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On alert for giant cell arteritis

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ALSO KNOWN AS temporal arteritis, giant cell arteritis (GCA) is a chronic vasculitis affecting medium and large vessels, commonly cranial branches of arteries originating from the aortic arch.[1,2] Affecting adults age 50 and older, it's the most commonly occurring vasculitis in Western countries, with the highest reported incidence in Scandinavian countries and in the state of Minnesota.[3-5] In these populations, which share a Northern European ethnic background, GCA has an annual incidence of approximately 20/100,000 in adults over age 50.[6]

GCA has a predisposition for cranial branches of both the external and internal carotid artery, including the superficial temporal and ophthalmic arteries (see *Superficial temporal arteries: Targets for GCA*).[7] Irreversible blindness, the most feared complication of GCA, can be prevented if the disorder is treated immediately, even before confirmed diagnosis. Consequently, GCA is a medical emergency.[6,8] This article reviews pathophysiology, diagnosis, and management of GCA.

Antigen-driven inflammatory process

Affecting women two to four times more often than men, GCA has a peak incidence among adults ages 75 to 85.[3,4,6,9] Its pathogenesis is thought to be a combination of environmental exposures and genetic polymorphisms, but the specific cause remains largely unknown.[3]

GCA is an antigen-driven inflammatory process. For unknown reasons, antigens stimulate release of antibodies that attach to the inner walls of medium- and large-sized arteries, including the superficial temporal arteries (STA) and ophthalmic

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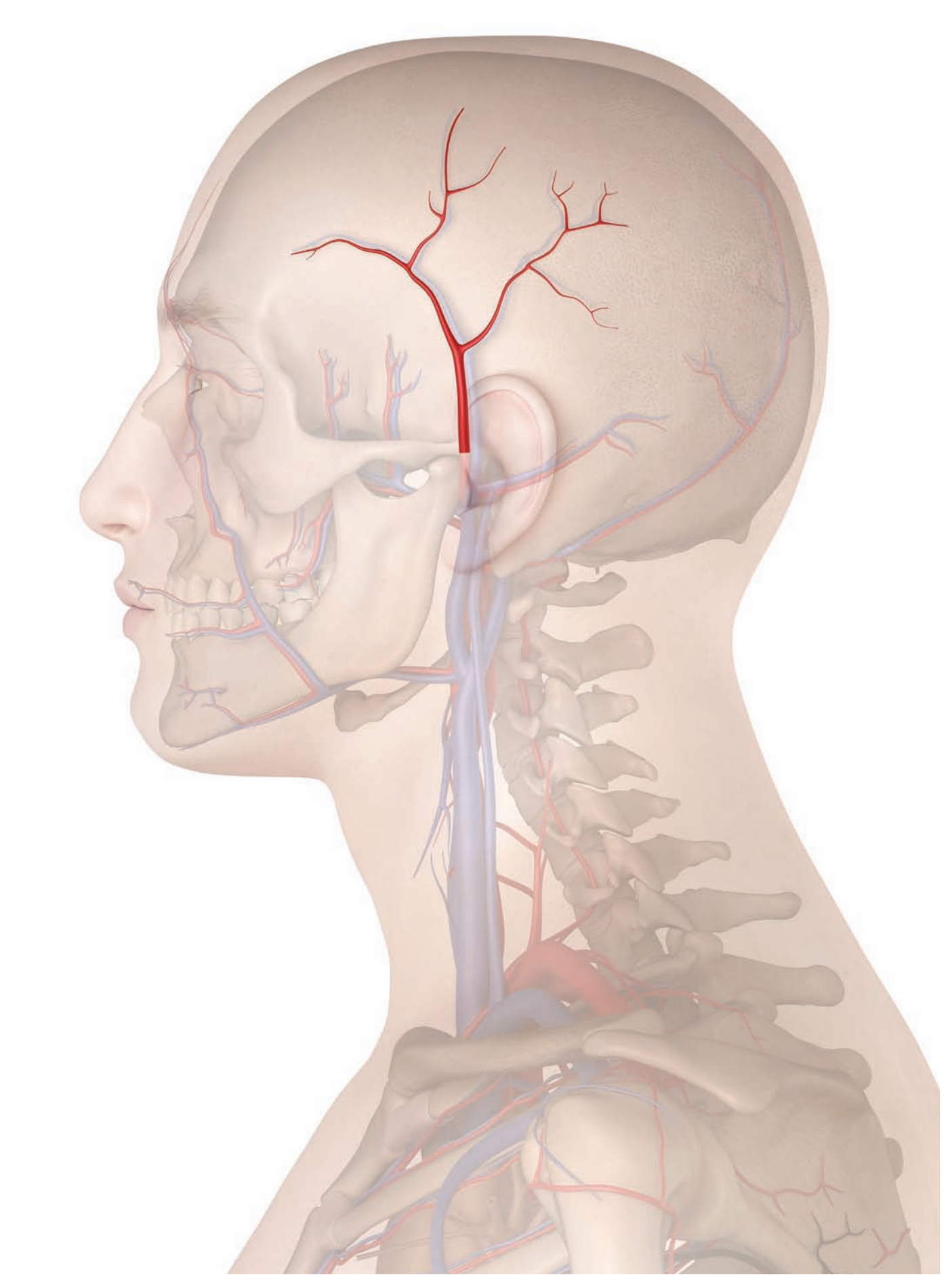


