OCULAR MANIFESTATIONS OF SYSTEMIC DISEASE

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Understanding the ocular manifestations of systemic disease is critically important for the emergency physician. Patients may present to the emergency department with or without visual symptoms, but with the threat of progressive visual loss or blindness. Some patients may present with obscure signs and symptoms and ocular manifestations may be the only clue for making a difficult diagnosis. Other patients may present with well-documented systemic diseases and eye findings may help to quantify the severity of their illness.

This review is divided into two parts. The first section discusses frequently encountered ocular abnormalities and provides a differential diagnosis of associated systemic diseases. The second section is devoted to a more detailed discussion of the systemic disorders with ocular findings that are important to the emergency physician. We discuss findings that are visible by direct inspection, slit-lamp examination, and direct ophthalmoscopy.

COMMON OCULAR FINDINGS

Systemic diseases characteristically affect more than one part of the eye concomitantly, and individual findings may not be specific. The eye should always be examined in a systematic fashion. The clinician should pay particular attention to invert the eyelids and to perform a complete slit-lamp and funduscopic examination for all patients.

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Eyelid Abnormalities

Any dermatologic disease can manifest itself on the eyelids, including psoriasis, discoid lupus, dermatomyositis, eczema, rosacea, erythema nodosum, dermatitis herpetiformis, scleroderma,[58] and infections, such as erysipelas and cellulitis.[40] Tumors affecting the lids include neurofibromas and the lesions of Kaposi's sarcoma in patients with the acquired immune deficiency syndrome (AIDS). Generalized swelling of the eyelids is nonspecific and may result from allergic reactions, generalized edema, hypothyroidism, trichinosis, or basilar skull fracture.[26] Swelling confined to the lateral aspect of the lid suggests infiltration of the lacrimal gland as seen in sarcoidosis, lymphoma, or mumps.[58] Spontaneous petechiae or ecchymosis of the lid may suggest a bleeding diathesis.

Dry Eyes

Dry eyes, or keratoconjunctivitis sicca (KCS) usually results from decreased tear formation by the lacrimal gland (either through infiltration or denervation), functional disorders of the lacrimal duct, or a defect in mucin or lipid secretion by the ocular glands.[44] Patients may complain of dry, gritty eyes, blurred vision, pain (especially at the end of the day), photophobia, or the sensation of a foreign body. Occasionally, patients report only the sensation of "eye awareness." Symptoms may be exacerbated by atmospheric pollutants or hot, dry weather.[84] Examination may show an absent lower lid meniscus or small filamentous changes on fluorescein staining. Definitive diagnosis is made with Shirmer's test. Filter paper is placed in the lower conjunctiva and allowed to absorb tear film. Less than 5 mm of absorption in 5 minutes suggests tear dysfunction.

Dry eyes are most commonly idiopathic, but may be a manifestation of many autoimmune and collagen vascular diseases (Table 1). Dry eyes may be an important clue to an associated systemic disease; however,

Table 1. DISEASES AND CONDITIONS THAT MAY MANIFEST WITH DRY EYES

Sjögren's syndrome	Vitamin A deficiency
Rheumatoid arthritis	Amyloidosis
Systemic lupus erythematosus (SLE)	AIDS
Systemic sclerosis	Lymphoma
Mixed connective tissue disease	Mononucleosis
Relapsing polychondritis	Lyme disease
Wegener's granulomatosis	Parkinson's disease
Polyarteritis nodosa	Multiple sclerosis
Waldenstrom's macroglobulinemia	Proptosis
Hepatic disease	Drugs causing dry eyes
Sarcoidosis	Beta-blockers
Psoriasis	Diuretics
Erythema multiforme	Anticholinergics

examination of patients without additional systemic signs or symptoms is usually not productive.[44]

Conjunctivitis

Conjunctivitis is inflammation of the mucous membranes lining the inner eyelids and anterior sclera.[45] It most commonly presents as an irritated or painful red eye, with or without discharge. Visual acuity is nearly always unaffected, and any change in vision should prompt suspicion of a more serious ocular disorder. Conjunctivitis is most often the result of direct viral, bacterial, or chlamydial infections. Conjunctivitis may be a manifestation of systemic diseases, such as Reiter's syndrome, Wegener's granulomatosis,[9, 38, 83] erythema multiforme, Stevens-Johnson syndrome,[90] psoriatic arthritis, Kawasaki's disease,[64] Crohn's disease,[45] gout,[27] or systemic infections, such as Lyme disease, mononucleosis, measles, or gonorrhea.[45, 58] Subconjunctival hemorrhage is usually idiopathic or traumatic but may also suggest a bleeding diathesis.[58]

Corneal Abnormalities

Keratitis

Keratitis refers to inflammation of the cornea and most commonly results from herpes simplex,[40, 49] herpes zoster,[40, 48, 49] Lyme disease,[4] syphilis,[40] and other viral,[49] bacterial,[48] and fungal infections.[30] Patients most often present with pain or sensation of a foreign body. Keratitis may also be seen in Wegener's granulomatosis,[9] Crohn's disease, Stevens-Johnson syndrome,[90] rheumatoid arthritis, and other connective tissue disorders.[45] Keratitis is an especially important diagnosis to suspect in patients who present to the emergency department with a painful eye because if left untreated, corneal opacification and ulceration may result. Diagnosis should be confirmed with fluorescein examination. Culture of corneal scrapings is critical to identify the offending organism and is usually performed by an ophthalmologist.

Corneal Deposits

Deposits on or in the cornea are almost always pathologic and frequently are the first sign of an associated systemic disease.[2] Patients may present with decreased visual acuity if deposits form within the visual axis. They most commonly result from excess tissue levels of various substances, including lipid (arcus juvenilis or arcus senilis), protein (myeloma, amyloidosis), minerals (copper, as in Wilson's disease), drugs (amiodarone, antimalarial agents, gold, indomethacin, phe-

nothiazines, tamoxifen, and silver), urate (gout), or from the rare inborn errors of metabolism.

