CHAPTER 15

Masquerade Syndromes

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Highlights

- Uveitic masquerade syndromes are neoplastic and nonneoplastic conditions that mimic immune-mediated entities. Because the underlying diseases often have serious consequences, early diagnosis and prompt treatment are vital.
- The most common condition to mimic uveitis is vitreoretinal lymphoma (VRL).
- VRL typically presents with vitritis, subretinal infiltrates, subretinal pigment epithelium infiltrates, and/or intraretinal infiltrates. Definitive diagnosis is made by cytologic analysis of intraocular fluid or tissue.
- More than two-thirds of patients with VRL will develop central nervous system (CNS) lymphoma; thus, all patients with suspected VRL should be evaluated for CNS lymphoma even in the absence of neurologic symptoms.

Introduction

Uveitic masquerade syndromes are a heterogeneous group of conditions noteworthy for mimicking immune-mediated uveitis and therefore are often difficult to diagnose. They can be divided into neoplastic and nonneoplastic conditions. The underlying diseases often have harmful consequences, so early diagnosis and prompt treatment may preserve life and/or vision.

Neoplastic Masquerade Syndromes

Neoplastic masquerade syndromes may account for 2%–3% of all patients evaluated in tertiary uveitis clinics. Vitreoretinal lymphoma is the most common entity.

Grange LK, Kouchouk A, Dalal MD, et al. Neoplastic masquerade syndromes in patients with uveitis. *Am J Ophthalmol.* 2014;157(3):526–531.

Read RW, Zamir E, Rao NA. Neoplastic masquerade syndromes. *Surv Ophthalmol.* 2002;47(2):81–124.

Vitreoretinal Lymphoma

Vitreoretinal lymphoma (VRL), formerly known as *primary intraocular lymphoma,* is a subset of primary central nervous system lymphoma (PCNSL). It is an uncommon but potentially fatal malignant neoplasm that may occur with or without CNS lesions. The mean age at onset is between 50 and 70 years, and there is no convincing gender predilection. Immunosuppressed patients are at increased risk of VRL. Nearly all (98%) cases of VRL are B-cell, non-Hodgkin lymphomas. Approximately 2% are T-cell lymphomas.

Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. *Oncologist*. 2011;16(11):1589–1599.

Clinical features and findings

Approximately 25% of patients with intracranial lymphoma will develop intraocular disease. The most common presenting symptoms are decreased vision and floaters. Sites of ocular involvement include the vitreous, retina, and subretinal or subretinal pigment epithelium (sub-RPE) spaces, or any combination thereof.

Examination reveals a variable degree of vitritis and anterior chamber cells. Posterior segment involvement may appear as cream-colored or yellow subretinal or sub-RPE infiltrates (Figs 15-1, 15-2) with overlying RPE detachments and discrete white lesions that may mimic those of acute retinal necrosis, toxoplasmosis, "frosted-branch" angiitis, or retinal arteriolar occlusion with coexisting multifocal chorioretinal scars and retinal vasculitis. Due to the challenge of diagnosing VRL, clinicians often prescribe anti-inflammatory medications that temporarily improve the vitreous cellular infiltration. In cases of presumed autoimmune uveitis that do not respond to appropriate noninfectious uveitis treatment, VRL should be a diagnostic consideration.

More than two-thirds of patients with VRL will develop CNS disease—usually within 29 months of diagnosis. CNS manifestations range from behavioral changes, hemiparesis, and cerebellar signs to epileptic seizures and cranial nerve palsies.