arteries (OA). The antibodies recruit macrophages that release inflammatory components, including peptides and proteins, that combine into immune complexes and granulomas. Formation of multinucleated giant cells follows, resulting in blood vessel dysfunction from intimal hyperplasia and vascular damage. This causes both thickening and narrowing of the arterial lumen, reducing blood flow and leading to ischemia (see *A deeper look at GCA*). Thrombi can also form, further obstructing arterial flow.[3] When the OA is affected, ischemia and infarction of the optic nerve may cause temporary vision loss or permanent blindness in the affected eye.[10]

Clinical manifestations

Onset of GCA signs and symptoms may be acute or chronic. General or nonspecific signs and symptoms include headaches, weight loss, fever, chills, night sweats, dry cough, fatigue, myalgia, arthralgia, depression, and general malaise. Although GCA accounts for only 2% of all fevers of unknown origin, it accounts for 16% of fever of unknown origin in those over age 65 and is often associated with rigors and sweats.[10]

Specific or classic signs and symptoms associated with GCA include sudden or abrupt unilateral new headache, scalp tenderness, jaw claudication, and vision changes.[4,10] Patients may report feeling scalp tenderness when combing or brushing hair.[7,11]

Because the STA passes behind the mandible, the mechanics of chewing compress the artery, causing painful jaw claudication. Patients develop significant aching in the jaw, which may prevent them from finishing meals and lead to weight loss.[11]

If the OA is affected, patients may experience vision disturbances such as blurry vision, diplopia, temporary or fleeting vision loss in one eye (amaurosis fugax), or permanent blindness. Amaurosis fugax is a worrisome sign indicating ischemia to the optic nerve; if untreated, it can lead to permanent blindness. However, clinicians should be aware that in the general population, amaurosis fugax is most commonly a symptom of atherosclerotic carotid artery disease, not GCA.[8]

The reported incidence of ocular involvement and vision loss in GCA varies greatly, between 6% and 70%.[3] Because blindness associated with GCA can occur in up to 30% of patients, any vision disturbances known or suspected to be associated with GCA is a medical emergency requiring immediate treatment to prevent further vision loss in the affected eye or involvement of the other eye. As discussed below, steroids should be initiated for suspected GCA even before the diagnosis is confirmed.[1,12]

