Ocular Manifestations of Autoimmune Disease

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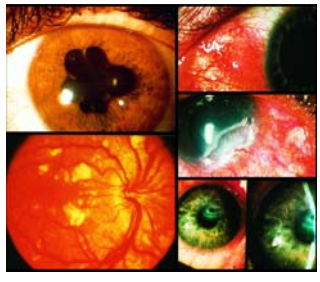
Rheumatoid arthritis, juvenile rheumatoid arthritis, Sjögren's syndrome, the seronegative spondyloarthropathies, systemic lupus erythematosus, multiple sclerosis, giant cell arteritis, and Graves' disease are autoimmune disorders commonly encountered by family physicians. These autoimmune disorders can have devastating systemic and ocular effects. Ocular symptoms may include dry or red eyes, foreign-body sensation, pruritus, photophobia, pain, visual changes, and even complete loss of vision. Because a number of these diseases may initially present with ocular symptoms, physicians should maintain a high index of suspicion to make a timely diagnosis. A thorough ophthalmic examination, including visual acuity, pupillary reaction, ocular motility, confrontation field testing, external inspection, and direct ophthalmoscopy with fluorescein staining, should be completed. In the patient with the complaint of a "dry eye" or a "red eye," simple tools such as the Schirmer's test or the blanching effect of phenylephrine can be useful in diagnosis. In general, managing the systemic effects with nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive agents controls the ocular symptoms. When visual function is threatened, surgical therapy may be necessary. Early and accurate diagnosis with prompt treatment or referral to an ophthalmologist may prevent systemic and ocular disabilities. (Am Fam Physician 2002;66:991-8. Copyright© 2002 American Academy of Family Physicians.)



See page 937 for definitions of strength-of-evidence levels contained in this article.

Patients with autoimmune diseases are frequently encountered by family physicians. It is important to understand not only the systemic effects of these diseases but also their ocular manifestations *(Table 1)*. Most ocular complications involve the cornea but may also include the conjunctiva, uvea, sclera, retina, and surrounding structures *(Figure 1)*. The majority of these diseases will ultimately need to be referred to an ophthalmologist.

Rheumatoid Arthritis

Approximately 25 percent of patients with rheumatoid arthritis (RA) will have ocular manifestations. These may include keratoconjunctivitis sicca, scleritis, episcleritis, keratitis, peripheral corneal ulceration, and less common entities such as choroiditis, retinal vasculitis, episcleral nodules, retinal detachments, and macular edema.[1,2]

Approximately 25 percent of patients with rheumatoid arthritis have ocular manifestations, most commonly keratoconjunctivitis sicca.

Keratoconjunctivitis sicca, or dry eye syndrome, is the most common ocular manifestation of RA and has a reported prevalence of 15 to 25 percent.[1,2] Symptoms are historically more prominent during the latter part of the day because of the evaporation of the tear film *(Table 2)*. A simple and easy-to-perform test assessing the function of the lacrimal glands is the Schirmer's test *(Figure 2)*. It is performed by first drying the tear film, then inserting a Schirmer strip into the lower conjunctival cul-de-sac toward the temporal aspect of the lower lid. No anesthetic should be used. After five minutes, if the strip measures less than 10 mm of wetting, the lacrimal glands are not functioning correctly. If a slit lamp is available, corneal examination may reveal punctate erosive keratopathy or filaments.[3,4]

The primary goal in managing dry eye is to replenish or preserve the tear film. Patients should be educated about simple measures such as using sunglasses and