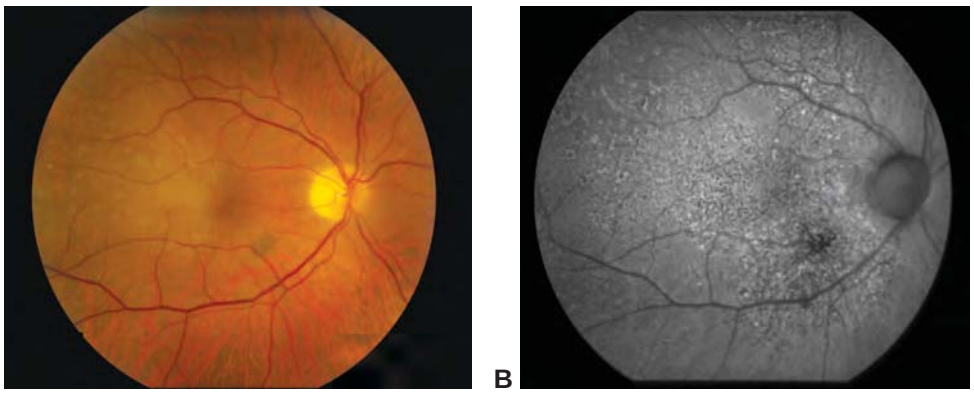

Figure 15-1 Ocular involvement in primary central nervous system (CNS) lymphoma. **A,** Fundus photograph demonstrates multifocal, cream-colored subretinal infiltrates. **B,** On fundus autofluorescence, these infiltrates appear as hyperautofluorescent and hypoautofluorescent granular changes. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

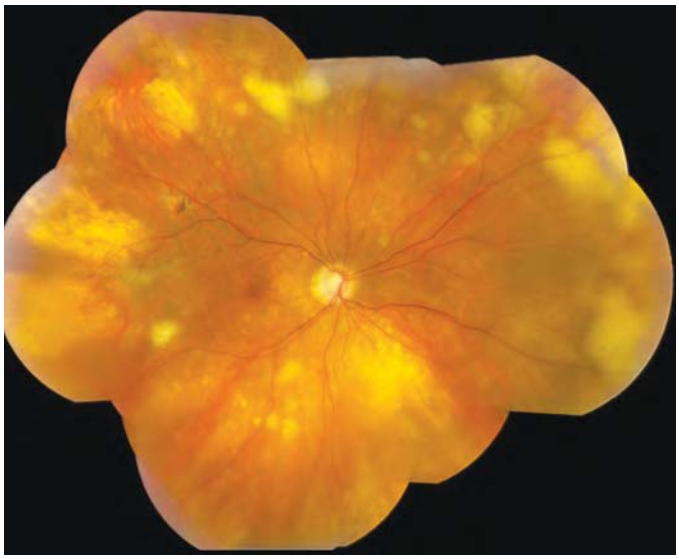

Figure 15-2 Vitreoretinal lymphoma. Fundus photograph montage shows varied multifocal lesions, some of which are cream colored/yellow and elevated while others are more atrophic. There are punctate and granular retinal pigment epithelial changes throughout the fundus. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

Diagnostic testing

Ultrasonography may reveal vitreous debris, elevated subretinal lesions, and exudative retinal detachment. Fluorescein angiography (FA) may show hypofluorescent areas due to choroidal fluorescence blockage from a sub-RPE tumor or from RPE clumping. Hyperfluorescent window defects may be caused by RPE atrophy from resolved RPE infiltration. An unusual leopard-spot pattern of alternating hyperfluorescence and hypofluorescence may also be noted on FA. Hyperautofluorescent and hypoautofluorescent granular changes may be present on fundus autofluorescence (Fig 15-3; see also Fig 15-1B), and optical coherence tomography may reveal nodular elevations at the level of the RPE and sub-RPE and/or vertical hyperreflective lesions. Indocyanine green angiography may show ill-defined hypofluorescent lesions in the late phase of the study.

All patients with suspected VRL should be urgently evaluated for CNS lymphoma, preferably with magnetic resonance imaging, even in the absence of neurologic symptoms. Cerebrospinal fluid analysis reveals lymphoma cells in one-third of patients with suspected VRL.

A vitreous biopsy is the most common procedure performed to definitively diagnose VRL. To increase diagnostic yield, systemic corticosteroids should be stopped at least 2 to 4 weeks before the diagnostic vitrectomy. As much vitreous as possible should be obtained. An ideal biopsy consists of at least 1 mL of undiluted vitreous and a cytospin preparation of diluted vitreous. Because the results of as many as one-third of vitreous biopsies may be falsely negative in VRL, a retinal biopsy and/or an aspirate of sub-RPE material may be considered if there is still a strong clinical suspicion for VRL after a negative result (Video 15-1).

VIDEO 15-1 Vitreoretinal lymphoma.
Courtesy of Emilio M. Dodds, MD.