Episcleritis

Episcleritis is an inflammatory disorder of the eye that is not infectious and is characterized by mild pain and scleral injection. Careful inspection shows preservation of the radial distribution of scleral vascular markings. It is most often monocular, and commonly occurs in young women.[35] Episcleritis is usually not related to any particular systemic disease and is usually self-limited.[84]

Scleritis

Scleritis is an inflammatory disorder of the sclera that presents with severe periorbital pain, swelling, and injection of the sclera in association with obliteration of its normal radial vascular pattern. It usually presents anteriorly but may also present posteriorly and may be difficult to diagnose unless associated with proptosis, reduced extraocular movements, or visual loss.[84] It is associated with myriad connective tissue and vasculitic disorders including rheumatoid arthritis, SLE, Wegener's granulomatosis, polyarteritis nodosa and relapsing polychondritis, Reiter's syndrome, ulcerative colitis, Crohn's disease, psoriatic arthritis, and ankylosing spondylitis.[35]

Uveitis

Uveitis is defined as inflammation involving the iris, ciliary body, or choroid. Anterior uveitis involves the iris (iritis) or iris and ciliary body (iridocyclitis), and posterior uveitis principally involves the choroid (choroiditis). Involvement of the entire uveal tract is termed panuveitis. Uveitis is further subdivided into acute or chronic, based on rate of onset and clinical course. A thorough review of systems should be performed in every patient who presents with uveitis because more than 50% of cases may be associated with systemic disease.[67, 73] Unless symptoms or signs of systemic illness are noted, however, laboratory evaluation is not generally helpful.

Anterior Uveitis

Anterior uveitis presents with pain, redness, watery discharge, and decreased vision. Photophobia is nearly always present and is often quite severe. Both decreased vision and the presence of photophobia (which is nearly always consensual) help differentiate anterior uveitis from simple conjunctivitis or episcleritis.[84] Examination of the anterior

chamber may display circulating cells or flare from increased protein in the aqueous humor. If severe, the pupil will be constricted from formation of posterior synechiae, and a hypopyon will be present. Anterior uveitis most commonly occurs between the ages of 20 and 50, and is frequently idiopathic[67]; however, about half of the cases are associated with a seronegative spondyloarthropathy[12] (Reiter's syndrome, ankylosing spondylitis), inflammatory bowel disease, interstitial nephritis, juvenile rheumatoid arthritis, psoriatic arthritis, Behçet's disease,[12, 14] or Sjögren's syndrome.[12, 45, 73] Kawasaki's disease,[64] multiple sclerosis, Rocky Mountain spotted fever,[20] syphilis, sarcoidosis,[12] Lyme disease,[4] herpes infection, Whipple's disease, and Wegener's granulomatosis[9] have also been implicated. Pupillary dilatation with a long-acting mydriatic will decrease pain and prevent formation of posterior synechiae. Topical steroids should only be applied after viral causes have been ruled out and only in consultation with an ophthalmologist. Urgent referral is mandatory.

Posterior Uveitis

Posterior uveitis is less common than anterior uveitis and characteristically presents with less pain and redness but greater disturbance in visual acuity. Floaters often appear, and direct ophthalmoscopic examination of the vitreous humor frequently reveals cells in the posterior chamber. Posterior uveitis most commonly results from hematogenous spread and seeding of the highly vascular choroid with infectious material. AIDS, toxoplasmosis, fungal infections,[23, 55] syphilis, toxocariasis, tuberculosis, and sarcoidosis are common causes.[67]

Lens Disorders

Abnormalities of the lens include cataracts from longstanding diabetes mellitus, parathyroid deficiency, trauma, or long-term use of corticosteroids.[45] Dislocation of the lens is seen in Marfan's syndrome, syphilis, and Ehlers-Danlos syndrome. Refractive errors are commonly seen in severe hyperglycemia and, rarely, in patients with botulism.[58]

Retinal Vascular Abnormalities

Retinal Hemorrhage

Retinal hemorrhages can take many forms. Flame-shaped hemorrhages involve the superficial nerve fiber layer and may result from hypertension, retinal vein occlusion, and diabetes. Dot and blot hemorrhages are most commonly associated with diabetic retinopathy. Roth's spots are larger hemorrhages with yellow-white centers that typically

result from endocarditis but may also occur in other hematologic and vascular diseases.

Cotton Wool Spots

Cotton wool spots appear as small, multiple, white or yellow, fluffy patches on funduscopic examination. Lesions are most common on the posterior pole of the retina and are generally less than one disc diameter wide (Color Plate 3, Fig. 9). Also known as soft exudates, cotton wool spots represent microinfarcts in the superficial retinal tissue, do not disrupt the vasculature, and resolve within a few months. They are most commonly seen in patients with diabetes, uncontrolled hypertension, and AIDS. Collagen vascular disease, endocarditis, Rocky Mountain spotted fever, high-altitude retinopathy, acute pancreatitis, and onchocerciasis[7, 8] have also been associated with cotton wool spots.

Hard Exudates

Hard exudates represent lipid deposition from long-term vascular leakage and appear as multiple, small, sharply demarcated, yellow lesions. They occur most frequently in diabetic and hypertensive disorders.