TABLE 1
Ocular Manifestations of Autoimmune Disease

Disease	*Ocular manifestations*	*Disease*	*Ocular manifestations*
Rheumatoid arthritis	Keratoconjunctivitis sicca, scleritis, episcleritis, keratitis, ulcerative keratitis, choroiditis, retinal vasculitis, episcleral nodules, retinal detachments, macular edema	Giant cell arteritis	Amaurosis fugax, diplopia, vision loss
Juvenile rheumatoid arthritis	Uveitis	Graves' disease	Proptosis/exophthalmos, lid lag and retraction, keratitis, decreased visual acuity, reduced visual fields, relative afferent pupillary defect, loss of color vision
Sjögren's syndrome	Keratoconjunctivitis sicca		
Ankylosing spondylitis	Uveitis		
Reiter's syndrome	Conjunctivitis, uveitis, keratitis	Myasthenia gravis	Diplopia, eyelid ptosis
Enteropathic arthritis	Uveitis, episcleritis, peripheral ulcerative keratitis	Sarcoidosis	Uveitis, conjunctival nodules, cranial nerve palsies, enlarged lacrimal glands, optic neuropathy
Psoriatic arthritis	Uveitis, conjunctivitis, keratitis		
Systemic lupus erythematosus	Keratoconjunctivitis sicca, conjunctivitis, uveitis, episcleritis, scleritis, keratitis, retinal hemorrhages, retinal vasculitis, proliferative retinopathy, optic neuritis, ischemic optic neuropathy, hemianopia, amaurosis, internuclear ophthalmoplegia, pupillary abnormalities, oculomotor abnormalities, visual hallucinations	Wegener's granulomatosis	Proptosis/exophthalmos, orbital cellulitis, uveitis, corneal ulcers, optic neuropathy
		Behçet's syndrome	Uveitis, hypopyon
		Antiphospholipid syndrome	Vaso-occlusive retinopathy, ischemic optic neuropathy
		Polyarteritis nodosa	Episcleritis, scleritis, optic neuropathy
		Takayasu's arteritis	Vaso-occlusive retinopathy, ischemic optic neuropathy, cataracts
Multiple sclerosis	Afferent: optic neuritis, retrobulbar neuritis, visual field defects Efferent: internuclear ophthalmoplegia, dysmetria, nystagmus, cranial nerve palsies	Dermatomyositis	Eyelid/conjunctival edema, retinopathy, uveitis

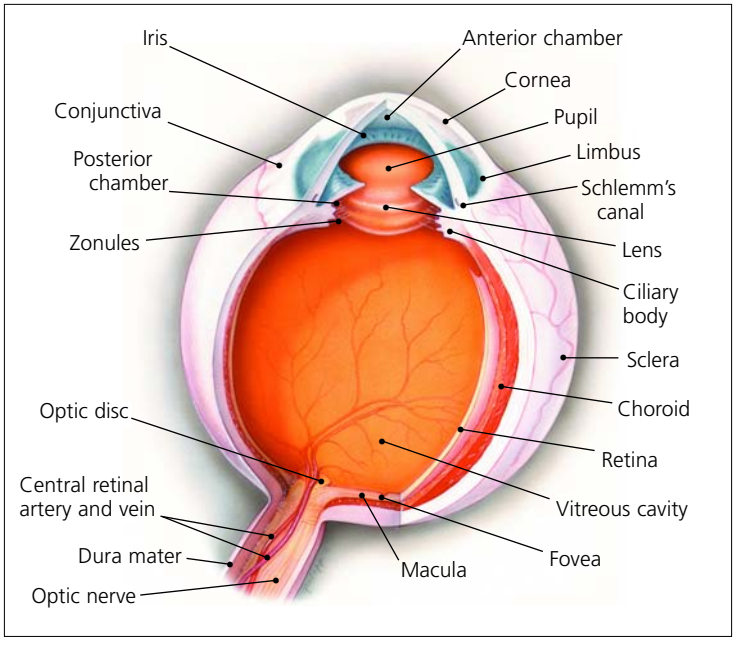


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FIGURE 1. Cross section of the eye.

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room humidifiers, and avoiding dry environments before turning to tear substitutes. Natural or artificial tear substitutes can help alleviate more severe symptoms, but most contain preservatives that can be toxic to the cornea.[5] In severe cases, occlusion of the lacrimal drainage puncta or tarsorrhaphy will be necessary.

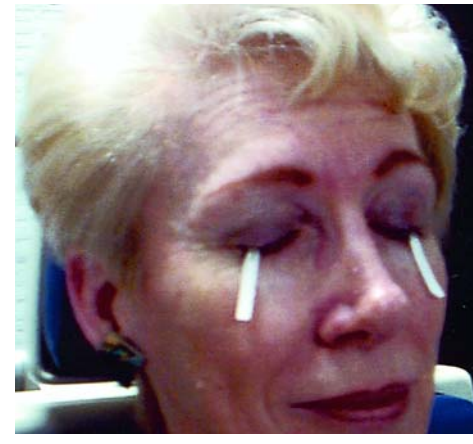

FIGURE 2. The Schirmer's test is used to assess the function of the lacrimal glands.

