extraction. See BCSC Section 10, *Glaucoma*, for additional discussion and images of phacolytic glaucoma.

Nche EN, Amer R. Lens-induced uveitis: an update. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(7):1359–1365.

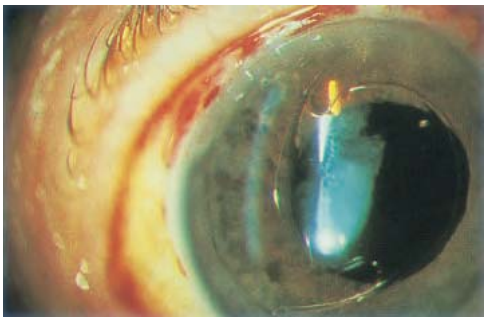

Figure 8-8 Low-grade postoperative uveitis in this patient could be secondary to retained lens cortex or to the anterior chamber intraocular lens (IOL). *(Courtesy of John D. Sheppard Jr, MD.)*

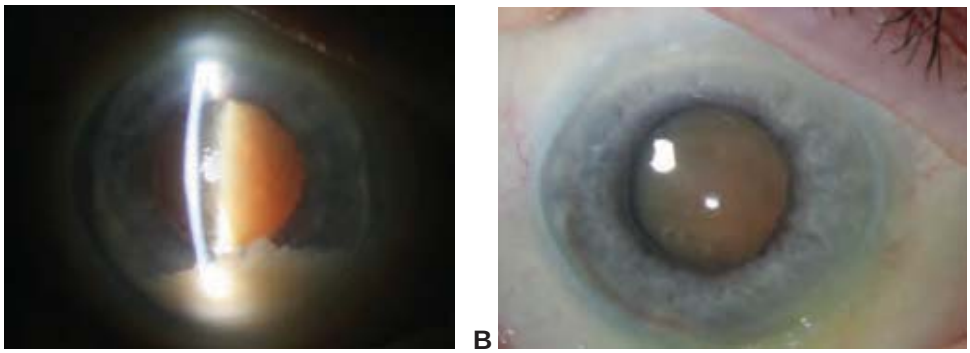

Figure 8-9 Phacolytic uveitis. **A,** Phacolytic uveitis with glaucoma, corneal edema, anterior uveitis, and pseudohypopyon in a patient with hypermature cataract. **B,** Resolution of anterior chamber inflammation with intense topical corticosteroid use; the patient eventually required cataract surgery. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

Postoperative inflammation: infectious endophthalmitis

Infectious endophthalmitis must be included in the differential diagnosis of postoperative inflammation, especially in the presence of hypopyon. Delayed or late-onset endophthalmitis may be caused by infection with low-virulence organisms such as *Cutibacterium acnes* (formerly, *Propionibacterium acnes*) and *Staphylococcus epidermidis,* as well as with fungal species. Chronic postoperative endophthalmitis is discussed in more detail in Chapter 14. See BCSC Section 12, *Retina and Vitreous,* for information about acute postoperative endophthalmitis.

Postoperative inflammation: intraocular lens–associated uveitis

All forms of surgical manipulation result in a breakdown of the blood–aqueous barrier, leading to vulnerability in the early postoperative period. Intraocular lens (IOL) implantation can activate complement cascades and promote neutrophil chemotaxis. This leads to cellular deposits on the IOL, synechiae formation, capsular opacification, and anterior capsule phimosis. Residual lens material can exacerbate the typically transient postoperative inflammation.

In general, the more biocompatible the IOL material, the less likely it is to incite an inflammatory response. Irregular or damaged IOL surfaces and polypropylene haptics have been associated with enhanced bacterial and leukocyte binding and should be avoided in patients with a preoperative diagnosis of uveitis. Acrylic IOLs appear to have excellent biocompatibility, with low rates of cellular deposits and capsular opacification.

IOL-associated uveitis can occur when chafing of the anterior or posterior surface of the iris by the edges or loops of an IOL causes mechanical irritation and inflammation. This uveitis ranges from mild inflammation to the uveitis-glaucoma-hyphema (UGH) syndrome.

The motion of an iris-supported IOL or anterior chamber IOL (ACIOL) can cause intermittent corneal touch and lead to corneal edema due to endothelial damage. Other ocular complications from IOL contact with anterior chamber structures include low-grade anterior uveitis, peripheral anterior synechiae, recurrent microhyphema, recalcitrant glaucoma, and macular edema (Fig 8-10). UGH syndrome and corneal decompensation are more likely to develop with older rigid ACIOLs versus newer ACIOLs and scleral-fixated IOLs. ACIOLs should be removed and exchanged when penetrating keratoplasty is performed.

Because ACIOL use is rare, UGH syndrome is encountered most commonly with unintentional sulcus placement of a single-piece hydrophobic acrylic IOL. UGH or IOL-associated uveitis can occur even with appropriate IOL placement; the IOL-capsule complex may be mobile, as for example in eyes with pseudoexfoliation syndrome. In cases of chronic pseudophakic uveitis, ultrasound biomicroscopy or anterior segment optical coherence tomography (OCT) can be used to evaluate the IOL position (Fig 8-11). Many cases can be managed with topical corticosteroids and/or cycloplegia, although some may require IOL repositioning or explantation. UGH syndrome and chronic uveitis are also discussed in BCSC Section 11, *Lens and Cataract.*

Ozdal PC, Mansour M, Deschênes J. Ultrasound biomicroscopy of pseudophakic eyes with chronic postoperative inflammation. *J Cataract Refract Surg.* 2003;29(6):1185–1191.

Patel C, Kim SJ, Chomsky A, Saboori M. Incidence and risk factors for chronic uveitis following cataract surgery. *Ocul Immunol Inflamm.* 2013;21(2):130–134.

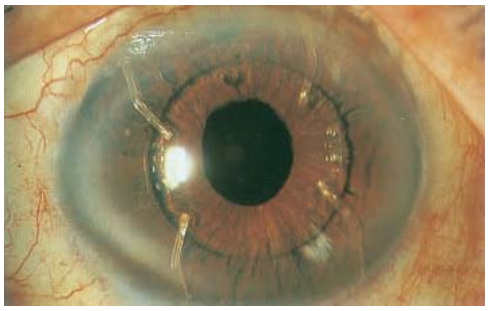

Figure 8-10 Fixed-haptic anterior chamber IOL associated with peripheral and superior corneal edema, chronic low-grade anterior uveitis, peripheral anterior synechiae, and intermittent microhyphema. *(Courtesy of John D. Sheppard Jr, MD.)*

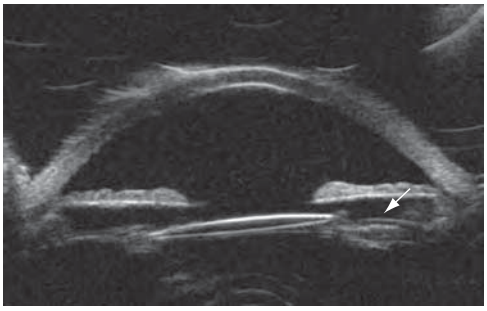

Figure 8-11 Evaluation of a patient who developed chronic anterior uveitis and macular edema after cataract surgery with IOL implantation. Ultrasound biomicroscopy shows a 1-piece posterior chamber IOL that is tilted with 1 haptic *(arrow)* in the sulcus. Clinically, an iris transillumination defect was observed overlying the haptic in the sulcus (not shown in the image). *(Courtesy of Wendy M. Smith, MD.)*

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):1609–1615.

