CHAPTER 10

Posterior Uveitis and Panuveitis With Possible Systemic Manifestations

Highlights

- Posterior uveitis and panuveitis can be isolated to the eye(s), or they may be associated with systemic infectious or inflammatory disease.
- The diagnosis of many systemic inflammatory diseases (ie, systemic lupus erythematosus, Behçet disease, and Vogt-Koyanagi-Harada syndrome) is based on a combination of clinical findings, not a single diagnostic test.
- Diagnostic ambiguity within the noninfectious uveitic entities should not preclude or delay appropriate therapy once infectious uveitis has been ruled out.
- Many patients with noninfectious posterior uveitis or panuveitis require systemic immunomodulatory therapy (IMT), and systemic and/or local corticosteroids are used as a bridge while IMT takes effect. Further details of the approach to systemic treatment are discussed in Chapter 6.

Introduction

Posterior uveitis is defined as intraocular inflammation that involves primarily the retina and/or choroid. Occlusive retinal vasculitis is also classified as posterior uveitis. In panuveitis, inflammation is present in all anatomical compartments of the eye without a single dominant site. Chapter 9 discusses the white dot syndromes, a group of noninfectious posterior uveitis entities that typically have no associated systemic inflammatory disease. This chapter discusses types of posterior uveitis and panuveitis that can occur as an isolated ophthalmic disorder or may have a systemic disease association. Such diseases include systemic lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis (antineutrophil cytoplasmic antibodies–associated vasculitis), sarcoidosis, Vogt-Koyanagi-Harada (VKH) syndrome, and Behçet disease. Ocular disease may be the first clue to a systemic diagnosis. Because untreated systemic inflammation may result in major morbidity and even mortality, proper ophthalmic evaluation leading to appropriate and early diagnosis can positively affect patient outcomes. In some cases, diagnostic ambiguity may make it challenging to establish a specific uveitis diagnosis. As long as infectious causes have been sufficiently investigated, treatment should not be delayed because of the inability to make an exact diagnosis.

Posterior Uveitis With Possible Systemic Manifestations

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disorder that affects primarily women of childbearing age, with higher incidence among Black and Hispanic women in the United States. Although incompletely understood, SLE is considered an autoimmune disorder that features B-lymphocyte hyperactivity, polyclonal B-lymphocyte activation, hypergammaglobulinemia, autoantibody formation, and T-lymphocyte autoreactivity with immune complex deposition, leading to end-organ damage. Autoantibodies associated with SLE include antinuclear antibodies (ANAs), antibodies to both single- and double-stranded DNA, antibodies to cytoplasmic components (eg, anti-Sm, anti-Ro, and anti-La), and antiphospholipid antibodies.

SLE is a clinical diagnosis based on criteria established by the European League Against Rheumatism/American College of Rheumatology. According to the literature, the association between SLE and uveitis is low. Recent analysis of laboratory tests typically used for uveitis shows a low (4.4%) positive predictive value of ANA testing in the context of intraocular inflammation. Thus, ANA testing should be limited to patients with signs or symptoms suggestive of SLE or to patients with juvenile idiopathic arthritis (JIA), for whom such testing helps determine the risk of uveitis. See BCSC Section 1, *Update on General Medicine,* for diagnostic criteria for SLE and for more information on interpreting diagnostic and screening tests.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71(9):1400–1412.

McKay KM, Lim LL, Van Gelder RN. Rational laboratory testing in uveitis: a Bayesian analysis. *Surv Ophthalmol.* 2021;66(5):802–825.

Manifestations

Systemic manifestations of SLE include acute cutaneous diseases (eg, malar rash, discoid lupus, photosensitivity, and mucosal lesions) in approximately 70%–80% of patients, arthritis in 80%–85%, renal disease in 50%–75%, Raynaud phenomenon in 30%–50%, and neurologic involvement in 35%. Cardiac, pulmonary, hepatic, and hematologic abnormalities may also develop.

Ocular manifestations occur in 50% of patients with SLE and include cutaneous lesions on the eyelids (discoid lupus erythematosus), secondary Sjögren syndrome, scleritis, cranial nerve palsies, optic neuropathy, and retinal and choroidal vasculopathy. As mentioned previously, uveitis is only rarely associated with SLE.

Lupus retinopathy (a non-uveitic marker for systemic SLE activity) is the most well-known posterior segment manifestation of SLE. Prevalence ranges from 3% among patients with mild systemic SLE to 29% among those with more active systemic disease. Fundamentally a vasculopathy, lupus retinopathy may produce cotton-wool spots and retinal nonperfusion (Fig 10-1) or infarction (Fig 10-2). In patients with lupus retinopathy, a hypercoagulable state caused by autoantibodies (rather than an inflammatory retinal vasculitis) provokes arterial and/or venous thrombosis. Although lupus retinopathy has similarities to hypertensive retinopathy secondary to SLE-induced hypertension and nephritis, the latter conditions may also result in arteriolar narrowing, retinal hemorrhage, and disc edema.

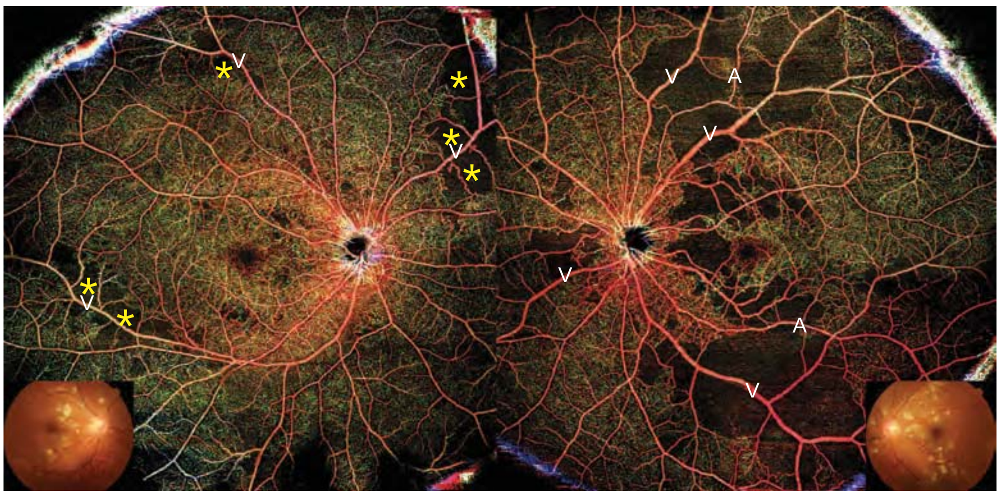

Figure 10-1 Systemic lupus erythematosus. Color fundus photographs *(lower left and right insets)* show multiple cotton-wool spots in both eyes. Optical coherence tomography (OCT) angiography shows multiple areas of capillary nonperfusion *(yellow asterisks)* associated with retinal veins *(V)* and arteries *(A)*. *(From Ishibashi T, Wakabayashi T, Nishida K. Purtscher-like retinopathy associated with systemic lupus erythematosus observed using wide-field OCT angiography.* Ophthalmol Retina. *2019;3(1):76.)*

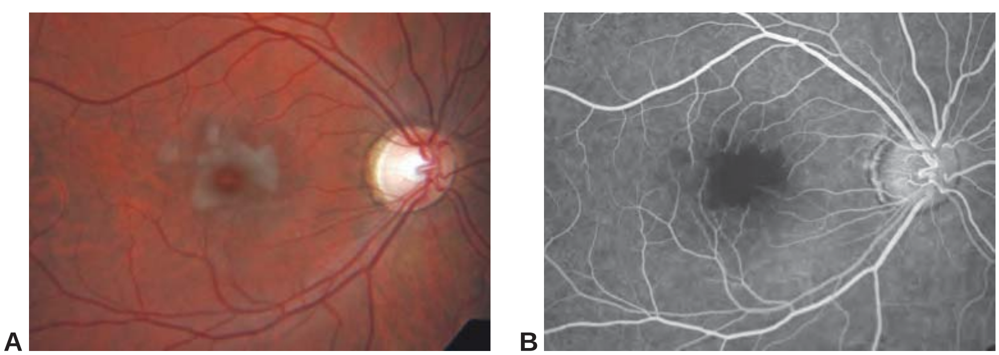

Figure 10-2 Systemic lupus erythematosus, initial presentation. **A,** Fundus photograph shows macular infarction in a 30-year-old woman who presented with diminished vision (counting fingers) and 1 week of myalgias. Laboratory test results were notable for positive antinuclear antibodies and double-stranded DNA. **B,** Early-phase fluorescein angiogram (FA). *(Courtesy of Sam S. Dahr, MD, MS.)*

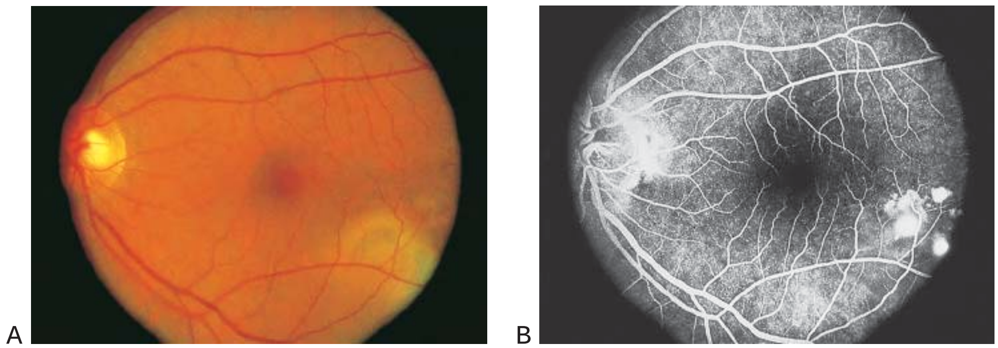

Figure 10-3 Systemic lupus erythematosus (SLE). **A,** Fundus photograph of multifocal choroiditis in a patient with SLE. **B,** FA showing multifocal areas of hyperfluorescence. *(Courtesy of E. Mitchel Opremcak, MD.)*

Retinal ischemia and nonperfusion may be extensive in lupus retinopathy, resulting in retinal neovascularization and vitreous hemorrhage. Severe retinal vascular occlusive disease can be associated with central nervous system (CNS) lupus and the presence of antiphospholipid antibodies (see BCSC Section 1, *Update on General Medicine,* for more information on antiphospholipid antibodies).

Autoantibodies associated with SLE also may trigger a *lupus choroidopathy* (Fig 10-3). Choroidal thrombosis may produce choroidal infarction, multifocal retinal pigment epithelium (RPE) detachments, and subretinal fluid.

Jabs DA, Fine SL, Hochberg MC, Newman SA, Heiner GG, Stevens MB. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol*. 1986;104(4):558–563.

Nguyen QD, Uy HS, Akpek EK, Harper SL, Zacks DN, Foster CS. Choroidopathy of systemic lupus erythematosus. *Lupus*. 2000;9(4):288–298.

Papagiannuli E, Rhodes B, Wallace GR, Gordon C, Murray PI, Denniston AK. Systemic lupus erythematosus: an update for ophthalmologists. *Surv Ophthalmol.* 2016;61(1):65–82.

