Progression of large-vessel giant cell arteritis despite tocilizumab treatment

Sirs,

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in the elderly population (1). Glucocorticoids (GC) have been the mainstay of therapy for GCA for over 7 decades (1). Tocilizumab is used as a GC-sparing agent for the treatment of GCA, as it has been shown to be effective both clinically and radiologically (2-4). However, little is known about the effect of tocilizumab on the risk of vascular complications in patients with GCA. We report a patient who developed new upper extremity arterial occlusive disease while on low-dose prednisone and tocilizumab.

A 72-year-old white female presented with a several-week history of constitutional symptoms plus bilateral hip and shoulder stiffness. She then developed persistent headache, scalp tenderness and progressive right upper extremity claudication. Physical examination showed reduced right radial pulse and systolic blood pressure in the left arm was 21 mm Hg higher than the right arm. The left radial and bilateral pedal pulses were normal. Non-invasive arterial studies demonstrated normal triphasic Doppler signal at the left subclavian and axillary compared to reduced biphasic findings at the right subclavian and axillary locations. Laboratory studies showed elevated C-reactive protein (CRP) of 186 mg/L (ref: <8.0 mg/L), and erythrocyte sedimentation rate (ESR) of 93 mm/hr (ref: 0-29 mm/hr). Whole body ^{18}F- fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scan was consistent with large-vessel GCA, including diffuse ^{18}FDG uptake in the aorta and great vessels, iliac and femoral arteries with max SUV 4 (Fig. 1A). Computed tomography angiography (CTA) of the right upper extremity showed multifocal arterial stenosis involving the right subclavian and proximal brachial artery and mild to moderate narrowing of the vertebral artery secondary to vasculitis (Fig. 1B).

Treatment for GCA was initiated with oral prednisone 1 mg/kg daily and weekly tocilizumab 162 mg by subcutaneous injection. Four weeks after treatment initiation her symptoms had resolved, and inflammatory markers normalised (ESR 5 mm/hr; CRP <3 mg/L). Prednisone was gradually tapered.

Two months later, while on prednisone 15 mg/day and tocilizumab, she reported new onset left upper extremity claudication, but no cranial symptoms. Non-invasive arterial studies identified new reduced biphasic Doppler signal at the level of the left subclavian and axillary artery. CTA of the left upper extremity showed a new high-grade focal narrowing of the subclavian and long segment stenoses in the left axillary and brachial arteries with associated wall thickening (Fig. 1 C-D). Markers of inflammation were normal (ESR 1 mm/hr and CRP < 3 mg/L), as expected given the mechanism of action of tocilizumab. Prednisone was increased to 40 mg/day with symptomatic improvement and the patient was enrolled in a clinical trial evaluating an investigational agent for the treatment of GCA.

Large-vessel involvement in GCA includes various vascular complications such as arterial stenosis, occlusion, aneurysm, dissection, and rupture (1, 5) A prospective longitudinal study showed that patients with large-vessel involvement at presentation were more likely to develop new lesions on follow up (5).

Clinical trials of therapeutic agents for GCA have not specifically addressed efficacy related to large-vessel manifestations (6). The American College of Rheumatology (ACR) recommends using a combination of glucocorticoid and non-glucocorticoid therapeutics in the management of patients with active extra-cranial large-vessel involvement (7).

This case suggests that progression of large-vessel GCA may occur despite standard of care treatment with prednisone and tocilizumab. This reinforces the concept that inflammatory markers are unreliable indicators of disease activity in such patients. Close clinical monitoring and periodic imaging studies are essential for the detection of vascular complications. Guidance for management of patients with tocilizumab-refractory large-vessel GCA is needed.