Taravati P, Lam DL, Leveque T, Van Gelder RN. Postcataract surgical inflammation. *Curr Opin Ophthalmol*. 2012;23(1):12–18.

Zhang L, Hood CT, Vrabec JP, Cullen AL, Parrish EA, Moroi SE. Mechanisms for in-the-bag uveitis-glaucoma-hyphema syndrome. *J Cataract Refract Surg*. 2014;40(3):490–492.

CLINICAL PEARL

For patients with persistent anterior uveitis following cataract surgery and IOL implantation:

- Assess for retained lens fragments.
- Evaluate for iris chafing even if the IOL is in the capsule.
- Investigate infectious causes, including *C acnes.*
- Use topical corticosteroids, tapered very slowly, to try to control the inflammation.
- Employ systemic IMT if necessary (only after infectious causes have been sufficiently investigated).

Drug-induced ocular inflammation

It is important to identify cases of drug-induced ocular inflammation, which is rare, because discontinuation of the offending agent may be curative. The causal relationship between a medication and an adverse reaction (eg, ocular inflammation) can be graded by using the Naranjo Algorithm, or Adverse Drug Reaction Probability Scale, which consists of 10 questions inquiring about the frequency of the patient's reaction and whether the reaction resolved with discontinuation of medication, worsened with dose increase,

and recurred with medication rechallenge. Point values are given to each response, and the total score indicates whether the reaction is definite, probable, possible, or doubtful. Medications associated with ocular inflammation include systemic, intravitreal, and topical formulations, as well as vaccines.

The systemic medications most strongly associated with ocular inflammation, including anterior uveitis, are the antiviral cidofovir and the antibiotic rifabutin (used in the treatment of *Mycobacterium avium* complex [*M avium-Mycobacterium intracellulare* infection]). Bisphosphonates (eg, pamidronate, alendronate) are highly associated with scleritis and uveitis. Systemic medications that are moderately associated with uveitis include systemic fluoroquinolones (especially moxifloxacin, which may induce iris depigmentation and uveitis), sulfonamides, and diethylcarbamazine (an antifilarial drug). Paradoxically, some TNF inhibitors (eg, etanercept, adalimumab) have also been associated with new-onset uveitis, psoriasis-like rash (Fig 8-12), and a systemic sarcoid-like syndrome. Vaccines such as BCG vaccine and influenza vaccines, as well as the purified protein derivative used in the tuberculin skin test, have been implicated in the development of uveitis. Intravesical BCG vaccine (sometimes used in the treatment of bladder cancer) can result in uveitis that may be immune mediated or infectious. More recently, cancer immunotherapy, particularly with immune checkpoint inhibitors (Fig 8-13), has been associated with a spectrum of intraocular inflammation—ranging from mild anterior uveitis to retinal vasculitis, choroiditis, and Vogt-Koyanagi-Harada syndrome–like panuveitis.

Numerous topical ocular hypotensive medications have been associated with uveitis, including brimonidine (α_2-adrenergic agonist), pilocarpine, and prostaglandin $F_{2\alpha}$ analogues.

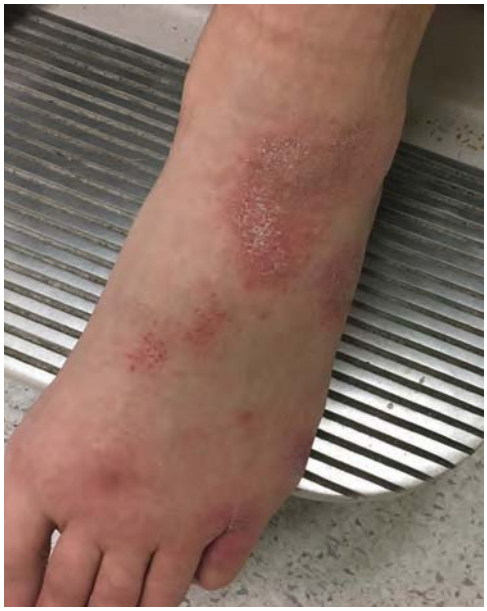

Figure 8-12 Adalimumab-induced psoriasis-like rash on the dorsal surface of the left foot of a young patient with chronic pars planitis. The rash resolved after discontinuation of the drug.

