Ocular Manifestations of Systemic Inflammatory Diseases

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ABSTRACT—Inflammation of the eye is often times seen in association with systemic inflammatory diseases. Understanding the various forms of ocular involvement in these conditions is important as untreated ophthalmic involvement can lead to severe vision loss. In addition to providing a basic framework for diagnosis and treatment, this review will highlight the ocular manifestations of the following systemic inflammatory conditions: rheumatoid arthritis, systemic lupus erythematosus, Wegener’s granulomatosis, Sjögren’s syndrome, polyarteritis nodosa, primary antiphospholipid syndrome, Behçet’s syndrome, Kawasaki disease, Cogan’s syndrome and relapsing polychondritis.

Introduction

Ocular inflammation is often seen in patients with systemic inflammatory conditions. Examples of systemic inflammatory conditions with ocular manifestations include rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, Wegener’s granulomatosis, Sjögren’s syndrome, polyarteritis nodosa, primary antiphospholipid syndrome, Behçet’s syndrome, Kawasaki disease, Cogan’s syndrome and relapsing polychondritis. The involvement of the eye in these processes can not only herald the onset of disease but can also serve as a marker of the severity of systemic inflammation. These conditions can affect various parts of the eye including the cornea, retina, sclera, conjunctiva, ocular adnexa and the vasculature with the potential of various ophthalmic complications and severe vision loss. Understanding the various presentations of these systemic inflammatory diseases with regard to the eye is important in order to be able to arrive expeditiously at the correct diagnosis and treatment plan with the goal of preserving visual function. This review will highlight the ocular manifestations of various systemic inflammatory diseases and provide a basic framework for diagnosis and treatment.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology that mainly affects the joints but can also have significant extra-articular involvement with nearly all organ systems affected. Women are affected three times more than men and there is evidence of a genetic component conferred through HLA-DQ and –DR alleles. The hallmark of RA is morning stiffness and this is probably the most widely noted presenting symptom. There are specific
criteria for the diagnosis of rheumatoid arthritis as set forth by the American College of Rheumatology. The criteria include the presence of synovitis in at least one joint, exclusion of alternate etiologies of the synovitis, and a score of at least six out of 10 in the categories of joint involvement, serology, acute-phase reactants, and duration of symptoms (Table 1).¹

Ophthalmic manifestations of RA are variable and include dry-eye syndrome, keratitis, episcleritis, and scleritis. Dry-eye syndrome is the most common eye finding and is characterized by irritation, foreign body sensation, redness, photophobia, burning, and fluctuating vision. Dry-eye syndrome can have various etiologies but in autoimmune disease the cause is usually decreased tear production. In addition to autoimmune disease, risk factors for dry-eye syndrome include age greater than 50 years, female sex, low environmental humidity, and systemic medications. Symptoms can be exacerbated during the winter months secondary to forced air heating systems and also during exposure to dry or windy conditions. Up to 90% of RA patients are affected by dry-eye syndrome and the severity can be independent of RA activity.² Patients with concomitant Sjögren’s syndrome (SS) and/or keratoconjunctivitis sicca (KCS) due to lacrimal gland involvement are at increased risk of corneal involvement secondary to an inadequate tear film.

Keratitis is inflammation of the cornea and in RA it classically presents as peripheral ulcerative keratitis (PUK). PUK results in corneal thinning due to complement and matrix metalloprotease activation and is often associated with adjacent scleral inflammation.³ As the name implies, PUK occurs in the peripheral cornea near the limbus (Fig. 1). The cornea is normally avascular and thus protected from the vascular system and inflammatory cells. However, the peripheral cornea by nature of its proximity to the limbal conjunctiva is able to derive the necessary components to mount an inflammatory response. Patients with PUK will typically complain of decreased vision, tearing, irritation, and pain. Examination will classically show crescent shaped peripheral corneal lesions with pooling of fluorescein and stromal thinning. If uncontrolled, PUK can progress to corneal melt which is a sterile avascular breakdown of corneal collagen fibers secondary to significant inflammation. Corneal melt is of great concern as it has the potential to lead to globe perforation and the loss of the eye. It is important to note that PUK is not specific to RA and can be seen in other systemic inflammatory conditions.

