CASE REPORT

Unmasking the elusive giant: an unusual case presenting as third nerve palsy in a patient with scleroderma

Wan Lin Ng,¹ John McManus,² James Anthony Joseph Devlin,¹ Alexander Fraser¹

¹Department of Rheumatology, University Hospital Limerick, Dooradoyle, Ireland

²Acute Medical Assessment Unit, University Hospital Limerick, Dooradoyle, Ireland

Correspondence to
Dr Wan Lin Ng,
ngwanlin@gmail.com

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SUMMARY

We report a case of an 80-year-old woman being treated with rituximab and maintenance corticosteroids for long-standing scleroderma who presented with right-sided third nerve palsy. Radiological investigations including CT, MRI and MR angiography of the brain were unremarkable. The patient was discharged with a diagnosis of probable microvascular third nerve palsy but was readmitted 1 week later with total visual loss in her left eye. Despite the absence of diagnostic clinical signs, giant cell arteritis (GCA) was suspected, and she was started on intravenous corticosteroids. Left temporal artery biopsy subsequently confirmed histological findings diagnostic of GCA. Unfortunately, she remained blind in the left eye.

BACKGROUND

Giant cell arteritis (GCA) causing visual loss is devastating and rarely reversible. However, GCA presenting as a third nerve palsy is extremely uncommon. Furthermore, GCA presenting de novo and leading to major visual loss while a patient is already maintained on significant immunosuppression is remarkable. We would like to highlight not only that GCA may present in this atypical way but that it may do so even if and perhaps because a patient is already immunomodulated. It is imperative to diagnose GCA early to prevent visual loss and other ischaemic complications such as cerebrovascular accident. Although a raised erythrocyte sedimentation rate (ESR) of more than 50 mm/first hour is a diagnostic criterion, one cannot exclude GCA even if the ESR is low or even within the normal range.

CASE PRESENTATION

An 80-year-old woman was admitted with a 2-week history of occipital headache partially relieved by analgesia, and intermittent double vision with right eye ptosis and squint. Her medical history included scleroderma (antinuclear antibody and anti-Scl 70 positive) with Raynaud's phenomenon and bilateral hearing impairment secondary to skull fracture. She was on maintenance corticosteroids of 10 mg daily and six-monthly rituximab infusions for her scleroderma. Her most recent rituximab infusions (500 mg intravenously 2 weeks apart) were 2 months prior to her presentation. She had worked as a nurse previously and had good baseline function prior to her current admission. She did not have any neurological

weakness of her limbs, numbness, painful joints, jaw pain or jaw claudication and fundoscopy was normal. Her radiological investigations were unremarkable. Computed tomography (CT) of the brain was normal apart from opacified right mastoid air cells. Magnetic resonance imaging (MRI) of the brain showed a focal abnormality involving the grey and white matter in the medial aspect of the left frontal cortex and right cerebellar hemisphere, which appeared to be old. MR angiography (MRA) of the brain did not reveal any evidence of intracranial aneurysm. Her ESR was 41 mm/first hour and C reactive protein (CRP) value was 37 mg/L. She was discharged with aspirin 75 mg daily and a diagnosis of microvascular third nerve palsy. However, she was readmitted 1 week later with total loss of vision in the left eye.

On examination, her vital signs were normal. Neurological, abdominal and cardiac examinations were normal. She had a right-sided pupil sparing third nerve palsy in which the right eye was positioned downward and outward. She had no perception of light in the left eye. The pupil was slightly dilated on the left but reacted to light and accommodation. Fundoscopy showed bilateral papilloedema (figure 1). Her other neurological findings were normal and there was no scalp or temporal tenderness. There was also neither pain nor stiffness in the shoulders or hips to suggest polymyalgia.

INVESTIGATIONS

On this admission, the patient's white cell count was elevated at $14.86 \times 10^9/L$, neutrophils at $13.21 \times 10^9/L$, ESR at 39 mm/first hour and CRP at 90 mg/L. Viral hepatitis and cryoglobulin screens were negative. Her chest radiography, Mantoux test and Quantiferon test were normal. MR venogram of the brain performed on this admission showed no thrombus. Her antinuclear antibody was positive at 1 in 800 titre and antineutrophil cytoplasmic antibody was negative. Based on the investigation findings, GCA was suspected. She subsequently underwent a left temporal biopsy, which was histologically positive for GCA, as demonstrated by disruption of the internal elastic lamina with the elastic Van Gieson stain and multinucleated giant cell along with lymphocytic infiltration with the haematoxylin and eosin (H&E) stain (figure 2A–D).