Treatment

Management of ophthalmic SLE focuses on treating the underlying systemic disease, which may involve corticosteroids and immunomodulatory therapy (IMT), including hydroxychloroquine. Patients with severe vaso-occlusive disease or antiphospholipid antibodies may require antiplatelet therapy or systemic anticoagulation, whereas those with severe sight-threatening disease may require aggressive therapy with intravenous immunoglobulin, cyclophosphamide, and/or plasma exchange. Ischemic complications, including proliferative retinopathy and vitreous hemorrhage, can be managed with panretinal photocoagulation, intravitreal anti–vascular endothelial growth factor, and vitrectomy.

Patients taking hydroxychloroquine should be counseled on the need for regular ophthalmic examinations to screen for retinal toxicity. For further information, see BCSC Section 12, *Retina and Vitreous.*

Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. *Arthritis Rheumatol.* 2021;73(6):908–911.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare systemic vasculitis (annual incidence, 0.7 per 100,000 individuals) that involves subacute or chronic focal, necrotizing inflammation of medium-sized and small arteries. The disease affects patients aged 40 to 60 years and occurs 1.5 times more frequently in men than in women. Hepatitis B and hepatitis C infection may play a pathogenic role in some cases of PAN, but most cases are idiopathic.

Manifestations and diagnosis

PAN vasculitis may affect multiple organ systems but characteristically spares the lungs. Skin features include subcutaneous nodules, purpura, livedo reticularis, and Raynaud phenomenon. Mononeuropathy multiplex with motor and sensory deficits affects up to 70% of patients. In approximately one-third of patients, kidney disease causes secondary hypertension. Gastrointestinal disease may result in small bowel ischemia and infarction, and cardiac manifestations include coronary arteritis and pericarditis.

Ocular involvement occurs in up to 20% of patients with PAN, with varying posterior segment manifestations. Retinal vasculitis may provoke amaurosis fugax or branch or central retinal artery occlusion (Fig 10-4). Choroidal or posterior ciliary artery vasculitis may cause lobular choroidal ischemia and infarcts, initially presenting as exudative retinal detachments and later resulting in *Elschnig spots* (focal areas of choroidal hyperpigmentation with margins of hypopigmentation; see BCSC Section 12, *Retina and Vitreous*). Systemic hypertension associated with kidney disease may cause hypertensive retinopathy. Neuro-ophthalmic manifestations include cranial nerve palsies, homonymous hemianopia, Horner syndrome, and ischemic optic neuropathy. In addition, scleral inflammatory diseases of all types, including necrotizing and posterior scleritis, have been reported. Peripheral ulcerative keratitis, often accompanied by scleritis, may be an early manifestation of PAN.

There is no definitive laboratory test for PAN, so laboratory evaluation is directed at ruling out other causes of systemic vasculitis. Unlike granulomatosis with polyangiitis (GPA; previously known as *Wegener granulomatosis*), PAN is *not* associated with antineutrophil

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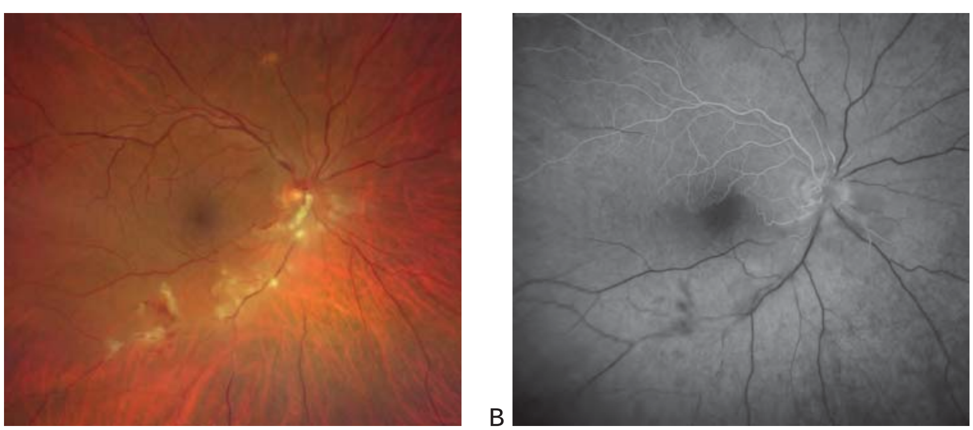


Figure 10-4 Polyarteritis nodosa. **A,** Fundus photograph indicates retinal vasculitis associated with vascular sheathing and intraretinal hemorrhage. **B,** Early-phase FA shows retinal infarction due to a hemiretinal artery occlusion. *(Courtesy of Sam S. Dahr, MD, MS.)*

cytoplasmic antibodies (ANCAs). The tissue biopsy (often skin or kidney) result may be confirmatory, but often the diagnosis is clinical and based on the presence of at least 3 of the following 10 criteria:

- weight loss >4 kg
- livedo reticularis
- testicular pain or tenderness
- diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
- development of mononeuropathy or multiple mononeuropathies or polyneuropathy
- development of hypertension with diastolic blood pressure >90 mm Hg
- elevation of blood urea nitrogen level >40 mg/dL or creatinine value >1.5 mg/dL, not due to dehydration or obstruction
- presence of hepatitis B surface antigen or antibody in the serum
- arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes
- biopsy of small or medium-sized artery showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

Hočevar A, Tomšič M, Perdan Pirkmajer K. Clinical approach to diagnosis and therapy of polyarteritis nodosa. *Curr Rheumatol Rep.* 2021;23(3):14. doi:10.1007/s11926-021-00983-2

Rothschild PR, Pagnoux C, Seror R, Brézin AP, Delair E, Guillevin L. Ophthalmologic manifestations of systemic necrotizing vasculitides at diagnosis: a retrospective study of 1286 patients and review of the literature. *Semin Arthritis Rheum*. 2013;42(5):507–514.

Treatment and prognosis

Mortality secondary to renal failure or mesenteric, cerebral, or cardiac infarction is common in PAN. In patients with untreated PAN, the 5-year survival rate is 13%; however, with treatment, the rate improves to 80%. Treatment usually includes systemic corticosteroids and IMT, typically cyclophosphamide. PAN should be considered in the differential diagnosis of ANCA-negative retinal vasculitis because appropriate diagnosis and management can be lifesaving.

Gayraud M, Guillevin L, le Toumelin P, et al; French Vasculitis Study Group. Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum.* 2001;44(3):666–675.

Pagnoux C, Mendel A. Treatment of systemic necrotizing vasculitides: recent advances and important clinical considerations. *Expert Rev Clin Immunol.* 2019;15(9):939–949.

Granulomatosis With Polyangiitis and Microscopic Polyangiitis

Granulomatosis with polyangiitis (GPA) is a multisystem inflammatory disorder that features the following classic triad:

- necrotizing granulomatous vasculitis of the upper and lower respiratory tract
- focal segmental glomerulonephritis
- necrotizing vasculitis of small arteries and veins

Paranasal sinus involvement is the most characteristic clinical feature of GPA, followed by pulmonary and renal disease. Glomerulonephritis eventually develops in 85% of patients and is a high risk for mortality, so early disease detection is important.

Like GPA, *microscopic polyangiitis (MPA)* is an ANCA-associated vasculitis. MPA and GPA may have similar clinical features, but biopsy specimens from patients with MPA lack granulomatous findings. In addition, MPA is associated with ANCA directed against myeloperoxidase (MPO; see the section "Diagnosis"), whereas GPA is usually associated with an elevated level of ANCA directed against proteinase 3 (PR3). Ophthalmic involvement is also less common in MPA than in GPA.

Manifestations

Patients with GPA may present with sinusitis featuring bloody nasal discharge, pulmonary symptoms, and arthritis. Dermatologic manifestations, including purpura (often in the lower extremities), ulcers, and subcutaneous nodules, occur in 50% of patients. Neurologic findings such as mononeuritis multiplex (most common), cranial neuropathies, seizures, stroke syndromes, and cerebral vasculitis are reported in one-third of patients.

Fifteen percent of patients with GPA have ocular or orbital involvement at presentation, and in up to 50% of patients with GPA, ocular involvement occurs over time. Orbital involvement may be due to contiguous spread of the granulomatous inflammatory process from the paranasal sinuses into the orbit. Orbital pseudotumor, distinct from the sinus inflammation, may also occur. Inflamed nasal and paranasal sinus mucosa may become secondarily infected and may progress to orbital cellulitis and/or dacryocystitis. Orbital disease can cause compressive ischemic optic neuropathy.

Up to 40% of individuals with GPA have scleritis of any type, particularly diffuse anterior or necrotizing disease, with or without peripheral ulcerative keratitis. Approximately 10% of patients with ophthalmic GPA have nonspecific unilateral or bilateral anterior, intermediate, or posterior uveitis, with varying degrees of vitritis. Retinal disease, while uncommon, may include cotton-wool spots, intraretinal hemorrhage, artery or vein occlusion, or retinitis. Complications such as retinal neovascularization (Fig 10-5),

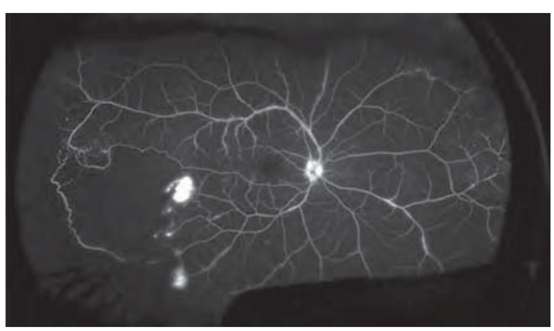


Figure 10-5 Granulomatosis with polyangiitis. FA shows peripheral nonperfusion and retinal neovascularization. *(Reproduced with permission from Huvard MJ, Pecen PE, Palestine AG. The clinical characteristics of noninfectious occlusive retinal vasculitis.* Ophthalmol Retina. *2022;6(1):43–48.)*

vitreous hemorrhage, and neovascular glaucoma may also arise. Vision loss occurs in up to 40% of patients with GPA, especially among those with long-standing or inadequately treated disease.

Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020;6(1):71.

Kubal AA, Perez VL. Ocular manifestations of ANCA-associated vasculitis. *Rheum Dis Clin North Am*. 2010;36(3):573–586.

Diagnosis

ANCAs are specific markers for a group of systemic vasculitides that include GPA, MPA, eosinophilic GPA (Churg-Strauss syndrome), renal-limited vasculitis, and pauci-immune glomerulonephritis. These antibodies are directed against cytoplasmic azurophilic granules within neutrophils and monocytes. Immunofluorescence staining patterns suggest 2 main classes of ANCAs:

- The cytoplasmic ANCA, or c-ANCA, pattern is both sensitive and specific for GPA and is present in up to 95% of affected patients. PR3 is the most common target antigen.
- The perinuclear ANCA, or p-ANCA, pattern is associated with MPA, renal-limited vasculitis, and pauci-immune glomerulonephritis. MPO is the most common antigenic target.

Two assays are available for these antibodies, and ideally, both assays are used for diagnosis:

- indirect immunofluorescence for c- and p-ANCA (more sensitive)
- enzyme-linked immunosorbent assay (ELISA) testing for the autoantibodies PR3-ANCA and MPO-ANCA (more specific)

Laboratory evaluation may also reveal proteinuria or hematuria and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. Chest radiography may show nodular, diffuse, or cavitary lesions. A tissue biopsy specimen showing necrotizing or granulomatous inflammation can establish a histologic diagnosis.