Optic Neuritis

Optic neuritis is an inflammatory process of the optic nerve characterized by an acute and rapid deterioration of vision. It is most often painful but may be painless. Optic neuritis is most commonly monocular in adults and binocular in children. Visual acuity is characteristically less affected than light, color, and depth perception. An afferent pupillary defect and visual field cuts are common. A well-characterized association between optic neuritis and multiple sclerosis exists. Other important causes include sarcoidosis, SLE, syphilis, toxoplasmosis, Lyme disease, cat-scratch disease, and diseases related to human immunodeficiency virus (HIV), especially cytomegalovirus (CMV) and *Cryptococcus*. Drugs, such as ethambutol and tamoxifen, may also precipitate optic neuritis. Postviral optic neuritis may develop approximately 4 to 6 weeks after a nonspecific viral illness.[54]

Ptosis

Ptosis, or drooping of the eyelids, may be unilateral or bilateral and may be a manifestation of neurologic disease with third nerve palsy (botulism, tumor, aneurysm), sympathectomy of the lid (Horner's syndrome), or a primary neuromuscular disorder, such as myasthenia gravis.

Extraocular Movement Disorders

Extraocular movements may be disturbed in myasthenia gravis, botulism, diabetic neuropathy, thyroid disease, the Miller-Fisher variant of Guillain-Barre syndrome,[28] or direct compression by tumor or aneurysm.[58]

SYSTEMIC DISORDERS WITH OCULAR FINDINGS

Cardiovascular Diseases

Endocarditis

Endocarditis is characterized by disruption of the endothelium lining the valves and chambers of the heart that leads to platelet and fibrin aggregation and subsequent embolization. Ocular manifestations include the classic Roth's spot (retinal hemorrhage characterized by a white center of focal retinitis or fibrin platelet aggregates), cotton-wool spots, and segmental retinal artery occlusions. Retinitis, choroiditis, vitreitis, uveitis, and endophthalmitis may also occur. Cranial nerve and other focal neurologic abnormalities may result from embolization to the CNS.[33]

Arteriosclerosis

Arteriosclerosis results from diffuse fibrosis and hyalinization in the vessels of the retina. Funduscopic changes occur with time and follow a predictable pattern. Initially, widening of the light reflex of the arteriole occurs. With time, "copper wiring" is seen, as lipid deposition turns the vessel wall opaque. "Silver wiring" is said to occur when enhanced vessel disease leads to lightening of the reflection. Ultimately, arteriolar obstruction results. These findings are associated with hypercholesterolemia and atherosclerosis.

Hypertension

Hypertension affects the eye in many ways. Hypertensive retinopathy secondary to arteriosclerosis, vasoconstriction, and vascular leakage follows a predictable pattern. Arteriosclerosis results in vessel wall thickening, leading to characteristic changes at arteriovenous crossings. Vasoconstriction causes narrowing of the retinal arteries, and if total obstruction occurs, cotton-wool spots can form. Leakage from vascular elements results in flame-shaped hemorrhages, hard exudates, retinal edema, and swelling of the optic disc if malignant hypertension is present. Retinal vein occlusion, retinal artery occlusion, and focal cranial nerve deficits may also occur. The grading of hypertensive retinopathy is shown in Table 2.

Table 2. GRADING OF HYPERTENSIVE RETINOPATHY

Grade	Characteristics
Grade I	Mild, generalized arteriolar constriction, widening of the arteriolar light reflex, and concealment of retinal veins at arteriovenous (AV) crossings.
Grade II	Severe generalized or focal vasoconstriction, and deflection of veins at AV crossings.
Grade III	Flame-shaped hemorrhages, cotton-wool spots, hard exudates, "copper wiring" of arterioles, and AV nicking.
Grade IV	"Silver wiring" of arterioles, disc swelling, and papilledema.

Infectious Diseases

Bacterial, Spirochetal, Rickettsial, Chlamydial, and Mycobacterial Diseases

Diphtheria. Diphtheria is caused by the gram-positive bacillus *Corynebacterium diphtheria.* Ocular involvement most commonly results in a minimally purulent conjunctivitis.[37] Severer ocular infections, cranial nerve abnormalities, and a characteristic accommodative paresis (in which pupillary response to accommodation is lost but response to light is retained) have also been reported.[29, 37]

Botulism. Ingestion of preformed exotoxin from poorly prepared canned foods or, rarely, systemic infection with the anaerobic gram-positive rod *Clostridium botulinum* results in interference with cholinergic nerve transmission. Patients present with a descending motor paralysis and autonomic dysfunction. Ocular manifestations include ptosis, impaired extraocular motions, diplopia, inability to focus to a near point, sluggish to nonreactive pupils, and decreased tear formation.[89]

Brucellosis. Brucellosis is a bacterial infection acquired through contact with infected livestock, domestic animals, or through ingestion of contaminated meat or unpasteurized dairy products. Infection manifests as fever, sweats, weight loss, weakness, headache, and myalgias. Ocular manifestations include severe optic neuritis in conjunction with papillary congestion and occasionally papilledema. Visual field defects and decreased visual acuity may result. Anterior uveitis, hypopyon, choroiditis, corneal lesions, conjunctivitis, and lid edema may also occur.[25] Vitreous inflammatory cells and posterior choroiditis have also been reported.[86]

Syphilis. Congenital syphilis is a common cause of interstitial keratitis that usually presents in the first or second decade of life. Patients present with pain, lacrimation, photophobia, and conjunctival injection involving both eyes.