Table 1

<table>
<thead>
<tr>
<th>A. Joint Involvement</th>
<th>Score</th>
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<tr>
<td>One large joint</td>
<td>0</td>
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<tr>
<td>Two to 10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>One to three small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>Four to 10 small joints (with or without involvement of large joints)</td>
<td>3</td>
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<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
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<th>B. Serology</th>
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<tbody>
<tr>
<td>Negative RF and negative anti-CCP</td>
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<tr>
<td>Low-positive RF or low-positive anti-CCP</td>
</tr>
<tr>
<td>High-positive RF or high-positive anti-CCP</td>
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<tr>
<th>C. Acute Phase Reactants</th>
</tr>
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<tr>
<td>Normal CRP and normal ESR</td>
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<tr>
<td>Abnormal CRP or abnormal ESR</td>
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<tr>
<th>D. Duration of Symptoms</th>
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<tbody>
<tr>
<td>&lt; 6 weeks</td>
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<td>≥ 6 weeks</td>
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As adapted from 2010 American College of Rheumatism diagnostic criteria.

Episcleritis and scleritis represent a spectrum of scleral involvement. Episcleritis is characterized by inflammation of the episcleral tissues which lie between the conjunctiva and sclera. Patients will present with minor eye pain/irritation, tearing, and injection. Episcleritis is usually a mild and self-limiting condition rarely requiring treatment. In contrast, scleritis is much more significant and associated with ocular morbidity. Scleritis can be broadly classified as either anterior or posterior with further subclassification to diffuse, nodular, or necrotiz-

Figure 1.—Peripheral ulcerative keratitis. Note perlimbal location of corneal inflammation and evidence of prior intraocular inflammation in the form of iris-lens synchiae.
The majority of scleritis presentations are anterior scleritis. In addition to eye redness, tearing, and light sensitivity, these patients will have a severe constant deep boring eye pain radiating to the face and periorbital regions. This deep boring pain is a major distinguishing factor compared to episcleritis. Studies have shown RA to be the most common disease associated with scleritis.

Rheumatoid arthritis patients are at special risk for the necrotizing scleritis and scleromalacia perforans variants. Necrotizing scleritis is the most severe form of scleritis and the most likely to be associated with ocular morbidity. These patients will complain of severe steady pain that will progressively worsen. Ocular findings will show significant scleral injection and edema with bluish discoloration representing the underlying choroid if thinning has occurred. Scleromalacia perforans is necrotizing anterior scleritis without inflammation. While patients with necrotizing scleritis will seek care due to severe pain, patients with scleromalacia perforans do not have pain and will not have an inflamed red eye. Examination will reveal a noninflamed eye with bluish thinning of the sclera and loss of normal episcleral vasculature. Patients may complain of blurred vision as the alteration in globe integrity can result in a change of corneal topography with resultant acquired astigmatism. It is thus important for clinicians taking care of patients with long-standing RA to examine the scleral wall for thinning. PUK and necrotizing scleritis together in RA indicates potentially fatal systemic disease requiring powerful immunosuppressive therapy.

Laboratory findings in RA include an elevated rheumatoid factor (RF) and cyclic citrullinated protein (CCP) antibodies. While elevated RF is nonspecific, anti-CCP has a specificity of 95% and has proven to be helpful in diagnosis. Elevated acute-phase reactants like erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) are consistent with active inflammation and are incorporated in the diagnostic criteria, but it is important to remember they are nonspecific.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem chronic inflammatory disease of unknown etiology in which individuals produce self-directed antibodies. These antibodies cause widespread tissue and cell destruction via the formation of immune complexes and the misdirection of the inflammatory response. Women are four times more commonly affected than men, mostly in the childbearing years. The disease is more common in black, Hispanic and Asian women than in Caucasians. Systemic lupus erythematosus can affect the entire body and thus patients can have highly variable presentations with periods of disease activity and remission. Constitutional symptoms are almost always present and include fatigue, weight loss, and fever. Organ specific complaints most commonly relate to those involving the joints, skin, or kidney. The classic SLE arthritis is symmetrical, nondeforming and involves the hands. The most common skin change is the butterfly rash which presents as erythema of the cheek and nose sparing the nasolabial folds. Occasionally, some will develop discoid lesions characteristic of discoid lupus. Kidney involvement is present in up to 60% of patients and is most commonly manifested as glomerulonephritis. Diagnostic criteria were set in 1982 by the American College of Rheumatology and were later updated in 1997. Four of the following 11 criteria are considered diagnostic of SLE: malar rash, discoid skin lesions, photosensitivity when the skin is exposed to UV light, pleuritis or pericarditis, arthritis, nasal or pharyngeal ulcers, seizures or psychosis, hematologic abnormalities (anemia, thrombocytopenia, lymphopenia, or leukopenia), renal abnormalities (proteinuria or nephritis), antinuclear antibody titer elevation, and other serologic abnormalities (autoantibodies such as antiphospholipid, antidouble stranded DNA, or anti-Smith).