Treatment

Without treatment of GPA, the 1-year mortality rate is 80%. Therefore, the condition is usually treated aggressively with systemic corticosteroids and IMT, such as rituximab or cyclophosphamide. The ophthalmologist's role in recognizing GPA-associated eye disease is critical, as timely diagnosis and treatment may prevent not only ocular morbidity but also patient mortality.

Susac Syndrome

Initially reported by Susac and colleagues in 1979, Susac syndrome (also referred to as *SICRET syndrome,* for *s*mall *i*nfarctions of *c*ochlear, *r*etinal, and *e*ncephalic *t*issue) is an immune-mediated, occlusive microvascular endotheliopathy. Patient age at onset is typically 20–40 years (range, 7–70 years), and women are more likely than men to be affected by a 3:1 ratio.

Manifestations

The clinical triad of Susac syndrome consists of

- encephalopathy
- low- to mid-frequency sensorineural hearing loss and/or tinnitus
- branch retinal artery occlusions

Most patients do *not* display the complete triad at disease onset, rendering diagnosis a challenge. The differential diagnosis includes multiple sclerosis, herpetic encephalitis, acute disseminated encephalomyelitis, sarcoidosis, and Behçet disease.

In patients with Susac syndrome, fundus examination may reveal yellow arteriolar wall deposits ("Gass plaques") that may represent an immunologic reaction in the arteriolar wall. Unlike cholesterol or Hollenhorst plaques, these deposits usually occur away from arteriolar bifurcations and may be transient. Retinal arteries may be diffusely or locally narrowed with a "boxcar" segmentation of the blood column at the level of peripheral retinal arteries (Fig 10-6A). Vitreous haze or cells are minimal or absent. In active disease, angiography shows focal, nonperfused retinal arterioles with arterial wall hyperfluorescence (Fig 10-6B). Embolic material or inflammatory reactions are not seen around the vessels. In magnetic resonance imaging, multifocal supratentorial white matter lesions involving the central corpus callosum are highly suggestive of Susac syndrome. When a diagnosis of Susac syndrome is being considered, formal audiology testing can be performed to assess for sensorineural hearing loss.

Treatment

Therapy for Susac syndrome often features a combination of high-dose corticosteroids, intravenous immunoglobulin, cyclophosphamide, antimetabolite therapy, and rituximab. The disease course varies, and patients may need long-term therapy. Serial fluorescein angiography helps monitor for ophthalmic disease recurrence.

Heng LZ, Bailey C, Lee R, Dick A, Ross A. A review and update on the ophthalmic implications of Susac syndrome. *Surv Ophthalmol.* 2019;64(4):477–485.

Rennebohm RM, Asdaghi N, Srivastava S, Gertner E. Guidelines for treatment of Susac syndrome – an update. *Int J Stroke.* 2020;15(5):484–494.

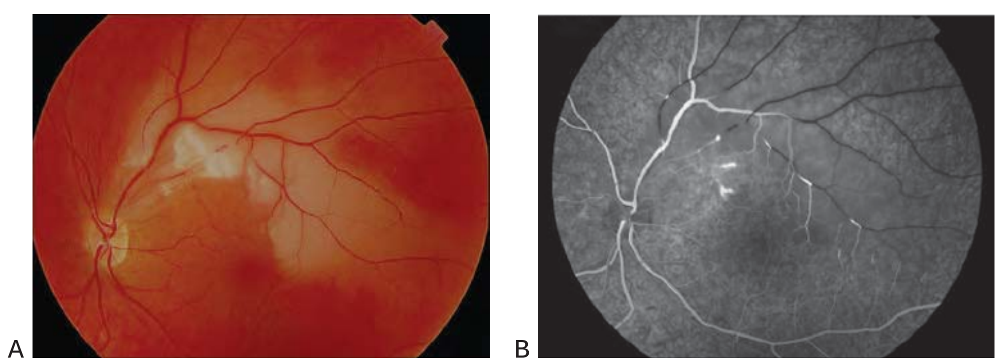


Figure 10-6 Susac syndrome. **A,** Color fundus photograph revealing an area of intraretinal whitening corresponding to a superotemporal branch artery occlusion in the left eye. **B,** FA showing a superotemporal branch artery occlusion with multiple areas of segmental staining well away from sites of bifurcation. *(Courtesy of Albert T. Vitale, MD.)*

Panuveitis With Possible Systemic Manifestations

Sarcoidosis

Sarcoidosis is a multisystem inflammatory disease of unknown etiology with a wide range of systemic and ocular manifestations. In patients with sarcoidosis, the lungs are most commonly affected (90% of cases); followed by the liver, spleen, or lymph nodes (25%–35%); the eyes (12%–50%); the skin (12%–25%); the joints (10%); and the CNS (5%–10%). Cardiac sarcoidosis is probably underdiagnosed; while 5% of patients with sarcoidosis may have clinically detectable cardiac disease, autopsy studies suggest cardiac involvement in 20%–30% of affected patients. The most common cause of sarcoidosis-related death is pulmonary disease, followed by cardiac disease. Overall, the sarcoidosis mortality rate is approximately 5%.

Sarcoidosis affects all ethnic groups worldwide; the highest prevalence is in northern European countries (40 per 100,000). In the United States, the disease is more common in Black patients than in White patients: the prevalence is 36 cases per 100,000 Black individuals versus 11 cases per 100,000 White individuals, and the cumulative lifetime risks are 2.4% versus 0.85%, respectively. No single etiologic agent or genetic locus has been definitively identified in the pathogenesis of sarcoidosis, although environmental exposures (ie, agricultural, infectious) likely play a role in directly triggering inflammation in those with a susceptible genetic background. Familial clustering also suggests a genetic predisposition; siblings of patients with sarcoidosis have a fivefold-increased risk of acquiring the disease. In the United States, lower socioeconomic status is associated with increased severity of disease and higher morbidity and mortality from sarcoidosis. Factors contributing to worse outcomes likely include limited access to medical care and physician implicit bias. See BCSC Section 1, *Update on General Medicine,* for further discussion of social determinants of health.

Although the age at onset for sarcoidosis is usually between 20 and 50 years, the disorder should be investigated as the cause of uveitis in patients of all ages; for example, epidemiologic studies suggest a second sarcoidosis peak between 50 and 65 years of age. Patients with late-onset sarcoidosis are more likely than younger patients to have uveitis, and they are less likely to have asymptomatic abnormalities on chest radiography.

Pediatric cases of sarcoidosis are rare. When children younger than 5 years are affected, they are less likely than adults to have pulmonary disease and more likely to have cutaneous and joint involvement. In this age group, pediatric sarcoidosis, JIA-associated anterior uveitis, and familial juvenile systemic granulomatosis may also overlap in terms of ocular and articular involvement. See Chapter 8 for a discussion of JIA-associated anterior uveitis.

In young patients, acute systemic sarcoidosis may present and spontaneously remit within 2 years. One form of acute sarcoidosis, *Löfgren syndrome,* is characterized by erythema nodosum, febrile arthropathy, bilateral hilar lymphadenopathy, and acute iritis. This syndrome responds well to systemic corticosteroids and has a good long-term prognosis. *Heerfordt syndrome* (uveoparotid fever), another form of acute sarcoidosis, is characterized by uveitis, parotitis, fever, and facial nerve palsy. In contrast, chronic sarcoidosis presents insidiously, persists longer than 2 years, and often involves lung disease and chronic uveitis.

Uveitis, along with granulomatous dermatitis and arthritis, is also observed in patients with *familial juvenile systemic granulomatosis* (ie, *Blau syndrome*), an autosomal dominant disease caused by mutations in the *NOD2* gene. The ophthalmic presentation is similar to that of ocular sarcoidosis and should be suspected when there is a family history of granulomatous disease.

Hena KM. Sarcoidosis epidemiology: race matters. *Front Immunol.* 2020;11:537382. doi:10.3389/fimmu.2020.537382

Moller DR, Rybicki BA, Hamzeh NY, et al. Genetic, immunologic, and environmental basis of sarcoidosis. *Ann Am Thorac Soc*. 2017;14(suppl 6):S429–S436.

Yee AM. Sarcoidosis: rheumatology perspective. *Best Pract Res Clin Rheumatol*. 2016;30(2):334–356.

Manifestations

The characteristic lesion of sarcoidosis is a noncaseating granuloma without histologic evidence of infection or foreign body (Fig 10-7). See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for additional details on histologic findings of sarcoidosis.

Ocular sarcoidosis can affect any ocular tissue, including the orbit and adnexa. Common findings include cutaneous lesions (Fig 10-8) as well as granulomas in the orbit and eyelids. Palpebral and bulbar conjunctival nodules can be easily biopsied to provide histologic confirmation of the diagnosis (Fig 10-9). Infiltration of the lacrimal gland, meanwhile, may cause dacryoadenitis and keratoconjunctivitis sicca.

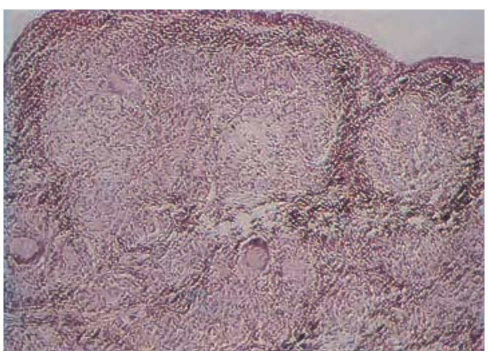


Figure 10-7 Sarcoidosis. Histologic view of conjunctival biopsy. Note the giant cells and granulomatous inflammation.

Figure 10-8 Sarcoidosis. Skin lesions.

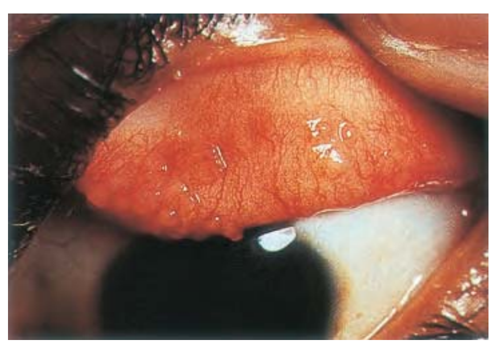


Figure 10-9 Sarcoidosis. Conjunctival nodules.

Uveitis is the most common manifestation of ocular sarcoidosis, occurring in 61% of patients. Overall, sarcoidosis accounts for 5%–10% of uveitis cases in tertiary care centers in the United States. Most sarcoidosis-associated uveitis cases (71%) are anterior. Presenting symptoms include acute onset of eye pain, redness, and photophobia. Alternatively, chronic granulomatous anterior uveitis may be more insidious, with the gradual development of blurred vision, floaters, and mild periorbital aching. Clinical findings of granulomatous anterior uveitis include *mutton-fat keratic precipitates (KPs)* (Fig 10-10), *Koeppe* (pupillary margin) and *Busacca* (iris stroma) iris nodules (Fig 10-11), and white clumps of cells in the anterior vitreous. The cornea is infrequently involved, but nummular infiltrates and inferior endothelial opacification have been observed. Band keratopathy may occur as a result of chronic uveitis or hypercalcemia. The formation of posterior synechiae and peripheral anterior synechiae

Figure 10-10 Sarcoidosis with keratic precipitates and anterior uveitis.