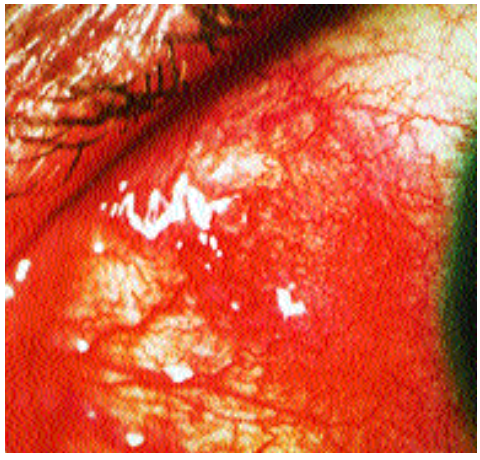

FIGURE 3. Scleritis. Engorged scleral vessels do not blanch with application of topical phenylephrine 2.5 percent.

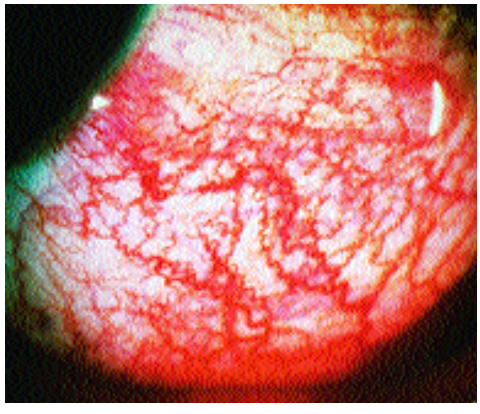

FIGURE 4. Episcleritis. Engorged episcleral vessels give the eye a bright red appearance. Blanching of the vessels occurs with application of topical phenylephrine 2.5 percent.

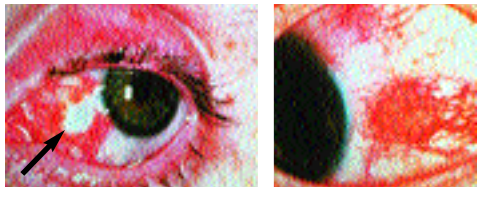

FIGURE 5. Necrotizing scleritis *(left)* and scleritis *(right)*. Note the avascular areas of sclera surrounded by edema *(arrow)*.

Scleritis *(Figure 3)* or episcleritis *(Figure 4)* in patients with RA occurs at a prevalence rate of 4 to 10 percent.[1] RA is the most common cause of scleritis, accounting for approximately 18 to 33 percent of cases.[1,2,6] Scleritis and episcleritis are distinguished on the basis of anatomy and appearance[1,2,7] *(Table 2)*. Symptoms may be similar, but the pain in scleritis is more evident and severe. Tenderness to palpation of the globe can help differentiate the two. After asking the patient to look down with eyelids closed, the physician gently presses the globe. Patients with scleritis have tenderness on palpation, while those with episcleritis do not.

Topical phenylephrine 2.5 percent (Neo-Synephrine) can help the physician distinguish dilated vessels caused by scleritis from those caused by episcleritis. The instillation of one to two drops in the affected eye will cause the engorged vessels caused by episcleritis to blanch while those caused by scleritis remain dilated. Patients should be warned that phenylephrine will cause blurred vision and dilation of the pupil for approximately three hours. This test should not be done in patients with a history of glaucoma.

Among the variations of scleritis, necrotizing scleritis with inflammation is the most destructive. In addition to the ocular findings in non-necrotizing scleritis, avascular areas of the sclera or necrosis may be seen, surrounded by scleral edema *(Figure 5)*. Complications include scleral thinning, staphyloma, or perforation.[1,7] Necrotizing scleritis without inflammation is a sign of long-standing RA and can lead to scleromalacia perforans *(Figure 6)*.

