Giant Cell Arteritis: Read the Fine Print!

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ANNALS CASE

"A 75 year-old female presented to the emergency department (ED) complaining of 11 days of a stabbing headache in the right temporal region, without associated jaw claudication or vision changes. She sought evaluation four times in the week prior, but those evaluation results were negative, including head computed tomography, magnetic resonance imaging, and laboratory testing. Physical examination in the ED showed prominent, nontender temporal arteries. Erythrocyte sedimentation rate (ESR) was 10 mm/hour."[1]

This time around, instead of ending with the diagnosis, we start with the final diagnosis: giant cell arteritis (GCA), also known as temporal arteritis. We skip right to the answer in immature retribution for the patient's not fully conforming to our handy medical school mnemonic.

First, let's take a step back and recall what some of us have been taught about GCA. A mnemonic sometimes used is the "rule of 50s": consider GCA in headache patients who are at least 50 years old and have a serum ESR greater than or equal to 50 mm/hour and then prescribe 50 mg of oral prednisone once a day. Patients should undergo urgent temporal artery biopsy for definitive confirmation, as they say. Not that we expect a mnemonic to carry the full weight of our jobs as diagnosticians, but clearly this "rule" failed us. Let's dig a little bit deeper.

SETTING THE CONTEXT

Let's give ourselves a break. GCA is pretty uncommon, with a prevalence in the general population of less than 1%.[2] It is a disease almost exclusively of older folks, with an average age at presentation of 73 years.[3] GCA almost never occurs in people younger than 50 years. In fact, of 1,435 pooled GCA cases, there are only 2 documented cases of GCA in patients younger than 50 years.[3] The specific cause of GCA remains unknown, although it does probably involve cytokines (doesn't everything?).[4,5] The problem with vascular inflammation is that it can result in luminal occlusion, leading to ischemic complications. In a GCA patient's case, we're worried about ischemic optic neuropathy leading to blindness. You may be wondering why we don't use the term "temporal arteritis" anymore. This term always helped trigger the association of temporal headaches with temporal arteritis. Turns out GCA can cause vasculitis anywhere from the thoracic aorta to its distal branches. Although many textbooks focus on ischemic optic neuropathy as a feared complication of GCA, we should know that GCA may lead to aortic dissection, aneurysm formation, or (extremely rarely) ischemic stroke.[4-6] Up to 25% of GCA patients have vasculitic involvement of the aorta and its major branches.[4]

MAKING THE GCA DIAGNOSIS

There is a point of confusion that needs some clarification. Some educational resources reference the American College of Rheumatology's classification criteria for GCA (Figure).[7] To be clear, these criteria were not developed for diagnosing GCA in the undifferentiated patient, but for distinguishing GCA from other vasculitides in patients with known vasculitis (when is the last time you checked the box for the criterion of biopsy-proven necrotizing arteritis?).[8] There are no validated diagnostic criteria for GCA,[4] and the one small study that looked at the diagnostic performance of these 1990 criteria left much to be desired: sensitivity and positive predictive value were 75%, and specificity and negative predictive value were 95%.[9]

That being said, GCA patients typically present with several common features, which can be divided into

Having 3 of the following 5 criteria is considered a positive result:

≥50 y at disease onset

Localized headache of new onset

Tenderness or decreased pulse of the temporal artery

ESR at least 50 mm/h

Biopsy revealing a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells

Figure. 1990 Classification criteria by the American College of Rheumatology.[8]

systemic and localized findings. Common systemic findings include fever, malaise or fatigue, myalgia, and anemia. Common localized findings include new-onset headache (usually constant and temporal in location), jaw claudication (fatigue, discomfort, or pain of the jaw muscles during chewing as a result of vascular insufficiency of the masseter and temporalis muscles), and visual abnormalities (such as amaurosis fugax or diplopia as a result of ocular vascular insufficiency).[5,6,10] Additionally, it is important to know that polymyalgia rheumatica occurs in up to 50% of GCA patients and may be undiagnosed.[6] So be sure to ask your patient with suspected GCA if he or she has chronic aching and morning stiffness in the proximal joints (shoulders and hips) or neck, which may suggest polymyalgia rheumatica and further increase your clinical suspicion for GCA.