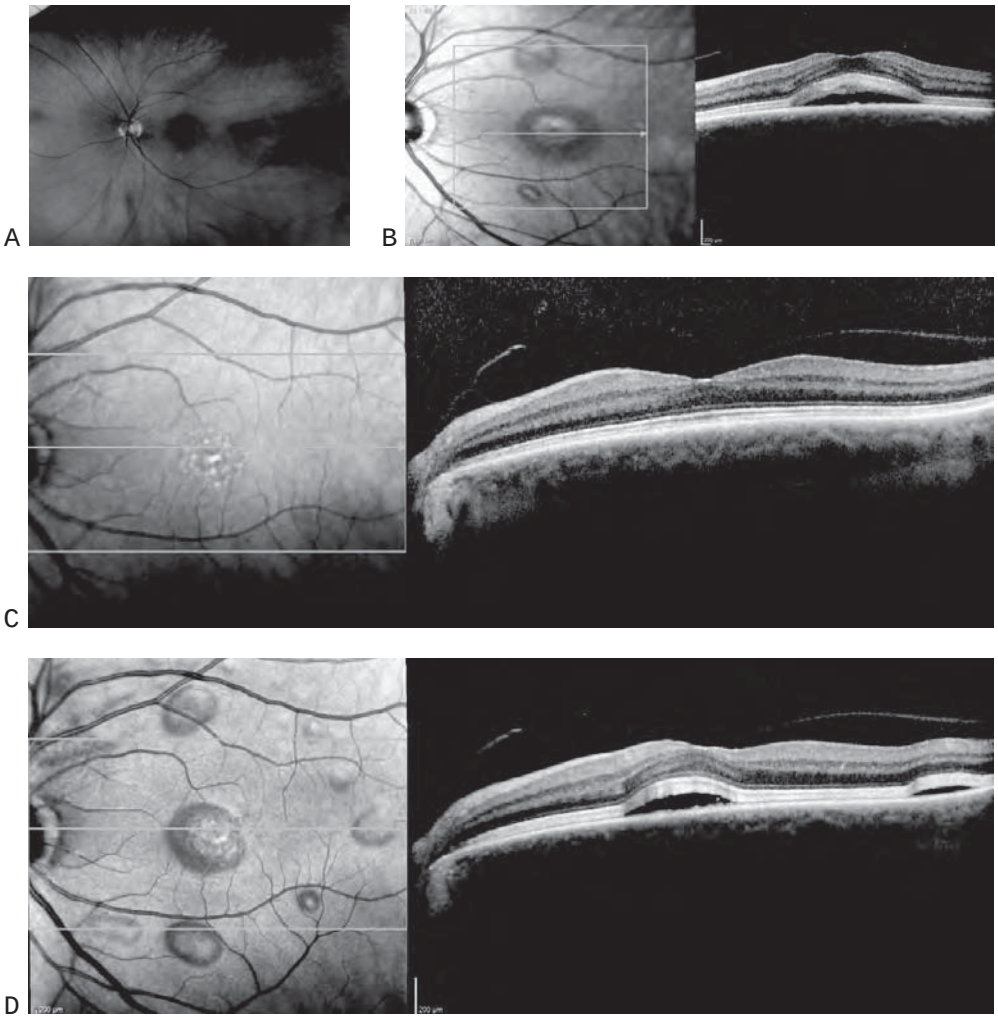

Figure 8-13 Immune checkpoint inhibitor (nivolumab)–induced Vogt-Koyanagi-Harada syndrome–like panuveitis in a patient with metastatic melanoma. **A, B,** Subretinal fluid noted on optical coherence tomography, despite relatively unremarkable fundus findings. **C,** Fluid resolved with periocular corticosteroids, but residual retinal pigment epithelium changes were noted on infrared imaging *(left).* **D,** There was recurrence when the next cycle of anticancer treatment was started. *(Courtesy of Bryn M. Burkholder, MD, and H. Nida Sen, MD.)*

A common presentation of brimonidine-associated uveitis is a red and irritated eye with extensive (often granulomatous) KPs and low-grade anterior uveitis in a patient receiving long-term brimonidine therapy. Corneal edema and vitreous inflammation may also be present. While prostaglandin analogues have been reported to induce or worsen macular edema, this adverse effect is rare; therefore, these glaucoma drops can be used in patients with uveitis when other medications are not sufficient to lower IOP.

Intravitreal medications associated with uveitis include antibiotics, urokinase (a plasminogen activator), cidofovir (a cytosine analogue effective against CMV), and vascular endothelial growth factor (VEGF) inhibitors (brolucizumab, aflibercept).

Treatment of drug-induced ocular inflammation often includes temporarily discontinuing the offending agent. If the inflammation is primarily anterior uveitis, topical corticosteroids can be effective. Scleritis and higher-grade uveitis or inflammation involving the posterior segment may require oral corticosteroids. If inflammation is vision threatening or recurs with medication rechallenge, the causative medication may need to be discontinued.

Conrady CD, Larochelle M, Pecen P, Palestine A, Shakoor A, Singh A. Checkpoint inhibitor-induced uveitis: a case series. *Graefes Arch Clin Exp Ophthalmol.* 2018;256(1):187–191.

Cunningham ET Jr, Pasadhika S, Suhler EB, Zierhut M. Drug-induced inflammation in patients on TNF-α inhibitors. *Ocul Immunol Inflamm.* 2012;20(1):2–5.

Horsley MB, Chen TC. The use of prostaglandin analogs in the uveitic patient. *Semin Ophthalmol.* 2011;26(4–5):285–289.

Moorthy RS, London NJ, Garg SJ, Cunningham ET Jr. Drug-induced uveitis. *Curr Opin Ophthalmol.* 2013;24(6):589–597.

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239–245.

Chronic Anterior Uveitis

Inflammation of the anterior segment that is persistent and relapses less than 3 months after discontinuation of therapy is termed *chronic anterior uveitis;* it may persist for years. This type of inflammation usually starts insidiously, with variable amounts of redness, discomfort, and photophobia. Some patients have no symptoms. The disease can be unilateral or bilateral, and the amount of inflammatory activity is variable. Uveitic macular edema, cataract progression, and secondary glaucoma are common complications. Common causes of chronic anterior uveitis include juvenile idiopathic arthritis–associated uveitis in children and sarcoidosis in adults. See Chapter 10 for further discussion of sarcoidosis.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA; formerly called *juvenile chronic arthritis* and *juvenile rheumatoid arthritis*) is the most common systemic disease associated with anterior uveitis in the pediatric age group. It is characterized by arthritis beginning before age 16 years and lasting for at least 6 weeks.

JIA subtypes and ocular involvement According to International League of Associations for Rheumatology guidelines, JIA can be classified into 7 subtypes on the basis of number of joints involved, extra-articular manifestations, and laboratory markers of antinuclear antibody (ANA) and HLA-B27 seropositivity:

- *Oligoarticular arthritis.* This subtype, previously called *pauciarticular onset,* accounts for 50%–60% of all cases of JIA and 60% of cases of JIA-associated uveitis. Four or fewer joints may be involved during the first 6 months of disease, and patients may have no joint symptoms. In 25%–35% of these patients, uveitis develops, with most cases occurring in the first 4 years after JIA diagnosis. Girls younger than 5 years who are positive for ANA are at increased risk of developing chronic anterior uveitis.

- *RF-negative, polyarticular arthritis.* This subtype represents 10%–30% of JIA cases and approximately 20% of cases of JIA-associated chronic anterior uveitis. Patients show involvement of more than 4 joints in the first 6 months of the disease.
- *RF-positive, polyarticular arthritis.* This subtype accounts for 2%–7% of JIA cases. Patients show involvement of more than 4 joints in the first 6 months of the disease. Individuals who are positive for RF may not develop uveitis.
- *Psoriatic arthritis* (or *psoriatic JIA*). This subtype accounts for approximately 2%–15% of JIA cases and 7% of JIA-associated chronic anterior uveitis.
- *Enthesitis-related arthritis (ERA).* ERA represents 1%–7% of JIA cases and approximately 8% of JIA-associated acute anterior uveitis. Enthesitis, axial disease, and HLA-B27 positivity are common. Compared with the course of uveitis in other JIA subtypes, uveitis in these patients is more likely to be acute and recurrent, with pain, redness, and photophobia.
- *Systemic arthritis (Still disease).* This subtype, usually found in children younger than 5 years, accounts for approximately 10%–20% of all JIA cases. It is characterized by fever, evanescent rash, lymphadenopathy, and hepatosplenomegaly. Joint involvement may be minimal or absent initially. Uveitis is rare.
- Undifferentiated. Cases are categorized as undifferentiated when they do not meet criteria for one of the categories listed here or when they meet criteria for more than one category.