Between the two forms of episcleritis, simple episcleritis is more common in patients with RA. The presence of subconjunctival

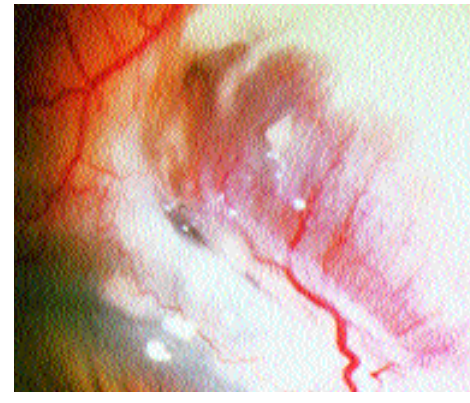

FIGURE 6. Scleromalacia perforans. Note the thinning of the sclera, which leaves the choroid bare and covered by a thin layer of conjunctiva.

TABLE 2
Ocular Signs and Symptoms in Autoimmune Disease

Condition	*Symptoms*	*Signs*	*Treatment*
Keratitis	Pain with photophobia, foreign body sensation, tearing, red eye, decreased vision	Inflammatory cell infiltrate, corneal opacification, corneal vascularization, corneal ulceration	NSAIDs, topical/oral/IV steroids, immunosuppressives, surgery
Keratoconjunctivitis sicca	Dry eye, burning, pain, blurred vision, pruritus, foreign-body sensation, mucous threads and crusting about the eyelids	Diminished corneal tear meniscus, abnormal Schirmer's test	Sunglasses, room humidifiers, tear substitutes, surgery
Scleritis	Gradual onset; deep, boring pain may radiate into cheek, eyebrows, and temples; blurred vision; photophobia	Decreased visual acuity; bluish appearance with engorged blood vessels; may have immovable, tender nodules over the sclera, general tenderness on palpation; engorged blood vessels do not blanch with phenylephrine (Neo-Synephrine); avascular areas over the sclera	NSAIDs, topical/oral/IV steroids, immunosuppressives, surgery
Episcleritis	Sudden onset; mild ache may radiate into cheek, eyebrows, and temples; no blurred vision; photophobia	No change in visual acuity; bright red appearance with engorged blood vessels; may have movable, nontender nodules over the episclera; no tenderness on palpation; engorged blood vessels blanch with phenylephrine	NSAIDs, topical/oral steroids
Uveitis	Red eye, pain, photophobia, blurred vision	Decreased visual acuity, inflammatory infiltrate in the anterior chamber, synechiae, pupillary miosis	Cycloplegics, topical steroids, immunosuppressives
Optic neuritis	Visual loss, pain with eye movement, photophobia	Decreased visual acuity, loss of color vision, central scotoma, afferent pupillary defect, swollen optic nerve	IV steroids with positive MRI findings
Exophthalmos	Irritable and gritty eyes, double or blurred vision, photophobia, increased tearing, orbital pressure	Protruding globe, widened palpebral fissures, conjunctival injection and chemosis, lid lag and retraction, exposure keratitis	Lubricating eye drops, sleeping with head elevated, sunglasses, eyelid taping at night, steroids, radiotherapy, surgery

NSAIDs = nonsteroidal anti-inflammatory drugs; IV = intravenous; MRI = magnetic resonance imaging.

nodules that are mobile over the sclera differentiates nodular episcleritis from simple episcleritis.[1,7] Both forms of episcleritis can be confused with severe conjunctivitis because of the bright-red appearance of the eye and should be differentiated with the help of a thorough history and physical examination.

The importance of correctly diagnosing and distinguishing between scleritis and episcleritis is based on the potential ocular and systemic complications associated with scleritis. Studies have shown that patients with RA-associated scleritis have more widespread systemic disease and a higher mortality rate than those without scleritis.[6-8] The initial treatment of scleritis and episcleritis should be focused on relieving discomfort and stopping progression of the disease. Initial therapy includes oral indomethacin (Indocin) or other nonsteroidal anti-inflammatory drugs (NSAIDs). Patients who do not respond to these medications should be referred to an ophthalmologist for possible treatment with topical steroids or systemic immunosuppressive medications.

