Case Study: Giant Cell Arteritis with Vertebral Artery Stenosis



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ABSTRACT: In giant cell arteritis (GCA), involvement of the vertebral arteries is rare with reported rates of 3%–4% for ischemic events secondary to vertebral artery stenosis or occlusion for those patients with GCA. This case study describes a patient who initially presented with acute onset of vertigo but was also found to have transient, side-alternating upper limb neurological findings. While initial imaging showed no vascular abnormalities, it was not until GCA was eventually confirmed with a temporal artery biopsy that the initial scans were shown to have bilateral narrowing of the vertebral arteries. While rare, vertebral artery involvement is an important complication to consider in the setting of GCA due to the high rate of associated mortality, despite immunosuppressive therapy.

KEYWORDS: giant cell arteritis, vertebral artery stenosis, Tocilizumab

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Introduction

Giant cell arteritis (GCA) is a chronic, systemic, inflammatory vasculitis of large and medium-sized vessels with unknown etiology.¹ The pathophysiology is thought to be an inflammatory response to endothelial injury via cell-mediated immunity. Possible triggers for the inflammatory cascade include genetic (higher frequency in Northern European heritage), environmental (Chlamydia pneumoniae, Mycoplasma pneumoniae, and parvovirus B19 infection), and autoimmune factors (granulomatous histopathology suggests antigen-driven disease).^{2,3} GCA predominantly affects the temporal arteries, but due to the diverse range of vessels affected, clinical manifestation for GCA are highly variable.³⁻⁶ Vertebral artery involvement is particularly rare with signs and symptoms including visual disturbances, cranial nerve palsies, affection of pyramidal and sensory tracts, cerebellar signs, and altered consciousness. Mortality rates associated with occlusion of the vertebral arteries are high unless an immediate high-dose immunosuppressive therapy is started.² Bilateral vertebral arteries occlusion (BVAO) resulting from GCA differs from BVAO of arteriosclerotic origin by much higher mortality rate (75% versus 19%, respectively).²

The gold standard for diagnosing GCA is temporal artery biopsy.⁷ Radiological investigation of GCA includes the following.

Temporal artery ultrasound. Demonstration of the typical halo sign surrounding the superficial temporal artery is secondary to edema within the inflamed vessel wall.² Doppler may show associated luminal stenosis. **CT angiography.** This shows nonspecific circumferential mural thickening.

Magnetic resonance imaging/angiography. This is the preferred test. T1 postcontrast images may demonstrate wall thickening and mural enhancement.² The degree of enhancement indicates inflammatory activity. With this modality, treatment response may also be monitored.

Fluorodeoxyglucose-positron emission tomography. There is an expanding role of this modality for this condition. The small caliber of the superficial temporal artery compared with comparatively increased cerebral uptake means that the artery may not be directly assessed; however, positron emission tomography (PET) is more useful for evaluation of the great vessels.²

The pathologic hallmark of GCA consists of a granulomatous inflammation of the inner half of the media centered on the internal elastic membrane. Mononuclear infiltrate, multinucleated giant, and fragmentation of the internal elastic lamina are the pathology findings. The involved arteries often reveal segmental involvement, leading to necrosis and subsequent disruption or thrombotic obstruction of the vessels.² The first two cases of BVAO resulting from GCA were published by Wilkinson, followed by three other cases.²

Case Report

A 72-year-old independent female living at home with her husband presented to the emergency department after waking

with an acute onset of vertigo. Her relevant past medical history included fallopian tube malignancy with hepatic metastasis, requiring surgical intervention, migraines, and fibromyalgia. Prior to admission, she suffered from temporal headaches, lethargy, generalized body aches, and bilateral jaw claudication post respiratory viral illness that was treated with a short course of prednisolone. Headaches were initially a prominent feature but were improving. One month prior to presentation, episodes of vertigo developed, which were followed by loss of balance.