Ocular involvement in SLE is variable affecting various parts of the eye. Similar to RA, SLE can demonstrate corneal involvement as manifested by dry-eye syndrome/KCS and keratitis and scleral involvement as manifested by episcleritis or scleritis. Interestingly, the prevalence of
dry-eye syndrome is approximately 25% which is higher than in RA.\textsuperscript{15} Dry-eye syndrome in SLE can be a significant cause of patient discomfort and decreased visual acuity. As opposed to RA, SLE frequently has an associated retinopathy which can parallel systemic disease activity.\textsuperscript{16,17} SLE can cause a retinal vasculitis which can present as a painless irreversible decrease in vision. Fundoscopic examination will demonstrate vascular sheathing (inflammation along vessel walls) which can lead to an ischemic retinopathy and choroidopathy characterized by retinal hemorhages, cotton wool spots, and artery occlusions (Fig. 2).\textsuperscript{18} In addition to retinal involvement, choroidopathy and optic nerve involvement have also been shown to occur.\textsuperscript{19,20} The presence of retinopathy in SLE is a sensitive marker for active systemic and central nervous system disease and must be treated aggressively even if there are no apparent systemic signs of activity.

Laboratory findings in SLE include an elevated ANA titer of 1:160 or higher, antidouble-stranded DNA, and anti-Smith antibodies. While ANA can also be seen in Sjögren’s syndrome, scleroderma, RA, and juvenile rheumatoid arthritis the titers are usually lower. Antidouble-stranded DNA and anti-Smith antibodies are specific for SLE with positive predictive values ranging from 89% to 100%.\textsuperscript{21} False positive VDRL tests are also commonly seen in SLE. Unfortunately, none of the antibody tests have been shown to uniformly indicate disease status. Disease activity is assessed according to patients’ symptoms, their physical examination, and organ specific laboratory findings.

Treatment options for SLE include NSAIDs, hydroxychloroquine, glucocorticoids, and immunosuppressants such as methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab. In addition, anti-TNF-α biologics like infliximab are also increasingly being used as therapy.

Primary Antiphospholipid Syndrome

The term “antiphospholipid antibodies” refers to antibodies against phospholipid-protein complexes on cell membranes. The presence of these antibodies when paired with clinical criteria (vascular event or pregnancy morbidity) is considered a pathologic autoimmune response predisposing a person to excessive arterial and venous thrombosis. Antiphospholipid syndrome (APS) is commonly seen in other autoimmune diseases such as SLE and is thus termed primary antiphospholipid syndrome (PAPS) in the absence of these associated conditions. PAPS is rare as approximately 5% of the population will have the antibodies as compared to the autoimmune associated APS (50% of SLE patients). The diagnosis is made by the presence of certain clinical criteria in conjunction with positive antiphospholipid antibody tests.\textsuperscript{22,23} Clinical criteria include arterial or venous thrombosis in any tissue and/or pregnancy morbidity. Pregnancy morbidity is defined as any of the following: unexplained fetal death at <10 weeks gestation of a morphologically normal fetus, premature birth before 34 weeks of gestation due to preeclampsia, eclampsia, or placental insufficiency, or at least three unexplained pregnancy losses <10 weeks gestation.

Laboratory criteria include the presence of antiphospholipid antibodies on two or more occasions at least 12 weeks apart and no more than five years prior to clinical manifestations. Three types of clinically defined antiphospholipid antibodies exist and must meet certain criteria to be considered valid for diagnosis: anticardiolipin IgG or IgM, anti-b2 glycoprotein-I IgG or IgM, and lupus anticoagulant. Of the various antiphospholipid antibodies, lupus anticoagulant is the strongest predictor of thrombosis with an odds ratio of up to 16 and irrespective of SLE status.\textsuperscript{24}

The range of ocular manifestations in antiphospholipid syndrome is broad and can include any of the following: decreased vision, amaurosis fugax, redness, pain, diplopia or transient visual field defects.\textsuperscript{25-27} However, the most common ocular manifestation of PAPS is retinal vascular occlusion and can be one of the presenting signs of the syndrome. Thus PAPS should be in the differential for unexplained retinal arterial and venous thrombosis especially in any individual without risk factors. It should also be suspected in cases of unusual intraocular inflammation and in any young individual without systemic risk factors.

Treatment for PAPS is similar to secondary antiphospholipid syndrome as seen in SLE. The emphasis of therapy is to prevent further episodes of thrombosis.
and thus therapy with anticoagulants like heparin, warfarin, and antiplatelets is mainstay. In addition, hydroxychloroquine has also been shown to reverse platelet activation in this condition and decrease the incidence of thrombotic events. If intraocular inflammation is seen, corticosteroids with or without immunosuppression must be instituted.