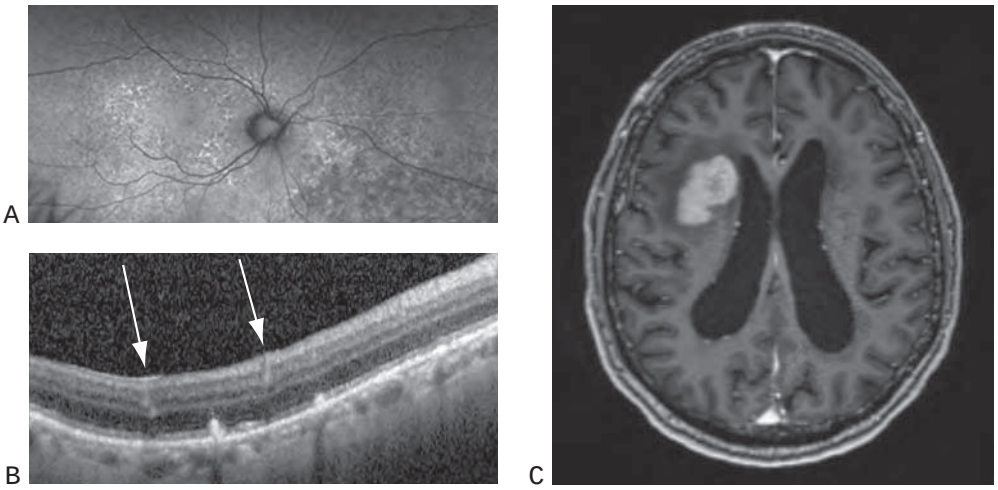

Figure 15-3 Primary CNS lymphoma. **A,** Wide-field fundus autofluorescence shows extensive mixed hyperautofluorescent and hypoautofluorescent granularities. **B,** Optical coherence tomography (OCT) shows vertical hyperreflective lesions *(arrows)* as well as subretinal infiltrates. **C,** The patient was evaluated for CNS lymphoma despite a lack of CNS symptoms, and a frontal lobe lesion was found on magnetic resonance imaging. *(Courtesy of Karen R. Armbrust, MD, PhD.)*

Prior to surgery, it is crucial to communicate with an experienced pathologist to ensure that specimens will be promptly and properly handled. Degeneration of the typically friable lymphoma cells may occur with delays in specimen handling and processing. The diagnosis may be difficult to establish because specimens from eyes with VRL may show sparse cellularity, or they may contain numerous reactive cells that hamper detection of the few lymphoma cells. Aliquots of the vitreous specimen are typically prepared for both cytologic analysis and cell surface marker determination by flow cytometry.

Cytologic specimens obtained from the vitreous typically contain pleomorphic lymphoid cells with scant cytoplasm, hyperchromatic nuclei with multiple irregular nucleoli, and an elevated nuclear-to-cytoplasm ratio (Fig 15-4). Samples that show hypercellularity may reveal numerous small reactive lymphocytes with rare tumor cells. Therefore, additional molecular techniques can be essential to confirm the diagnosis of lymphoma. Because VRL cells can be monoclonal, immunohistochemical immunophenotyping or flow cytometry is used to demonstrate the clonality of B lymphocytes by the presence of (1) abnormal immunoglobulin κ or λ light chain predominance; (2) specific B-lymphocyte markers (CD19, CD20, and CD22); and/or (3) gene or oncogene translocations or gene rearrangements. Abnormal lymphocytes isolated manually or by laser capture can be analyzed in polymerase chain reaction (PCR)–based assays to improve the diagnostic yield of paucicellular samples. A specific mutation (proline for leucine substitution mutation at position 265, L265P) in the gene *MYD88* (myeloid differentiation primary response 88) is present in 62%–88% of VRL cases; thus, detection of this mutation by PCR can be strong

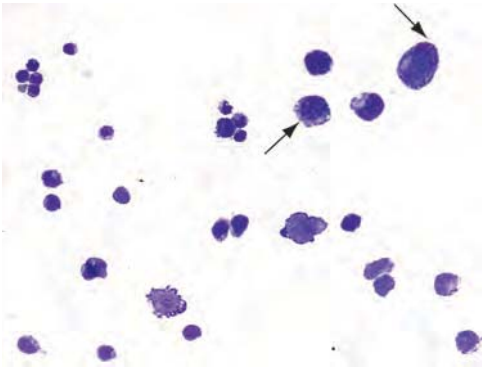

Figure 15-4 Cytologic appearance of vitreoretinal lymphoma in a vitreous specimen. Note the large atypical lymphoid cells *(arrows),* large irregular nuclei, and scant basophilic cytoplasm consistent with large B-cell lymphoma. *(Courtesy of Chi Chao Chan, MD, and H. Nida Sen, MD/National Eye Institute.)*

evidence for the diagnosis of VRL. See also BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for discussion of intraocular lymphoma.