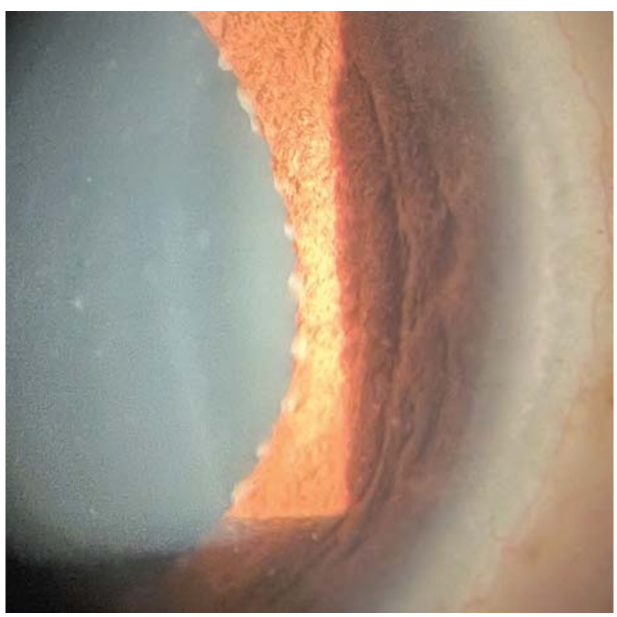


Figure 10-11 Koeppe nodules. *(Courtesy of Sam S. Dahr, MD, MS.)*

can be extensive, leading to iris bombé and secondary angle closure; glaucoma due to sarcoid uveitis complications is a poor prognostic sign associated with severe vision loss.

Posterior segment manifestations occur in up to 20% of patients with ocular sarcoidosis. Vitreous involvement includes cellular-proteinaceous clumps *(snowballs)* with or without vitreous inflammatory cell infiltrate. Vitreous cells may also form semi-linear strands or "string of pearls." Vitreous inflammation may be the primary site of involvement (ie, intermediate uveitis) or accompany sarcoidosis-associated panuveitis. Acute chorioretinal disease can present as multiple small yellow choroidal granulomas (Fig 10-12) that can evolve into hypopigmented atrophic spots, sometimes with a rim of pigment hyperplasia. Large choroidal granulomas may cause exudative retinal detachment. Granulomas also may involve the retina or optic nerve. *Dalen-Fuchs nodules,* a mixture of lymphocytes and epithelioid histiocytes located between the RPE and Bruch membrane, can occur. Linear or segmental venous sheathing or periphlebitis is common, and retinal macroaneurysms may also develop. *Candlewax drippings,* or *taches de bougie* (Fig 10-13), are irregular nodular granulomas along venules. Retinovascular involvement may also manifest as branch or central retinal vein occlusion and peripheral retinal capillary nonperfusion.

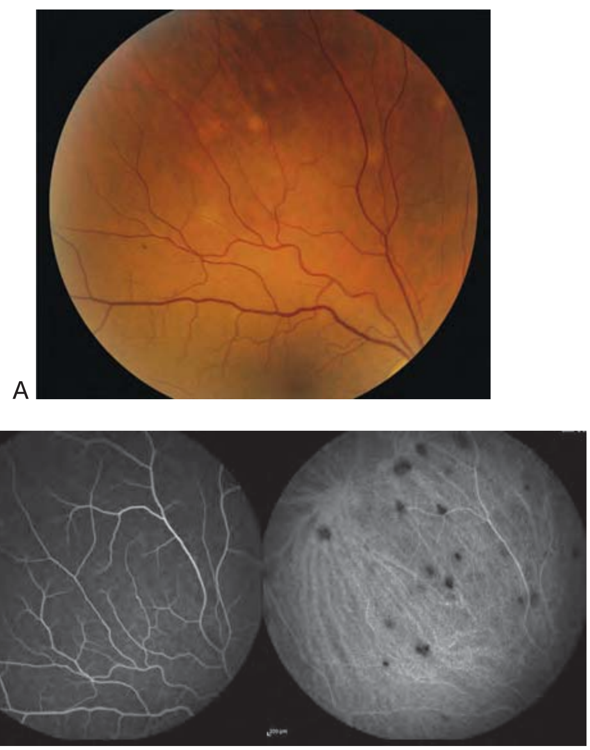


Figure 10-12 Sarcoidosis. **A,** Color fundus photograph of small, deep yellow lesions. **B,** FA *(left)* shows no hyperfluorescence associated with clinically seen lesions. Indocyanine green imaging *(right)* shows multiple small hypocyanescent lesions more numerous than appreciated clinically. *(Courtesy of Wendy M. Smith, MD.)*

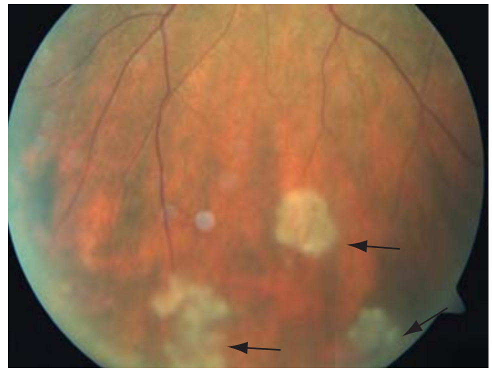


Figure 10-13 Sarcoidosis. Color fundus photograph of taches de bougie, or candlewax drippings *(arrows)*. *(Courtesy of Sam S. Dahr, MD, MS.)*

Complications of posterior segment inflammation include macular edema, retinal neovascularization and vitreous hemorrhage, and choroidal neovascularization (CNV) associated with choroidal lesions. Papillitis secondary to uveitis can develop, although more prominent optic disc swelling from papilledema may occur with neurosarcoidosis. Sarcoidosis can also cause an inflammatory optic neuropathy without uveitis.

Acharya NR, Browne EN, Rao N, Mochizuki M; International Ocular Sarcoidosis Working Group. Distinguishing features of ocular sarcoidosis in an international cohort of uveitis patients. *Ophthalmology*. 2018;125(1):119–126.

Kidd DP, Burton BJ, Graham EM, Plant FT. Optic neuropathy associated with systemic sarcoidosis. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(5):e270.

Standardization of Uveitis Nomenclature (SUN) Working Group. Classification criteria for sarcoidosis-associated uveitis. *Am J Ophthalmol*. 2021;228:220–230.

Diagnosis

The diagnosis of sarcoidosis is based on cumulative evidence obtained from clinical observations, laboratory testing, radiologic studies, and tissue biopsy. As noted previously, definitive diagnosis requires the presence of characteristic histologic findings (noncaseating granuloma with no infectious or neoplastic etiology) in a biopsy specimen; in some cases, however, the diagnosis may be considered probable because of clinical and radiologic evidence, as long as other causes such as tuberculosis (TB) and syphilis have been ruled out.

For the ophthalmologist who is investigating suspected ocular sarcoidosis, a starting point could be a chest x-ray, as abnormalities are present at some point in up to 90% of patients with the disorder. Bilateral hilar with or without mediastinal lymphadenopathy is strongly suggestive of sarcoidosis. However, pulmonary pathology may not persist throughout the disease course, or it may not be detectable by chest radiography. When clinical suspicion for sarcoidosis is high, high-resolution chest computed tomography (CT) is more sensitive than chest x-ray for confirmation. However, the potential clinical utility of the CT scan (ie, the likelihood of changing management of the ocular disease when there are no other signs or symptoms of extraocular sarcoidosis) must be weighed against the risk of increased radiation and the higher cost of the test. If the chest image is abnormal, pulmonary function testing and a pulmonology consultation may be considered. Bronchoscopy with bronchoalveolar lavage and/or endobronchial ultrasound-guided transbronchial needle aspiration may provide histologic proof of sarcoidosis. The characteristic finding from lavage is mononuclear alveolitis with increased $CD4^+$ lymphocytes.

Laboratory testing may include serum levels of angiotensin-converting enzyme (ACE) and lysozyme. If the patient is taking a systemic ACE inhibitor, the ACE level is unlikely to be significantly elevated; however, the lysozyme value may still be informative. A series of biopsy-proven or probable cases of ocular sarcoidosis reported a combined sensitivity of 61% and specificity of 88% for elevated levels of ACE, lysozyme, or both. It is important to note that lysozyme levels can be elevated in patients with chronic renal failure, especially end-stage disease. Other serum test results such as calcium and liver enzyme levels may be abnormal in patients with sarcoidosis, but they are not very useful for diagnosis.

The review of systems should be the guide for additional evaluations of sarcoidosis because other disease sites may have substantial associated morbidity. Signs and symptoms of neurologic involvement may include new-onset headaches, seizures, bowel/bladder dysfunction, gait disturbance, and paresthesias. A patient with suspected ocular sarcoidosis should be asked about symptoms of cardiac arrhythmia (ie, unexplained fainting) or heart failure. Cardiac sarcoidosis is rare, but it can be asymptomatic as well as a cause of sudden cardiac arrest; therefore, some advocate obtaining a screening electrocardiogram in all patients with suspected ocular sarcoidosis, as definitive proof of sarcoidosis could be lifesaving for patients with cardiac disease. Fluorine-18-fluorodeoxyglucose positron emission tomography may be used to identify occult sarcoidosis disease activity and potential sites for biopsy. However, this imaging modality is expensive and involves extensive radiation exposure, so it should be reserved for scenarios in which the correct diagnosis would truly change management (ie, differentiating between neoplastic, inflammatory, and infectious diseases.)

Han YS, Rivera-Grana E, Salek S, Rosenbaum JT. Distinguishing uveitis secondary to sarcoidosis from idiopathic disease: cardiac implications. *JAMA Ophthalmol*. 2018; 136(2):109–115.

McKay KM, Lim LL, Van Gelder RN. Rational laboratory testing in uveitis: a Bayesian analysis. *Surv Ophthalmol*. 2021;66(5):802–825.

Mochizuki M, Smith JR, Takase H, Kaburaki T, Acharya NR, Rao NA; International Workshop on Ocular Sarcoidosis Study Group. Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. *Br J Ophthalmol.* 2019;103(10):1418–1422.

Treatment

Local and systemic corticosteroids are appropriate for initial treatment and short-term control of ocular sarcoidosis. Topical cycloplegia should be utilized to prevent synechiae formation until anterior segment inflammation is well controlled. Posterior segment disease usually requires systemic corticosteroids; for sarcoid uveitis, intravitreal corticosteroids, including implants, can be adjunctive or primary treatment, but systemic disease will be untreated.

Systemic IMT should be used when there is persistent or recurrent vision-threatening ocular sarcoidosis despite administration of corticosteroids or when complications arise with their use. Repeated short courses of systemic corticosteroids or monotherapy with serial intravitreal corticosteroids can lead to cumulative damage from waxing and waning ocular inflammation. Options for systemic IMT include methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and leflunomide. The tumor necrosis factor (TNF) inhibitors adalimumab and infliximab have been shown to be effective in treating sarcoid uveitis. Paradoxically, a sarcoid-like syndrome is a rare adverse effect of etanercept, another TNF inhibitor.

Factors associated with vision loss from ocular sarcoidosis include chronic intermediate or posterior uveitis, glaucoma, and delayed involvement of a uveitis specialist.

Takase H, Acharya NR, Babu K, et al. Recommendations for the management of ocular sarcoidosis from the International Workshop on Ocular Sarcoidosis. *Br J Ophthalmol.* 2021;105(11):1515–1519.

