ABSTRACT

Purpose: The purpose of this article is to review giant cell arteritis, with a focus on ophthalmic manifestations, and provide a quick reference for clinical identification, diagnosis and appropriate management.

Summary: Giant cell arteritis is one of a few true medical emergencies that may present initially to the eyecare professional. An understanding the disease course and management will help the eyecare professional detect and manage this condition early in the disease process, potentially preventing blindness and life-threatening systemic manifestations.

KEYWORDS
Giant cell arteritis, ischemic optic neuropathy, polymyalgia rheumatica, temporal artery, glucocorticoid

INTRODUCTION
Giant cell arteritis (GCA), also known as temporal arteritis, is classified as a systemic vasculitis affecting medium and larger vessels. GCA is the most common of the systemic vasculitides that primarily affect people over 50 years of age. The clinical presentation of GCA, when it affects blood flow to the eye, is typically a sudden, unilateral, painless vision loss with or without other ocular findings. GCA affects women three times more than men, with an estimated incidence of 27 cases per 100,000 in those 50 years or older and a peak incidence of 70-80 years of age. Individuals of northern European, particularly Scandinavian, descent carry a higher risk than other ethnic groups. Suspected GCA is a medical emergency and must be managed as such until proven otherwise. In addition to significant vision loss, GCA can present as other ocular and/or systemic manifestations, such as headache, jaw claudication, cranial nerve palsies, peripheral neuropathies, scalp necrosis, altered mental status, congestive heart failure, myocardial infarction, aortitis, aortic aneurysm rupture, and thromboembolic events. The goal of this article is to provide the eyecare professional an update on the clinical presentation, diagnosis, and treatment options for GCA.
ETIOLOGY AND PATHOPHYSIOLOGY
The exact etiology and pathogenesis of GCA remain unknown. However, several studies have demonstrated that the etiology may be multifactorial in nature, and involve both genetic and environmental factors. Temporal artery histopathology demonstrates segmental and focal panarteritis with non-necrotizing inflammation. In addition, CD4+ T lymphocytes, macrophages, and giant cells are found infiltrating the arterial walls, suggesting an immune response to a triggering antigen. Herpes zoster virus has been a proposed inciting antigen, however the literature remains inconclusive. Although a specific mechanism remains elusive, aging is accompanied by physiological changes leading to a reduction in the immune response, increased inflammation and oxidation, and an increased production of auto-antibodies, which creates an environment for an autoimmune response to antigens. The resultant inflammatory process leads to vascular compromise and tissue ischemia.

CLINICAL PRESENTATION
Approximately one in five patients diagnosed with GCA will present with only ocular signs or symptoms, without other systemic symptoms. It is estimated that one in three patients with GCA will present with either transient (amaurosis fugax) or permanent visual symptoms. Amaurosis fugax has been reported to affect 10-30% of patients with GCA and carries a poorer visual prognosis. Transient visual symptoms may present uni- or bilaterally.

Permanent vision loss, to varying degrees, occurs in 5-20% of patients with confirmed GCA. The most common ocular manifestation is acute, painless, unilateral vision loss secondary to ischemic optic neuropathy. Arteritic ischemic optic neuropathy (A-AION) affects approximately 80%-85% of individuals with ocular GCA and the presenting acuity may range from 20/200 to no light perception. Ischemia to the posterior ciliary arteries and the short branches supplying the optic nerve head leads to a clinical appearance of an edematous, chalky-white colored nerve with or without surrounding intra-retinal hemorrhages. Optic atrophy develops within 6-8 weeks of the inciting event and typically appears as sectoral pallor without other retinal exam findings. A relative afferent pupillary defect will be present in unilateral cases without previous significant retinal or neurological events to the fellow eye. The automated visual field will show signs of either a complete or incomplete altitudinal defect that may or may not be absolute in nature (Figure 2). Although inferior or superior defects (relative or absolute) are the more commonly reported visual field defects associated with ischemic optic neuropathy, the pattern defects can take on an array of appearances based on the type of field (kinetic vs. static) as well as the testing size (i.e., I-1e to I-4e, V-4e).