Cytokine analysis of vitreous samples can also provide supportive evidence. Interleukin (IL)-10 levels are elevated in the vitreous of patients with lymphoma, while high levels of IL-6 are found in the vitreous of patients with inflammatory uveitis. An elevated ratio of IL-10 to IL-6 supports the diagnosis of VRL.

Carbonell D, Mahajan S, Chee SP, et al; Study Group for Vitreoretinal Lymphoma Diagnostics. Consensus recommendations for the diagnosis of vitreoretinal lymphoma. *Ocul Immunol Inflamm.* 2021;29(3):507–520.

Deák GG, Goldstein DA, Zhou M, Fawzi AA, Jampol LM. Vertical hyperreflective lesions on optical coherence tomography in vitreoretinal lymphoma. *JAMA Ophthalmol.* 2019;137(2):194–198.

Gangaputra S, Kodati S, Kim M, Aranow M, Sen HN. Multimodal imaging in masquerade syndromes. *Ocul Immunol Inflamm*. 2017;25(2):160–168.

Treatment

Treatment of VRL may involve intravitreal chemotherapy (methotrexate and/or rituximab), local external beam radiation of the eye, and/or systemic chemotherapy depending on CNS involvement. In cases with concomitant PCNSL, high-dose systemic chemotherapy in conjunction with intrathecal therapy, whole-brain radiotherapy, and/or autologous stem cell transplantation is considered. There are various chemotherapy regimens. Among the most commonly used is high-dose systemic methotrexate with rituximab. Some specialists use prophylactic treatment of the CNS even in patients with seemingly isolated ocular disease.

Pulido JS, Johnston PB, Nowakowski GS, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: a review. *Int J Retina Vitreous.* 2018 May 7;4:18. doi:10.1186/s40942-018-0120-4

Prognosis

Vitreoretinal lymphoma responds well to initial treatment; however, it is associated with high rates of relapse and CNS involvement, which usually lead to poor prognosis and limited survival. The prognosis for survival depends on whether there is CNS involvement. Despite

the availability of multiple treatment modalities and regimens, the long-term prognosis for patients with PCNSL remains poor. The median survival with supportive care alone is 2–3 months, and with surgery alone, median survival is in the range of 1–5 months. In various reports, the longest median survival approaches 40 months with treatment, and the 5-year overall survival is approximately 60%. Factors that negatively influence outcome include advanced age, worse neurologic functional classification level, multiple CNS lesions, and deep nuclei/periventricular lesions rather than superficial cerebral and cerebellar hemispheric lesions.

Uveal Lymphoma

The uveal tract may be a site for low-grade lymphoma that can mimic chronic posterior uveitis. Presenting symptoms may include vision loss that is gradual, painless, and unilateral or bilateral. Early-stage disease shows multifocal cream-colored or yellow choroidal lesions that may mimic those of sarcoidosis-associated uveitis or birdshot chorioretinopathy (Fig 15-5). Macular edema may be present. Anterior uveitis with acute signs and symptoms of pain, redness, and photophobia may also occur. Angle structures may be infiltrated by lymphocytes, resulting in elevation of intraocular pressure (IOP). The presentation may overlap with that of posterior scleritis and uveal effusion syndrome.

Fleshy salmon-pink episcleral or conjunctival masses may be present. Unlike subconjunctival lymphomas, these masses are not mobile and are attached firmly to the sclera. Histologic examination of biopsy specimens demonstrates mature lymphocytes and plasma cells, quite different from the histologic appearance of VRL specimens. In cases of uveal lymphoma, ancillary testing to evaluate for systemic lymphoma is indicated. This testing typically consists of skull base to mid-thigh computed tomography with or without positron emission tomography.

Therapy consisting of corticosteroids, radiation, or both has been used with variable results. Systemic and periocular corticosteroid therapy can lead to rapid regression of the lesions, as can external beam radiotherapy.