Sympathetic Ophthalmia

Sympathetic ophthalmia (SO) is a rare, bilateral granulomatous panuveitis that develops after surgical or accidental trauma to one eye (the *exciting eye*). After a latent period ranging from months to years, uveitis develops in the uninjured fellow eye (the *sympathizing eye*). In a recent series, one-third of patients developed SO within 3 months of ocular injury or surgery, and less than one-half did so within 1 year of the event. Earlier studies found that SO was more likely to occur after accidental penetrating ocular trauma than after ocular surgery; however, owing to improved access to emergency surgical care after ocular trauma (particularly in combat situations), SO is now more commonly associated with ocular surgery such as pars plana vitrectomy. In rare cases, SO may develop after nonpenetrating ocular surgery, such as transscleral ciliary body laser, panretinal photocoagulation, and radioactive plaque therapy.

The precise etiology of SO is unknown, but it is hypothesized to be an autoimmune reaction to previously sequestered ocular antigens from the RPE or choroid that reach conjunctival lymphatic channels and initiate an immunopathologic T-lymphocyte response. There may be a genetic predisposition to SO, as affected patients are more likely to express human leukocyte antigen (HLA)-DR4, HLA-DRw53, and HLA-DQw3 haplotypes compared with the general population. Of note, SO and VKH syndrome have nearly identical immunogenetics and share many of the same pathologic ophthalmic features.

Anikina E, Wagner S, Liyanage S, Sullivan P, Pavesio C, Okhravi N. The risk of sympathetic ophthalmia after vitreoretinal surgery. *Ophthalmol Retina*. 2022;6(5):347–360.

Chu XK, Chan CC. Sympathetic ophthalmia: to the twenty-first century and beyond. *J Ophthalmic Inflamm Infect*. 2013;3(1):49.

Fromal OV, Swaminathan V, Soares RR, Ho AC. Recent advances in diagnosis and management of sympathetic ophthalmia. *Curr Opin Ophthalmol*. 2021;32(6):555–560.

He B, Tanya SM, Wang C, Kezouh A, Torun N, Ing E. The incidence of sympathetic ophthalmia after trauma: a meta-analysis. *Am J Ophthalmol*. 2022;234:117–125.

Manifestations

As mentioned previously, in SO the injured/postsurgical eye is the exciting eye and the fellow eye is the sympathizing eye. Patients with SO typically present with asymmetric bilateral panuveitis, in which the exciting eye exhibits more severe inflammation than the sympathizing eye, at least initially. However, prior enucleation, phthisis, or corneal opacity may preclude observation of inflammation in the exciting eye. Early SO symptoms may also include near vision loss (secondary to ciliary body edema), photosensitivity, pain, floaters, photopsia, and metamorphopsia. In rare cases, there may be extraocular signs and symptoms similar to those observed in VKH syndrome (ie, cerebral spinal fluid pleocytosis, sensory neural hearing disturbance, alopecia, poliosis, and vitiligo).

Anterior segment findings include granulomatous KPs, thickening of the iris from lymphocytic infiltration, and posterior synechiae. Intraocular pressure (IOP) may be elevated because of trabeculitis, or it may be low as a result of ciliary body hyposecretion. Moderate to severe vitritis is usually present. Fundus examination typically shows multiple serous retinal detachments and yellow-white midperipheral lesions known as *Dalen-Fuchs nodules* (Fig 10-14). With time, these lesions can coalesce into areas of chorioretinal atrophy. Optic nerve edema followed by optic atrophy, chronic macular edema, CNV, and cataract may also develop.

Two fluorescein angiography (FA) patterns may be seen in acute SO, sometimes concurrently: (1) multiple areas of early pinpoint hyperfluorescence (Fig 10-15) with late pooling corresponding to areas of serous retinal detachments; and (2) early hypofluorescence and late staining of chorioretinal lesions. Indocyanine green angiography (ICGA) shows numerous hypocyanescent foci (Fig 10-16), whereas fundus autofluorescence (FAF)

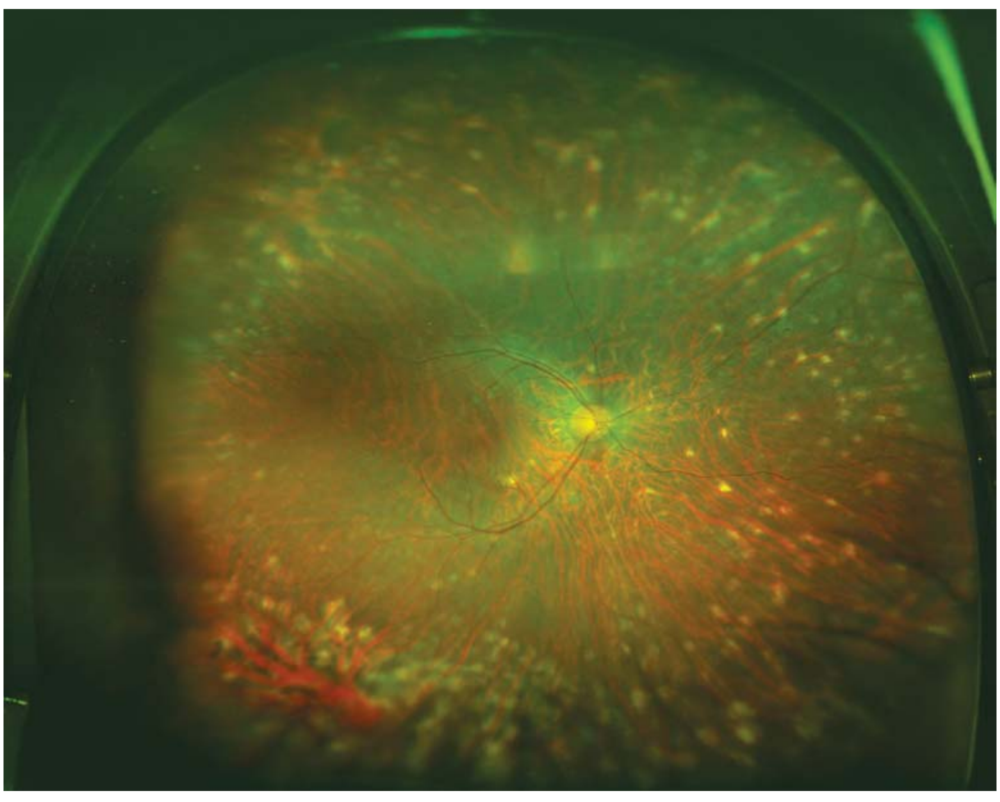


Figure 10-14 Sympathetic ophthalmia. Wide-field fundus photograph shows multiple yellow-white lesions known as *Dalen-Fuchs nodules*. *(Courtesy of Emilio M. Dodds, MD.)*

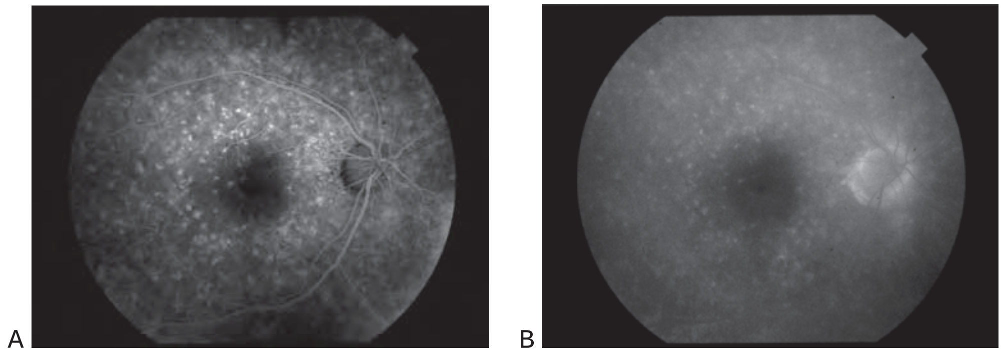


Figure 10-15 Sympathetic ophthalmia. **A,** Early FA demonstrates pinpoint hyperfluorescence. **B,** Late FA shows staining. *(Courtesy of Emilio M. Dodds, MD.)*

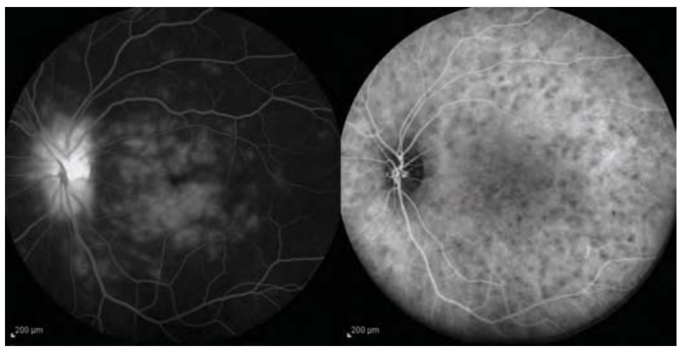


Figure 10-16 Sympathetic ophthalmia. *Left,* FA shows substantial late disc leakage with moderate late central macular leakage. *Right,* Indocyanine green angiography demonstrates multiple hypocyanescent lesions that are more numerous than lesions found on clinical examination or FA. *(Courtesy of Wendy M. Smith, MD.)*

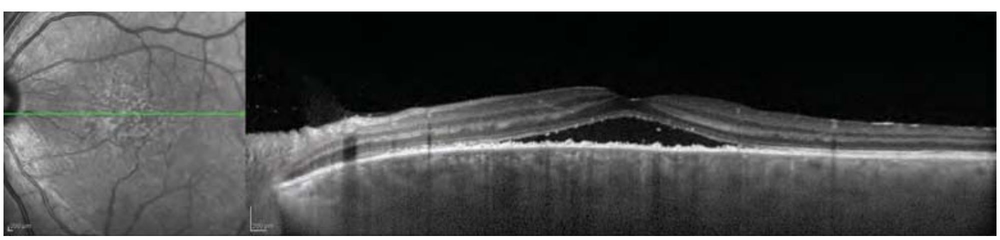


Figure 10-17 Sympathetic ophthalmia. Enhanced depth imaging (EDI)-OCT of the same patient as in Figure 10-16 shows subfoveal fluid with massive, diffuse choroidal thickening. *(Courtesy of Wendy M. Smith, MD.)*

shows hypoautofluorescence secondary to blockage by nodules or atrophy. Optical coherence tomography (OCT) may show choroidal folds and thickening, retinal edema, and/or subretinal fluid (Fig 10-17). Choroidal thickening may also be demonstrated by B-scan ultrasonography.

The histologic features of SO are similar for both the exciting and sympathizing eyes. The entire uveal tract is infiltrated by a diffuse granulomatous, nonnecrotizing inflammatory response that is composed primarily of lymphocytes plus epithelioid cells and a few giant cells. In the choroid, the choriocapillaris is classically spared, at least in the early stage. Dalen-Fuchs nodules, also found in sarcoidosis and VKH, are composed of lymphocytes and epithelioid histiocytes and are located between the RPE and Bruch membrane (see BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors*).

Mahajan S, Invernizzi A, Agrawal R, Biswas J, Rao NA, Gupta V. Multimodal imaging in sympathetic ophthalmia. *Ocul Immunol Inflamm*. 2017;25(2):152–159.

Diagnosis

The diagnosis of SO is clinical and should be suspected in any patient with bilateral uveitis after ocular trauma or surgery. The differential diagnosis includes TB, sarcoidosis, syphilis, traumatic or postoperative endophthalmitis, and endogenous fungal endophthalmitis. SO and lens-associated uveitis (phacoantigenic) may occur concurrently and share similar clinical features; in the absence of SO, lens-associated uveitis can be differentiated by the absence of choroidal thickening. SO and VKH can also have very similar clinical presentations; however, by definition patients with VKH have no history of ocular injury.