Although disc edema may be more diffuse in A-AION, presentation can also be sectoral in nature. Arteritic posterior ischemic optic neuropathy (A-PION) is far less common than A-AION and presents similarly to A-AION without the typical fundoscopic findings. As such, A-PION is a diagnosis of exclusion.
Other presentations of GCA-associated ocular findings include retinal ischemia (retinal artery occlusion, cilio-retinal artery occlusion, cotton wool spots), choroidal ischemia (small retinal hemorrhages and/or retinal pigmentary changes), anterior segment ischemia (hypotony, corneal edema, uveitis, rubeosis irides), ophthalmoplegia (cranial nerve palsy/palsies, orbital pseudotumor), scleritis, and ocular ischemic syndrome.26

Although GCA is typically characterized as a “head and neck” disease, systemic manifestations should be explored as part of the case history of a suspected GCA-related ocular complication presenting to the eyecare professional. Headache is the first symptom in 32-40% of GCA cases.27-29 Characteristic presentation is a new acute headache or a change in the pattern of previous headaches. The headache may often be localized, and occurs in the temporal region 25-50% of the time.29 The headache may be accompanied by jaw claudication (mandibular pain from repeti-
tive chewing motion), pain in the tongue, or chest pain and odynophagia (pain on swallowing foods or fluids) due to aortitis. Giant cell arteritis can present with symptoms of fever, weight loss (40% of cases) and general malaise.

Other systemic manifestations associated with GCA are listed in Table 1.

**Table 1: Other systemic manifestations of GCA**

<table>
<thead>
<tr>
<th>System</th>
<th>Signs/Symptoms</th>
</tr>
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<tbody>
<tr>
<td>central nervous</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td></td>
<td>stroke</td>
</tr>
<tr>
<td></td>
<td>dementia</td>
</tr>
<tr>
<td></td>
<td>cranial neuropathy (other than ocular)</td>
</tr>
<tr>
<td>peripheral nervous</td>
<td>mono- and polyneuropathies</td>
</tr>
<tr>
<td></td>
<td>median nerve</td>
</tr>
<tr>
<td></td>
<td>C5-C6 roots</td>
</tr>
<tr>
<td>cardiovascular</td>
<td>aortitis, aortic dissection, aortic aneurysm, aortic stenosis</td>
</tr>
<tr>
<td></td>
<td>thoracic or abdominal aortic dissection or aneurysm</td>
</tr>
<tr>
<td></td>
<td>stenosis of cervical, brachial, subclavian, axillary or lower extremity artery</td>
</tr>
<tr>
<td>respiratory</td>
<td>cough</td>
</tr>
<tr>
<td>gastrointestinal and renal</td>
<td>elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td>small-bowel infarction</td>
</tr>
<tr>
<td></td>
<td>renal and bladder disease (rare)</td>
</tr>
<tr>
<td>reproductive</td>
<td>vascular involvement of breast and female genital tract</td>
</tr>
<tr>
<td>integumentary</td>
<td>scalp necrosis, otherwise rare</td>
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In terms of systemic manifestations of GCA, the discussion must include polymyalgia rheumatica (PMR), due to the apparent association of the two disease processes. Approximately 40-60% of patients diagnosed with GCA have PMR, and approximately 16-21% of PMR patients have GCA. A PMR diagnosis is based on clinical features that include acute, bilateral shoulder pain and stiffness and/or pelvic girdle aching for more than two weeks. In addition, constitutional symptoms of fever, fatigue, weight loss, depression, and night sweats are frequent.

**DIAGNOSTIC WORK-UP**

The 1990 American Academy of Rheumatology criteria for the classification of GCA are currently used as the standard for diagnosis of the condition (Table 2). The presence of three or more of the five criteria carries a sensitivity of 93.5% and a specificity of 91.2%.