Ocular manifestations of acquired syphilis can take many forms, but ocular involvement is most common in the second stage of the disease.[18] Anterior uveitis (iritis) occurs in about 5% of patients with secondary syphilis and is the most common ocular manifestation.[87] Iritis usually coincides with development of the typical rash. Choroiditis,

retinal vasculitis, scleritis, and conjunctivitis may also result.[52] If left untreated, neurosyphilis may result in an optic neuritis and the classic Argyll-Robertson pupil (pupillary response to light lost while accommodative response is retained). Concurrent HIV infection may lead to a more aggressive presentation of ocular syphilis, and therapy with high doses of intravenous penicillin is often necessary to eradicate the infection.[56, 66]

Lyme Disease. Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted to humans by ticks. The disease is characterized by a viral-like illness, a distinctive annular, erythematous, expanding, circular or ovoid rash known as erythema chronicum migrans, migratory arthralgias, fever, malaise, headache, central and peripheral neuropathies, and heart block.[82] Ocular findings may include conjunctivitis and periorbital edema in the initial stages of the disease, uveitis, Bell's palsy, or other cranial nerve abnormalities in the intermediate stages, and a bilateral keratitis with multiple and irregular lesions involving all layers of the cornea in the later stages.[80] Optic neuritis, temporal arteritis, retinal detachment, macular edema, and papilledema secondary to meningitis have been reported rarely.[4]

Borreliosis. This tick-borne disease, also known as relapsing fever, caused by the spirochete *Borrelia recurrentis,* is most common in the western United States. The disease presents with fever, chills, headache, malaise, and arthralgias.[82] Ocular manifestations include conjunctivitis and anterior uveitis (iritis).[51]

Rocky Mountain Spotted Fever. Caused by the tick-borne *Rickettsia rickettsii,* Rocky Mountain Spotted Fever (RMSF) is a medical emergency and an important cause of preventable death. Patients present with fever, malaise, headache, and myalgias, and a characteristic maculopapular rash that begins on the wrists and ankles and spreads to involve the palms, soles, face, and trunk. If left untreated, it results in vasculitis, disseminated intravascular coagulation, and ultimately death in roughly 25% of patients.[82] Ocular manifestations may include retinal edema, cotton wool spots, retinal hemorrhage, and anterior uveitis.

Chlamydia. Infection with *Chlamydia trachomatis* can be acquired in a number of ways. Patients can inoculate the eye after acquiring the organism through sexual contact, newborns can acquire infection after passing through an infected birth canal, or patients can inoculate the eye after infection with lymphogranuloma venereum. Trachoma is a chronic form of conjunctivitis caused by repeated infections with *Chlamydia trachomatis* and is one of the leading causes of blindness in the world.[40, 85] Patients with chlamydial conjunctivitis present with injection, lacrimation, and purulent discharge. Chronic or multiple infections lead to poor tear formation, corneal drying, lid problems, and cicatrix formation, with possible visual loss.

Tuberculosis. Ocular infection with *Mycobacterium tuberculosis* is uncommon but usually occurs via the hematogenous route.[71] Patients present with pain, decreased visual acuity, and anterior uveitis. Patients with severe miliary tuberculosis present without pain, and ophthalmos-

copy may reveal numerous minute, gray or yellow nodules or tubercles on the ocular fundus. Disseminated choroidal hemorrhages have also been reported.[81]

Leprosy. Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* that primarily affects the skin and mucous membranes. The most common ocular complication is exposure keratitis from ectropion and seventh nerve paralysis. Scleritis and anterior uveitis occur frequently and chronic uveitis and glaucoma rarely.[76]

Viral Diseases

Herpes simplex. Infection with herpes simplex virus (HSV) is the most frequent cause of corneal opacities in developed nations and is responsible for more than 300,000 cases of ocular disease yearly in the United States. Once infecting a host, the virus lies dormant in the sensory root and autonomic ganglia. Reactivation of the virus leads to recurrent vesicular eruptions along the territory of a particular nerve. When the ophthalmic distribution of the trigeminal nerve is involved, vesicular eruption on the eyelid often occurs, and patients present with pain, redness, photophobia, foreign body sensation, or visual disturbance. Active replication of HSV in the cells of the cornea leads to an epithelial keratitis with a characteristic dendritic pattern on fluorescein staining. Early in the course of ophthalmologic involvement, a punctate keratitic pattern may be seen. Stromal keratitis (inflammation of the thick stromal layer of the cornea), corneal edema, corneal scarring, blepharitis, and conjunctivitis may also occur. Diagnosis is made by viral culture of corneal scrapings, and treatment is with localized debridement and topical antiviral agents, including vidarabine and trifluorothymidine (Viroptic).[49] Steroids are absolutely contraindicated and should be avoided in any case of possible HSV infection.[40]

Herpes zoster. Herpes zoster ophthalmicus (HZO) results from reactivation of varicella zoster virus infection in the distribution of the ophthalmic branch of the trigeminal nerve. This infection can involve nearly any part of the eye. Corneal involvement is most common, and 65% of patients with HZO display evidence of corneal disease.[47] Patients present with pain, paresthesias, lacrimation, and vesicular eruption over the skin of the eye that progresses to crusting and scarring. Early corneal lesions take the form of a punctate keratopathy. These lesions later coalesce to form a branching pattern similar to the corneal involvement in HSV keratitis.[49] Conjunctivitis, scleritis, uveitis, and optic neuritis are also seen.[40] Vesicular eruption along the side or tip of the nose known as Hutchinson's sign, indicates involvement of the nasociliary nerve and portends a higher incidence of potential ophthalmologic complications because this nerve innervates the eye directly.[49]

Patients with HIV infection have an increased risk of HZO, and patients with AIDS who develop HZO are at risk of developing a syndrome known as acute retinal necrosis (ARN). ARN is a severe infection of the retina thought to be related to either hematologic dissem-

ination or direct spread of varicella zoster virus to the eye in immunocompromised patients. In one series, more than 25% of patients who presented with HZO had HIV or AIDS, and 17% of immunocompromised patients with HZO developed ARN.[78] Some experts recommend that all patients who develop HZO and are younger than 45 should consider HIV testing, and all patients with HZO suspected of concomitant HIV infection should be followed closely for the development of ARN.