Corneal disease in patients with RA can be an isolated complication, but it is most commonly associated with keratoconjunctivitis sicca or a form of anterior scleritis. The spectrum of disease may include keratitis, sclerosing keratitis, and peripheral or paracentral ulcerative keratitis[1,2,6,7] *(Table 2)*. The drying effects of keratoconjunctivitis sicca lead to devitalized epithelial cells and punctate epithelial erosions. Keratitis associated with scleritis may be acute or sclerosing. Acute keratitis has been identified in 30 to 70 percent of patients with scleritis or episcleritis-associated RA.[1,6] It is marked by an inflammatory cell infiltrate that may result in corneal scarring, ulceration, or melting.[1,6]

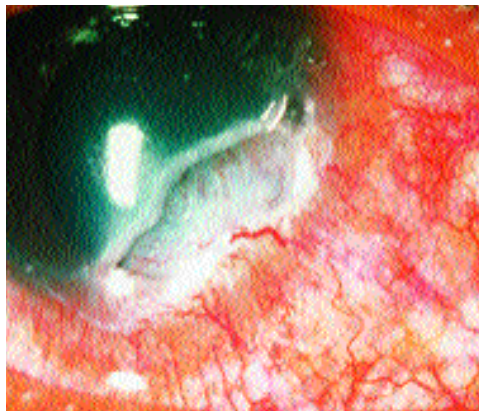

FIGURE 7. Peripheral corneal ulceration. Note the crescent-shaped destructive inflammation of the juxtalimbal cornea.

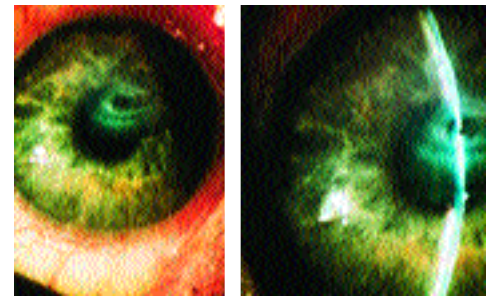

FIGURE 8. Corneal perforation. Severe tear deficiency leads to breakdown of the corneal epithelial layer.

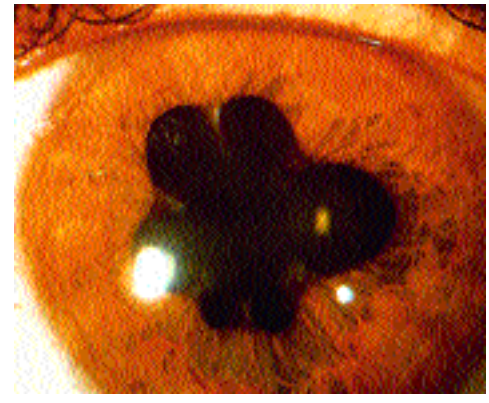

FIGURE 9. Posterior synechiae caused by adhesion of the iris to the lens, resulting in an irregularly shaped pupil.

Sclerosing keratitis is a chronic process marked by an area of opacified and vascularized cornea that progresses toward the visual axis. This area of opacification may be more evident with fluorescein staining. Peripheral and paracentral ulcerative keratitis can occur in association with, or in the absence of, scleritis and are marked by corneal thinning in the juxtalimbal cornea (peripheral) or the central (paracentral) cornea[1,2] *(Figure 7)*. Without treatment, perforation *(Figure 8)* and visual loss may occur. Care must be taken when prescribing steroids to prevent further thinning of the cornea. It is important that the patient receive a thorough ocular examination with frequent slit lamp follow-up evaluations. Typically, topical steroids, immunosuppressive therapy, surgical intervention, or a combination of the above will be required to preserve vision. Surgical options include ulcer debridement, conjunctival resection, corneal graft, application of tissue adhesives, sclerectomy, and scleral patch grafting.[1,2,8]

Other, less common ocular manifestations of RA include choroiditis, retinal vasculitis, episcleral nodules, exudative or serous retinal detachments, and macular edema.[1,2,6] A high index of suspicion can preserve vision and prevent further ocular complications.