See also BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* Chapter 25 for additional information.

Children with JIA, especially those who are ANA positive or who have oligoarticular disease, should undergo regular slit-lamp examinations. Table 8-2 outlines the schedule for screening eye examinations in patients with JIA as recommended by the American College of Rheumatology/Arthritis Foundation in 2019.

The average age at onset of uveitis in patients with JIA is 6 years. Uveitis generally develops within 5–7 years of the onset of joint disease but may occur as long as 28 years after the development of arthritis. There is usually little or no correlation between severity or timing of ocular and joint inflammation. Most patients test negative for RF. HLA-DRB1*11 and *13 may be associated with increased risk of uveitis among patients with JIA.

Table 8-2 Uveitis Screening Schedule for Patients With JIA

Eye examination every 3 months for patients with the following characteristics:

- oligoarthritis or undifferentiated
- ANA positive
- JIA onset before age 7 years
- JIA diagnosis for 4 years or less

Eye examination every 6–12 months for patients without the characteristics listed above.

ANA = antinuclear antibody; JIA = juvenile idiopathic arthritis.

Adapted from Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken).* 2019;71(6):703–716.

In JIA-associated uveitis, the eyes are frequently white and asymptomatic. The eye disease may be found incidentally on routine examination. When they occur, symptoms may include mild to moderate pain, photophobia, and blurred vision. Signs of inflammation include fine KPs, band keratopathy, anterior chamber cells and flare, posterior synechiae, and cataract (Fig 8-14). When JIA is suspected, ANA, RF, and HLA-B27 testing can be performed in addition to evaluation by a pediatric rheumatologist, as the joint disease may be minimal or absent at the time of uveitis diagnosis. The differential diagnosis includes TINU, Fuchs uveitis syndrome, sarcoidosis, Blau syndrome, Behçet disease, seronegative spondyloarthritis, and herpetic uveitis.

Angeles-Han ST, Pelajo CF, Vogler LB, et al; and the CARRA Registry Investigators. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. *J Rheumatol.* 2013;40(12):2088–2096.

Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. *Rheum Dis Clin North Am.* 2007;33(3): 441–470, vi.

Prognosis Because the uveitis is frequently asymptomatic, profound ocular damage can occur. The long-term prognosis often depends on the extent of structural complications at the time of diagnosis. Sequelae of inflammation are frequent and often severe; they include band keratopathy, cataract, glaucoma, macular edema, chronic hypotony, and phthisis bulbi.

Treatment of JIA-associated uveitis The American College of Rheumatology and the Arthritis Foundation expert panels developed evidence-based recommendations for the screening, treatment, and monitoring of JIA-associated anterior uveitis. As mentioned previously, Table 8-2 summarizes screening recommendations. In general, the goal of treatment is to eliminate active inflammation and prevent the development of new complications. Although topical corticosteroids may be used initially, long-term use of topical treatment increases the risk of complications such as corticosteroid-induced glaucoma and cataract formation. There is evidence that even low-grade inflammation, when present for a prolonged period, can result in unacceptable ocular morbidity and vision loss. Therefore, if topical corticosteroids cannot be tapered to a frequency of 2 times daily or less, if steroid-induced ocular hypertension develops, or if the ocular inflammation is severe, there is a low threshold to begin systemic treatment. Systemic corticosteroids may be used in the

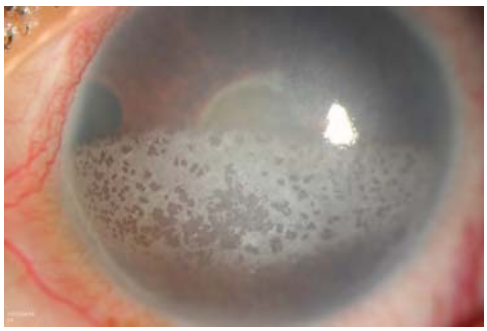

Figure 8-14 JIA-associated uveitis with complicated chronic calcific band keratopathy, cataract, and glaucoma in a patient with peripheral iridectomy superonasally. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

short term; however, children are uniquely at risk for growth retardation from premature closure of the epiphyses, so corticosteroid-sparing systemic IMT is usually necessary.

To reduce the risk of complications of treatment and inflammation, the clinician should maintain a low threshold for beginning an antimetabolite such as methotrexate (MTX) in children with JIA-associated chronic anterior uveitis. Numerous studies have shown that this treatment approach can effectively control the uveitis, is generally well tolerated, and can spare patients the complications of long-term corticosteroid use. If uveitis is not adequately controlled with MTX, the TNF inhibitor adalimumab is often prescribed in addition to the antimetabolite. See Chapter 6 for discussion of the SYCAMORE trial, which demonstrated that there was significant improvement in the control of JIA-associated uveitis with the addition of adalimumab to MTX. Although etanercept can effectively treat the joint inflammation associated with JIA, it is usually not effective for JIA-associated uveitis.

In patients with chronic anterior chamber flare, short-acting mydriatic drugs may be useful to keep the pupil mobile and to prevent posterior synechiae formation. Use of systemic NSAIDs may permit a lower dose of corticosteroids. Treatment of JIA-associated uveitis is usually prolonged (ie, years) due to the chronic nature of the inflammatory disease. Patients with inactive uveitis (or <1+ anterior chamber cells) should be monitored every 3 months, unless tapering or discontinuing treatment. Patients should be seen at least 1 month after each change in topical medication, and within 2 months of changing systemic treatment.

Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken).* 2019;71(6):703–716.

Gregory AC 2nd, Kempen JH, Daniel E, et al; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Research Group. 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):186–192.

Horton S, Jones AP, Guly CM, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE trial. *Am J Ophthalmol.* 2019;207:170–174.

Mehta PJ, Alexander JL, Sen HN. Pediatric uveitis: new and future treatments. *Curr Opin Ophthalmol.* 2013;24(5):453–462.

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.* 2020;127(4S):S21–S26.

Zannin ME, Birolo C, Gerloni VM, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol.* 2013;40(1):74–79.

Management of cataract Cataract surgery in patients with JIA remains a challenge. There is a high risk of complications due to the difficulty controlling the more aggressive inflammatory response present in these children. However, good visual outcomes can be attained if uveitis is meticulously controlled before cataract surgery as well as during the postoperative period. Band keratopathy should be treated using chelation with sodium

EDTA, and the cornea should be well healed before cataract surgery is attempted. Pars plana lensectomy with removal of the lens complex and anterior vitreous has been advocated to avoid posterior capsule opacification.

