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An atypical manifestation of Giant cell arteritis (GCA): constitutional symptoms & lingual ulcer in a 78-Year-Old male with negative temporal artery biopsies

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Abstract

Background Giant cell arteritis (GCA) is a large vessel vasculitis characterized by granulomatous inflammation classically affecting the carotid artery branches. GCA most often presents with one or more classic clinical features which include headache, jaw claudication, temporal scalp tenderness, and polymyalgia rheumatica. In a minority of cases, GCA can adopt an "occult" presentation (i.e., failure to thrive in the setting of unexplained inflammation) where vascular manifestations affect vascular beds, such as lingual ulceration, not amenable to biopsy. While the diagnosis of GCA is often supported by temporal artery biopsy or imaging studies, such as temporal artery ultrasound or magnetic resonance angiography, these techniques are known to have limited sensitivity. As a result, there is the potential for GCA to be misdiagnosed where it presents both in the absence of classic clinical manifestations and without clear diagnostic evidence by imaging or histopathology.

Case presentation A 78-year-old male presented to rheumatology on the inpatient consult service with unexplained headaches, failure to thrive, and persisting elevated acute phase reactants. He was admitted for unexplained fevers three times in as many months, with an unrevealing infectious and malignancy workup. His past medical history was remarkable for a shallow right lateral tongue ulcer that was non-healing despite weeks of acyclovir treatment. Two bitemporal artery ultrasounds did not suggest features of GCA and subsequent temporal artery biopsies failed to show healing or active arteritis. The patient was started on empiric corticosteroids tapered to discontinue over six months in conjunction with tocilizumab. He had rapid normalization of inflammatory markers (prior to tocilizumab initiation), anemia of chronic inflammation, and correction of his serum Na + without need for ongoing fluid restriction. Clinically, his headaches and unexplained weight loss improved and his serial exams showed complete resolution of his tongue ulcer, suspected to be end-organ damage from GCA.

Conclusions Although the hospitalist service suspected GCA in this elderly patient with headaches, failure to thrive, recurrent fever of unknown origin, and elevated inflammatory markers, they were deterred from this diagnosis by repeat negative bitemporal artery ultrasounds and negative biopsies. This case demonstrates the need to survey for atypical vascular beds of GCA involvement, even in the presence of negative imaging and biopsy results.

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Keywords Case report, Lingual ulcer, Biopsy-negative vasculitis, Giant cell arteritis

Background

Giant cell arteritis (GCA) is a large-vessel vasculitis which typically affects the carotid artery branches. The characteristic granulomatous inflammation of this disease leads to transmural damage of arterial walls. This can result in intimal hyperplasia and fragmentation of the elastic lamina [1]. Classic manifestations of GCA result from ischemia of the external carotid artery and its distal branches and include headache, jaw claudication, and temporal scalp tenderness. Diagnostic modalities include diminished temporal artery pulse, temporal artery ultrasound, neck CT/MR angiography, and biopsy of the temporal artery – which is the gold standard. If unrecognized and left untreated, the disease process can progress to potentially involve the internal carotid artery leading to irreversible cranial ischemic complications. These may include permanent loss of vision (most commonly anterior ischemic optic neuropathy), extraocular motility disorders, and uncommonly, cerebral infarct in the internal carotid or vertebrobasilar arterial distributions [2–4]. Thus, recognizing this disorder by its clinical features and diagnostic techniques is critical to preventing these life-altering complications.