**Sarcoidosis**

Sarcoidosis is a multisystem immune-mediated disease of unknown etiology in which T-cells and macrophages proliferate and collect in affected tissues. The immune aggregates eventually organize into the characteristic noncaseating granulomas and mechanically disrupt the structure of vital organs. Sarcoidosis most frequently presents in the lung (95%) and this involvement accounts for the majority of the morbidity and mortality associated with the disease. After the skin and lymph nodes, the eye is the fourth system to be the most commonly affected with 25% to 60% of patients having ocular involvement. It affects all races and both genders, but in the United States the majority of sarcoidosis patients are African-Americans, with a prevalence of 35 per 100,000 compared to 10 per 100,000 among Caucasians. Interestingly, this trend does not hold elsewhere in the world. Globally, the disease is most prevalent in Northern European countries, and the highest annual incidence of 60 per 100,000 is found in Sweden and Iceland. Most patients present between 20 and 40 years of age.

Clinical presentation is highly variable ranging from an asymptomatic disease that resolves spontaneously to a chronic debilitating condition. As the majority of sarcoidosis patients have lung involvement, the most common presenting symptoms include shortness of breath, cough, and chest pain. Almost all patients will have lung symptoms and/or a positive chest x-ray at some point. Constitutional symptoms including fatigue, fever, and weight loss can be present. Extrapulmonary involvement includes lymphadenopathy, erythema nodosum, hematologic abnormalities due to bone marrow involvement, and joint pains.

Several syndromes associated with sarcoidosis have been described. Löfgren’s syndrome is the constellation of erythema nodosum, hilar lymphadenopathy, fever, and migratory polyarthralgias. This syndrome has been shown to have a genetic component and a good prognosis. Heerfordt’s syndrome (uveoparotid fever) is characterized by the combination of anterior uveitis, parotitis, fever, and facial nerve palsy. Mikulicz’s syndrome is the term for sarcoidosis with lacrimal and parotid swelling and keratoconjunctivitis sicca.

After pulmonary, ocular complaints are one of the most common initial manifestations of sarcoidosis seen in approximately 20% to 33% of patients on presentation. As mentioned previously, ophthalmic manifestations have been reported to occur in 25% to 60% of patients throughout the disease course. As such, a complete ophthalmic examination has been recommended in most patients regardless of ocular symptoms. An anterior granulomatous uveitis is the most common manifestation and has been reported in up to 70% of patients with ocular involvement. Mutton fat keratoprecipitates can be seen on the corneal endothelium and iris nodules on the pupillary border and within the stroma. Posterior segment involvement is characterized by intermediate uveitis, vitritis, retinal vasculitis and/or optic nerve involvement. Candle wax drippings, cystoid macular edema, and periphlebitis are the most common posterior segment abnormalities. Some patients can develop yellow-orange round retinal spots scattered diffusely in the periphery. Occasionally, discreet round sarcoid choriretinal nodules can be seen near the equator that after resolving leave scars roughly 500 microns in size. External eye findings include dacroyoadenitis, millet seed lids, and conjunctival nodules.

As there is no one single definitive test, the diagnosis of sarcoidosis involves a comprehensive evaluation requiring both laboratory and radiological studies, exclusion of other diseases with similar presentations, and a tissue diagnosis demonstrating noncaseating granulomas. Ninety percent of patients with sarcoidosis will have pulmonary involvement with the most common finding being hilar lymphadenopathy. In the setting of a negative chest x-ray and strong clinical suspicion a chest CT scan is recommended. Serum angiotensin converting enzyme and serum lysozyme can be elevated but they are not necessary for the diagnosis. Other laboratory abnormalities include a decreased white blood cell count and hemoglobin when there is bone marrow involvement, increased creatinine with kidney involvement, and abnormal liver enzymes with hepatic involvement. Biopsy of conjunctival nodules or lung nodules can be performed to assess the presence of noncaseating granulomas. In 2009, the International Workshop on Ocular Sarcoidosis sought to establish a regimented approach and proposed four levels of certainty for the diagnosis of ocular sarcoidosis each with its own set of criteria: definite, presumed, probable, and possible. While these categories have still not yet been validated they have set a basic framework on which to build.

