

Clinical Diagnosis of Temporal Arteritis With Seronegative and Negative Biopsy Studies

Angel Bayas ¹, Octavio Carranza ¹, Marc A. Swerdloff ²

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1. Neurology, Florida Atlantic University Charles E. Schmidt College of Medicine, Boca Raton, USA 2. Marcus Neuroscience Institute, Boca Raton Regional Hospital, Boca Raton, USA

Corresponding author: Angel Bayas, abayas@health.fau.edu

Abstract

Giant cell arteritis (GCA), also known as temporal arteritis is the most common of the systemic vasculitides. It occurs in individuals older than 50 years of age and peaks in incidence in the seventh decade. The gold standard for diagnosis of GCA is temporal artery biopsy (TABx) which will show transmural inflammation, but a negative biopsy does not rule out the disease. We present a case of a 66-year-old male with a classic clinical presentation of temporal arteritis with a normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and negative bilateral temporal artery biopsies. He was discharged on prednisone. Ten days later, he unilaterally stopped his corticosteroid treatment leading to a recurrence of symptoms and conversion to seropositivity (ESR negative and CRP positive). The objective of this article is to point out that the diagnosis of temporal arteritis is clinical and is not discarded by a negative TABx. Patients with classic clinical manifestations of temporal arteritis but with a negative TABx should be treated aggressively.

Categories: Neurology

Keywords: giant cell arteritis, temporal arteritis, erythrocyte sedimentation rate, c-reactive protein, c-reactive protein (crp), erythrocyte sedimentation rate (esr), temporal artery biopsy, temporal arteritis, giant cell arteritis (gca)

Introduction

Giant cell arteritis (GCA), also known as temporal arteritis is the most common of the systemic vasculitides. Temporal artery biopsy (TABx) is the gold standard for diagnosis of GCA with a sensitivity of 15%-40% and a specificity of 100%. Unfortunately, TABx has a false negative rate as high as 7% [1]. Elevation in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are variables for diagnosis criteria of GCA but may be normal in 7%-20% of patients with GCA [2].

The American College of Rheumatology (ACR), in 1990 created a criterion for the diagnosis of GCA in the "Traditional Format." Later the ACR presented the Tree format that used the same traditional format, except that ESR was excluded, and two other variables were included [3]. The last revision from the ACR for diagnosis criteria of GCA, (rACR) was published in 2016. This revision contains 11 points (p). It proposed that in the existence of three points or more, with at least one point included in Domain 1, the diagnosis of GCA can be accepted, however, this is yet to be evaluated [4].

The objective of this article is to point out that the diagnosis of temporal arteritis is clinical and is not discarded by a negative TABx. Patients with classic clinical manifestations of temporal arteritis but with a negative TABx should be treated aggressively.

Case Presentation

A 66-year-old male presented to the emergency room complaining of a right temporal headache, difficulty with balance, and blurry vision. The headache woke him from sleep two days in a row. It was intermittent throughout the day. He never experienced headaches prior to this. He did not take medication to alleviate this headache. The day before his presentation, he experienced transient vertigo with diaphoresis, nausea, and heaviness in his lower extremities. He felt off balance while walking. He had jaw claudication. He denied falls, loss of consciousness, fevers, or chills. He was initially treated as a stroke alert; however, the duration of symptoms and an NIHSS score of 0 made acute stroke intervention unlikely. On physical examination, his visual fields were intact. Pupils were equally round and reactive to light to direct and indirect light bilaterally. Extraocular movements were intact. No nystagmus was noted. The facial sensation was intact. The face was symmetric. No dysarthria. MRI and CT scan of the head was negative. Laboratory values are listed in Table 1.