Though the classic features of GCA are well established, the current framework for diagnosis of GCA is limited due to the vast spectrum of manifestations resulting from its involvement of various large- and medium-sized arteries, both intra- and extra-cranial. Other manifestations of GCA include persistent unexplained fever, significant unintended weight loss, normocytic or microcytic anemia, and syndrome of inappropriate antidiuresis (SIADH) – a challenging diagnostic tetrad due to its mimic of occult malignancy or infection [5, 6]. In addition, lingual necrosis/ischemia is also a known, though rare, initial manifestation of GCA which should not be overlooked as GCA is its most common etiology [7, 8]. Lingual involvement is especially critical to identify due to its correlation with increased risk for visual involvement [9]. Overall, these less common manifestations should increase clinical suspicion for GCA even in the absence of classic diagnostic evidence or clinical features due to the potential complications of the disease going untreated. Here, we discuss a rare case of a patient with presumptive GCA who presented with recurrent unexplained fevers, SIADH, and normocytic, hyperferritinemic anemia and was later discovered to have a lingual ulcer concerning for lingual ischemia.

Case presentation

A 78-year-old male with no relevant past medical history, up-to-date age-appropriate cancer screening, and no smoking history presented to the rheumatology service with a 3-month history of fever of unknown origin, headaches, fatigue, anemia of chronic disease, SIADH, and significant unintended weight loss. The patient was in his normal state of health until 3 months prior when he presented to the emergency room with intermittent fevers, fatigue, day-time somnolence, shortness of breath, and significant unintended weight loss (20lbs over 1–2 month period). Notably at this presentation a right-sided shallow, oval-shaped, approximately 2 cm long (anteroposterior) and 1 cm wide (mediolateral) tongue ulceration without bleeding was observed, which was at that time thought to be the result of a bite wound or infection – though it was non-healing for >1 month and refractory to antibiotics and antiviral therapy. Work-up revealed significant elevation in acute phase reactants (CRP 13 mg/dL, ESR 113 mm/hr, Ferritin 883 ng/mL). The patient received an extensive infectious disease evaluation which was negative except for COVID-19, and rheumatology did not suspect autoimmune disease at the initial evaluation. The patient was discharged without a definitive diagnosis.

Three days later, the patient was readmitted for altered mental status and had a 2-day hospital course without new findings on work-up. Three weeks later, the patient was admitted for his third inpatient stay due to outpatient finding of significant anemia (HgB 7.9 g/dL). Acute phase reactants remained elevated (CRP 7.72 mg/dL, ESR 145 mm/hr, Ferritin 714 ng/mL), and anemia of chronic disease was confirmed. The absence of a unifying diagnosis prompted a bone marrow biopsy which was unremarkable for malignancy or myelodysplasia.

With infection and malignancy workups both failing to yield a diagnosis after 3 months, rheumatology was again consulted. At this evaluation, he denied having headache, vision changes, scalp tenderness, jaw claudication, and pain/stiffness in the hip/shoulders. A repeat temporal artery duplex found no "halo sign" or other expected evidence of arteritis. Persistent suspicion for GCA prompted temporal artery biopsy. Bilateral biopsies of >3 cm in length were obtained by vascular surgery; however, pathology identified no evidence of vasculitis and noted only purportedly age-related focal disruption of the internal elastic lamina with highlights of intimal thickening. MRA of the neck, including survey of the carotids, subclavian arteries, and the great vessels, did not show features consistent with large vessel vasculitis.