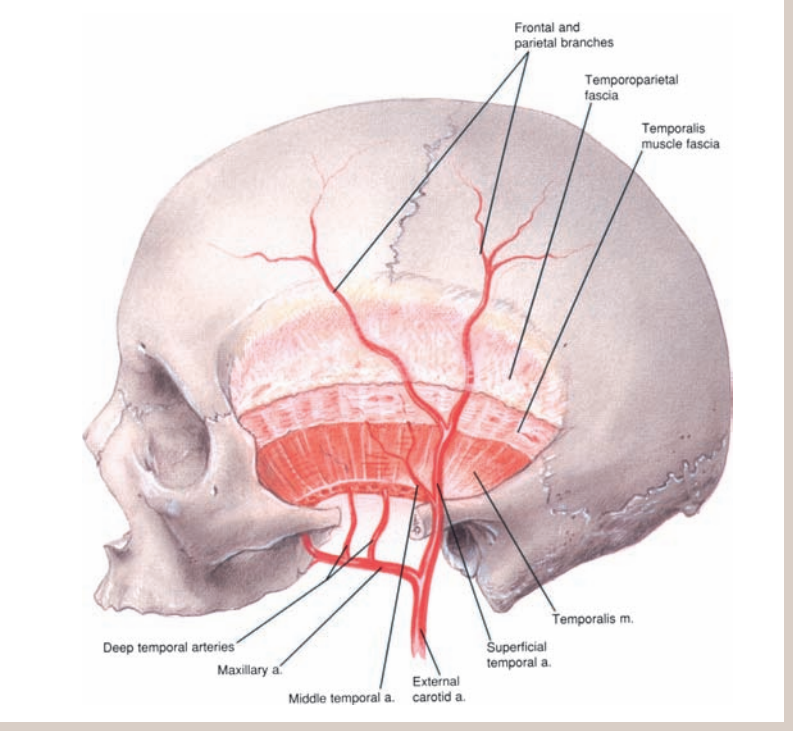
Diagnostic indicators

The combination of nonspecific and specific signs and symptoms of GCA makes diagnosis challenging. Clinicians should assess for enlarged, nodular, or nonpulsatile temporal arteries and auscultate for a bruit indicating reduced flow. However, not all patients with GCA have these signs. For some patients, nonspecific complaints such as weight loss, fever, fatigue, and anorexia are the only manifestations of GCA.[13]

If the clinician suspects GCA based on clinical presentation, patient age, and patient history, testing for evidence of inflammation is indicated. Both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are biomarkers of a systemic inflammatory process; pretreatment elevation in both ESR and CRP levels are useful indicators supporting a GCA diagnosis.[1]

The American College of Rheumatology (ACR) lists elevated ESR as one of the essential criteria required

Superficial temporal arteries: Targets for GCA



to diagnose GCA (see *ACR criteria for diagnosing GCA*). Almost all patients with GCA have a markedly elevated ESR, averaging about 100 mm/h (normal, <20-30 mm/h for both men and women). Very rarely, however, the ESR may be normal in a patient with GCA; for example, if the patient is taking immunosuppressants such as steroids.

Most patients with GCA have mild normochromic normocytic anemia; serum alkaline phosphatase is elevated in 20% to 30% of patients. The leukocyte count is usually normal, which helps distinguish GCA from infection or malignancy.[10]

Confirming the diagnosis

The gold standard for confirming a GCA diagnosis is temporal artery biopsy (TAB), which should be performed in all patients suspected to have GCA.[4,14] The procedure, which can usually be performed with a local anesthetic, should be performed within 1 to 2 weeks of initiating standard treatment with steroids.[15] Reports suggest that TAB results will remain positive for 2 to 6 weeks following initiation of steroids.[1,4,14]

False-negative TAB results may occur due to multiple factors, such as sampling error due to irregular or separated lesions, sample size that's too small, and/or presence of disease not associated with GCA. These patients may have GCA involving only large vessels (such as the subclavian, aorta, or carotid arteries) without any cranial vessel involvement. Subclavian artery involvement causes arm claudication; aortic involvement leads to aneurysms and dissection. In cases where TAB is negative but significant clinical suspicion for GCA remains, the TAB can be repeated either on the same or opposite side.[4]

Magnetic resonance imaging (MRI) is an option to assess for the presence of isolated large-vessel GCA not associated with cranial arteries.[16] In addition, other diagnostic imaging studies, including ultrasonography and positron emission tomography, are being evaluated as tools to aid in the diagnosis of GCA. These studies don't replace TAB as confirmatory testing for GCA and more research is needed to define their role. However, ultrasonography may reveal a halo sign around affected segments of the temporal artery indicating the area of the vessel to biopsy.[8,16,17]