Because children who are left aphakic may develop amblyopia, it may be appropriate to place an IOL in some cases. For patients with JIA-associated uveitis who receive an IOL implant at the time of cataract surgery, it is important for the clinician to do the following:

- Ensure that uveitis is well controlled for at least 3 months before surgery without the need for frequent topical corticosteroids or high-dose systemic corticosteroids.
- Use systemic IMT preoperatively and postoperatively, not just perioperatively.
- Place an acrylic lens in the capsular bag whenever possible.
- Monitor patients frequently after cataract surgery and treat postoperative inflammation aggressively.
- Maintain a low threshold for IOL explantation in patients with chronic postoperative inflammation and recurrent cyclitic membranes.
- Strongly advise patients about the need for lifelong follow-up to detect late complications.

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):657–662.

Management of glaucoma Glaucoma should be treated with medical therapy initially, although surgical intervention is often necessary in severe cases. Standard filtering procedures are usually unsuccessful, and the use of antifibrotic drugs or aqueous drainage devices is usually required for successful IOP control. See Chapter 16 in this volume and BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for further discussion of treatment of band keratopathy, pediatric cataract, and glaucoma.

Fuchs uveitis syndrome

Fuchs uveitis syndrome (sometimes called *Fuchs heterochromic iridocyclitis* or *Fuchs heterochromic uveitis*) accounts for 2%–3% of patient referrals to uveitis clinics. Studies have shown an association between Fuchs uveitis syndrome and several infectious agents, including rubella virus, CMV, and *Toxoplasma*. Fuchs uveitis syndrome is usually unilateral, and symptoms vary from none to mild blurred vision and ocular discomfort. Signs include

- heterochromia
- diffuse iris stromal atrophy with variable pigment epithelial layer atrophy (Fig 8-15)
- small, white, stellate KPs scattered diffusely over the entire endothelium (Fig 8-16A)
- iris nodules (Fig 8-16B)
- cells in the anterior chamber and anterior vitreous
- late staining of the optic nerve on fluorescein angiography (FA)
- glaucoma and cataract, which occur frequently

Posterior synechiae, chorioretinal scars, and retinal periphlebitis are rare or absent; likewise, macular edema is seldom present. Occasionally, patients may develop extensive vitreous opacification.

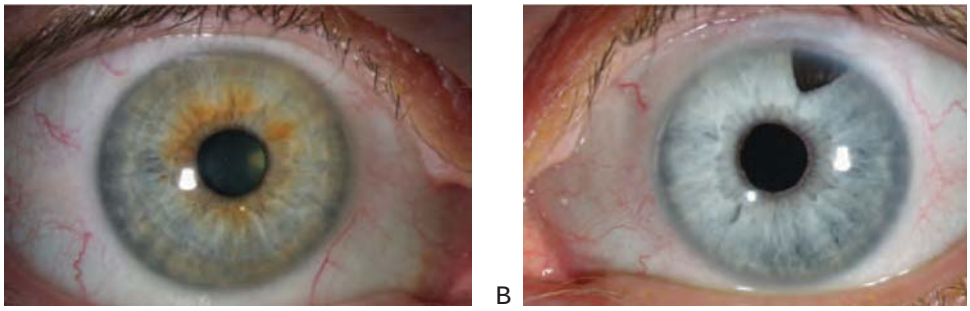

Figure 8-15 Heterochromia in Fuchs uveitis syndrome. **A,** Right (unaffected) eye. **B,** Left (affected) eye in the same patient. Note the lighter iris color and stromal atrophy ("moth-eaten appearance") in the affected eye, which underwent iridectomy at the same time as cataract surgery. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

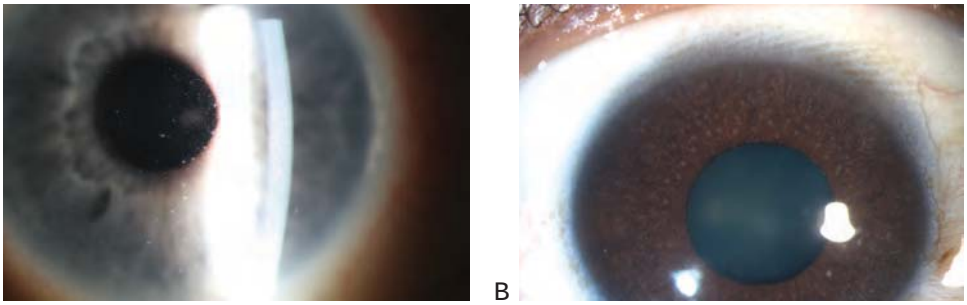

Figure 8-16 Fuchs uveitis syndrome. **A,** Diffusely distributed stellate keratic precipitates. **B,** Iris nodules have a "pasted on" appearance. *(Part A courtesy of H. Nida Sen, MD/National Eye Institute; part B courtesy of Wendy M. Smith, MD.)*

The diagnosis is made according to the distribution of KPs, presence of heterochromia, lack of synechiae, and minimal or no symptoms. The heterochromia may be subtle in brown eyes, and the clinician must look carefully for signs of iris stromal atrophy. Often, the inflammation is discovered during a routine examination, such as when a unilateral cataract develops. Usually, but not invariably, a lighter-colored iris indicates the involved eye. In patients with blue eyes, however, the affected eye may become darker as the stromal atrophy progresses and the darker iris pigment epithelium shows through.

Although topical corticosteroids can lessen the inflammation, they typically do not resolve it; thus, aggressive treatment to eradicate the cellular reaction is not indicated. Cycloplegia is usually unnecessary. Patients can have symptomatic exacerbations of uveitis that may be treated by restarting or increasing topical corticosteroids. Topical corticosteroids may also be used long-term to decrease the accumulation of KPs and inflammatory deposits on IOLs after cataract surgery. Glaucoma may be difficult to control, but otherwise the prognosis is good in most cases, even when the inflammation persists for decades.

Since the anterior chamber cellular reaction may not completely subside with treatment, cataract surgery and IOL implantation may be performed even if the eye has not

been quiet for at least 3 months. Abnormal vessels bridging the angle may bleed during surgery, resulting in postoperative hyphema. In general, however, outcomes are usually good after cataract surgery. Some patients may still experience substantial visual disability after surgery, because of diffuse KPs or extensive vitreous opacification; pars plana vitrectomy may be carefully considered for such patients. See BCSC Section 10, *Glaucoma,* for further discussion of Fuchs uveitis syndrome.

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. doi:10.1155/2016/1458624

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(3):424–428.

de Groot-Mijnes JD, de Visser L, Rothova A, Schuller M, van Loon AM, Weersink AJ. Rubella virus is associated with Fuchs heterochromic iridocyclitis. *Am J Ophthalmol.* 2006;141(1):212–214.