Examination of the patient demonstrated left upper limb dysmetria and distal dysesthesia. She was admitted under the neurology team, and her blood test showed an elevated white cell count of 12.5, C-reactive protein of 77 mg/L, and erythrocyte sedimentation rate (ESR) of 66 mm/hour. A noncontrast computed tomography (CT) brain was performed, with no acute intracerebral abnormality identified. CT cerebral angiogram revealed short segments of symmetrical irregular luminal narrowing to 1 mm, involving bilateral distal vertebral arteries as they curve posteriorly to the lateral masses of C1 (Fig. 6A, 6B). This reflective finding was realized only after a magnetic resonance imaging (MRI), and a magnetic resonance angiography of the brain showed appearances suggestive of a number of small emboli within the posterior circulation on the right side of the brain, involving the posterior inferior cerebellar artery (PICA) and posterior cerebral artery (PCA), despite negative transthoracic echocardiogram for a cardiac cause of emboli. Endovascular therapy was not pursued by the managing team, as there was a lack of substantial evidence to support this intervention.¹ The neurological symptoms improved, the inflammatory markers decreased after a five-day pulse of methylprednisolone, and the patient was discharged home with a reduced prednisolone dose, atorvastatin, aspirin, and perindopril. Outpatient investigations and follow-up regarding the possibility of temporal arteritis or a prothrombotic condition were arranged. Rheumatology team was not consulted at that time.

The patient returned to hospital two days later with blurred vision, headaches, and gradually increasing right side upper limb paresthesia, as opposed to her previous presentation where the left side was affected. This time her examination revealed right-sided nystagmus and dysmetria, but there was no palpable temporal artery and fundoscopy was normal. She was readmitted and repeated MRI of the brain showed multiple small acute infarcts involving the posterior aspect of the medulla, cerebellum, and temporal lobes, with all infarcts being in the distribution of the posterior circulation. The vascular surgical team then performed a biopsy on the left temporal artery with histopathology consistent with GCA (Figs. 1–3).

While the histopathology was pending, further investigation was done using a six-vessel angiogram as well as a separate MRI, which showed bilateral vertebral artery disease with multiposition stenosis, suggesting a vasculitic process. She was given methylprednisolone pulse and an oral dose of



Figure 1. Lumen narrowing.

60 mg prednisolone to be continued at home, and aspirin was changed to clopidogrel.

An outpatient MRI three weeks later revealed further posterior circulation infarcts. Six days after this scan, she was presented to the hospital, with gradually worsening bilateral lower limb weakness and increasing confusion, despite normal erythrocyte sedimentation rate (ESR). Further imaging on CT showed a small mature lacunar infarct in the right thalamus, and repeat MRI showed further posterior circulation infarcts. Paraneoplastic survey including a CT scan of the chest, abdomen, and pelvis did not reveal any abnormalities. Given unusual GCA presentation, a PET/CT was obtained, which showed nonspecific generalized reduction of cortical uptake that can be seen in acute or chronic brain syndromes (data not shown). There was also a focal region of hypometabolism in the right cerebellum, which could reflect prior posterior cerebral artery infarction. Multifocal regions of increased arterial uptake were also observed in keeping with inflammation (Figs. 4 and 5).

She was commenced on warfarin and was planned for six courses of cyclophosphamide after liaising with the rheumatology team. Tocilizumab (TCZ), an IL-6 inhibitor,



Figure 2. Chronic transmural inflammation.



Figure 3. Mural necrosis.

was considered during her admission but not initiated. She was discharged to transitional care due to her functional and cognitive deterioration and her inability to participate in rehabilitation.

Unfortunately, the transitional care staff were unable to deal with the patient's confusion and impulsive behavior, which prompted a return to the hospital. It was also noted that she was struggling to have the cyclophosphamide treatments as an outpatient due to her confusion and high degree of falls risk. Thus, her fourth admission prompted the use of TCZ, as new infarcts were detected on repeat MRI, despite the cyclophosphamide treatment (rituximab was considered, but at that time, there was more objective evidence, in the form of successful case reports, for the use of TCZ⁶). Over the next few weeks, evolving right-sided choreoathetosis, dysphagia, right-sided gaze preference, and loss of gag reflex led



Figure 4. Increasing metabolic activity in left vertebral artery.



Figure 5. Both common carotid arteries showing increased metabolic uptake.

to the decision to transfer to high-level care, and a second dose of TCZ was not used as originally planned due to progression of her disease, poor prognosis, and quality of life. The patient's condition deteriorated rapidly and she passed away shortly after her last admission for choking. Written consent was obtained from the patient's relative to reproduce information and images appearing in this work.

Discussion

As described earlier, the clinical presentation of GCA can be highly variable. GCA may occasionally affect the extradural vertebral and internal carotid arteries.⁸ But the only intracranial area that has been documented to be involved includes the first few millimeters of the vertebral arteries as they enter the dura.⁸ However, our patient developed distal vertebral narrowing evident in cerebral angiogram, which has not been reported previously.