HZO in immunocompetent subjects is treated with orally administered acyclovir (800 mg five times a day for 7 to 10 days). Treatment shortens the course of disease, reduces viral shedding, and prevents corneal complications, especially if given early in the presentation.[13] Because of poor bioavailability of oral acyclovir, intravenous acyclovir is recommended for immunocompromised patients, both to prevent ocular sequelae and to decrease the risk of viral dissemination.[77] Any patient with suspected HIV who develops HZO should receive immediate ophthalmologic consultation and follow-up to monitor for ARN. Treatment of ARN requires aggressive parenteral therapy with acyclovir and/or foscarnet.

Fungal Diseases

Candidiasis. Candidal infection in the eye can be local or systemic. Infection of the eyelids can result from contiguous involvement of facial skin and is occasionally associated with an allergic conjunctivitis.[40] *Candida* is a frequent cause of fungal keratitis, especially in the northern United States,[30] and is the most common cause of fungal endophthalmitis.[68] Ocular manifestations of systemic candidiasis occur in 10% to 50% of patients.[23, 55] The disease usually presents as focal areas of necrotizing granulomatous retinitis that appear as multiple, fluffy white, cotton-like lesions on direct ophthalmoscopy that are frequently associated with vitreous cellular infiltrate. The presence of these signs should prompt further investigation for other manifestations of systemic candidiasis in susceptible hosts because their presence is highly suggestive of invasive disease.[55] Roth's spots, retinal detachment, and endophthalmitis may also result.[23]

Mucormycosis. Infection with any of the fungal genera *Rhizopus, Absidia, Cunninghamella,* and *Mucor* can result in a devastating, rapidly destructive, and fatal orbital infection. Patients with uncontrolled diabetes and other immunocompromised patients, such as those with AIDS, hematologic malignancies, sepsis, or those receiving chemotherapy or prolonged courses of corticosteroids, are at particular risk. Patients may present with proptosis, facial swelling, pain, visual disturbances, cranial nerve abnormalities, or retinal artery occlusion. The diagnosis should be suspected in any immunocompromised patient who presents with proptosis or decreased extraocular movements.[40] Prompt diagnosis, debridement, and intravenous administration of amphotericin B is absolutely necessary to avoid disfiguration and death.

Parasitic Diseases

Onchocerciasis. Onchocerciasis (microfilariasis, river blindness) is the most common cause of blindness in the world. Caused by the parasite *Onchocerca volvulus*, the disease is most common in West Africa, although multiple endemic areas exist along the equator. Damage to the eye results from localized inflammation elicited by dead parasites. Long-term infection leads to accumulation and confluence of affected areas and to visual impairment. Anterior chamber involvement occurs initially[50]; organisms can be seen in the anterior chamber on slit-lamp examination and result in an anterior uveitis.[62] Posterior segment involvement includes chorioretinal scarring.[5, 59] Keratitis, optic neuritis, and optic atrophy may also occur.[50] Early treatment with ivermectin can potentially save the patient's vision.[88]

Acquired Immune Deficiency Syndrome

It has been estimated that between 40% and 90% of patients with AIDS or AIDS-related complex (ARC) develop ophthalmologic complications. In pediatric patients, the frequency of ocular complications is considerably less.[17] Opportunistic infections and a well-characterized microangiopathic retinopathy are the most frequent ophthalmologic abnormalities in patients with AIDS.[53] Neurophthalmologic, adnexal, and conjunctival disease are also seen.[6, 41] The frequency of ocular lesions correlates inversely with the number of circulating CD4 lymphocytes. In one study, ocular lesions occurred in more than 75% of patients with AIDS, 37% of patients with ARC, and only 6% of asymptomatic HIV carriers.[31] Therefore, ocular disease may be seen as a marker of immunologic decline in patients with HIV infection. Any patient with HIV seen in the emergency department who has suspicious eye findings should receive prompt ophthalmologic and medical follow-up because ocular findings may be the first sign of AIDS. The eye should be examined in every patient with HIV and presumed systemic opportunistic infection, not only because ocular signs may provide a clue to the organism involved[22] but also to prevent progressive visual loss due to CMV retinitis[19] or acute retinal necrosis.

AIDS Retinopathy

Cotton wool spots (see Color Plate 3, Fig. 9) and retinal hemorrhages are the most prevalent ocular findings in patients with AIDS,[63] occurring in up to 66% of patients with AIDS, 40% of patients with ARC, and fewer than 2% of patients with asymptomatic HIV infection.[41] Lesions are thought to occur from direct infection of retinal blood vessels with HIV-1, circulating immune complexes, or rheologic abnormalities. Most patients with AIDS retinopathy have little to no visual disturbance, and lesions tend to come and go with time. Visual loss from AIDS retinopa-

thy is decidedly rare. The importance of finding AIDS retinopathy is the association with deteriorating immune function; cotton wool spots in formerly asymptomatic HIV infected persons may herald the onset of full-blown AIDS.

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) retinitis is the most frequently encountered ocular opportunistic infection in patients with HIV, occurring in more than 20% to 25% of patients with AIDS.[42] It is the most common manifestation of systemic CMV disease (Color Plate 3, Fig. 10). CMV retinitis is a medical emergency. Immediate referral to an ophthalmologist is mandatory for urgent treatment. Patients may present with progressive loss of vision; however, asymptomatic infection is common early in the presentation. Characteristic ocular findings include patchy white, granular lesions on the retina associated with hemorrhage. CMV produces a necrotizing retinitis that destroys retinal cells and heals by scarring. Retinal detachment occurs in roughly 25% of patients.[43] Left untreated, progressive visual loss and blindness can result.[36] Patients develop pain, redness, photophobia, or anterior chamber findings rarely, and these findings should prompt investigation into another cause.[22] Ganciclovir and foscarnet have both been used for treatment for CMV retinitis,[42, 69] with a response rate of more than 90%. Relapse of active disease is common, and maintenance therapy is necessary. Either agent needs to be administered intravenously on a daily basis indefinitely. Orally administered ganciclovir has recently been licensed for maintenance therapy.