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| Test | Result | Normal range | Test | Result | Normal range |
|---------|---------------|---------------------|----------------------|-------------------|-------------------|
| WBC | 7.900 K/mcL | 4.1–10.9 K/mcL | Na | 139 mmol/L | 138–148 mmol/L |
| RBC | 4.71 mcL | 4.20–6.30 mcL | K | 3.7 mmol/L | 3.6–5.2 mmol/L |
| HGB | 15.0 g/dL | 12.0–18.0 g/dL | Glucose | 106 mg/dL | 70–99 mg/dL |
| HCT | 44.5% | 37.0%–51.0% | BUN | 21 mg/dL | 7–18 mg/dL |
| PLT | 211 K/mcL | 140–440 K/mcL | Creatinine | 1.3 mg/dL | 0.6–1.3 mg/dL |
| ESR | (12) mm/h (N) | 0–20 mm/h | GFR | 59 mL/min/1.73 m2 | >59 mL/min/1.73 |
| CRP | 0.39 mg/dL | <0.80 mg/dL | AST | 24 Int/Unit/L | 10–31 Int/Unit/L |
| INR: PT | 1.0/136 s | 0.9–1.2/11.5–14.4 s | ALT | 37 Int/Unit/L | 12–78 Int/Unit/L |
| PTT | 30.9 s | 22–34.8 s | Alkaline phosphatase | 41 Int/Unit/L | 45–117 Int/Unit/L |

TABLE 1: Laboratory values.

BUN, blood urea nitrogen; GFR, glomerular filtration rate; ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; PLT, platelet count; INR, international normalized ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PTT, partial thromboplastin time; PT, prothrombin time

A vascular surgery consultation refused to perform a biopsy citing the low yield of a positive biopsy in a seronegative setting. A rheumatology consultation concluded the case was compelling for GCA and recommended long-term steroids even if a TABx was negative. The vascular neurosurgical team performed a bilateral TABx. The pathology report was negative for bilateral temporal arteritis.

After one dose of prednisone, he was able to sleep uninterrupted by headache. His other symptoms also ceased. He was sent home on 60 mg prednisone daily. Ten days later, he presented to the hospital after abruptly stopping his medication after a week of treatment. He developed chills, dizziness, numbness in his hands, and slight blurring in his distance vision. He returned to the hospital where a CRP was elevated to 4 mg/dL.

Ophthalmology evaluation described floaters in both eyes. Visual acuity with correction was oculus sinister (OS): 20/40 and oculus dextrus (OD): 20/40. Visual fields were intact to finger confrontation. No dyschromatopsia on Ishihara testing oculus uterque (OU). Pupils were equally round and reactive to light bilaterally. There was no afferent pupillary defect (APD). Extraocular movements were intact without nystagmus. Fundoscopic examination was normal. He was discharged home on 60 mg prednisone daily.

Discussion

The American College of Rheumatology (ACR), in 1990 created a criterion for the diagnosis of GCA the "Traditional Format." In this format, the presence of three or more of these five variables can suggest the diagnosis of GCA and was associated with a sensitivity of 93.5% and a specificity of 91.2%. See Table 2, for the traditional format for the diagnosis of GCA [3].

| |
|---|
| Age at disease onset >= 50 years. New onset of or new type of localized headache. Temporal artery abnormality (tenderness to palpation or decreased temporal artery pulse). Elevated ESR greater than or equal to 50 mm/h abnormal biopsy of an artery. |
|---|

TABLE 2: 1990 Criteria for the classification of GCA (Traditional format).

ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis

Reference: The American College of Rheumatology

Later the ACR presented the Tree format that used the same traditional format, except that ESR was excluded, and two other variables were included: scalp tenderness and claudication of the jaw or tongue or on deglutition. The Tree format was associated with a sensitivity of 95.3% and a specificity of 90.7%, as listed in Table 3 [3].

| Criterion | Definition |
|--|--|
| Age at disease onset >= 50 years | Development of symptoms or findings beginning at age 50 or older |
| New headache | New onset of or a new type of localized headache |
| Claudication of jaw, tongue, or on deglutition | Temporal artery abnormality (tenderness to palpation or decreased temporal artery pulse, unrelated to arteriosclerosis of cervical arteries) |
| Scalp tenderness or nodules | Development of tenderness areas or nodules over the scalp, away from the temporal artery or other cranial arteries |
| Abnormal artery biopsy | Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells |

TABLE 3: Criteria and definition used for the classification of GCA (Tree format).