Treatment for sarcoidosis is not always required as many patients with pulmonary involvement do not require treatment and are likely to experience spontaneous remission. Those requiring treatment to reduce the long-term sequelae of inflammation can be treated with oral glucocorticoids. The presence of active posterior
uveitis is an indication of chronic ophthalmic disease. Mild anterior uveitis can be treated with topical steroids and cycloplegia while posterior uveitis necessitates oral prednisone at a starting dose of 1 mg/kg/day. Periocular and intravitreal corticosteroid treatments are alternate routes of drug delivery which are utilized in particular patients. Patients intolerant to long-term corticosteroid treatment may benefit from chemotherapeutic agents like methotrexate and azathioprine.

**Sjögren’s Syndrome**

Sjögren’s syndrome (SS) is a systemic autoimmune disease of the exocrine glands in which patients develop sicca symptoms characterized by dryness of the mucous membranes and skin. Sjögren’s syndrome is one of the most prevalent autoimmune diseases with an estimated half-million to three-million affected in the United States. Ninety percent of affected patients are women, most of whom are aged 40 to 60 years old. The disease is termed primary Sjögren’s syndrome when sicca symptoms occur in a previously healthy person without another associated systemic disease. When these findings occur in the setting of another autoimmune illness, frequently L.E or R.A, the term secondary Sjögren’s syndrome is used.

Dry mouth and dry eyes are the most common systemic manifestations while nose, throat, vaginal and skin involvement can also occur. Dry mouth can be severe enough to limit intake and cause dental disease. Women may also complain of dyspareunia and vaginal discomfort when walking due to vaginal dryness. Ophthalmic manifestations are typified by corneal involvement. Dry eye syndrome is the mildest form of ocular involvement but can progress to a punctate epithelial keratopathy, corneal filaments, and corneal epithelial erosions.

Schirmer testing to evaluate tear production, Rose Bengal staining to assess conjunctival and corneal damage, and measurement of tear break-up time are essential parts of the ophthalmic workup in any patient with dry-eye symptoms. Laboratory workup in Sjögren’s syndrome patients will often demonstrate an elevated ANA and elevated RF, 90% and 75% of patients respectively. Sity-five percent of patients will also have the cytoplasmic autoantibodies anti-Ro (SS-A) and anti-La (SS-B). Autoimmune thyroid related abnormalities are also common in Sjögren’s syndrome.

Treatment can be challenging in these patients. Frequent use of preservative free artificial tears and lubricating ointment at night are the mainstays of treatment. Punctal occlusion with plugs or cautery and autologous serum tears can also be helpful. Topical cyclosporine (Restasis) has been proven to be effective in increasing tear production via its anti-inflammatory properties.

The use of serum tears derived from the patients own blood have been shown to be beneficial in SS patients. Patients with severe disease may benefit from systemic therapy of oral cyclosporine. In patients with systemic vasculitis, glucocorticoids and biologic agents like Rituximab have been proven to be effective in treating active disease. It is important to remember that while sicca symptoms are troublesome to the patient, the major long-term concern is the development of lymphoma. Sjögren’s syndrome patients are 44 times more likely to develop non-Hodgkin lymphoma than the general population with the mean time of presentation being seven years after diagnosis.

**Relapsing Polychondritis**

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by immune mediated inflammation and destruction of cartilaginous structures throughout the body. It appears to affect mostly Caucasians in the fourth decade, and nearly 25% have another autoimmune disease. Clinical manifestations vary considerably. Ear inflammation is the most common feature but the nose, joints, heart, respiratory tract, vascular system and eye can be affected.

Ocular manifestations are seen in up to 60% of affected patients at some point during the disease course and 18% have been shown to have eye involvement at presentation. Eye involvement can manifest as episcleritis, scleritis, peripheral ulcerative keratitis, or anterior uveitis (Fig. 3). While rare, retinitis and exudative retinal detachments have been reported.

Diagnosis of RP requires a combination of clinical findings with supporting laboratory abnormalities, imaging studies, and biopsy of involved tissues. The newly revised criteria include the positive histological finding of chondritis at two or more separate anatomic locations.
with a positive response to steroids in addition to three or more of the McAdam’s criteria which include: bilateral auricular chondritis, nasal chondritis, respiratory tract chondritis, cochlear/vestibular dysfunction, nonerosive seronegative inflammatory polyarthritis, and ocular inflammation. It is important to note that tracheal involvement in RP can be fatal and patients must be educated on warning signs of throat involvement.

Laboratory testing is of no diagnostic use in RP. An elevated ESR is typically seen but this is a nonspecific finding. Treatment is largely empiric as the rarity of the disease has precluded rigorous clinical trials. Patients with local active disease may be managed with NSAIDs. If this does not achieve control then corticosteroids or dapsone can be used. However, if there is a potential for organ compromise, then high dose corticosteroids plus an immunomodulatory agent depending on severity of disease. The choice of immunomodulatory agent is provider dependent due to lack of studies but medications that have been used include cyclophosphamide, cyclosporine, azathioprine, and methotrexate. Physical examination and findings will guide therapy during the disease course.