Toxoplasma Chorioretinitis

Toxoplasmosis is caused by the parasite *Toxoplasma gondii.* Infection frequently involves the eye. Patients usually complain of a painless decrease in vision. Significantly decreased visual acuity suggests macular involvement and is an ophthalmologic emergency. Lesions appear as single yellow-white, circular or oval or areas of focal necrotizing retinitis that affect the macula or central retina preferentially.[32] Scarred "satellite" lesions are often present (Color Plate 3, Fig. 11). Floaters, inflammatory cells, and permanent opacities in the vitreous humor also can be noted. Less commonly, anterior uveitis, cataracts, iris abnormalities, and glaucoma will be seen. The appearance contrasts well with CMV retinitis, which primarily affects the peripheral retina diffusely. Despite this difference, however, ocular toxoplasmosis is frequently confused with CMV retinitis, syphilis, TB, fungal infections, and sarcoidosis.[61] If left untreated, lesions can enlarge, and the inflammatory response may worsen, leading to blindness.[57] Patients without AIDS or HIV infection can also develop ocular toxoplasmosis. Although common in South America, the disease is less severe, and untreated ocular toxoplasmosis often results in no permanent sequelae. Treatment is absolutely required

for immunocompromised patients and often must continue indefinitely. Pyrimethamine and sulfadiazine or pyrimethamine and clindamycin, alone or in conjunction with steroids, are the most commonly employed treatments. It was once thought that most cases of toxoplasmosis were acquired congenitally, although recently this assumption has been challenged.[61]

Lymphoma

CNS lymphoma is common in patients with AIDS, especially in patients with severely reduced T-cell counts. CNS lesions produce focal neurologic signs that can manifest as ocular cranial nerve abnormalities. Primary ocular lymphoma also has been reported.[75]

Pneumocystis Carinii

Pneumocystis carinii is the most common opportunistic infection in patients with AIDS and most often presents as an interstitial pneumonia. Ocular complications are less common but do occur with disseminated *Pneumocystis carinii* infection. Lesions appear as multiple, light-yellow, plaque-like foci on the retina and choroid (Color Plate 3, Fig. 12).[6] Disseminated *Pneumocystis carinii* infection most frequently presents in patients receiving aerosolized pentamidine prophylaxis because the drug is distributed solely to the lungs. Ocular involvement may be the earliest clue to disseminated *Pneumocystis carinii* infection.[21]

Vasculitic and Rheumatologic Diseases

Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune multisystem disease. Ocular manifestations are frequent and may be a helpful clue for making the diagnosis. They include retinal involvement[84] (cotton-wool spots, retinal edema, and superficial hemorrhages), dry eyes[44] (Sjögren's syndrome, keratoconjunctivitis sicca), which occur in as many as 50% of patients, and scleritis.

Polyarteritis Nodosa

Polyarteritis nodosa is a multisystemic necrotizing vasculitis affecting small- and medium-sized vessels. Characterized by fever, malaise, weight loss, and other constitutional symptoms, the disease can affect any organ system, but the kidneys, heart, liver, and gastrointestinal tract are most commonly involved. Ocular manifestations include cotton wool spots, retinal microhemorrhages, edema from retinal vasculitis, episcleritis, scleritis, and ophthalmoplegia from involvement of the vasa ner-

vorum.[70] Treatment consists of systemic steroid administration and cyclophosphamide.

Behçet's Disease

Behçet's disease is a disease of unknown cause diagnosed on the clinical presentation of recurrent oral aphthous ulcerations, recurrent genital ulceration, and uveitis.[12] Synovitis, cutaneous vasculitis, and meningoencephalitis also may occur. Ocular involvement occurs in 60% to 70% of patients and may occur late in the course of the disease.[14] Not all patients have the classic triad of symptoms. Anterior uveitis is the most common manifestation and is frequently severe enough to cause hypopyon. Posterior uveitis may also occur and manifests as vitreous cellular infiltrate (floaters). Retinal vascular inflammation, conjunctivitis, episcleritis, and keratitis also may occur. Oral corticosteroids may be of some benefit.

Temporal (Giant Cell) Arteritis

Temporal arteritis is a devastating, preventable cause of blindness caused by an idiopathic vasculitis that affects medium and large arteries. An important consideration in the differential diagnosis of elderly patients who present to the physician with headache, temporal arteritis presents most commonly in the seventh and eighth decades of life as a severe unilateral cephalgia that is typically associated with pain and tenderness over the temporal artery. Occasionally, patients may present with blindness as an initial feature. Fever, malaise, and other constitutional symptoms may also be present, and jaw claudication from involvement of the arterial supply to the masseter muscle is highly suggestive of temporal arteritis. If left untreated, about one quarter of patients will develop anterior ischemic optic neuropathy resulting in sudden, near complete, monocular loss of vision, pain, and an afferent pupillary defect. Cranial nerve abnormalities, cortical blindness, and central retinal artery occlusion also may result. Funduscopic examination reveals a pale, swollen optic nerve head. The diagnosis is suggested by tenderness over the temporal artery and a high erythrocyte sedimentation rate and is confirmed with a temporal artery biopsy. Prompt administration of systemic corticosteroids may prevent complications in the contralateral eye.

Kawasaki's Disease

Kawasaki's disease, also known as mucocutaneous lymph node syndrome, is a rare, febrile, multisystem disease, characterized by fever, oropharyngeal lesions, cervical lymphadenopathy, a maculopapular rash, and other skin and nail changes. It is most common in Japanese boys younger than 2 years.[46] Ocular manifestations include bilateral conjunctival injection, punctate keratitis, subconjunctival hemorrhage,

iridocyclitis, vitreous opacities, and papilledema in severe cases.[64] Conjunctivitis occurs in about 90% of cases, involves primarily the bulbar conjunctiva, is bilateral, and usually is not severe. Anterior uveitis is also common.