Undifferentiated anterior uveitis

In many cases of chronic anterior uveitis, it may not be possible to identify a cause. As long as infectious etiologies have been appropriately investigated, the uveitis should be treated with topical corticosteroids and/or cycloplegics, as well as systemic corticosteroids or IMT or both as needed. If the clinical picture evolves or new systemic signs or symptoms arise, additional diagnostic testing may be warranted. However, if the result of initial HLA-B27 testing was negative, this test does not need to be repeated.

Intermediate Uveitis

Intermediate uveitis accounts for up to 15% of all cases of uveitis. It is characterized by inflammatory cells and haze in the vitreous (see Chapter 5, Fig 5-7). Inflammation may also occur in the vitreous base overlying the ciliary body and peripheral retina–pars plana complex. Other signs may include *snowballs* (aggregates of inflammatory cells in the vitreous) and *snowbanks* (inflammatory exudative accumulation on the inferior pars plana). Snowbanks seem to correlate with a more severe disease process. Retinal phlebitis is often present peripherally or diffusely. Anterior chamber reaction of varying severity may also occur.

Intermediate uveitis can be associated with various conditions, including sarcoidosis, multiple sclerosis (MS), peripheral toxocariasis, syphilis, tuberculosis, TINU, primary Sjögren syndrome, and human T-cell lymphotropic virus type 1 infection. The most common form of intermediate uveitis is idiopathic or undifferentiated.

Pars Planitis

The term *pars planitis* refers to a form of idiopathic intermediate uveitis with snowballs as well as inflammatory membranes on the pars plana and snowbanks. It is the most common form of intermediate uveitis, constituting approximately 85%–90% of such cases. The condition most commonly affects persons aged 5–40 years in a bimodal distribution,

concentrating in younger (5–15 years) and older (20–40 years) age groups. No overall sex predilection is apparent.

Approximately 80% of cases of pars planitis are bilateral, but disease activity may be asymmetric with 1 eye more affected. The initial presentation in children may include eye redness, photophobia, and discomfort with considerable anterior chamber inflammation as well as vitreous cells. The onset in teenagers and young adults may be more insidious, and the presenting symptom is often just floaters.

In addition to snowballs (Fig 8-17A), pars plana inflammatory membranes, and snowbanks (Fig 8-17B), ocular manifestations can include anterior chamber inflammation and vitreous cells and haze. Inferior peripheral retinal phlebitis with retinal venous sheathing is common. With long-standing inflammation, macular edema often develops; this condition becomes chronic and refractory in approximately 10% of patients and is the major cause of vision loss. Ischemia from retinal phlebitis, combined with angiogenic stimuli from intraocular inflammation, can lead to neovascularization along the inferior snowbank in up to 10% of cases. These neovascular complexes can result in vitreous hemorrhages, which are more common in children than in adults; the complexes also may contract, leading to peripheral tractional retinal schisis and rhegmatogenous retinal detachments. In rare cases, the complexes evolve into secondary peripheral retinal vasoproliferative tumors—vascular masses with exudative retinopathy and minimally dilated vessels—years after the initial diagnosis. Rhegmatogenous retinal detachments are rare, but localized peripheral detachments (exudative [also called *serous*] or tractional) occur in 4%–10% of patients with pars planitis. With chronic inflammation, posterior synechiae and band keratopathy may also develop. Other possible causes of vision loss include cataract, epiretinal membrane, and vitreous opacification.

Histologic examination of eyes with pars planitis shows vitreous condensation and cellular infiltration in the vitreous base. The inflammatory cells consist mostly of macrophages, lymphocytes, and a few plasma cells. Pars planitis is also characterized by peripheral lymphocytic cuffing of venules and a loose fibrovascular membrane over the pars plana.

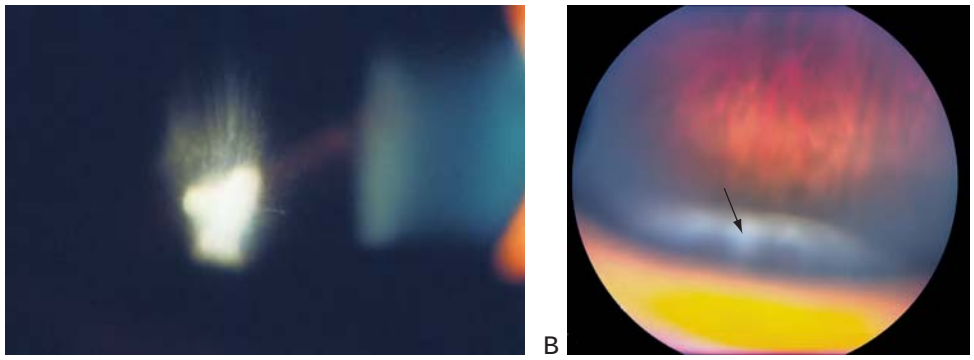

Figure 8-17 Pars planitis. **A,** Snowball opacity in the retrolental vitreous. **B,** Inferior pars plana snowbank *(arrow)*. *(Part A courtesy of Ramana S. Moorthy, MD/National Eye Institute; part B courtesy of H. Nida Sen, MD/National Eye Institute.)*

Workup and ancillary tests

The diagnosis of intermediate uveitis is based on the clinical findings, and the subtype pars planitis is established by ruling out specific etiologies. The workup should investigate any pertinent positive responses on a comprehensive review of systems and may include evaluations for sarcoidosis and MS. Sarcoidosis-associated uveitis presents as an intermediate uveitis in 7% of cases. Up to 15% of patients with pars planitis eventually develop MS. Anterior uveitis and intermediate uveitis occur in up to 20% of patients with MS; if the patient has current neurologic symptoms or a previous episode of an unexplained symptom like footdrop, magnetic resonance imaging (MRI) of the brain may be obtained to assess for evidence of demyelinating disease. Syphilis testing should be performed in all patients with new-onset uveitis, including those with intermediate uveitis. Although Lyme-associated uveitis is very rare, Lyme enzyme-linked immunosorbent assay (ELISA) screening may be appropriate in a patient who has erythema chronicum migrans ("bull's eye" rash), new-onset arthritis, and a history of tick bite in a Lyme-endemic region. A child with toxocariasis may have a peripheral or posterior pole retinal granuloma that resembles a snowbank. The complete absence of inflammation in the contralateral eye and a positive *Toxocara* antibody test result may help confirm the diagnosis of ocular toxocariasis.

The new onset of vitreous cells in an older patient should raise suspicion for vitreoretinal lymphoma. These patients are often older than the typical pars planitis patient, usually 50–60 years of age or older. Visual acuity may be better than expected despite substantial sheets of dense vitreous cells, and macular edema is usually absent. See Chapter 15 for additional discussion of vitreoretinal lymphoma.