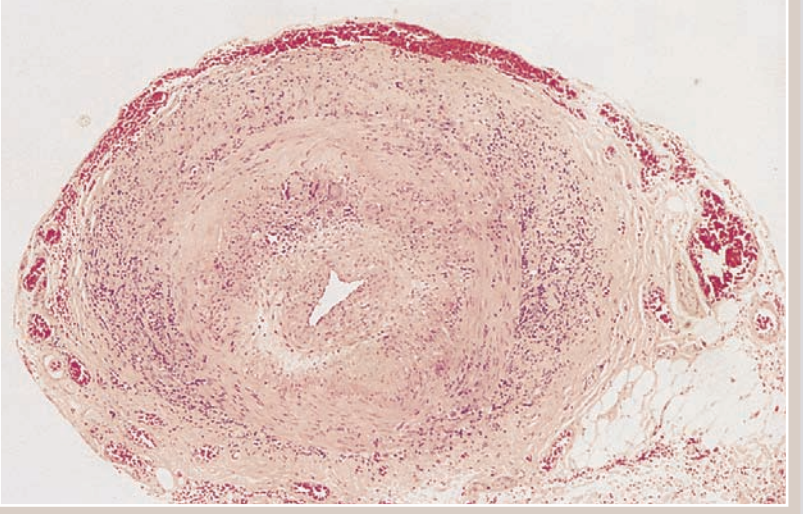
Fluorescein angiography (FA) can further help distinguish GCA from nonarteritic disorders by showing absent or markedly delayed filling of the retinal circulation. FA can reveal retinal perfusion abnormalities before permanent vision loss.[8,17]

Treatment options

Although no clinical trials have been conducted to compare dosing regimens, steroids remain the cornerstone of treatment for GCA and should be prescribed immediately whenever GCA is suspected. Steroids act as an anti-inflammatory and can effectively control inflammatory processes, manage symptoms, and prevent ischemic manifestations such as jaw claudication and vision loss

A deeper look at GCA

A photomicrograph of a temporal artery shows chronic inflammation throughout the wall, giant cells, and a lumen severely narrowed by intimal thickening.



Source: Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

ACR criteria for diagnosing GCA[8,14]

For a GCA diagnosis, the American College of Rheumatology (ACR) recommends that patients meet at least three of these five criteria.

- age ≥50 years
- new onset or new type of localized pain in the head
- elevated ESR ≥50 mm/h (by Westergren method). Note: ESR is one of the most useful markers of GCA. A normal ESR value makes GCA unlikely but doesn't rule it out.
- temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries
- biopsy specimen showing vasculitis characterized by mononuclear infiltration or granulomatous inflammation, usually with multinucleated giant cells.

associated with GCA.[1,4,8,9] In most cases, steroids provide complete symptomatic relief in 24 to 48 hours.[6]

In cases of vision loss suspected or known to be due to GCA, high-dose I.V. methylprednisolone followed by an oral regimen of a glucocorticoid such as prednisone is typically prescribed.[4] The total duration of high-dose prednisone is usually governed by clinical response, such as resolution of symptoms and improvement in lab test abnormalities. If symptoms remain under control and ESR and other inflammation biomarkers remain at an acceptable level, the daily dose can be titrated.[1,4]

The optimal duration and dosage of steroid therapy vary from patient to patient, as does the need to add other immunosuppressant drugs to control disease activity and reduce steroid toxicity.[6] Patients at risk for adverse reactions to a glucocorticoid may benefit from the addition of methotrexate. Cyclophosphamide and the interleukin-6 blocker tocilizumab are also options for these patients and for those who don't respond well to standard treatment. However, little research has been done on the effectiveness of these drugs in patients with GCA.[2]

Most patients will require steroid therapy for months to years and some indefinitely, emphasizing the importance of close monitoring and patient teaching to prevent and treat steroid-related adverse reactions. The burden of high-dose steroids is considerable, especially in older adults, with over 80% of patients experiencing significant treatment-related adverse reactions.[6] Proven et al. have reported a high number of major adverse reactions related to long-term glucocorticoid use in patients with GCA, including posterior subcapsular cataract (41%), bone fractures (38%), infections (31%), hypertension (22%), diabetes mellitus (9%), and gastrointestinal bleeding (4%).[18]