DIFFERENTIAL DIAGNOSIS

It was crucial to exclude a posterior communicating aneurysm, cavernous sinus thrombosis and

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Figure 1 Fundoscopy showing papilloedema.

space occupying lesions in a patient presenting with pupil sparing third nerve palsy. However, her CT, MRI and MRA of the brain had excluded the above. Hence, the initial diagnosis of microvascular third nerve palsy was made on her first admission.

Her second presentation of blindness, papilloedema and raised CRP value triggered the suspicion of a vasculitic condition, which was subsequently confirmed by the temporal artery biopsy. Although GCA has been described in patients with disseminated tuberculosis, this patient had neither signs nor symptoms in keeping with active tuberculosis and, but had negative chest radiography and negative Mantoux and Quantiferon tests.¹ Other forms of infection-related vasculitis do enter the differential diagnosis, including cryoglobulinaemia and

granulomatosis with polyangiitis, but this patient's cryoglobulin screen was negative as was a viral hepatitis screen.

Another rare condition of rituximab-induced vasculitis was considered as a differential diagnosis. However, our patient did not have systemic symptoms such as fever, skin lesions or limb pain, and she had several rituximab infusions, with the last being 2 months prior to presentation of her current symptoms.^{2 3}

TREATMENT

In view of the patient's rapidly deteriorating condition and blindness secondary to the aggressive GCA, intravenous 1000 mg methylprednisolone was administered following consultation with neurology and rheumatology colleagues. After 3 days, the patient was started on oral prednisolone, which was tapered slowly over 2 months, without relapse, to 15 mg of prednisolone once daily.

OUTCOME AND FOLLOW-UP

This patient's vision and the right-sided third nerve palsy did not improve at all but her ESR and CRP value dramatically reduced within days after the start of corticosteroid therapy. On follow-up, she had no new symptoms and remained well.

DISCUSSION

GCA is a granulomatous vasculitis of large and medium-sized arteries that typically occurs in people above 50 years of age.⁴ Women are affected two to four times as often as men.⁴ GCA is devastating when irreversible loss of vision due to optic nerve ischaemia occurs.⁴ The aetiology of this condition remains unknown but it is speculated that it may be triggered by an environmental cause in a genetically predisposed person.⁴ It has

Figure 2 (A) Elastic Van Gieson stain showing inflammation in the tunica adventitia with intact elastic lamina. (B) Elastic Van Gieson stain demonstrating the disruption of internal elastic lamina secondary to inflammation. (C) H&E stain (×10) showing inflammatory cells. (D) H&E stain (×20) showing multinucleated giant cell and lymphocytic infiltration.

been shown that inflammatory cytokines interleukin-1 and interleukin-6 that are produced by macrophages are responsible for systemic inflammation occurring in GCA.⁴

GCA presenting as isolated third nerve palsy is rare. Sixteen cases have been reported in the literature to date.^{5–14} It is believed that ischaemic demyelination of the nerve is the cause of the third nerve palsy in GCA.⁵ Fisher reported that vasculitis affecting the branches of the posterior cerebral artery that supply the third nerve may be the cause of ischaemia.¹⁵ Our patient had a complete right-sided palsy of the third cranial nerve without involvement of the pupil. Although she had headaches, she did not have the typical symptoms of jaw claudication or tenderness over her temple on palpation.

ESR is usually raised at 50 mm/first hour or above in GCA and is one of the diagnostic criteria for GCA.⁴ Our case demonstrated a mildly raised ESR and CRP value at initial presentation, which might have been due to the patient being on maintenance oral corticosteroids and regular rituximab infusions.

Recent studies have demonstrated significant benefits from the use of rituximab, an anti-CD20 monoclonal antibody, in treating scleroderma.¹⁶ This monoclonal antibody has also been documented to be one of the alternative treatments for GCA.^{17,18} In the case report by Bhatia *et al*,¹⁸ improvement in symptoms and inflammatory markers was seen although the patient developed some side effects from treatment with rituximab. However, in our case, the patient suffered a catastrophic deterioration in her symptoms and signs leading to blindness despite being on maintenance corticosteroids and rituximab for her previous diagnosis of scleroderma. The low dose of maintenance prednisolone might have been insufficient to suppress the inflammatory response, leading to neovascularisation and resulting in optic nerve ischaemia and subsequent blindness. Following a literature search, there has been no reported case of patients developing GCA while receiving biological and steroid treatment.