Treatment

In primary penetrating ocular trauma, every effort should be made to salvage eyes with a reasonable prognosis for useful vision, as SO is rare and treatable. When the globe is grossly disorganized with no discernible visual potential, enucleation within 2 weeks of injury may be considered to reduce the risk of SO. Although controversial, enucleation may still be preferred to evisceration, because it removes all residual uveal tissue that may predispose patients to the development of SO. See BCSC Section 7, *Oculofacial Plastic and Orbital Surgery,* for further discussion of enucleation versus evisceration. Regardless of visual potential, once SO has developed, enucleation of the exciting eye does not appear to reduce inflammation in the sympathizing eye. In fact, the exciting eye may eventually become the better-seeing eye.

Treatment of SO usually involves local and/or systemic corticosteroids combined with systemic IMT. Long-term therapy is necessary in most patients, and if the inflammation is severe and vision threatening, alkylating agents should be used. With prompt and aggressive systemic therapy, the visual prognosis of SO is good; 60% of patients achieve a final visual acuity of 20/40, although up to 25% decline to 20/200 or worse in the sympathizing eye.

Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia: a clinicopathologic review of 105 cases (1913–1978). *Ophthalmology.* 1980;87(2):109–121.

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada (VKH) syndrome is a multisystem disease characterized by bilateral granulomatous posterior uveitis or panuveitis that is usually accompanied by auditory, neurologic, and integumentary manifestations. Ethnic groups affected by VKH include individuals of East Asian, South Asian, Middle Eastern, Hispanic, and Native American ancestry. Accordingly, the incidence of VKH varies geographically: in tertiary referral centers for uveitis, VKH accounts for 6%–8% of cases in Asia, 1.2% in the Middle East, 1%–4% in North America, and 2%–4% in Brazil.

The precise pathogenesis of VKH is unknown, but current evidence implicates a T-cell–mediated process directed against melanin-containing cells in the eyes, ears, skin, and meninges. A genetic predisposition for VKH is supported by a strong association with HLA-DR4 among Japanese patients and with HLA-DR1 or HLA-DR4 among Hispanic patients in Southern California.

Abu El-Asrar AM, Van Damme J, Struyf S, Opdenakker G. New perspectives on the immunopathogenesis and treatment of uveitis associated with Vogt-Koyanagi-Harada disease. *Front Med (Lausanne)*. 2021;8:705796. doi:10.3389/fmed.2021.705796

Rao NA. Pathology of Vogt-Koyanagi-Harada disease. *Int Ophthalmol*. 2007;27(2–3):81–85.

Sakata VM, da Silva FT, Hirata CE, de Carvalho JF, Yamamoto JH. Diagnosis and classification of Vogt-Koyanagi-Harada disease. *Autoimmun Rev*. 2014;13(4-5):550–555.

Manifestations

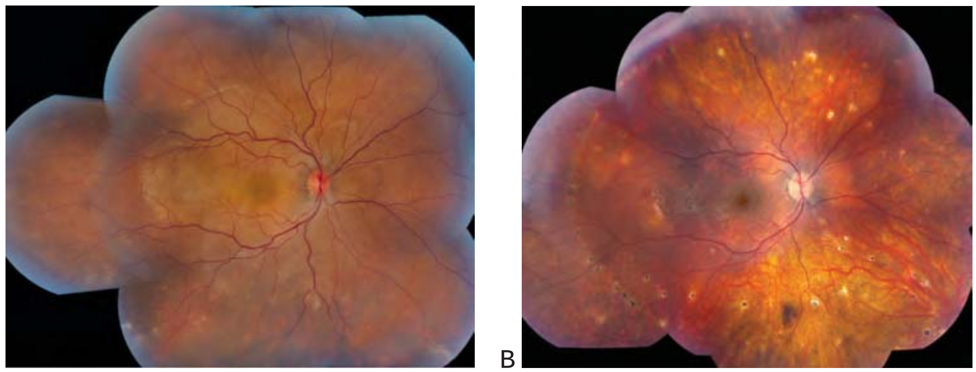
Prodrome Before the onset of ocular symptoms, patients with VKH may experience headache, nausea, meningismus, dysacusia, tinnitus, fever, orbital pain, photophobia, and hypersensitivity of the skin to touch. Focal neurologic signs are rare but may include cranial neuropathies, hemiparesis, aphasia, transverse myelitis, and ganglionitis. Cerebrospinal fluid analysis reveals lymphocytic pleocytosis with normal levels of glucose in more than 80% of patients. Central dysacusia of the higher frequencies occurs in approximately 30% of patients early in the disease course, usually improving within 2–3 months.

Previous investigators described 4 stages of VKH uveitis, but multimodal imaging suggests VKH is a continuum from early- to late-stage disease.

Early stage The early stage of VKH is characterized by bilateral granulomatous anterior uveitis, a variable degree of vitritis, thickening of the choroid, optic nerve edema, and multiple serous retinal detachments (Fig 10-18A). Rare cases may be unilateral. The focal serous retinal detachments are often small and shallow, forming a cloverleaf pattern around the posterior pole, but they may coalesce and evolve into bullous exudative detachments. The posterior pole exudative retinal detachments may be associated with substantial vision loss. Other findings include granulomatous KPs and pupillary margin nodules. IOP may be elevated with shallowing of the anterior chamber because of ciliary body edema or annular choroidal detachment. Alternatively, ciliary body shutdown may result in low IOP.

Late stage In late-stage VKH, there may be features of a smoldering panuveitis including anterior chamber inflammation, vitritis, and choroiditis/choroidal thickening. Repeated bouts of granulomatous anterior uveitis may occur, but recurrent serous retinal detachment is uncommon in late-stage disease. Additional sequelae of chronic inflammation include posterior subcapsular cataract, glaucoma, CNV, and subretinal fibrosis.

The orange-red "sunset-glow" fundus of VKH evolves as a result of depigmentation of the choroid, and juxtapupillary depigmentation may also occur. Small, round, discrete, depigmented, atrophic chorioretinal spots may develop in the peripheral fundus (Fig 10-18B). Perilimbal vitiligo (Sugiura sign) is present in up to 85% of Japanese patients with VKH but is rarely observed among White patients with the disease (Fig 10-19). In up to 30% of patients, integumentary changes such as vitiligo, alopecia, and poliosis develop (Fig 10-20), which can coincide with fundus depigmentation as a later finding. Among Hispanic patients, the incidence of cutaneous and other extraocular manifestations is relatively low.



A B

Figure 10-18 Vogt-Koyanagi-Harada syndrome. **A,** Color fundus photograph montage from initial presentation shows exudative retinal detachments. **B,** After treatment, residual depigmented deep lesions in the periphery and diffuse sunset-glow fundus changes are seen. *(Courtesy of Jared E. Knickelbein, MD, PhD, and Nida Sen, MD/National Eye Institute.)*

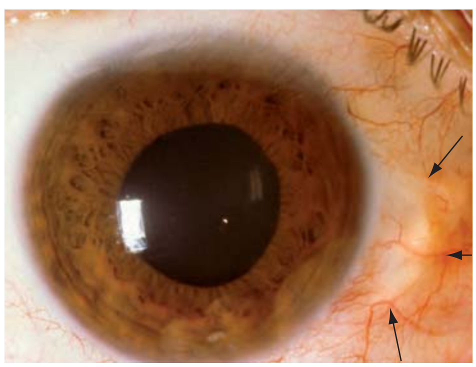


Figure 10-19 Perilimbal vitiligo (Sugiura sign) *(arrows)*. *(Courtesy of Albert T. Vitale, MD.)*

Figure 10-20 Vogt-Koyanagi-Harada syndrome. Vitiligo of the upper eyelid and marked poliosis in the late stage. *(Courtesy of Ramana S. Moorthy, MD.)*

Imaging findings

In the early stage of VKH, FA reveals punctate hyperfluorescent foci followed by pooling in areas of neurosensory detachment (Fig 10-21). Optic disc leakage occurs in most cases, but macular edema and retinovascular leakage are less common. In late-stage disease, alternating areas of hyperfluorescent window defects (from RPE loss) and hypofluorescence (from chorioretinal atrophy and pigment migration) are seen.

ICGA in early-stage VKH shows initial choroidal perfusion delay and subsequent segmental or diffuse choroidal vessel hypercyanescence indicating inflammatory vasculopathy. Hypocyanescent dark dots, likely corresponding to choroidal granulomas, are also seen. These hypocyanescent dark dots are often more widespread than clinical examination findings, and thus ICGA can be used to detect and monitor subclinical choroidal inflammation.

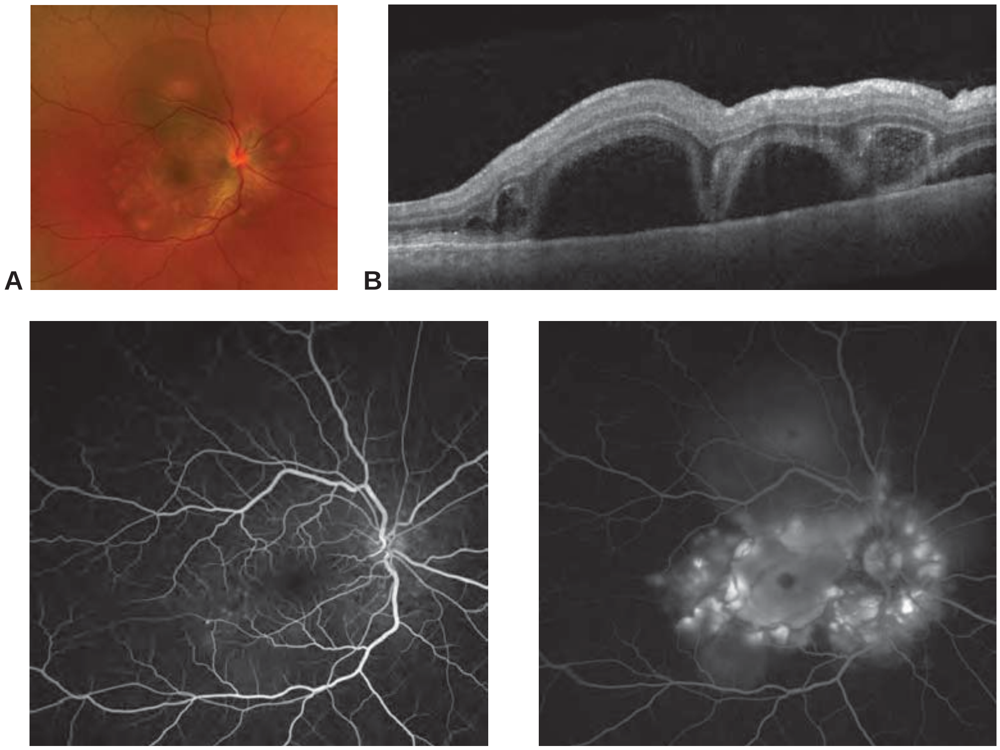


Figure 10-21 Vogt-Koyanagi-Harada syndrome. **A,** Color photograph shows multiple serous retinal detachments. **B,** OCT scan reveals characteristic loculated spaces of subretinal fluid with fibrinous septa extending from the outer retina to the retinal pigment epithelium. **C,** FA shows early pinpoint hyperfluorescence. **D,** Late-phase FA shows leakage and pooling within multiple serous detachments. *(Courtesy of Karen R. Armbrust, MD, PhD.)*

Ultrasonography may display low to medium reflective thickening of the posterior choroid, exudative retinal detachment, vitreous opacities, and posterior thickening of the sclera and/or episclera.