**Wegener’s Granulomatosis**

In 2011, the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that Wegener’s Granulomatosis (WG) be renamed to granulomatosis with polyangiitis (gPA) to better reflect the disease process and to eliminate political associations with the name. This disease is an immune mediated process resulting in tissue injury secondary to necrotizing granulomas formation and vasculitis of small vessels. The disease is more typical in adults but can occur in all ages. Caucasians are much more commonly affected than blacks.

Presentation can be variable as any organ can be affected. However, this disease has a predilection for the respiratory tract and kidney. Upper respiratory tract involvement can manifest as epistaxis, sinus disease, nasal discharge, or cough. Renal involvement is characterized by glomerulonephritis which is typically asymptomatic unless severe damage has occurred. While no specific diagnostic criteria exist for Wegener’s granulomatosis, the American College of Rheumatology has proposed the following findings helpful in distinguishing Wegener’s from other vasculitis: 1) oral ulcers or nasal discharge, 2) abnormal chest radiograph, 3) abnormal urinary sediment and, 4) granulomatous inflammation on biopsy. The presence of two or more is 88% sensitive and 92% specific for Wegener’s. In addition, the presence of positive c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody) has been found in 80% to 90% of patients. As opposed to other systemic inflammatory conditions where dry-eye syndrome is the most common finding, Wegener’s eye involvement is most often associated with orbital and scleral disease. Orbital disease can manifest as proptosis, diplopia, optic nerve compression, or decreased vision. An analysis of 140 patients with biopsy-proven Wegener’s granulomatosis demonstrated eye involvement in 29% with the following distribution: 15% with orbital disease, 8% with corneal disease, 7% with scleral involvement, 7% with nasolacrimal involvement, and 3.5% with episcleral findings. In a separate study analyzing 158 patients, early ocular involvement was found in 15% of patients with up to 52% eventually developing one or more ocular symptoms. Scleritis and conjunctivitis were the most common eye findings on presentation with close to 18% eventually developing dacryocystitis at some point during the disease course. Retinal vasculitis and uveitis, while rare, have also been reported to occur.

Laboratory findings include the presence of c-ANCA antibodies in 80% to 90% of patients as previously mentioned. Urinalysis can demonstrate hematuria or proteinuria. Biopsy is often performed to establish a tissue diagnosis of necrotizing granulomas and vasculitis affecting arteries, veins and capillaries. Treatment for severe disease is a combination of oral cyclophosphamide and corticosteroids. Methotrexate can be used in mild disease and for maintenance of disease activity once control is achieved. In patients intolerant to cyclophosphamide therapy, rituximab has been shown to be as effective in achieving immediate control. While eye disease usually occurs in the context of systemic disease, the presence of eye disease by itself warrants systemic therapy. In addition, surgical intervention in the form of orbital decompression for optic nerve compression or refractory diplopia, and dacryocystorhinostomy for nasolacrimal duct obstruction may be beneficial. As with all patients taking potent immunosuppressive agents, careful vigilance for secondary ocular infections, especially retinitis, is important.

**Polyarteritis Nodosa**

Polyarteritis nodosa (PAN) is a necrotizing vasculitis of the medium sized arteries. Men are affected almost twice as often as women, usually in the fourth to sixth decades. Essentially all organs can be involved. While the exact pathogenesis is not well understood, circulating immune complexes have been implicated.

Patients with PAN typically present with systemic complaints. Fever, malaise, or weight loss were shown to be present in 80% of patients on presentation, neurological changes in the form of mononeuritis multiplex and polyneuropathy in 75%, and arthralgias/myalgias in 60%. The diagnosis is based on symptoms, physical examination, and laboratory workup. Ideally, tissue
biopsy should be obtained for diagnosis. Ten criteria for diagnosis have been established. Three out of 10 of the following criteria yield a sensitivity of 82% and a specificity of 87% have been found in patients with documented vasculitis: unexplained weight loss of more than 4 kg, livedo reticularis, testicular pain, myalgias–weakness–polynuropathy, mononeuropathy–polynuropathy, new onset diastolic blood pressure greater than 90 mm Hg, elevated blood urea nitrogen > 40 mg/dl or creatinine > 1.5 mg/dl, positive hepatitis B serology, arteriographic abnormalities, and biopsy of a small or medium sized artery showing granulocytic or mixed leukocytic infiltration.