GCA has been known to cause vertebral artery stenosis and occlusion more common than internal carotids, a rare but serious neurologic condition that can present with initial severe headache, followed by progressive, side-alternating neurologic deficits.² The initial CT scans did not report the vertebral artery involvement, but on review, the findings were visualized. There is some literature describing the use of Doppler ultrasound, but the sensitivity and specificity is not well established in diagnosing GCA. One confounding factor in using ultrasound in this particular case may have been the patient's recent course of prednisolone, which has been shown to reduce sensitivity of color-coded duplex sonography and MRI for detecting GCA. In one particular study, it was demonstrated that a two-day course (similar to this patient's duration at presentation) can drop the sensitivity by approximately 10% (from 92%–90% to







Figure 6. (**A**,**B**) Digital subtraction angiography demonstrates bilateral (right: a, left: b) severe extracranial vertebral artery stenosis, worse on the left.a.

80%–78%), but for greater than four days, the sensitivity of Doppler US falls to 50%.⁹ The vertebral artery sample was not obtained postmortem; however, the imaging findings, especially PET/CT, MRI, and cerebral angiogram, were all highly suggestive of GCA vasculitic process.

One other consideration for this patient is that of vasculitis as a paraneoplastic syndrome. While paraneoplastic vasculitides are rare and more frequently associated with hematological malignancies than with solid tumors, our patient ultimately did not respond to the treatment that was instituted, prompting a wider range of diagnostic consideration.^{10,11} Our patient had a history of ovarian cancer with liver metastasis requiring resection. Follow-up CT scans taken shortly before her presentation with vasculitis did not indicate any recurrence of the disease and repeat chest, abdomen, and pelvis scans as well as PET/CT during admission again showed no evidence of recurrence. If the patient was in fact suffering from a paraneoplastic vasculitis, the treatment would involve treating the underlying cancer but this seems unlikely, given the negative findings of our investigations.

GCA and TCZ (IL-6 blocker). In GCA patients, IL-6 is upregulated within the inflamed arteries and in the peripheral circulation. Serum IL-6 levels mirror the activity of the disease and decline with effective glucocorticoid therapy.³ It has been suggested that the pharmacologic inhibition of the IL-6 cytokine can control vascular inflammation in this setting through different mechanisms that include promoting the generation of Treg cells, targeting downstream aspects of the inflammatory cascade, and altering upstream differentiation of autoreactive lymphocytes.³

About two dozen case series and case reports have reported that TCZ may be effective in patients with GCA in whom it has been difficult to taper glucocorticoids to an acceptable level or in whom disease has been refractory or relapsing, even despite therapy with additional agents.⁶ However, there is no previous data regarding trial of IL-6 blocker in refractory GCA with vertebral artery occlusion.

In the largest of these studies, seven patients with GCA, two patients with Takayasu arteritis, and one patient with polymyalgia rheumatica (all of whom had relapsing or refractory disease) were treated for a mean period of 7.8 months with TCZ (8 mg/kg once monthly in eight patients, administered intravenously, and 4 mg/kg once monthly in two of the patients with GCA).¹² Clinical improvement was seen within 8–12 weeks, clinical remission was achieved during therapy by all patients, and prednisone doses were successfully decreased significantly (from a mean dose of 20.8 mg daily before receiving TCZ to 4.1 mg daily while receiving TCZ). Acute-phase reactants were also markedly reduced by TCZ treatment with an acceptable adverse-effect profile (Medscape).

Conclusion

We reported a fatal GCA with intracranial involvement, which was refractory to all immunosuppressives. Cerebrovascular accidents have been reported in 3%–4% of patients with GCA. Vertebral artery involvement is a rare, yet serious, CNS complication of GCA. In any case, the vertebral arteries have a rare chance to develop giant cell vasculitis, which can be potentially fatal, despite an aggressive immunosuppressive therapy.

Author Contributions

Conceived and designed the experiments: RDC, FG, MD. Analyzed the data: RDC, FG, MD. Wrote the first draft of the manuscript: RDC, FG, MD. Contributed to the writing of the manuscript: RDC, FG, MD. Agreed with manuscript results and conclusions: RDC, FG, MD. Jointly developed the structure and arguments for the paper: RDC, FG, MD. Made critical revisions and approved the final version: RDC, FG, MD. All the authors reviewed and approved the final manuscript.

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