Because vertebral compression fractures, the most common type of osteoporotic fracture, develop in one-third of patients taking steroid therapy, prevention and treatment of osteoporosis should be part of initial management.[19] Patients should be encouraged to maintain adequate dietary calcium and vitamin D intake, with calcium and vitamin D supplementation as indicated. Biphosphonate use should be considered. Low-dose aspirin may reduce the risk of ischemic events and the incidence of vision loss, both at presentation and at follow-up in patients with GCA.[1,4] Proton pump inhibitors may be prescribed for gastrointestinal protection in patients on long-term steroid therapy, although evidence for efficacy is weak.[6,20]

Duplex ultrasonography can help track disease status during treatment. A trend toward normalization of blood-flow velocities should be seen following treatment with steroids in patients with GCA.[1]

Case reports and small studies describe angioplasty for lesions seen in GCA, but results have been conflicting; some studies report success and resolution of symptoms when stenting or angioplasty is used in conjunction with steroids, others report as many as 50% of patients needing additional procedures such as vascular bypass.[7] Additionally, one case study on endovascular interventions reported arterial dissections complicating 16 of 40 angioplasties.[8]

Long-term follow-up for progression of GCA is required to detect late recurrences, including the late onset of thoracic aortic aneurysms with aortic regurgitation, heart failure, and aortic dissection.[1] Some practitioners recommend annual chest X-rays to monitor for asymptomatic thoracic aortic aneurysms.[2]

Ongoing care

Consultation with a rheumatologist is recommended. At each visit, the following investigations should be performed: complete blood cell (CBC) count, ESR, CRP, blood urea nitrogen (BUN), serum electrolytes, and blood glucose to monitor for steroid-induced diabetes. At least every 2 years, the patient should undergo chest X-rays to monitor for aortic aneurysm; more detailed investigations using MRI and echocardiography and bone mineral density scans may also be indicated.[4,6]

Follow-up schedules can vary. For example, the British Society of Rheumatology recommends close monitoring at weeks 0, 1, 3, and 6 and then at months 3, 6, 9, and 12 in the first year. Unscheduled visits are advised in the event of relapse.[4,12]

Patient education is essential to promote understanding of the disease's clinical manifestations, treatments (especially adherence to medication administration), importance of follow-up appointments, awareness of complications suggesting treatment failure or relapse, and instructions for responding to a medical emergency. Specific instructions

Polymyalgia rheumatica: A mysterious companion[5,21,22]

The immune complexes associated with GCA can spread via the circulatory system and accumulate in joints, including the shoulders and hips, causing a widespread and painful condition known as polymyalgia rheumatica (PMR). PMR is characterized by morning stiffness, pain, and decreased range of motion in the shoulders, neck, and pelvis.

From 40% to 50% of patients with GCA also have PMR, and about 15% of patients with PMR also have GCA. However, although the two disorders often occur together, their relationship is unclear. Relapses or exacerbations of both GCA and PMR are common, even during treatment.

include description of signs and symptoms of GCA, such as unilateral headache, jaw claudication, joint and muscle pain, and scalp tenderness. Patient education should include an explanation of visual disturbances associated with GCA.

Patients should be made aware that symptom improvement may take a few days once medical therapy is initiated, and that the duration of medical therapy varies but may continue for a year or longer. Supplements such as calcium, vitamin D, and possibly a proton pump inhibitor will be prescribed to address potential adverse reactions associated with long-term steroid use.

Nurses should emphasize that following up with scheduled appointments is essential to monitor for disease progression, response and effectiveness of interventions, and indications to modify the therapeutic plan.

Review symptoms that need to be reported such as new onset of headache, fever, and especially vision disturbances. Because GCA can affect systemic arteries including the aorta, teach patients to recognize all signs and symptoms that indicate a medical emergency.

A case in point

DK, 72, a woman of Scandinavian heritage, presents to her primary care provider (PCP) reporting recent vision changes, including diplopia, blurry vision, and transient vision loss in her right eye. She also reports other nonspecific symptoms that have bothered her for the past couple of months, including fatigue, malaise, and myalgia and arthralgia that mainly affect her shoulders. She says the pain is worse in the morning, making activities of daily living difficult. Her health history includes hypertension and osteoarthritis. Vital signs are all within normal limits.