GCA, giant cell arteritis

Reference: The American College of Rheumatology

The last revision from the ACR for diagnosis criteria of GCA, (rACR) was published in 2016. This revision contains 11 points (p) as listed in Table 4. It proposed that in the existence of three points or more, with at least one point included in Domain 1, the diagnosis of GCA can be accepted, however, this is yet to be evaluated [4].

| Score | Entry |
|-------|--|
| N/A | Age at onset >50 years old absence of exclusion criteria |
| | Domain I |
| 1 | New onset localized headache |
| 1 | Sudden onset of visual disturbances |
| 2 | PMR |
| 1 | Jaw claudication |
| 2 | Abnormal temporal artery |
| | Domain II |
| 1 | Unexplained fever and/or anemia |
| 1 | ESR > 50 mm/h |
| 2 | Compatible pathology |

TABLE 4: Revised ACR criteria (rACR) for diagnosis of GCA.

rACR, revision for American College of Rheumatology; ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatica; GCA, giant cell arteritis

Reference: International Journal of Surgery Open, Vol 9., 2017, pp. 19-23

Our case meets the age criteria, absence of exclusion criteria, and in Domain I, new onset of localized headache, sudden onset of visual disturbance, and jaw claudication.

Table 5 listed the comparison of the sensitivity and specificity of potential criteria variables for GCA [3].

| Criterion | #. Of patients (n=214) | #. Of controls (n=593) | Sensitivity | Specificity |
|------------------------------------|------------------------|------------------------|-------------|-------------|
| History | | | | |
| Age at disease onset >=50 years | 213 | 588 | 98.6 | 63.8 |
| Headache, new, localized | 214 | 590 | 64.5 | 81.9 |
| Jaw claudication | 213 | 579 | 38.5 | 97.9 |
| Tongue claudication | 213 | 578 | 2.8 | 99.8 |
| Claudication on deglutition | 212 | 577 | 4.2 | 99.0 |
| Claudication, variables 3-5 | 212 | 576 | 40.6 | 97.6 |
| AM stiffness neck/torso | 211 | 586 | 50.2 | 86.5 |
| AM stiffness shoulders/arms | 210 | 586 | 52.9 | 77.5 |
| AM stiffness hips/thighs | 211 | 586 | 46.9 | 79.7 |
| PMR | 210 | 585 | 52.9 | 79.3 |
| Diplopia | 213 | 587 | 11.3 | 93.9 |
| Physical | | | | |
| Ischemic optic neuritis | 212 | 580 | 7.5 | 98.4 |
| Amaurosis fugax | 214 | 588 | 11.2 | 95.7 |
| Partial unilateral loss of vision | 213 | 587 | 4.2 | 99.0 |
| Complete unilateral loss of vision | 212 | 585 | 3.3 | 99.7 |
| Partial bilateral loss of vision | 214 | 584 | 2.3 | 99.1 |
| Optic atrophy | 212 | 586 | 4.7 | 99.0 |
| Visual abnormality | 210 | 573 | 27.6 | 88.8 |
| Right TA tenderness | 212 | 495 | 23.1 | 99.6 |
| Decrease right TA pulse | 210 | 477 | 35.2 | 97.9 |
| Left TA tenderness | 211 | 494 | 21.3 | 99.2 |
| Decrease left TA pulse | 209 | 476 | 28.7 | 97.9 |
| TA abnormality | 211 | 473 | 57.3 | 96.8 |
| Scalp tenderness | 212 | 584 | 40.6 | 97.9 |
| Scalp nodules | 212 | 585 | 13.7 | 99.5 |
| Scalp tenderness or nodules | 212 | 581 | 43.9 | 97.4 |

TABLE 5: Comparison of the sensitivity and specificity of potential criteria variables for GCA.