OCT is useful for monitoring serous macular detachments, macular edema, and choroidal neovascular membranes. In the presence of multiple serous detachments, OCT may show loculated areas of subretinal fluid with fibrinous septa extending from the retina to the RPE (see Fig 10-21B). Enhanced depth imaging OCT displays massive choroidal thickening in the early stage that decreases with treatment (Fig 10-22). Recurrent choroidal thickening may precede the appearance of anterior chamber cells if VKH activity increases. FAF may show hyperautofluorescence in early-stage disease (early damage to RPE from inflammation) with areas of hypoautofluorescence corresponding to serous detachments. Later, hypoautofluorescent spots may develop as a result of RPE loss and chorioretinal atrophy.

Histologic findings

In early-stage VKH there is a diffuse, nonnecrotizing, granulomatous inflammation that is virtually identical to the pattern seen in SO. The uveal inflammation consists of

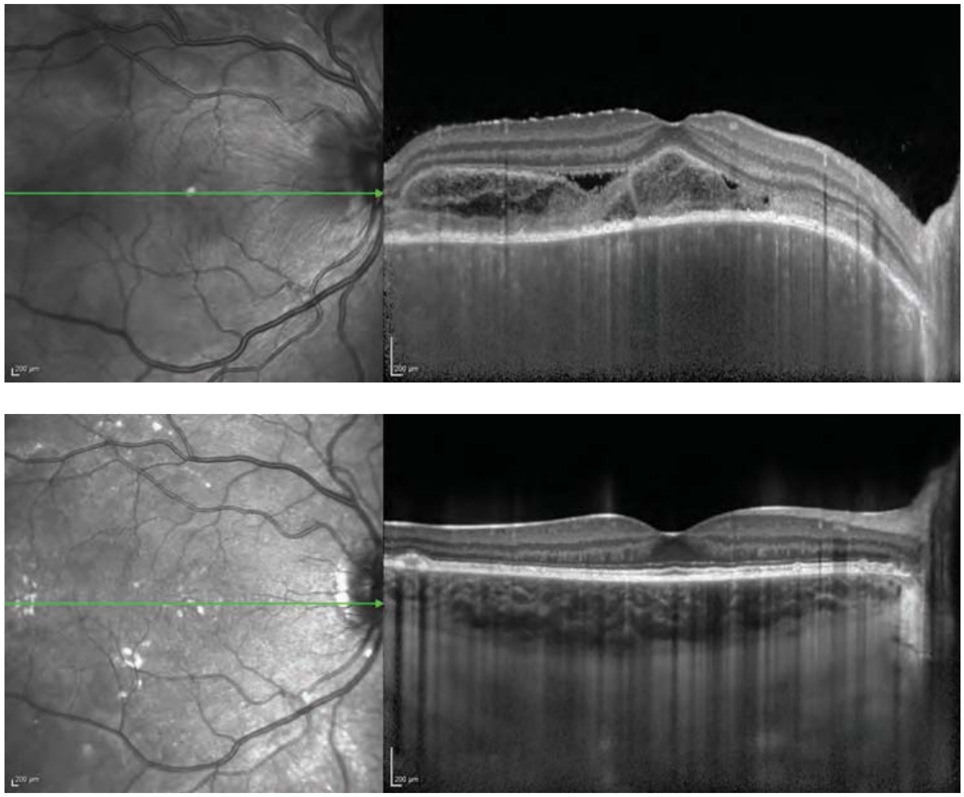
A

B

Figure 10-22 Vogt-Koyanagi-Harada syndrome. **A,** EDI-OCT shows turbid subretinal fluid and massive choroid thickening. **B,** After treatment, the subretinal fluid and choroidal thickening resolved. *(Courtesy of Jared R. Knickelbein, MD, PhD, and Nida Sen, MD/National Eye Institute.)*

lymphocytes, macrophages, and epithelioid and multinucleated giant cells with preservation of the choriocapillaris. The peripapillary choroid is the predominant site of inflammation, but the ciliary body and iris may also be involved.

In late-stage VKH, the choriocapillaris is damaged and sometimes obliterated. The number of choroidal melanocytes decreases with loss of melanin pigment (corresponding to the sunset-glow fundus).

Diagnosis

Vogt-Koyanagi-Harada syndrome is a clinical diagnosis; no confirmatory diagnostic tests exist. The 2001 International Committee Revised Diagnostic Criteria included categories of "complete," "incomplete," and "probable" VKH. More recently, the Standardization of Uveitis Nomenclature (SUN) Working Group sought to minimize misclassification by dividing cases into early-stage (Table 10-1) and late-stage (Table 10-2) diseases. Patients may have overlap of early- and late-stage diseases.

The differential diagnosis of VKH includes SO, uveal effusion syndrome, posterior scleritis, vitreoretinal lymphoma, choroidal lymphoma, acute posterior multifocal placoid

Table 10-1 Classification Criteria for Early-Stage Vogt-Koyanagi-Harada Syndrome

Criteria: require #1 or #2 below

1. Evidence of Vogt-Koyanagi-Harada syndrome (posterior uveitis with serous detachment) and no history of penetrating trauma or vitreoretinal surgery prior to disease onset
   a. Serous (exudative) retinal detachment AND
   b. Multiloculated appearance on fluorescein angiogram or septa on optical coherence tomography

OR

2. Panuveitis[a] with ≥2 of the following within 4 weeks and no history of penetrating trauma or vitreoretinal surgery prior to disease onset:
   a. Headache OR
   b. Tinnitus OR
   c. Dysacusis OR
   d. Meningismus OR
   e. Cerebrospinal fluid pleocytosis

Exclusions

1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomas)

[a]Patients with uveitis should have evidence of choroidal involvement on clinical examination, fluorescein angiography, indocyanine green angiography, or optical coherence tomography.

Adapted with permission from SUN Working Group. Classification criteria for Vogt-Koyanagi-Harada disease. *Am J Ophthalmol*. 2021;228:205–211.

Table 10-2 Classification Criteria for Late-Stage Vogt-Koyanagi-Harada Syndrome

Criteria: history of early-stage Vogt-Koyanagi-Harada syndrome plus #1 or #2 below

1. Sunset-glow fundus

OR

2. Uveitis[a] AND at least 1 of the following: vitiligo, poliosis, or alopecia

Exclusions

1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomas)

[a]Uveitis may be (1) chronic anterior uveitis, (2) anterior and intermediate uveitis, or (3) panuveitis with multifocal choroiditis (Dalen-Fuchs–like nodules).

Adapted with permission from SUN Working Group. Classification criteria for Vogt-Koyanagi-Harada disease. *Am J Ophthalmol*. 2021;228:205–211.

pigment epitheliopathy, bilateral diffuse uveal melanocytic proliferation, TB-associated uveitis, and sarcoidosis.

Abouammoh MA, Gupta V, Hemachandran S, Herbort CP, Abu El-Asrar AM. Indocyanine green angiographic findings in initial-onset acute Vogt-Koyanagi-Harada disease. *Acta Ophthalmol*. 2016;94(6):573–578.

Jap A, Chee SP. Imaging in the diagnosis and management of Vogt-Koyanagi-Harada disease. *Int Ophthalmol Clin*. 2012;52(4):163–172.

Jap A, Chee SP. The role of enhanced depth imaging optical coherence tomography in chronic Vogt-Koyanagi-Harada disease. *Br J Ophthalmol*. 2017;101(2):186–189.

Treatment and prognosis

Aggressive therapy for VKH can produce good visual outcomes, especially when used early in the disease course. Initial treatment is high-dose systemic corticosteroids followed by a taper. Within 3 months, oral corticosteroids are tapered to 10 mg or less daily and then decreased very slowly (often at a rate of 1 mg per month) over the subsequent 6–12 months to prevent late-stage VKH. Local steroid injections should be used with caution, as patients with VKH may have an increased risk of developing elevated IOP.

Most practitioners also initiate systemic IMT at the onset of VKH to reduce the risk of chronic inflammation with subsequent pigment loss, chorioretinal atrophy, and loss of visual function. Systemic treatment with corticosteroids or IMT reduces the risk of vision loss and the development of structural complications such as CNV and subretinal fibrosis.

Greco A, Fusconi M, Gallo A, et al. Vogt-Koyanagi-Harada syndrome. *Autoimmun Rev.* 2013;12(11):1033–1038.

Herbort CP Jr, Abu El Asrar AM, Takeuchi M, et al. Catching the therapeutic window of opportunity in early initial-onset Vogt-Koyanagi-Harada uveitis can cure the disease. *Int Ophthalmol*. 2019;39(6):1419–1425.

Behçet Disease

Behçet disease (BD) is a chronic, relapsing, multisystem vasculitis known for the triad of (1) painful oral ulcers, (2) genital lesions, and (3) recurrent (often high-grade) uveitis. BD may also affect the joints, skin, heart, gastrointestinal system, and CNS. No environmental or infectious factors have been definitely linked to BD. The disorder is clinically and experimentally unlike other autoimmune diseases.

The disease has been described for more than 2,500 years; in the early 20th century, it was formally characterized by Adamantiades and Behçet. Affected patients often have ancestry derived from the ancient Silk Road, extending from Greece and Turkey in the eastern Mediterranean to China, Korea, and Japan along the eastern rim of Asia.

The prevalence of BD varies from as high as 20–421 cases per 100,000 inhabitants in Turkey to 13.5–30 cases per 100,000 people in Asia. The estimated prevalence in the United States is 5.2 cases per 100,000 people. Onset typically occurs in the third and fourth decades, but the disease can also present in childhood or after age 50 years. Both sexes are affected equally, but BD may have a more severe course in males. Uveitis may be especially severe in young males aged 15–25 years, and diagnosis of BD is often delayed in this demographic. Although some familial cases exist, most are sporadic.

Hammam N, Li J, Evans M, et al. Epidemiology and treatment of Behçet's disease in the USA: insights from the Rheumatology Informatics System for Effectiveness (RISE) Registry with a comparison with other published cohorts from endemic regions. *Arthritis Res Ther*. 2021;23(1):224.

Yazici H, Seyahi E, Hatemi G, Yazici Y. Behçet syndrome: a contemporary view. *Nat Rev Rheumatol*. 2018;14(2):107–119.

Figure 10-23 Behçet disease. Mucous membrane ulcers (oral aphthae).

Nonocular manifestations

In patients with BD, painful oral aphthae can occur on the lips, gums, palate, tongue, uvula, and posterior pharynx (Fig 10-23). These discrete, round lesions are white with red rims, vary in size from 2 to 15 mm, and last 7–10 days until healing with zero to minimal scarring. Genital ulcers, which occur on the scrotum or penis in men and on the vulva and vaginal mucosa in women, are deeper and larger and heal with more scarring.

Skin lesions include painful or recurrent erythema nodosum, often over extensor surfaces such as the tibia, but also on the face, neck, and buttocks. Pustular acnelike spots called *pseudofolliculitis* may occur on the upper thorax and face. Skin lesions may resolve with minimal or no scarring. Nearly 40% of patients with BD exhibit cutaneous pathergy: the development of a sterile pustule at the site of a venipuncture or an injection; however, this is not pathognomonic.