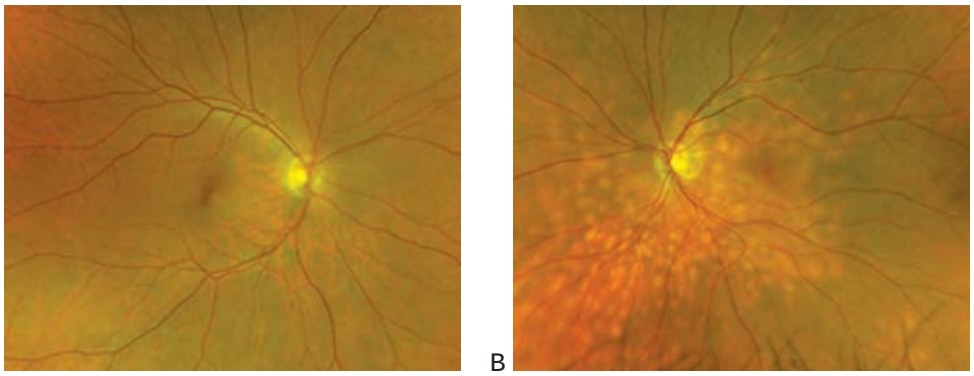

Figure 15-5 Primary uveal lymphoma. **A,** Fundus image of the right eye is unremarkable. **B,** Fundus image of the left eye shows multifocal yellow choroidal lesions. *(Courtesy of Karen R. Armbrust, MD, PhD.)*

Aronow ME, Portell CA, Sweetenham JW, Singh AD. Uveal lymphoma: clinical features, diagnostic studies, treatment selection, and outcomes. *Ophthalmology.* 2014;121(1):334–341.

Ocular Manifestations of Systemic Lymphoma

Systemic lymphomas can spread hematogenously to the choroid, subretinal space, vitreous, and anterior chamber, although this is rare. These entities can manifest with a pseudohypopyon, vitritis, cream-colored subretinal infiltrates, retinal vasculitis, necrotizing retinitis, and diffuse choroiditis or uveal masses.

Ocular Manifestations of Leukemia

Patients with leukemia may have retinal findings, including intraretinal hemorrhages, cotton-wool spots, white-centered hemorrhages, microaneurysms, and peripheral neovascularization. In rare instances, leukemic cells may invade the vitreous cavity. If the choroid is involved, exudative retinal detachment (Fig 15-6) and angiographic findings may be reminiscent of Vogt-Koyanagi-Harada syndrome. Leukemia may also manifest with a hypopyon or hyphema; iris heterochromia; or a pseudohypopyon, which can be gray yellow.

Nonlymphoid Tumors

Uveal melanoma

Approximately 5% of patients with uveal melanoma present with signs of ocular inflammation, including episcleritis, anterior or posterior uveitis, or panuveitis. Most tumors that manifest in this fashion are epithelioid-cell or mixed-cell choroidal melanomas. Ultrasonography

Figure 15-6 Exudative retinal detachment in acute leukemia. **A,** Wide-field fundus image shows inferior exudative retinal detachment. **B,** OCT shows that subretinal fluid and infiltration extend to the fovea. **C, D,** Resolution with systemic treatment of leukemia. *(Courtesy of Polly A. Quiram, MD, PhD, and Karen R. Armbrust, MD, PhD.)*

is useful in diagnosing atypical cases because of the characteristically low internal reflectivity of these lesions. Diagnosis and management of uveal melanomas is discussed in BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors.*

Retinoblastoma

Approximately 1%–3% of retinoblastomas, primarily the relatively rare form of retinoblastoma termed *diffuse infiltrating retinoblastoma,* may manifest with the appearance of inflammation. Affected patients are usually between age 4 and 6 years at presentation. Diffuse infiltrating retinoblastoma can be diagnostically confusing because of the limited visibility of the fundus and minimal or absent calcification on radiography or ultrasonography. Patients may have conjunctival chemosis, anterior chamber cells, pseudohypopyon, iris nodules (Fig 15-7), and vitritis. The pseudohypopyon typically shifts with changes in head position and is usually white as opposed to the yellowish color of inflammatory hypopyon.

Juvenile xanthogranuloma

Juvenile xanthogranuloma is the result of a histiocytic process affecting mainly the skin and eyes and, in rare instances, viscera. Patients usually present before 1 year of age with characteristic reddish-yellow skin lesions. Histologic examination of the lesions shows large histiocytes with foamy cytoplasm and Touton giant cells. Ocular lesions can involve the iris and result in a spontaneous hyphema (Fig 15-8). Histologically, iris biopsy samples show fewer foamy histiocytes and fewer Touton giant cells than do skin biopsy specimens. In rare cases, other ocular structures may be affected. If the eyelid skin is involved, the globe is usually spared.