Macular OCT may show macular thickening with or without frank intraretinal edema. The pattern of thickening can be diffuse or focal over macular vessels. Epiretinal membrane may also be present. FA should be obtained in all patients with substantial clinical signs of inflammation, such as higher-grade vitreous cell and haze and pars plana membranes or snowbanks. Reliance on clinical findings and OCT may result in underassessment of uveitis activity. FA may show peripheral or diffuse leakage of venules and capillaries as well as optic disc and macular leakage (Fig 8-18). Ultrasound biomicroscopy can demonstrate peripheral exudates or membranes on the pars plana.

Prognosis

The clinical course of pars planitis varies. Approximately 10% of cases have a self-limited, benign course; 30% have a smoldering course with remissions and exacerbations; and 60% have a chronic course without exacerbations. Chronic forms of pars planitis can remain active for many years. As mentioned previously, macular edema is the foremost vision-threatening complication. If macular edema is resolved, the long-term visual prognosis can be good, with nearly 75% of patients maintaining visual acuity of 20/40 or better after 10 years.

Treatment

Occasionally, pars planitis is very low grade and can be observed without treatment, but a substantial proportion of patients will need either long-acting regional corticosteroid injections or systemic IMT. Indications for treatment may include substantial vitritis and macular thickening with or without intraretinal fluid. Although patients may have

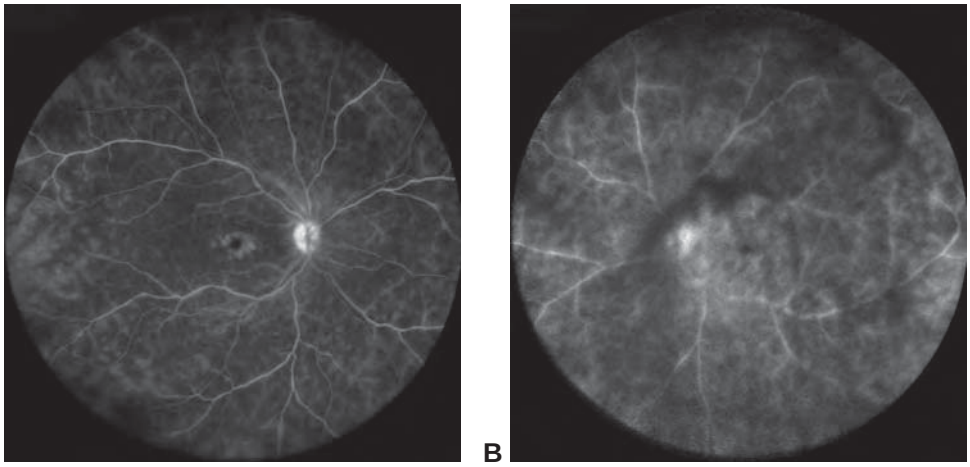

Figure 8-18 Pars planitis. **A,** Wide-angle fluorescein angiography shows diffuse venular and small-vessel leakage in the right eye. **B,** Imaging of the left eye shows a similar pattern of leakage, as well as shadowing from vitreous inflammatory debris. *(Courtesy of Wendy M. Smith, MD.)*

objectively good visual acuity, floaters and glare can be debilitating and may warrant treatment. FA may show more inflammation than is clinically apparent and should be used to monitor response to treatment.

Corticosteroids are first-line therapy. In unilateral cases, local treatment with corticosteroid injections is a particularly appealing approach as long as infectious causes of uveitis have been sufficiently investigated. Triamcinolone acetonide or methylprednisolone acetate may be given as depot injections into the posterior sub-Tenon space or orbital floor (see Chapter 6). In many cases, the inflammation resolves, and the macular edema improves; however, both conditions may persist, or they may recur within 2–3 months. Patients must be carefully monitored for corticosteroid-induced IOP elevation, which can develop weeks to years after corticosteroid injections. Cataract formation can occur with any form of corticosteroid therapy.

Intravitreal corticosteroids may also be utilized in pars planitis. The POINT (Peri-Ocular vs. INTravitreal corticosteroids for uveitic macular edema) Trial showed that intravitreal corticosteroids were more effective than periocular corticosteroid injections as treatment for uveitic macular edema. (See Chapter 6 for further discussion of POINT.) IOP elevation and cataract progression can also occur with intravitreal corticosteroids. Additional risks include retinal tear and detachment, vitreous hemorrhage, and endophthalmitis. Injections should be administered away from areas of snowbanking or other peripheral retinal pathology. Longer-acting forms of intravitreal corticosteroids, such as dexamethasone or fluocinolone acetonide implants, are FDA approved for the treatment of noninfectious intermediate uveitis.

In severe or bilateral cases, systemic corticosteroid therapy is required. Patients are treated with an initial dosage of 1 mg/kg/day (up to a maximum of 60–80 mg/day), with gradual tapering every 1–2 weeks to dosages of less than 7.5 mg/day after 8–10 weeks of treatment. As with all cases of noninfectious uveitis, if corticosteroid therapy fails or high doses of corticosteroids are needed to control the inflammation, systemic corticosteroid-sparing agents

are added. Systemic IMT options include antimetabolites, T-cell inhibitors, and biologic agents. Several reports from the SITE (Systemic Immunosuppressive Therapy for Eye Diseases) Cohort Study and the FAST (First-line Antimetabolites as Steroid-sparing Treatment) uveitis trial indicated that methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine were effective in achieving sustained control of inflammation in 70%–80% of patients with intermediate uveitis. (See Chapter 6 for more details on these studies.) The TNF inhibitor adalimumab is approved by the FDA for the treatment of noninfectious uveitis, including intermediate uveitis. Because TNF inhibitors can exacerbate MS, it is important to consider a workup for demyelinating disease, including brain MRI, before initiating this therapy. See Table 6-1 in Chapter 6 for more detailed information on IMT in uveitis.

Some practitioners utilize supplementary therapies for pars planitis, including peripheral ablation of snowbanks with cryotherapy and/or laser photocoagulation to the peripheral retina. In patients receiving systemic IMT who have persistent inflammation or retinal neovascularization, gentle, limited cryotherapy might be applied; however, there is a risk of inducing further inflammation. Peripheral laser photocoagulation to ischemic retina may prevent or involute retinal neovascularization and prevent vitreous hemorrhage; laser does not seem to increase the risk of rhegmatogenous retinal detachment. Intravitreal anti-VEGF agents can also be used for retinal or choroidal neovascularization in otherwise quiet eyes.

Pars plana vitrectomy (PPV) may be necessary to treat non-resolving vitreous hemorrhage or tractional adhesions, retinal detachment, or epiretinal membrane. In cases involving epiretinal membrane or vitreomacular traction, separation of the posterior hyaloid membrane during PPV may have a beneficial effect in reducing macular edema. PPV may also be considered for patients with substantial vitreous opacities despite adequate IMT. Potential complications of PPV include retinal detachment, endophthalmitis, and cataract formation. A perioperative increase in systemic immunosuppression and/or corticosteroids should be considered.