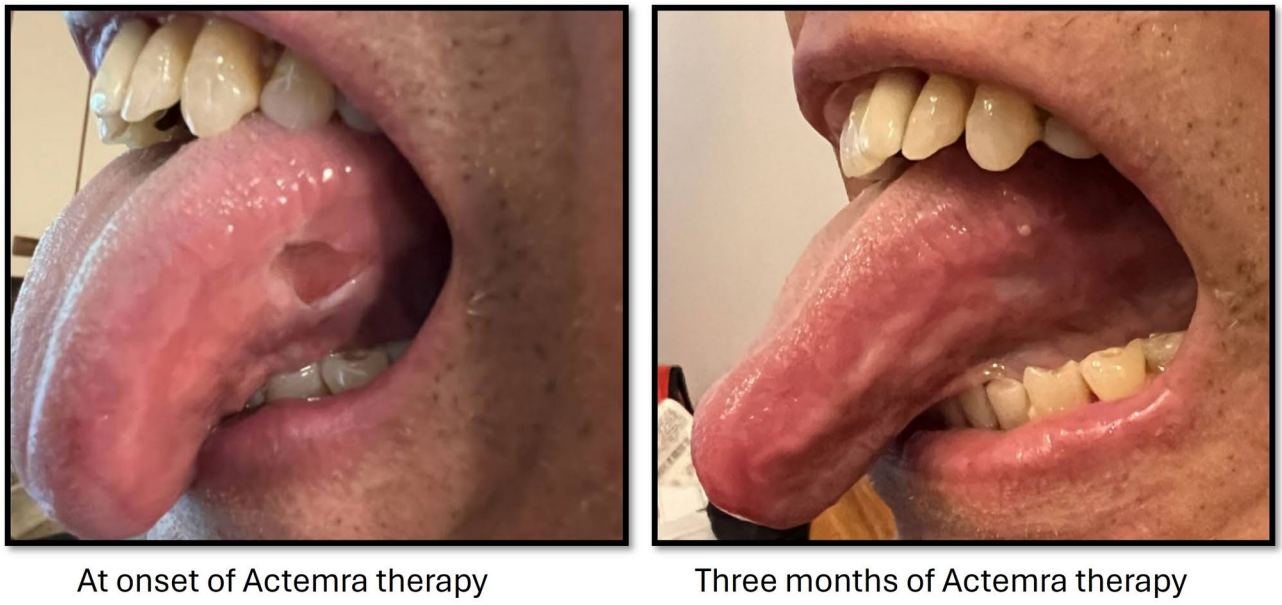

Fig. 1 Left-sided tongue ulcer pre- and post-treatment with prednisone/Actemra. (**a**) Patient-acquired image of a left-sided tongue ulceration at the time of initial observation by rheumatology. (**b**) Patient-acquired image of the resolved lesion after completion of a full course of high-dose prednisone and continued Actemra therapy

The patient was discharged to follow-up with rheumatology and initiated on 1 mg/kg/day of oral prednisone for 4 weeks. Shortly after commencement of steroid therapy, the patient's anemia and thrombocytosis improved along with normalization of his serum Na + and concomitant reduction in CRP (5 mg/dL) and ESR (2 mm/hr). Prednisone taper was planned in conjunction with initiation of tocilizumab (Actemra) 162 mg subQ/week. Additionally, thorough examination for evidence of GCA end-organ damage at this time revealed a new-left sided tongue ulceration (Fig. 1a), which resolved completely by the conclusion of the steroid taper (Fig. 1b). The patient continued to follow up outpatient with rheumatology on tocilizumab monotherapy over the next 8 months, with no relapse of failure to thrive, anemia, thrombocytosis, SIADH, or fever, and no recurrence of lingual ulceration.

Discussion & conclusions

Giant cell arteritis (GCA), historically known as temporal arteritis, is classically associated with specific symptoms such as temporal headaches, jaw claudication, scalp tenderness, and symptoms of polymyalgia rheumatica. In addition, it can affect more atypical cranial vascular beds manifesting as findings like lingual ulceration/necrosis. Atypical presentations of GCA without cranial involvement, also called "occult" or "Large Vessel (LV)-GCA", have also been documented where the primary complaint is exclusively constitutional symptoms like fever, malaise, weight loss, and failure to thrive [6]. These atypical cases likely contribute to the false negatives observed with the diagnostic scoring system established by the American College of Rheumatology (ACR) & European Alliance of Associations for Rheumatology (EULAR), which reports a sensitivity of only 87.0% (95% CI 82.0–91.0%) [10]. Thus, GCA should remain on the differential in those with prolonged systemic inflammation, even in the absence of typical features.