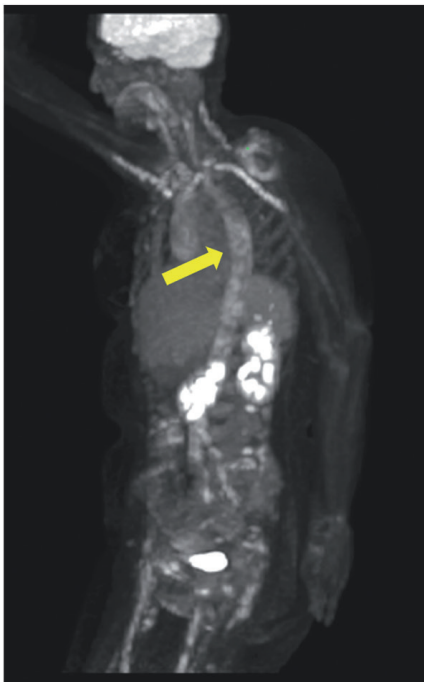
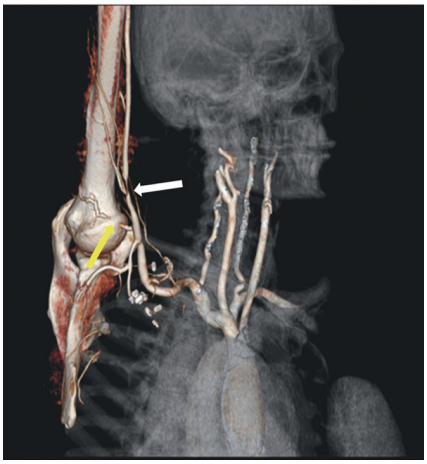
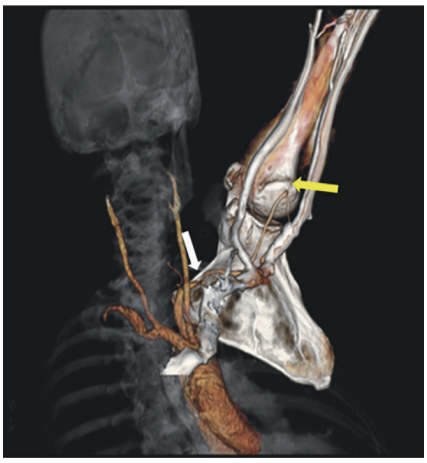


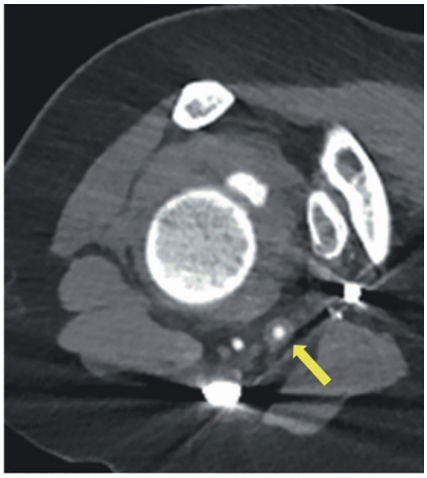
Fig. 1. (**A**) ^{18}FDG-PET at GCA diagnosis demonstrating diffuse ^{18}FDG uptake throughout the aorta (yellow arrow) with extension into the great vessels, axillary, iliac, and femoral arteries.



(**B**) CTA with 3D reconstruction at GCA diagnosis shows focal severe narrowing of the right posterior circumflex humeral artery (yellow arrow) and focal severe narrowing of the proximal right brachial artery (white arrow).



(**C**) CTA with 3D reconstruction shows high-grade focal narrowing of the left subclavian artery just distal to the origin of the left vertebral artery (white arrow), and high-grade stenosis of the left brachial artery (yellow arrow).



(**D**) On cross-section imaging of CTA, mural thickening of the left axillary artery (yellow arrow) is seen, consistent with vasculitis.

Letters to the Editors

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Competing interests: K.J. Warrington has received research support from Eli Lilly, GSK and Kiniksa, and honoraria from Chemocentryx. The other authors have declared no competing interests.

References

1. GARVEY TD, KOSTER MJ, WARRINGTON KJ: My treatment approach to giant cell arteritis. *Mayo Clin Proc* 2021; 96: 1530-45. https://doi.org/10.1016/j.mayocp.2021.02.013
2. QUINN KA, DASHORA H, NOVAKOVICH E, AHLMAN MA, GRAYSON PC: Use of 18F-fluorodeoxyglucose positron emission tomography to monitor tocilizumab effect on vascular inflammation in giant cell arteritis. *Rheumatology* 2021; 60: 4384-9. https://doi.org/10.1093/rheumatology/keaa894
3. FERRO F, QUARTUCCIO L, MONTI S *et al.*: One year in review 2021: systemic vasculitis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 129): S3-12. https://doi.org/10.55563/clinexprheumatol/v1tpfo
4. LA ROCCA G, DEL FRATE G, DELVINO P *et al.*: Systemic vasculitis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40: 673-87. https://doi.org/10.55563/clinexprheumatol/ozhc85
5. KERMANI TA, DIAB S, SREIH AG *et al.*: Arterial lesions in giant cell arteritis: A longitudinal study. *Semin Arthritis Rheum* 2019; 48: 707-13. https://doi.org/10.1016/j.semarthrit.2018.05.002
6. STONE JH, TUCKWELL K, DIMONACO S *et al.*: Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; 377: 317-28. https://doi.org/10.1056/nejmoa1613849
7. MAZ M, CHUNG SA, ABRIL A *et al.*: 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. *Arthritis Rheumatol* 2021; 73: 1349-65. https://doi.org/10.1002/art.41774