Ophthalmic manifestations are highly variable and have been shown to be present in up to 20% of patients at time of diagnosis and include retinal/choroidal vasculitis, retinal exudates, conjunctivitis, keratitis, scleritis, disc edema, uveitis and decreased vision. Laboratory testing is nondiagnostic but can aid in determining which organs are involved and the extent of tissue injury. Basic laboratory tests that should be ordered include serum creatinine, BUN, liver function tests. Hepatitis testing should be obtained as both hepatitis B and C have been shown to be associated with PAN. While acute phase reactants like the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are typically elevated they are nonspecific. The most valuable information to aid in establishing a diagnosis is tissue biopsy. Treatment is based on disease severity. Mild cases can be managed with oral corticosteroids while more advanced cases will require combination therapy with corticosteroids and cyclophosphamide.

Kawasaki Disease

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome is a systemic vasculitis of medium-sized arteries of unknown etiology affecting mostly children under five years old. An infectious etiology has been suggested but no definitive evidence has been put forth. East Asians have the greatest prevalence of the disease alluding to a possible genetic predisposition. It is typically a self-limited disease but it does have cardiac complications that can lead to significant morbidity and mortality. KD begins as a fever secondary to the systemic inflammation and then progresses to involve multiple organ systems. The diagnosis of KD is made in patients with a fever lasting at least five days without any identifiable source plus four of the following criteria: bilateral conjunctival injection sparing the limbus, oral changes (erythema of the lips or mouth, cracking of the lips, strawberry tongue), peripheral extremity changes (edema or erythema of the hands and feet), polymorphous rash, and acute nonpurulent cervical lymph node enlargement with at least one node > 15 mm in diameter. It is important to note that in small children there can be variations in presentation falling into atypical KD and thus diagnosis can be made with fewer criteria in special circumstances. Cardiovascular manifestations of KD include tachycardia, myocarditis, arrhythmia, conduction abnormalities, and coronary artery aneurysms. Coronary artery aneurysms are the most well characterized and worrisome consequence and can lead to myocardial infarction and death. While the greatest risk of myocardial infarction is in the first year after diagnosis the risk continues through adulthood. Thus, KD is an important and possibly under recognized cause of myocardial infarction in children and young adults.

The classic ophthalmic manifestation is conjunctival injection which is present in approximately 90% of patients. We generally do not treat conjunctival injection by itself as it will resolve when the disease itself resolves or with treatment. If symptomatic, cool compresses and artificial tears can be used. A small subset of patients will develop an anterior uveitis.

Laboratory workup is nonspecific with findings consistent with KD include an elevated ESR, anemia, leukocytosis, and pyuria. The most important test is echocardiography to look for coronary aneurysms. Treatment is undertaken with the goal of reducing the cardiac sequelae of the disease. Intravenous gamma globulin (IVIG) and aspirin have been shown to reduce the incidence of coronary artery aneurysms and myocardial infarction.

Behçet’s Disease

Behçet’s disease is a multisystem vasculitis first described in 1937 by a Turkish dermatologist who identified three patients with the following triad of findings: hypopyon uveitis, aphthous oral ulcers, and genital ulcers. As our understanding of the disease has increased, we now know that it can affect multiple organ systems with neurologic, gastrointestinal, vascular, and rheumatic manifestations. The etiology of this disorder is unclear but a geographic predisposition is present with more people of Middle Eastern, Japanese, and Mediterranean descent being affected. It has been hypothesized that the prevalence of the disease coincides with the ancient Silk Road which connected eastern and southern Asia to the Mediterranean, southern Europe and northeastern Africa. Infectious etiologies have been proposed but not fully accepted. Genetic analysis has revealed that those with the major histocompatibility group HL-B5 and its subtype HLA-B51 are more susceptible to having the
disease.63 Men are more commonly affected than women with ratios depending on country as high as 4.8:1.64 The disease is more common among those in third and fourth decades of life.

Ocular involvement is a major cause of disease associated morbidity. Approximately one-third of patients will have ocular inflammation as the initial manifestation of the disease.65 Up to 95% of men have been noted to have ocular involvement at some point during the disease course.66 Patients that present with systemic manifestations initially may develop eye involvement within two to three years. The most common ophthalmic manifestation is a nongranulomatous uveitis without hypopyon. Interestingly, the hypopyon noted initially as part of the diagnostic triad is only seen in approximately one-third of cases. With regard to the posterior examination, retinal vasculitis is the most common finding. This vasculitis can affect both arteries and veins and is frequently associated with retinal ischemia, cystoid macular edema and retinal exudates. The incidence of vision loss increases when retinal vasculitis and posterior uveitis are present.