Temporal artery biopsy, the gold standard for diagnosing GCA, has historical limitations in sensitivity. While reported sensitivity has improved from ~ 50% in 1990 to 77% in 2023, variability in its diagnostic accuracy across different sites remains, as shown by a recent meta-analysis [6, 11]. This limitation is partly due to segmental nature of temporal artery involvement in GCA; however, absence of temporal artery vasculitis in cases of occult GCA also likely contributes. The use of temporal artery ultrasound (TAUS) has improved upon the detection of skip lesions, with sensitivity estimated from 62% to 87%. However, TAUS still cannot detect occult GCA which lacks cranial vessel involvement [12]. MR/CT angiography, offering a wider field of view, holds promise for detecting occult GCA without cranial involvement, but its sensitivity may also be limited, as seen in this case [13]. Consequently, patients with atypical GCA presentation (e.g., exclusively constitutional symptoms) may have negative temporal artery biopsies and unremarkable findings on TAUS and MR/CT angiography, placing them at risk for misdiagnosis and deterioration due to delayed or absent immunosuppressive treatment. This diagnostic delay may explain the increased trend in all-cause mortality previously observed in occult GCA, despite a

reduced rate of severe ischemic complications with standard GCA treatment [14].

In this case report, we have characterized a case of biopsy-negative, atypical GCA who fails to meet ACR/EULAR classification criteria [10]. This case highlights the importance of considering atypical GCA in elderly patients with chronic failure to thrive and signs of systemic inflammation without other unifying diagnosis, even in the context of negative biopsy and imaging.

The hospitalist team was appropriately concerned for GCA in this elderly patient with recurrent fever of unknown origin; however, were limited in terms of treatment options in the setting of a diagnostic dead-end: he had an extensive infectious and malignancy work-up, and now faced absence of evidence for GCA, interpreted as evidence of absence of GCA. Importantly, other autoimmune causes of systemic inflammatory symptoms had also been ruled out, including systemic lupus erythematosus (-ve anti-dsDNA, -ve anti-Smith), ANCA vasculitis (-ve anti-PR3 and -ve anti-MPO) and IgG4-related disease (persistent high-grade fever and hypogammaglobulinemia by SPEP/IFE).

Surveying for a site of end-organ damage from GCA (e.g., his tongue lesion) prompted suspicion for GCA and empiric therapy in the absence of imaging or biopsy evidence of the disease. This presumptive diagnosis was supported by complete resolution of his constitutional features (e.g., fever, weight loss, malaise), end-organ damage (e.g., tongue ulceration), inflammatory markers, and the inflammatory-related abnormalities seen on bloodwork (e.g., profound anemia of chronic disease requiring transfusion, SIADH without an alternative cause).

Abbreviations

GCA	Giant cell arteritis
CT	Computed tomography
MR	Magnetic resonance
SIADH	Syndrome of inappropriate antidiuresis
Lbs	Pounds
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
mg	Milligram
dL	Deciliter
mm	Millimeter
hr	Hour
ng	Nanogram
mL	Milliliter
HgB	Hemoglobin
g	Gram
kg	Kilogram
cm	Centimeter
subQ	Subcutaneous
TAUS	Temporal artery ultrasound
ACR	American College of Rheumatology
EULAR	European Alliance of Associations for Rheumatology
CI	Confidence interval
MRA	Magnetic resonance angiography
-ve	Negative
ANCA	Anti-neutrophil cytoplasmic antibodies
PR3	Proteinase 3
MPO	Myeloperoxidase
SPEP	Serum Protein Electrophoresis
IFE	Immunofixation Electrophoresis

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Author contributions
DR was the attending rheumatologist involved in the management of the case and provided the original concept of the manuscript and clinical case. JG performed literature review to support the background section and completed retrospective review of patient's clinical course to inform the case presentation and discussion. JG and DR collaborated in the drafting of the manuscript and revision process. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient reported in this case provided written consent for the publication of the details and images related to this case in BMC Rheumatology via the BioMed Central standard consent form.

Competing interests
The authors declare no competing interests.

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