GCA, giant cell arteritis; PMR, polymyalgia rheumatica; TA, temporal artery

Reference: The American Academy of Rheumatology

Studies showed that ESR, CRP, and platelets are moderate, equivalent diagnostic tests for GCA [5]. These studies can help to guide the GCA diagnosis, but they are not specific to the diagnosis. Approximately four percent of patients have normal ESR and CRP values [6].

The gold standard for diagnosis of GCA is TABx with or without temporal artery color Doppler ultrasound (CDUS). TABx should be performed in any patient with suspected temporal arteritis. The treatment with systemic corticosteroids should not be delayed until after TAB is done [7]. TABx has a specificity of 100%, but poor sensitivity when compared with clinical diagnosis with a false-negative rate reported as high as

44% [8]. The characteristic histologic finding of GCA is transmural inflammatory infiltrate of lymphocytes, macrophages, and, in 75% of cases, giant cells [1].

The following are reasons for a high false negativity rate in TABx:

1. Skip lesions: The pathology is segmental, and a biopsy may miss the area of involvement.
2. Length of specimen: With non-continuous pathology, the lesion cannot be localized a longer biopsy specimens and bilateral sites are recommended [9].
3. Number of sections evaluated: In order not to miss inflammatory changes, at least three additional slices should be evaluated in all negative TABx specimens [9].
4. Effect of therapy: Glucocorticoid treatment may reduce the sensitivity of TABx. Resolution of the inflammatory infiltrate of GCA occurs slowly, and histopathologic evidence will be evident for at least a month after glucocorticoid therapy has.

The most common complications of TABx are bleeding, surgical site infection, nerve injury involving the auriculotemporal nerve or branches of the facial nerve. In a series of 75 biopsies performed on 68 patients, 16% of patients developed new frontalis muscle weakness with complete recovery after one year (two cases) [10]. A rare complication of TABx seen by one of us (M Swerdloff), was an operating room fire triggered by electrocautery applied to a flammable local disinfectant. The patient was transferred to a regional burn unit with burns to her scalp. She was lost to follow up.

Other noninvasive vessel wall imaging to complement the diagnosis of GCA such as high-resolution contrast enhanced magnetic resonance angiography (MRA) may identify mural edema in the temporal artery [11]. There is evidence supporting the use of Doppler ultrasound, dedicated post-contrast T1-weighted spin echo MRI of the scalp arteries, and positron emission tomography (PET) scan. These studies can improve diagnostic accuracy of GCA in cases in which TABx is inconclusive or negative [12]. In our case we did not use these studies due to the strong clinical findings that our patient presented.

Some of the differential diagnoses to consider are Takayasu arteritis, small- and medium-sized vessel vasculitides, primary angiitis of the central nervous system, idiopathic aortitis, non-arteritic anterior ischemic optic neuropathy, and infection [13].

Steroid treatment should not be delayed awaiting TABx results. The 2016 revised ACR criteria (rACR) help us to have strong guidance for the GCA diagnosis in patients who meet the criteria. Clinical improvement after high-dose glucocorticoids is nonspecific and should not be the sole reason for establishing the diagnosis of GCA but it is supportive. Close follow-up to monitor the clinical course of the disease and to mitigate long-term corticosteroid treatment side effects is necessary.

Conclusions

The 2016 rACR criteria for the diagnosis of GCA are still in review. New imaging strategies such as temporal ultrasound, MRI, MRA, and PET scans may reinforce the diagnosis. There remain economic barriers to instituting all these modalities. The objective of this article is to point out that the diagnosis of temporal arteritis is clinical and is not discarded by a negative TABx. Patients with classic clinical manifestations of temporal arteritis but with a negative TABx should be treated aggressively. The treating physicians should follow clinical symptoms and signs during the tapering process when serological guidance is not present. We recommend a rheumatology consultation to support a full workup and treatment when disagreements arise among the treating specialties.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Marc Swerdloff, MD issued approval 561-955-4600. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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