Wegener's Granulomatosis

Wegener's granulomatosis is a granulomatous disease that characteristically involves the lungs, sinuses, and kidneys. Ocular involvement is common and results in proptosis, ptosis, and ophthalmoplegia from granuloma formation and inflammation within the orbit (Fig. 1). Conjunctivitis, episcleritis, scleritis, obstruction of the nasolacrimal duct, and corneal ulceration also may occur.[9, 38]

Sarcoidosis

Sarcoidosis is an idiopathic multisystem disease characterized by the presence of noncaseating granulomas in the lungs, lymph nodes, and skin. Ocular involvement occurs in as many as 50% of patients and most commonly takes the form of a granulomatous anterior uveitis. Patients present with pain, decreased visual acuity, and photophobia. Floaters also may occur. Sarcoidosis may result in keratic precipitates on the corneal epithelium.[12] Posterior synechiae, conjunctivitis, iris nodules, and posterior uveitis also can be seen. Treatment is with cycloplegics and topical corticosteroids.

Sjögren's Syndrome

Sjögren's syndrome is the name given to a disorder characterized by keratoconjunctivitis sicca and xerostomia (dry mouth) that occurs secondary to lymphocytic infiltration and destruction of the lacrimal and salivary glands. It may occur primarily, or may be secondary to SLE, scleroderma, or other collagen vascular disease. Ocular manifestations include keratitis, corneal ulceration, and recurrent infections secondary to decreased tear formation. Frequent use of artificial tears is usually sufficient treatment.

Reiter's Syndrome

Reiter's syndrome is an idiopathic disease that presents with the classic triad of arthritis, urethritis, and conjunctivitis. Circinate balanitis also may occur. This syndrome is much more common in men than in women and has a particular predilection for patients with HLA-27 histocompatability complex. Ocular findings most commonly seen include a conjunctivitis that is both bilateral and purulent and an anterior uveitis (iritis).[12, 65]

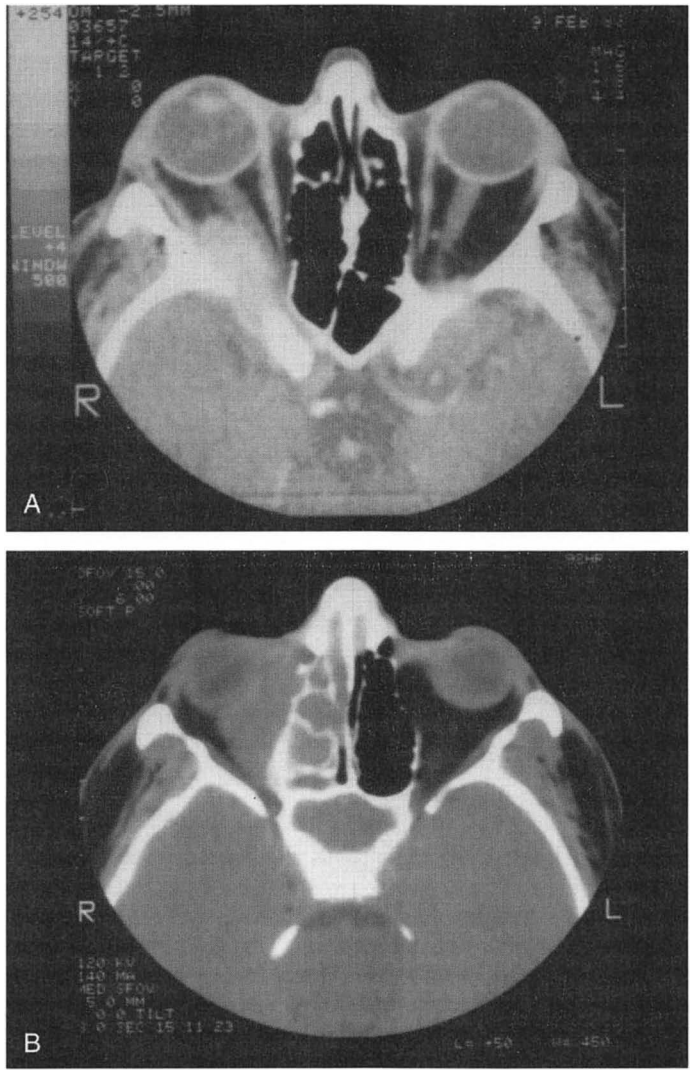

Figure 1. Wegener's granulomatosis involving the orbit *(A)* at presentation and *(B)* involving the posterior orbital space and ethmoid sinuses.

Metabolic and Endocrine Diseases

Diabetic Retinopathy

Diabetes causes myriad changes in the eye and is one of the most common causes of blindness in developed countries.[15] Diabetic retinopathy is the most common ophthalmologic complication and relates to both the duration of diabetes and the adequacy of glycemic control over

time. About two thirds of patients with diabetes for 20 years or more will develop retinopathy. Changes begin with microaneurysm formation and retinal "dot and blot" hemorrhages. Severer disease leads to macular edema, cotton-wool spots, and venous hemorrhage. Ultimately, neovascularization occurs, leading to vitreous contraction and hemorrhage and retinal detachment.

Lens changes, including refractive changes[72] and cataracts, also occur. Diabetes should be considered in any patient with a sudden change in visual acuity. The term *diabetic cataract* refers to the sudden opacification of the lens seen with type I diabetes. *Senile cataract* is the term used for slow, progressive, opacification that occurs primarily in type II diabetes. Tight control of blood sugar may limit ocular complications.