Temporal artery biopsy remains the gold standard for diagnosing GCA, and biopsy specimens may still be positive even after more than 2 weeks of corticosteroid therapy.¹⁹ However, the tremendous advancement of radiological imaging has led to its emerging importance in diagnosing GCA in recent years. Colour Doppler sonography, which allows full length visualisation of the temporal arteries, in contrast to biopsy, contributes in the atraumatic diagnosis of GCA.²⁰ This complementary method demonstrates concentric hypoechogenic mural thickening, which is considered as a typical ultrasonographic finding in GCA.²⁰ Imaging techniques such as positron emission tomography (PET) and MRI are helpful in patients with large vessel GCA, especially when they present with systemic symptoms, limb claudication or persistently high inflammatory markers despite adequate glucocorticoid therapy.²¹ A piece of literature in the British Society for Rheumatology (BSR) guidelines has also highlighted the promising role of fluorodeoxyglucose positron emission tomography (PET) (FDG-PET) in assessing disease activity and the extent of GCA, where there was a decrease in vascular FDG uptake in patients with GCA on treatment.²¹

In a retrospective study performed by Ezeonyeji *et al*,²² the mean time from onset of symptom to diagnosis of GCA was 35 days and there was a high incidence of irreversible ischaemic complications, which may have been contributed to by diagnostic and treatment delays. Once visual loss is established, it rarely improves and therefore early treatment with high-dose intravenous methylprednisolone of 500–1000 mg daily for 3 days is recommended when GCA with visual involvement is suspected.²¹ If there are no contraindications, low-dose aspirin

should be considered as it has been shown to decrease the rate of visual loss and cerebrovascular accidents in GCA.²³ The early introduction of methotrexate or alternative immunosuppressants as adjuvant therapy should also be considered.²¹ A small meta-analysis in Spain showed that the use of methotrexate reduced the number of relapses and the cumulative corticosteroid dose.²⁴

Biologics are emerging as an alternative treatment to corticosteroids in treating GCA, particularly in refractory cases. Published case reports have demonstrated the successful treatment of GCA with antitumour necrosis factor α agents such as infliximab, etanercept and adalimumab.^{25–27} However, a randomised double-blind, placebo-controlled, multicentre study showed that infliximab did not reduce the number of first relapses nor the cumulative corticosteroid dosage.²⁸ The interleukin-6 receptor antagonist, tocilizumab, has demonstrated promising results in treating GCA in several studies.^{29–33} Of the 19 patients with GCA treated with tocilizumab with a combination of prednisolone, all achieved disease remission and a reduction of corticosteroid doses, while only three patients developed a relapse.³⁴

Monitoring of therapy in our patient was based on clinical response and measurement of inflammatory markers, as recommended by the BSR guidelines.²¹ She has had no relapse of symptoms and her ESR and CRP value decreased following treatment.

Reviewing the literature, it appears that the coexistence of scleroderma and GCA is extremely rare. At present, there have been only four reports in the literature, of GCA occurring in association with scleroderma, and no genetic links have been found for the association between the two.^{35–39} Perez-Jinenez *et al*³⁷ have discussed the possibility that alterations of the immune system may play a role in the development of GCA in patients with underlying scleroderma.

Learning points

- ▶ Giant cell arteritis can present in multiple and atypical ways.
- ▶ Ongoing immunosuppressive treatment for other immunological diseases does not necessarily prevent the development of giant cell arteritis.
- ▶ Erythrocyte sedimentation rate may not necessarily be helpful in diagnosing giant cell arteritis, especially if the patient concerned is on immunosuppressants.
- ▶ Always be ready to reconsider a diagnosis should there be deterioration of existing symptoms, occurrence of new symptoms and/or poor response to treatment.

Contributors WLN was a major contributor to acquisition of data, analysis of data, writing the manuscript and reviewing the literature. JM was a major contributor to critically reviewing the manuscript and supervising the development of work. JAJD and AF were major contributors to manuscript revision and critically reviewing the manuscript for intellectual content.

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