**Table 2: Criteria for diagnosis of GCA**

<table>
<thead>
<tr>
<th>System</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at disease onset ≥50 years</td>
<td>Development of symptoms or findings beginning at age 50 or older</td>
</tr>
<tr>
<td>2. New headache</td>
<td>New onset or new type of localized pain in the head</td>
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<tr>
<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries</td>
</tr>
<tr>
<td>4. Elevated erythrocyte sedimentation rate</td>
<td>Erythrocyte sedimentation rate ≥50 mm/hour by the Westergren method</td>
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<tr>
<td>5. Abnormal artery biopsy</td>
<td>Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
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The combination of ESR with C-reactive protein (CRP) increases the specificity of a GCA diagnosis than is available with either test alone, whereas a few studies have shown that CRP (>2.45 mg/dL) alone is highly sensitive to this condition. Of note, approximately 4-14% of temporal artery biopsy-proven cases of GCA may have a normal ESR.
Laboratory testing and patient symptoms help predict the likelihood of GCA. However, temporal artery biopsy (TAB) remains the standard test for clinically-proven GCA. TAB carries a diagnostic sensitivity of 70-90%. Among patients with negative TAB studies, further GCA investigation may be indicated in cases with high suspicion based on lab work-up and clinical signs and symptoms. For those with large-vessel disease, such as GCA affecting the aorta, immediate branches of the aorta, larger upper and lower extremity vessels, or individuals carrying a high suspicion of GCA despite a negative TAB, recent literature suggests that imaging techniques may be useful for confirming a diagnosis. Additional techniques for the diagnosis of GCA include Doppler ultrasonography, computed tomography (CT) and computed tomography angiography (CTA), magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), and positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG).

MANAGEMENT
Given the potential negative visual and systemic outcomes of GCA, medical therapy is generally initiated upon a diagnosis of suspicion. For the eyecare professional managing a patient with signs or symptoms of GCA, the most likely course of action will be immediate referral to a tertiary eyecare specialist or local emergency room with instructions for suspicion of GCA. If available, a cursory blood work-up is appropriate and should focus on complete blood count, ESR, and CRP.

Gluocorticoid therapy is the primary treatment in suspected or biopsy-proven GCA. However, the optimal dosage and regimen for initial therapy and long-term management remains a matter of debate and focuses more on individualized management. Current practice is to dose anywhere from 20 to 60mg/day of prednisolone with the aim of suppressing GCA-related symptoms. While the tapering of glucocorticoids is desired given systemic side effects, therapy may go on for months to years based on the individual response to treatment.

For visually-symptomatic GCA, existing recommendations are for intravenous glucocorticoid therapy (methylprednisolone 1g/day for 3 consecutive days) with oral prednisolone (15mg/kg/day) and continued oral glucocorticoid tapering based on the individual patient signs and symptoms. For patients who already have visual impairment, earlier treatment (within 24hrs) yields the best chance of visual recovery. Visual symptoms without strong evidence of GCA may initially be treated with oral therapy alone. Like large-vessel non-ocular disease treatment, there are no clear guidelines on effective dosage or duration, and management is individualized to the patient’s signs and symptoms.

As with any glucocorticoid treatment, especially long-term care, systemic side effects and the risk of complications associated with steroid therapy raise the question of other management options for GCA. FDA-approved sub-cutaneous administration of tocilizumab (TCZ) has been shown to offer immediate and long-term efficacy in GCA treatment. Several studies have shown that it is effective for inducing remission of initial GCA-related signs/symptoms. The GaACTA trial demonstrated that tocilizumab is effective for the management of new or relapsing GCA in conjunction with a glucocorticoid taper of 52 weeks, where the overall dosage of glucocorticoids is reduced as needed to prevent relapse. The role of TCZ in the management of occult visual changes associated with GCA is unclear at this time. Adjunctive therapy may include aspirin, statins, and/or angiotensin II receptor blockers due to their anti-inflammatory properties, anti-coagulative properties, and potential for reduced relapse, and has been found to be beneficial in observational studies and animal models. Large-scale randomized clinical trials are needed to confirm their roles in the management of GCA.

PROGNOSIS
The prognosis of GCA-related vision loss is typically guarded for the initial event. Although significant recovery from ischemic optic neuropathy events has been documented, management is focused on prevention of fellow-eye involvement, with approximately 50% of individuals affected within days to weeks of the initial event. Relapse of GCA is a concern for the managing healthcare professional. It is estimated that 43-80% of patients experience GCA-related relapse within 1 to 2 years after the initial event. Although ischemic events, such as ischemic optic neuropathy, are not characteristic in relapse events, headache, PMR symptoms, and constitutional symptoms (myalgia, malaise, fever, nausea) may reflect recurrence.

CONCLUSION
Giant cell arteritis may initially present as acute vision loss. Signs or symptoms associated with GCA-related vision loss must be handled as a medical emergency. The eyecare professional must take immediate action and assess the true risk of GCA based on the findings. If the diagnosis is uncertain given the case history, exam findings, or cursory blood work-up, the ocular manifestations should be treated as GCA until proven otherwise.
REFERENCES

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