DK reports that the vision changes in her right eye are new, persistent, and worsening. She denies any vision changes in her left eye.

Questioned about scalp sensations, DK describes significant right-sided scalp tenderness, which is more noticeable when she brushes her hair. When the PCP palpates the area, DK reports tenderness over the superficial right temporal artery, but the PCP finds no palpable nodules or bruits indicating reduced blood flow. DK reports moderate-to-severe right-sided headaches as well as right-sided jaw pain, particularly when chewing, which prevents her from finishing her meals.

DK has decreased range of motion in her major joints and complains of stiffness and tightness, particularly in her shoulders, hips, and knees, which is worse in the morning. She also reports significant muscle pain, more than what she's used to with her osteoarthritis.

The PCP suspects GCA as the cause of the patient's vision symptoms and as a contributor to many of her other symptoms, the PCP immediately administers I.V. methylprednisolone and prescribes oral prednisone for 4 weeks.[17] The PCP also prescribes a nonsteroidal anti-inflammatory drug for muscle and joint pain.

The PCP orders bloodwork including CBC count, metabolic panel, creatine kinase, rheumatoid factor, and antinuclear antibody. Because of suspicion for GCA, the PCP also orders testing for systemic inflammatory markers including CRP and ESR.

DK is discharged home with medication instructions. The nurse teaches her what to do if symptoms worsen and instructs her to follow up with an ophthalmologist.

DK sees her ophthalmologist later that week. At that point, her lab work shows that her ESR was elevated at 100 mm/h and her CRP was also elevated. All other lab results were within normal limits.

The funduscopic exam doesn't reveal any abnormalities. However, because of DK's transient vision loss (amaurosis fugax), the ophthalmologist suspects GCA and notes that DK meets 4 of the 5 ACR criteria for the diagnosis. Knowing that the presence of jaw claudication and diplopia strongly predicts the presence of GCA, the ophthalmologist continues DK on high-dose oral steroids and schedules her for TAB.

The TAB is positive, confirming the diagnosis along with other key findings: age of onset >50 years, northern European ethnicity, new type of headache, and ESR >50 mm/h. DK is referred to a rheumatologist for follow-up, including instructions on the maintenance of steroids and when and how to taper the dosage. The ophthalmologist also prescribes low-dose aspirin daily, a proton pump inhibitor, and calcium/vitamin D supplements, with weekly bisphosphonates for bone protection while DK is on steroids. Her serum glucose will be monitored as surveillance for steroid-induced diabetes.

DK is told to follow up with the rheumatologist at weeks 1, 3, 6; and then at months 3, 6, 9, and 12. Her bloodwork, including CBC, ESR, CRP, BUN, electrolytes, and glucose, will be checked with each appointment.

Because long-term glucocorticoid use is anticipated, DK is to undergo bone density measurements annually. Chest X-rays will be performed to monitor for changes such as development of an aortic aneurysm. In the future, other specific diagnostic tests may be required, such as an ECG or MRI.

DK is instructed to see her rheumatologist immediately if she experiences signs and symptoms of a relapse, such as unilateral headache, jaw claudication, joint and muscle pain, and scalp tenderness. The nurse emphasizes that vision deficits must be reported immediately to minimize the risk of permanent vision loss. DK understands the

importance of maintaining scheduled appointments, being alert for signs and symptoms associated with long-term glucocorticoid use, and adhering to the medication regimen.

DK improves on oral glucocorticoid therapy and is prescribed a slow taper schedule to follow unless she experiences an exacerbation of symptoms. If she experiences a relapse, she'll be restarted on a short-term, higher dose regimen for several weeks, followed by a similar slow taper schedule based on clinical response, ESR results, and symptom control.

DK responds well to the treatment regimen and her vision changes and other symptoms are controlled on steroid and prophylactic therapies. To give her the best chance for long-term management of her GCA and control of symptoms and disease progression, DK will be followed closely for the rest of her life. ■

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On alert for giant cell arteritis

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