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis accounts for approximately 80 percent of cases of uveitis in children.[1,2,9] Delay in diagnosis can lead to cataracts, glaucoma, and blindness. Although uveitis can be found in all forms of juvenile RA, it is most commonly found in the pauciarticular subtype. Most patients will be symptom-free or have blurred vision *(Table 2)*. On examination, the patient may have decreased visual acuity, band keratopathy, synechiae *(Figure 9)*, cataracts, or elevated ocular pressure. Diagnosis or suspicion of juvenile RA should prompt a referral to a pediatric ophthalmologist. Recommendations for ocular screening examinations are based on the risk of developing uveitis *(Table 3)*.[10] Therapy involves close monitoring by an ophthalmologist, with the use of cycloplegic agents, steroids, NSAIDs, or immunosuppressive agents.[1,2]

Sjögren's Syndrome

The primary ocular manifestation of Sjögren's syndrome is keratoconjunctivitis sicca. The signs and symptoms are similar to those of keratoconjunctivitis sicca associated with RA. In addition to the treatment noted above, 5 mg of oral pilocarpine (Salagen) four times daily may improve the symptoms of dry eyes and dry mouth.[11,12] [Reference 11, Evidence level A, randomized controlled trial] Patients should be cautioned that the side effects of diaphoresis and poor night vision may occur.

TABLE 3
JRA Risk Categories for Developing Uveitis and Recommended Ocular Examinations

Risk	*Recommendations*
High: should have ocular examination every three months	Pauci- or polyarticular arthritis; positive for antinuclear antibodies Onset of arthritis ≤ 7 years Duration of arthritis ≤ 4 years
Moderate: should have ocular examination every six months	Pauci- or polyarticular arthritis; positive for antinuclear antibodies Onset of arthritis ≤ 7 years Duration of arthritis > 4 years
Low: should have ocular examination every 12 months	Pauci-, polyarticular, or systemic arthritis; negative for antinuclear antibodies Onset of arthritis > 7 years Duration of arthritis > 4 years

JRA = juvenile rheumatoid arthritis.

Adapted with permission from American Academy of Pediatrics, Subcommittees of Rheumatology and Ophthalmology. Guidelines for ophthalmic examinations in children with juvenile rheumatoid arthritis. Pediatrics 1993;92:295-6.

Spondyloarthropathies

Among the seronegative spondyloarthropathies, uveitis in ankylosing spondylitis is the most common ocular manifestation. It occurs in approximately 25 percent of patients with ankylosing spondylitis, in up to 37 percent of patients with Reiter's syndrome, in approximately 20 percent of patients with psoriatic arthritis, and in up to 9 percent of patients with enteropathic arthritis (arthritis associated with Crohn's disease or ulcerative colitis).[2,13-15] Ocular symptoms can be unilateral or bilateral, and pain is caused by ciliary spasm in response to anterior chamber inflammation. As noted earlier, patients suspected of having uveitis should be referred to an ophthalmologist. Complications include glaucoma, cataracts, or blindness.

Systemic Lupus Erythematosus

Ocular disease occurs in 20 percent of patients with systemic lupus erythematosus (SLE). In some cases, ocular disease may indicate reactivation of SLE that was thought to be in remission.[16] External ocular manifestations include keratoconjunctivitis sicca, conjunctivitis, uveitis, episcleritis, scleritis, keratitis, and a discoid lupus rash over the eyelids that is often confused with blepharitis.[16,17] Neuro-ophthalmic involvement in SLE is primarily caused by microinfarction, hemorrhage, or vasculitis in various locations of the eye and along the visual pathway. Typical complications include optic neuritis, ischemic optic neuropathy, hemianopia, amaurosis, internuclear ophthalmoplegia, pupillary abnormalities, oculomotor abnormalities, pseudotumor cerebri, and visual hallucinations.[16]

Retinal disease primarily occurs in patients with active SLE and may include cotton-wool spots *(Figure 10)*, retinal hemorrhages, retinal vasculitis, or proliferative retinopathy. Treatment of ocular disease is based on specific pathology and underlying disease.[16] Keratoconjunctivitis sicca is thought to be the most common manifestation and can be treated as noted above.