Mackensen F, Jakob E, Springer C, et al. Interferon versus methotrexate in intermediate uveitis with macular edema: results of a randomized controlled clinical trial. *Am J Ophthalmol.* 2013;156(3):478–486.

Rathinam SR, Gonzales JA, Thundikandy R, et al; FAST Research Group. Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: a randomized clinical trial. *JAMA*. 2019;322(10):936–945.

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. doi:10.1155/2017/5946240

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.

Thorne JE, Sugar EA, Holbrook JT, et al; Multicenter Uveitis Steroid Treatment Trial Research Group. 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. *Ophthalmology.* 2019;126(2):283–295.

Complications

Complications of pars planitis include cataract, glaucoma, macular edema, macular or foveal atrophy, retinal neovascularization, vitreous hemorrhage, retinoschisis, and tractional or rhegmatogenous retinal detachment. Cataract occurs in up to 60% of cases. Cataract surgery with IOL implantation may be complicated by smoldering low-grade inflammation, recurrent posterior capsule opacification, and chronic macular edema. Combining PPV with cataract extraction and IOL implantation may reduce the risk of these complications. Glaucoma—both angle-closure and open-angle—occurs in approximately 10% of patients with pars planitis. Macular edema is a hallmark of pars planitis and occurs in 50% of patients. Neovascularization of the retina, optic disc, and peripheral snowbank can develop. Occasionally, vitreous hemorrhage is the presenting sign of pars planitis, especially in children. Tractional and rhegmatogenous retinal detachments occur rarely and may require scleral buckling, sometimes combined with vitrectomy. Risk factors for rhegmatogenous retinal detachment include severe inflammation, use of cryotherapy at the time of a vitrectomy, and neovascularization of the snowbank.

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):812–817.

Lauer AK, Smith JR, Robertson JE, Rosenbaum JT. Vitreous hemorrhage is a common complication of pediatric pars planitis. *Ophthalmology.* 2002;109(1):95–98.

Multiple Sclerosis

Uveitis is 10 times more common in patients with MS than in the general population. The frequency of uveitis in patients with MS is reported to be as high as 30%, and the onset of uveitis may precede the diagnosis of MS by 5–10 years. MS usually affects White women 20–50 years of age; however, patients with intermediate uveitis who are in this demographic do not warrant an MRI or neurologic workup unless they have neurologic signs and symptoms of MS. An MRI might also be considered before treatment with a TNF inhibitor is initiated.

The immunopathogenesis of MS is not well understood but appears to involve humoral, cellular, and immunogenetic components directed against myelin. Studies have shown some cross-reactivity between myelin-associated glycoprotein and Müller cells. HLA-DR15 has been associated with the combination of MS and uveitis.

Intermediate uveitis is the most common manifestation of MS-associated uveitis. It is bilateral in 95% of cases, and most patients have mild vitritis with periphlebitis (Fig 8-19). In contrast to idiopathic intermediate uveitis, MS-associated intermediate uveitis is milder, and macular edema is less common. Periphlebitis in MS-associated uveitis is not clearly related to optic neuritis, systemic exacerbations, or disease severity. As in all types of intermediate uveitis, FA may show more inflammation than might be appreciated clinically.

Some of the medications used as disease-modifying therapy for MS may also treat MS-associated uveitis and associated macular edema. Interferon has been shown to be effective for macular edema in MS-associated uveitis. Ocrelizumab is a humanized anti-CD20 monoclonal antibody with a mechanism of action similar to that of rituximab, a biologic that has been used to treat other forms of noninfectious uveitis and scleritis. Of

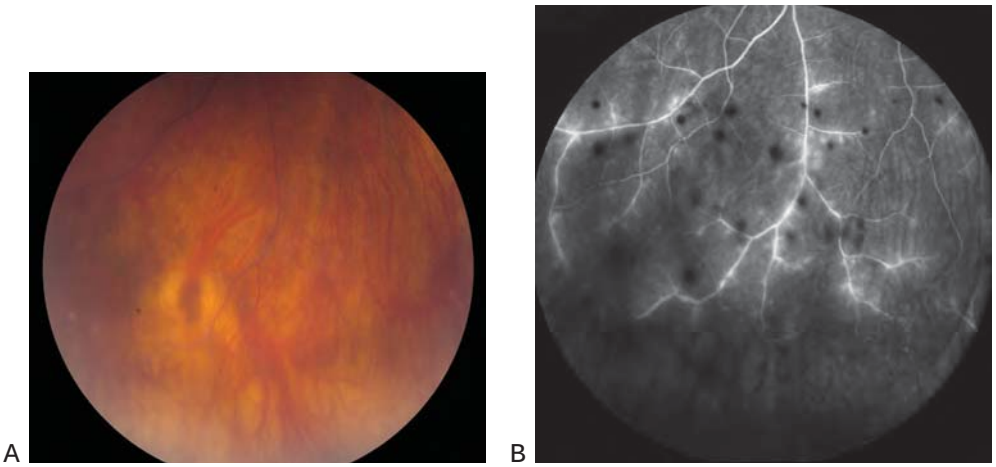

Figure 8-19 Multiple sclerosis–associated intermediate uveitis. **A,** Color fundus photograph demonstrates subtle vascular sheathing and vitreous snowballs. **B,** Corresponding fluorescein angiogram shows venular leakage and shadowing from vitreous snowballs. *(Courtesy of Wendy M. Smith, MD.)*

note, one disease-modifying therapy for MS, fingolimod, can cause macular edema, although this is a rare complication.

TNF inhibitors, a class of biologic medications that is FDA approved to treat noninfectious uveitis, are contraindicated with demyelinating disease. Therefore, before these agents are started in patients with suspected idiopathic intermediate uveitis, a brain MRI should be obtained to rule out demyelinating disease.

Abraham A, Nicholson L, Dick A, Rice C, Atan D. Intermediate uveitis associated with MS: diagnosis, clinical features, pathogenic mechanisms, and recommendations for management. *Neurol Neuroimmunol Neuroinflamm.* 2020;8(1):e909.

Becker MD, Heiligenhaus A, Hudde T, et al. Interferon as a treatment for uveitis associated with multiple sclerosis. *Br J Ophthalmol.* 2005;89(10):1254–1257.

Chen L, Gordon LK. Ocular manifestations of multiple sclerosis. *Curr Opin Ophthalmol.* 2005;16(5):315–320.

Chirpaz N, Kerever S, Gavoille A, et al. Relevance of brain MRI in patients with uveitis: retrospective cohort on 402 patients. *Ocul Immunol Inflamm.* 2021;1–7. doi:10.1080/09273948.2020.1870145

Zein G, Berta A, Foster CS. Multiple sclerosis–associated uveitis. *Ocul Immunol Inflamm.* 2004;12(2):137–142.