Hyperthyroidism

Hyperthyroidism results in a constellation of ocular findings, including lid retraction, lid lag, exophthalmos, and optic neuropathy. Lid retraction and lid lag are thought to occur secondary to sympathetic stimulation. Graves's disease causes a cellular increase in glycosaminoglycans that results in extraocular muscle enlargement and proliferation of orbital fat and leads to an increase in orbital pressure. Proptosis, restriction of extraocular movements, and pressure on the optic nerve ultimately lead to visual changes and optic neuropathy. Conjunctivitis, especially around the lateral rectus muscle, is seen commonly also.

Gout

Although rare, ocular manifestations of gout include conjunctival injection, episcleritis, and deposition of urate crystals in the cornea.[27]

Wilson's Disease

This rare disorder of copper metabolism leads to neurologic impairment, hepatitis, and cirrhosis. Corneal deposits of copper lead to the pathognomonic Kayser-Fleischer ring, which appears as a single, thin, yellow, red or green peripheral band in more than 95% of patients. Cataracts may also occur as a late manifestation of the disease.[2]

Hematologic Diseases

Sickle Cell Disease

Sickle cell disease is an inherited hemoglobinopathy characterized by red cell deformation and painful crises. Ocular complications are most common in patients who are heterozygous for sickle cell disease. These complications include conjunctival "comma"-shaped capillaries known as the "sickling sign" and retinal arterial ischemia from vascular

occlusion.[60] Retinal ischemia eventually leads to neovascularization, vitreous hemorrhage, and occasionally retinal detachments.[34] Lid edema and iris atrophy also may occur.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a disorder characterized by thrombotic occlusion of small vessels associated with consumption of platelets and clotting factors. Ocular manifestations include thrombosis and hemorrhage of the choroidal vessels resulting in yellow-grey, plaque-like lesions on fundoscopic examination. Decreased visual acuity and afferent pupillary defect also have been reported.[74]

Bleeding and Coagulation Disorders

Polycythemia and other hyperviscosity syndromes may result in venous dilatation and congestion, retinal hemorrhages, cotton-wool spots, and retinal vein occlusion.[45] Leukemia can result in spontaneous subconjunctival hemorrhage, anterior uveitis, spontaneous hyphema, and retinal hemorrhages. Vitreous hemorrhage is a rare but serious complication of systemic anticoagulation, and spontaneous hyphema from overzealous anticoagulation has also been reported.[39]

Neurologic Diseases

Myasthenia Gravis

Myasthenia gravis is a disorder caused by impaired transmission at the neuromuscular junction that leads to generalized motor weakness. Ocular involvement occurs in almost 90% of patients and is frequently the first symptom to appear. Manifestations include diplopia, ptosis, and nystagmus, which are nearly always bilateral and frequently worse at the end of the day. Pupillary activity is always spared.[79]

Multiple Sclerosis

Multiple sclerosis (MS) is a disorder characterized by demyelination of the central nervous system and recurrent, unpredictable attacks of motor, sensory, autonomic, and cortical dysfunction. The most common ocular manifestation of MS, occurring in up to 40% of cases, is optic neuritis. Patients present with painful monocular loss of vision. Loss of color vision occasionally occurs, and a central scotoma (loss of central vision) is particularly common but not unique. In every case of presumed optic neuritis, referral to an ophthalmologist and neurologist is essential because early treatment with large doses of corticosteroids may reduce the short-term risk of developing MS.[3] Cranial nerve dysfunction is also common and can lead to diplopia, nystagmus, and inability to

adduct the affected eye when the opposite eye is abducted secondary to intranuclear ophthalmoplegia (INO). INO results from involvement of the tracts connecting the third, fourth, and sixth cranial nerves and is seen almost entirely in patients with MS. Facial hypesthesia, tic-douloureux, and Bell's palsy leading to dry eye syndrome also may occur.

Trauma and Environmental Injury

Trauma and Child Abuse

Child abuse may be particularly difficult to diagnose, especially in children with no external signs of trauma. Detailed ophthalmoscopic examination may reveal changes suggestive of child abuse from blunt head trauma, the shaken baby syndrome,[11] or other significant trauma,[1] including retinal hemorrhage, hyphema, subconjunctival hemorrhage, and lens subluxation. Retinal hemorrhage is most often seen and occurs in approximately 70% of patients thought to be abused.[24] Intraocular hemorrhage may be the only sign of abuse in children, and any child without a documented reason for the finding should be referred to child protective services.

High-Altitude Illness

Exposure to high altitudes results in a clinical spectrum of physiologic abnormalities ranging from mild acute mountain sickness to high-altitude pulmonary edema and high-altitude cerebral edema. Exposure to high altitude also results in predictable changes to the retina known as high-altitude retinopathy (HAR). Initial changes include dilation of the retinal veins and arteries. Severer exposure results in peripheral retinal hemorrhages, macular hemorrhages, vitreous hemorrhage, and papillary hemorrhage. With the onset of cerebral edema, peripapillary hyperemia and, ultimately, papilledema result. HAR is important not only for its potential for major visual loss but also because retinal changes are a sensitive indicator of more severe high-altitude illness.

Dysbarism

Decompression sickness occurs when a rapid decrease in ambient pressure results in the release of inert gas from the blood and formation of gas bubbles in the circulation. These changes lead to a myriad of effects, including joint pain (the "bends"), subcutaneous emphysema, pulmonary edema, and neurologic abnormalities. Ocular abnormalities are common[16] and include scotomas, diplopia, visual field defects, hemianopsia, cortical blindness, eye pain, accommodative and convergence difficulties, and retinal artery occlusion.[10] Hyperbaric therapy is the only method of treatment.

SUMMARY

Systemic diseases can present with ocular manifestations to the emergency physician. Although most ocular findings serve to alert the physician to a possible ocular complication, many are different enough to aid the physician in making an obscure diagnosis. Knowledge of the characteristic ophthalmologic manifestations of systemic disease can aid the physician in diagnosing a particular disorder, limit the progression of more common diseases, and prevent further visual loss or blindness in patients with serious ophthalmologic complications.

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