Systemic findings include recurrent painful aphthous ulcers up to 1 cm involving the buccal, lingual, labial, and gingival mucosa. Genital involvement is generally nodular with central ulceration. Other skin manifestations include erythema nodosum and pseudofolliculitis. Nonerosive recurrent arthritis of the wrists and ankles is typical. When the disease affects the central nervous system it is termed neuro-Behçet’s disease. Approxi-

The diagnosis of Behçet’s is clinical and several similar sets of criteria have been put forth.68 For clinical purposes, we consider the disease “complete” in patients with oral ulcers, genital ulcers, migratory thrombophlebitis and uveitis. When three of these findings are present, we subscribe to the use of the term “incomplete” Behçet’s, while patients with two such findings may be referred to as “Behçet’s suspect.” HLA-B51 testing, if present, supports the diagnosis in questionable cases.

Treatment is based on severity and organ systems involved. Anterior uveitis can be treated with topical corticosteroids but if posterior uveitis or vasculitis is present more potent therapies in the form of systemic steroids will be required. For immediate control of severe vasculitis, we begin with intravenous methylprednisolone 1mg pulse daily for three days followed by 1mg/kg/day oral prednisone. If the vasculitis is not severe, then one can proceed with oral steroids directly. Due to the need for long-term therapy and the toxic side effects from high-dose steroids, many patients require immunomodulatory therapy in some form. Choice of agent is provider depen-

Cogan’s Syndrome

Cogan’s syndrome (CS) is a rare immune mediated disorder affecting young adults characterized by ocular inflammation and audiovestibular dysfunction. The disease was first described in 1945 in patients presenting with interstitial keratitis and audiovestibular symptoms.69,70 Since that time the disease has also been found to be associated with a medium or large vessel vasculitis in approximately 10% of cases.71,72 When present, the vasculitis can manifest as an aortitis or aortic regurgitation and is an important cause of morbidity and mortality in these patients.73–75 Patients are typically in the second to third decades of life and with a roughly equal male:female ratio.72 While the cause is unknown, there is speculation of an infectious etiology due to chlamydial infection.72,76,77

Ocular disease is typified by a nonsyphilitic interstitial keratitis which manifests as pain, redness, photophobia, and decreased vision. However, eye involvement in CS can also present in the forms of conjunctivitis, uveitis, episcleritis, scleritis, or retinal vasculitis.78,79 Ear involvement can manifest as a Ménière’s disease-like attack with nausea, vomiting, vertigo, tinnitus, and hearing loss.71 The hearing loss can be acute and severe resulting in complete deafness in 60% of patients.80 We suspect CS in any patient with ocular inflammation and symptoms referable to the ears.

There are no diagnostic laboratory findings for CS. However, laboratory workup is indicated when CS is suspected to rule out other diseases that can mimic the presentation including syphilis, tuberculosis, and chlamydia. Treatment is organ specific. Ocular inflammation is treated with topical corticosteroids in the form of drops or injections. More extensive involvement will require systemic corticosteroids at doses of 1mg/kg/day to achieve control. Various immunomodulatory regimens have been used depending on the severity of disease and organ system involved.

Conclusion

Ocular involvement in systemic autoimmune inflammatory diseases cannot only be the initial presenting symptom but can also provide important information regarding disease activity. While each of the conditions discussed has different presentations and characteristics, it is important to remember several key points relevant to all. Firstly, the most common ophthalmic manifestation
of systemic inflammatory disease is dry-eye syndrome. Dry eye by itself can be a disabling symptom with the potential of causing blindness secondary to corneal disease. Patient complaints with regard to this symptom must not be trivialized and treated promptly. If necessary, a referral to a cornea specialist should be made. Secondly, concurrent ocular manifestation indicates that a systemic inflammatory process is more severe and requires increased therapy, regardless of the control of systemic disease or the patients subjective complaints. Thirdly, ocular inflammation due to the blood-retina barrier in these patients is generally more difficult to treat than inflammation present in other organ systems and often times requires higher doses of antiinflammatory agents. Lastly, the immunosuppressive agents used to treat these conditions can result in opportunistic ocular infections presenting in atypical and severe forms. Ocular herpetic, bacterial, fungal and toxoplasmosis infections are the most common pathogens encountered in these settings. Patients with systemic autoimmune disease will need routine ophthalmic evaluation to assess the presence of ocular inflammation. In addition, if these patients are on potent immunosuppression, they will warrant a low threshold for examination of any ophthalmic complaint.

REFERENCES