To make sense of what clinical features are important, the good folks from the Rational Clinical Examination series broke down the performance characteristics of several of these findings.[3] Even better, Widico and Newman[11] highlighted and reviewed those findings for us right here in *Annals of Emergency Medicine* (Table). Jaw claudication and diplopia had the highest positive likelihood ratios, at 4.2 and 3.4, respectively. Of the temporal artery abnormalities commonly noted in GCA patients (tender temporal artery, absent temporal artery pulse, prominent or enlarged temporal artery, or beaded temporal artery), beaded and prominent or enlarged temporal artery had the highest positive likelihood ratios, at 4.6 and 4.3, respectively. Despite the verification bias of this study, no features effectively ruled the diagnosis in or out (shocker).

ESR: CLINICAL LORE?

What about our patient's ESR of 10 mm/hour? Many of us want to believe that a normal ESR effectively rules out GCA. However, a 2012 study of 764 patients with suspected GCA who underwent temporal artery biopsy, with 177 biopsy-confirmed cases, looked at the performance characteristics of serum ESR and C-reactive protein. Using an abnormal cutoff value of ESR greater than 22 mm/hour in men and greater than 29 mm/hour in women, the study found ESR to have 84% sensitivity, 30% specificity, 26% positive predictive value, and 86% negative predictive value.[12] That sure doesn't sound like a great screening test. Some recommend obtaining both ESR and C-reactive protein level to increase diagnostic yield[5,12-14]; however, 4% of biopsy-confirmed GCA patients had normal ESR and C-reactive protein level at the diagnosis (using an abnormal C-reactive protein cutoff value of >8 mg/L).[12] Basically, Rosen's textbook said it best: GCA is "substantially less likely in patients with an ESR below 50 mm/hr and a C-reactive protein level below 2.45 mg/dL, although patients in whom there is high suspicion of disease should be referred for biopsy even if both of these biomarkers are normal."[10]

BACK TO THE CASE

This 75-year-old woman with new temporal headache fits the GCA demographic. The ischemic features we were

Table. Positive and negative likelihood ratios and sensitivities for selected symptoms and signs among patients with positive temporal artery biopsy results.[11]

Symptom/Sign	LR+ (95% CI)*	LR− (95% CI)*	Sensitivity (95% CI)†
Jaw claudication	4.2 (2.8–6.2)	0.72 (0.65–0.81)	0.34 (0.29–0.41)
Diplopia	3.4 (1.3–8.6)	0.95 (0.91–0.99)	0.09 (0.07–0.13)
Beaded temporal artery	4.6 (1.1–18.4)	0.93 (0.88–0.99)	0.16 (0.07–0.28)
Prominent/enlarged temporal artery	4.3 (2.1–8.9)	0.67 (0.5–0.89)	0.47 (0.40–0.54)
Tender temporal artery	2.6 (1.9–3.7)	0.82 (0.74–0.92)	0.41 (0.30–0.52)
Absent temporal artery pulse	2.7 (0.55–13.4)	0.71 (0.38–1.3)	0.45 (0.26–0.66)
Any temporal artery abnormality	2.0 (1.4–3.0)	0.53 (0.38–0.75)	0.65 (0.54–0.74)
ESR abnormal	1.1 (1.0–1.2)	0.2 (0.08–0.51)	0.96 (0.93–0.97)

LR+, Positive likelihood ratio; *CI*, confidence interval; *LR−*, negative likelihood ratio.
*Pooled data including results for patients with both positive and negative biopsy results. Refer to Smetana and Shmerling[3] for specific references to studies cited.
†Pooled data including results of all eligible studies, including those that reported clinical features for patients with positive biopsy results only.

hoping to elicit, such as jaw claudication or vision deficits, were absent. That being said, not having jaw claudication and vision deficits does not rule out GCA. Moreover, the accompanying image demonstrates a prominent and beaded temporal artery, which increases the likelihood of GCA. Especially in light of the apparently recent extensive evaluation excluding many other causes of headache, and despite an ESR of 10 mm/hour, GCA is still left on the differential. The classic textbook presentation of GCA that we were all hoping for didn't pan out (welcome to medicine).

Perhaps we should listen more often to Swadron's[15] voice in the back of our heads, talking about "visual signs from above" and making sense of all of the clinical data, instead of relying on a single laboratory test. In the end, this case is yet another great reminder of the limitations of mnemonics and screening tests. The "rule of 50s" may be a great rule to use to pass the written boards, but it is more of a guideline in actual clinical practice.

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