Intraocular lesions may respond to topical, periocular, or systemic corticosteroid therapy. Resistant cases may require local resection, radiation, or immunomodulatory therapy. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for additional discussion.

Samara WA, Khoo CT, Say EA, et al. Juvenile xanthogranuloma involving the eye and ocular adnexa: tumor control, visual outcomes, and globe salvage in 30 patients. *Ophthalmology.* 2015;122(10):2130–2138.

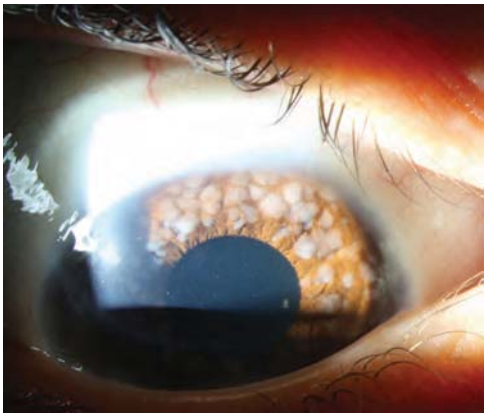

Figure 15-7 Diffuse infiltrating retinoblastoma. Slit-lamp photograph from a child with retinoblastoma shows iris tumor nodules and anterior chamber cells. *(Courtesy of Laura J. Kopplin, MD, PhD.)*

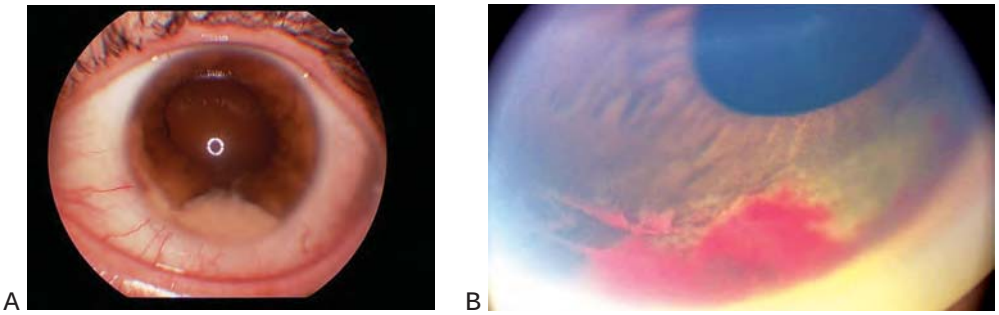

Figure 15-8 Juvenile xanthogranuloma (JXG). **A,** Iris JXG. **B,** JXG presenting as a yellow iris lesion with associated atraumatic hyphema in a child. *(Part A courtesy of Emilio M. Dodds, MD; part B courtesy of Raymond G. Areaux Jr, MD.)*

Metastatic Tumors

Most intraocular malignancies in adults are metastatic tumors. The most common primary cancers metastasizing to the eye include lung and breast carcinoma. Patients with anterior uveal metastasis may present with cells in the aqueous humor, iris nodules, neovascularization of the iris, and elevated IOP. Anterior chamber paracentesis may help confirm the diagnosis. Retinal metastases are extremely rare. Primary cancers metastatic to the retina include cutaneous melanoma (the most common), followed by lung, gastrointestinal, and breast cancer. Metastatic melanoma often produces brown spherules in the retina, whereas other metastatic cancers appear white to yellow and may result in perivascular sheathing, simulating a retinal vasculitis or necrotizing retinitis. Choroidal metastasis may be marked by vitritis, exudative retinal detachment, and occasionally macular edema. These lesions are often bilateral and multifocal. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for additional discussion and images showing metastases to the eye.

Bilateral Diffuse Uveal Melanocytic Proliferation

Bilateral diffuse uveal melanocytic tumors have been associated with systemic malignancy. Such tumors can be accompanied by rapid vision loss, cataracts, multiple pigmented and nonpigmented placoid iris and choroidal nodules, and exudative retinal detachments. This condition can mimic Vogt-Koyanagi-Harada syndrome. Histologic examination shows diffuse infiltration of the uveal tract by benign nevoid or spindle-shaped cells. Necrosis within the tumors may be present, and scleral involvement is common. The cause of this entity is unknown. Treatment should be directed at finding and treating the underlying malignancy. See BCSC Section 12, *Retina and Vitreous,* for additional information about this condition.