Retinal disease has a high morbidity and should be treated aggressively by an ophthalmologist.[16,17] Ophthalmic screening programs in SLE are controversial. Most physicians agree that patients on antimalarial or steroid regimens should receive a full dilated-eye examination on initiation of therapy then with routine examinations in low-risk patients and yearly for high-risk patients. High risk is defined by medication

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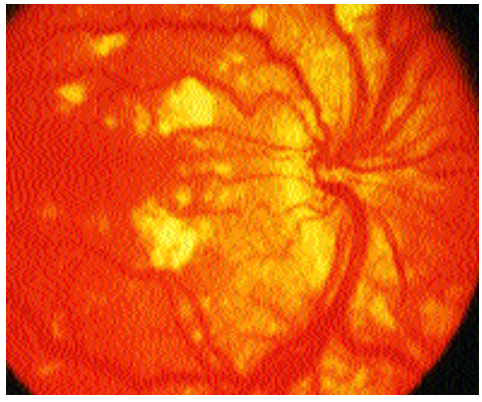

FIGURE 10. Cotton-wool spots in a patient with systemic lupus erythematosus.

dosage (>6.5 mg per kg hydroxychloroquine or >3 mg per kg chloroquine), duration of use (more than five years), high body fat level, presence of renal or liver disease, presence of concomitant retinal disease, and age greater than 60 years.[16,18]

Multiple Sclerosis

The ocular manifestations of multiple sclerosis (MS) can be divided into afferent and efferent disorders[19] *(Table 1)*. Optic neuritis is diagnosed in 75 percent of patients with MS and is the presenting symptom in 14 to 25 percent of cases[19,20] *(Table 2)*. Visual field defects in patients with MS are a result of demyelination along the visual pathway. Bilateral internuclear ophthalmoplegia is almost always caused by a demyelinating disorder.[19] Dysmetria, nystagmus, and cranial nerve palsies, especially involving the sixth and third nerves, may result from lesions of the brain stem and cerebellum.

Nystagmus, which may be the first neurologic finding in patients with MS, is commonly horizontal but may also be rotary or vertical.[19] Patients with suspected ocular involvement should receive magnetic resonance imaging (MRI), a full dilated-eye examination, and treatment with intravenous corticosteroids if the MRI is positive.[20] Periodic follow-up evaluations should be done to monitor the progression of disease.

Ocular disease may occur in 50 percent of patients with giant cell arteritis and is commonly present in patients who are still without systemic signs or symptoms.

Giant Cell Arteritis

Up to 50 percent of patients with giant cell arteritis present with ocular symptoms that include pain, diplopia, visual loss, and amaurosis fugax, in addition to headache, jaw claudication, and neck pain.[21,22] It is important to note that ocular involvement is common in the absence of systemic signs and symptoms.[21,22] Patients may have temporal artery tenderness or a decreased temporal artery pulse, but diagnosis is confirmed with biopsy of the artery and elevated titers of erythrocyte sedimentation rate and C-reactive protein. Biopsy will remain positive for up to two weeks after the initiation of corticosteroid therapy.[21] Intravenous corticosteroids should be used in patients with visual symptoms.[21] Immediate therapy can be dramatic in effect and prevent further vasculitic complications, permanent blindness, or death.

Graves' Disease

Exophthalmos *(Figure 11)* occurs in approximately 50 percent of patients with thyroid disease[23] *(Table 2)*. It is strongly associated with smoking and may also be found in patients who are euthyroid or hypothyroid.[23] If signs of optic nerve compression, such as decreased visual acuity, reduced visual fields,

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FIGURE 11.

relative afferent pupillary defect, and loss of color vision are present, computed tomography or MRI of the orbit is recommended.[23-25]

Patients with suspected ocular disease should be referred to an ophthalmologist for a full dilated ocular examination. Mild ocular disease can be treated with simple methods such as lubrication drops applied hourly, sleeping with the head elevated, wearing sunglasses during the daytime, and taping eyelids closed at night. Systemic corticosteroid therapy or radiotherapy is reserved for more severe cases, and surgical decompression of the orbit or tarsorrhaphy may be required in patients with sudden visual loss or extensive corneal damage, respectively.[23,25]

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A list of terms and definitions is available on the Web site at www.aafp.org/afp/20020915/991x.html.

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