Systemic vasculitis affecting any size artery or vein in the body occurs in up to 25% of patients with BD. Examples include arterial occlusions and aneurysms and superficial or deep venous thrombosis and varices. Cardiac involvement can manifest as granulomatous endocarditis, myocarditis, endomyocardial fibrosis, coronary arteritis, or pericarditis. Gastrointestinal lesions, such as ulcers involving the esophagus, stomach, and intestines, are seen in more than 50% of Japanese patients with BD, for whom it is a major cause of morbidity. Lung involvement is mainly pulmonary arteritis with aneurysmal dilatation of the pulmonary artery. Moreover, 50% of patients with BD develop arthritis, commonly of the knee, elbow, hand, or ankle.

Thirty percent of patients with ocular BD have neurologic involvement, and 10% of patients with *neuro-BD* have ocular disease. Brain or brainstem white matter lesions may cause motor dysfunction, stroke, and cognitive/behavioral changes. CNS vasculitis or meningeal inflammation may provoke headaches and aseptic meningitis, respectively. Neuro-ophthalmic involvement may also include cranial nerve palsies, papillitis, and papilledema from venous sinus thrombosis.

Ocular manifestations

Up to 70% of patients with BD have ocular manifestations; however, ocular involvement is not usually an initial presenting symptom or sign, and it may develop years after involvement of other organs. In addition, ocular BD usually does not cause chronic inflammation; it is typically an acute and explosive inflammation that spontaneously resolves in a few weeks, potentially with substantial vision loss when there is retinal ischemia from vaso-occlusive disease.

When uveitis occurs in patients with BD, it is most often bilateral and nongranulomatous and can occur in all potential anatomical sites. However, the most common forms of ocular BD are posterior uveitis and panuveitis (50%–80% of cases), which may be profoundly sight threatening as well as more severe in men. A characteristic finding is occlusive retinal vasculitis affecting arteries and veins, which may manifest as multifocal chalky white retinitis, often with surrounding retinal hemorrhage (Figs 10-24, 10-25). Other posterior manifestations of ocular BD include vitritis with or without dense haze, retinal artery and vein occlusions, macular edema, and macular atrophy. Repeated occlusions cause whitening and sclerosis of retinal vessels. Retinal ischemia can stimulate retinal and iris neovascularization. The optic nerve is affected in 25% of patients with ocular BD. Vasculitis affecting the posterior ciliary vessels may cause optic papillitis and subsequent optic atrophy.

In a minority of cases, anterior uveitis may be the only ocular manifestation of BD. Although BD is associated with hypopyon, this is not a common occurrence. A classic description is a sudden-onset hypopyon that shifts with patient head position or disperses with head shaking. The eye may appear relatively quiet despite the hypopyon, or the patient may experience symptoms of acute anterior uveitis (ie, redness, photophobia, and pain). In addition, relapses of anterior uveitis can lead to posterior synechiae, iris bombé, and

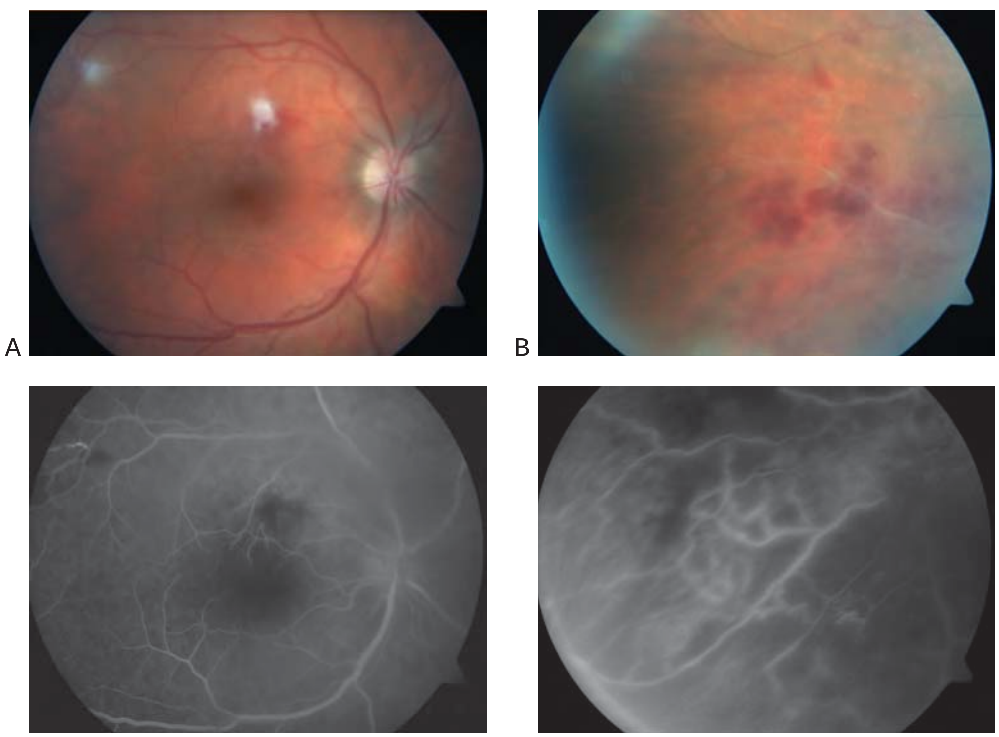


Figure 10-24 Behçet disease with retinitis and vasculitis in a 17-year-old male. **A,** Fundus photograph shows retinitis and hemorrhage in the macula. **B,** Fundus photograph shows retinitis, hemorrhage, and vascular occlusion in the midzone. **C,** Mid-phase FA of the macula. **D,** Peripheral FA shows nonperfusion and vessel staining. *(Courtesy of Sam S. Dahr, MD, MS.)*

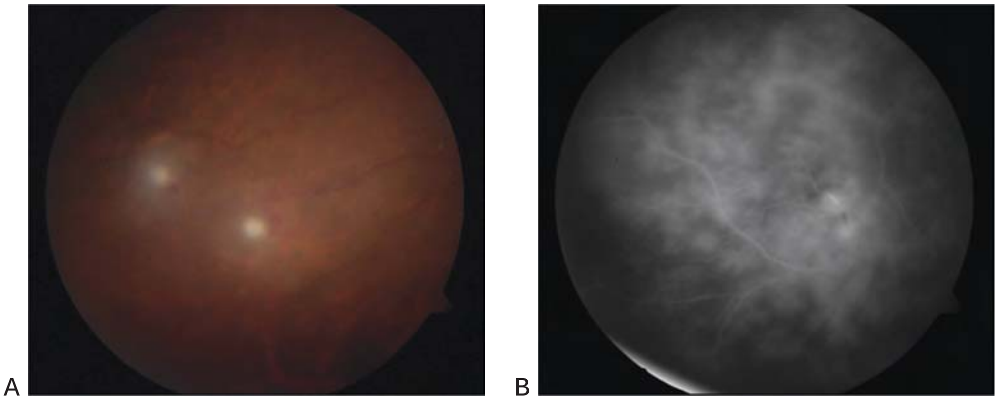


Figure 10-25 Behçet disease. **A,** Fundus photograph of retinitis. **B,** FA shows a ferning pattern of small vessel leakage and focal areas of more intense hyperfluorescence. *(Courtesy of Sam S. Dahr, MD, MS.)*

angle-closure glaucoma. Less common anterior segment features include episcleritis, scleritis, conjunctival ulcers, and corneal immune ring opacities.

In cases of acute ocular BD, FA may show islands of hyperfluorescence corresponding to capillaritis in the posterior and midzones of the retina (see Fig 10-25B). These islands may or may not correspond to clinically visible retinitis and are important indicators of active or impending inflammation. Larger vessels as well as the optic nerve may leak and/or stain. When early signs of inflammation are observed on FA, treatment may prevent an explosive attack. Later sequelae on FA include foveal capillary pruning, islands of capillary nonperfusion, telangiectasias and remodeling, and neovascularization (see Fig 10-24C, D). OCT can show inflammatory retinal edema as well as later macular atrophy.

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Pathogenesis

Histologically, neutrophils, T lymphocytes, macrophages, and plasma cells accumulate around the vasa vasorum and perivascular area, generating immunoglobulin and complement-containing immune complexes (Fig 10-26). Necrotizing, neutrophilic, obliterative perivasculitis with or without fibrinoid necrosis develops in capillaries, arteries, and veins of all sizes. Local aggregates of B lymphocytes and plasma cells may be present, contributing to immune complex deposition. The vascular endothelium, meanwhile, shows upregulated expression of adhesion molecules.

Diagnosis

The differential diagnosis of BD includes HLA-B27–associated anterior uveitis, reactive arthritis, JIA, inflammatory bowel disease–associated uveitis, sarcoidosis, and Susac

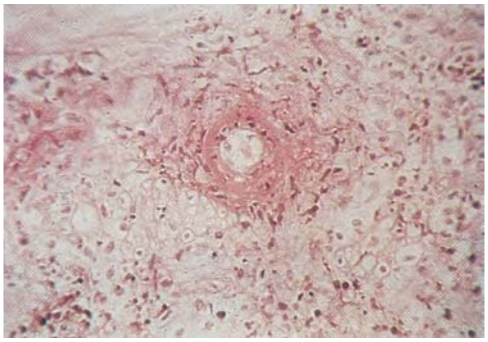

Figure 10-26 Behçet disease. Histologic view of perivascular inflammation.

Table 10-3 International Study Group Criteria for the Diagnosis of Behçet Disease

Recurrent oral aphthous ulcers (at least 3 times per year) plus 2 of the following criteria:

1. Recurrent genital ulcers
2. Ocular inflammation
3. Skin lesions
4. Positive cutaneous pathergy test result

Adapted from International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet.* 1990;335(8697):1078–1080.

syndrome. Systemic vasculitides such as SLE, PAN, and GPA are also included in the differential. In addition, infections such as acute retinal necrosis, toxoplasmosis, and syphilis and masquerade syndromes such as lymphoma may cause a retinitis that mimics BD.

BD is a clinical diagnosis (Table 10-3). Although HLA typing, cutaneous pathergy testing, and blood tests such as ESR and CRP can provide supportive evidence for BD, none definitively establishes the diagnosis. Of note, although the HLA-B51 allele is strongly associated with BD, it is not one of the diagnostic criteria. This association—much like the association between mucocutaneous BD and HLA-B12—is not reproducible in all populations, and testing lacks the sensitivity and specificity necessary to support routine diagnostic use.

Yazici Y, Hatemi G, Bodaghi B, et al. Behçet syndrome. *Nat Rev Dis Primers*. 2021;7(1):67.

Treatment of ocular Behçet disease

The goals of ocular BD treatment are twofold: (1) quickly control acute inflammation to minimize damage; and (2) treat chronic inflammation and reduce the frequency and severity of future attacks. Close collaboration with other specialists, such as rheumatologists, dermatologists, neurologists, and gastroenterologists, is often indicated to treat this multisystem disease.

Systemic corticosteroids are usually necessary to control acute inflammation. Periocular and intravitreal corticosteroids may be a useful adjunct in select patients. Corticosteroid monotherapy should be avoided in sight-threatening ocular BD because of the risk of severe rebound attacks during tapering.

Posterior segment ocular BD is an absolute indication for prompt initiation of systemic IMT. An American expert panel recommended TNF inhibitor therapy with infliximab or