Nonneoplastic Masquerade Syndromes

Retinitis Pigmentosa

Patients with retinitis pigmentosa (RP) often have variable numbers of vitreous and anterior chamber cells and can develop macular edema. Features of RP that differentiate it from

uveitis include nyctalopia, positive family history of RP, waxy optic disc pallor, attenuation of arterioles, and a bone-spicule pattern of pigmentary changes in the midperiphery. Electroretinographic responses of patients with RP often appear severely depressed or extinguished, even early in the disease. However, these findings can also occur in some types of posterior uveitis, such as late-stage birdshot chorioretinopathy, making differentiation between the entities very difficult in some cases. See BCSC Section 12, *Retina and Vitreous,* for additional information.

Ocular Ischemic Syndrome

Ocular ischemic syndrome (OIS) results from hypoperfusion of the entire eye and sometimes the orbit, usually because of carotid artery obstruction. Patients with OIS are typically men aged 65 years or older. Examination findings may include corneal edema, anterior chamber cells, and moderate anterior chamber flare that is often greater than and out of proportion to the number of cells. Anterior segment neovascularization may also be present.

Dilated fundus examination and FA help distinguish OIS from uveitis. In OIS, fundus examination typically shows dilated retinal venules, narrowed arterioles, and medium to large intraretinal blot hemorrhages scattered in the midperiphery and far periphery. FA shows delayed arteriolar filling, diffuse leakage in the posterior pole as well as from the optic disc, and signs of capillary nonperfusion.

Diagnostic studies for OIS include carotid Doppler ultrasonography; ipsilateral carotid stenosis greater than 90% supports the diagnosis of OIS. See BCSC Section 12, *Retina and Vitreous,* for discussion of OIS treatment.

Mendrinos E, Machinis TG, Pournaras CJ. Ocular ischemic syndrome. *Surv Ophthalmol.* 2010;55(1):2–34.

Chronic Peripheral Rhegmatogenous Retinal Detachment

Chronic peripheral rhegmatogenous retinal detachment can be associated with anterior chamber cell and flare and vitreous inflammatory and pigment cells. Patients often have good vision unless they develop macular edema. Careful dilated fundus examination with scleral depression is crucial to establishing the diagnosis. Findings may include peripheral pigment demarcation lines, subretinal fluid, retinal breaks, subretinal fibrosis, and peripheral retinal cysts.

Photoreceptor outer segments liberated from the subretinal space may be present in the anterior chamber, simulating inflammatory cells. In such situations, the photoreceptor outer segments may obstruct trabecular outflow, resulting in elevated IOP and secondary open-angle glaucoma. This condition is called *Schwartz-Matsuo syndrome.*

Matsuo T. Photoreceptor outer segments in aqueous humor: key to understanding a new syndrome. *Surv Ophthalmol.* 1994;39(3):211–233.

Intraocular Foreign Bodies

Open-globe injury may result in an intraocular foreign body. Retained intraocular foreign bodies may produce chronic intraocular inflammation as the result of mechanical, chemical,

toxic, or inflammatory irritation of uveal tissues (particularly the ciliary body). In some cases of retained intraocular foreign bodies, the ocular trauma is unrecognized or perceived as mild by the patient. A high index of suspicion and the following are essential for accurate diagnosis: a careful history; clinical examination; and ancillary testing, including gonioscopy, ultrasonography, and computed tomography of the eye and orbits. If this condition is suspected and recognized quickly, removal of the foreign body is often curative. If the diagnosis is delayed, ocular complications, such as proliferative vitreoretinopathy and endophthalmitis, result in a poorer visual prognosis.

Pigment Dispersion Syndrome

Pigment dispersion syndrome is characterized by pigment granules released into the anterior chamber from the iris and/or ciliary body. These granules may be confused with the cells of anterior uveitis. Careful examination of the corneal endothelium, iris, and iridocorneal angle can help distinguish between uveitis and pigment dispersion syndrome. See BCSC Section 10, *Glaucoma,* for a complete discussion of pigment dispersion syndrome.

Infectious Uveitis

Certain infectious uveitic entities may be mistaken for immune-mediated uveitis and thus are included in nonneoplastic masquerade syndromes. These entities are discussed in Chapters 11 and 12.