Masked giant cell arteritis

Peter Pak Moon Cheung
MBBS, is rheumatology registrar, Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, New South Wales. cheungppm@yahoo.com.au

Griffith Richards
FRACP, is visiting rheumatologist, Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, New South Wales.

BACKGROUND
Giant cell arteritis (GCA) is the most common vasculitis in the western world and often presents as a diagnostic problem for general practitioners. Prompt diagnosis and treatment is important to prevent potential irreversible complications, with a favourable outcome.

OBJECTIVE
This article discusses a case of GCA presenting with mild anaemia, weight loss and high erythrocyte sedimentation rate.

DISCUSSION
Anaemia and high inflammatory markers are common blood abnormalities encountered in the elderly population. Even though anaemia as a primary presentation of GCA has been well documented in the past, our case highlights the importance of considering this as a differential diagnosis in the community. Ways of assessing the so-called 'masked GCA' which may enable a better awareness of the diversity of this disease, is also discussed.

Case history

A previously well woman, 65 years of age, was referred by her general practitioner for investigation of anaemia, weight loss and a high erythrocyte sedimentation rate (ESR). She had initially presented 5 months earlier complaining of nonspecific fatigue and general malaise. Investigations revealed a mild normocytic anaemia and significantly raised ESR which precipitated her referral.

On review, aside from anorexia and a 2–3 kg weight loss over a 5 month period, the patient was otherwise asymptomatic. Specifically, there was no history of headache, rash, arthralgia, myalgia, morning stiffness, jaw claudication, visual disturbance, night sweats or fevers. Although there was a family history of colorectal cancer, there were no symptoms to suggest gastrointestinal bleeding or any change in bowel habit.

Clinical examination was unremarkable. In particular, the patient was apyrexial, weight 50 kg, height 158 cm with blood pressure 135/80 in both arms. The temporal arteries were not tender, nodular nor thickened, and there was no detectable reduction in pulsation. Musculoskeletal examination revealed no evidence of weakness, synovitis or neurological deficit. Abdominal examination revealed no organomegaly or masses and rectal examination was normal. Examination of the cardiovascular system revealed no peripheral stigmata of bacterial endocarditis and there were no murmurs audible. There were also no bruits in the carotid, brachial or subclavian areas, and fundoscopy was normal.

Initial blood results showed a normocytic anaemia (haemoglobin 108 g/L, mean corpuscular volume 83.4 fL), and normal reticulocyte count. Iron studies were consistent with anaemia of chronic disease. The ESR was 105 mm/hr and the C-reactive protein was 84.40 mg/L. Electrolytes, urea, creatinine, liver function tests and thyroid function tests were all normal. Serum electrophoresis revealed increased beta-globulins and alpha-globulins consistent with a chronic inflammatory disorder and no monoclonal bands. Autoimmune serology including rheumatoid factor (RF), antinuclear antibody (ANA), double stranded DNA antibody (ds DNA), extractable nuclear antigens (ENA), and antineutrophil cytoplasmic antibodies (ANCA) were all negative; angiotensin converting enzyme (ACE) level was normal. Septic workup including blood cultures and echocardiography revealed no evidence of infection or endocarditis. Chest X-ray was unremarkable. Due to continued unexplained anaemia, the patient was admitted and underwent gastroscopy, which showed mild reflux oesophagitis, and colonoscopy, which was normal. Furthermore, faecal occult blood testing and computerised tomography (CT) scanning of the abdomen revealed no evidence of malignancy.

The lack of explanation for her high ESR and anaemia prompted a biopsy of her right temporal artery that revealed histology consistent with giant cell arteritis (GCA) (*Figure 1, 2*). The patient was commenced on 50 mg of prednisone (1 mg/kg/day), a proton pump inhibitor, and prophylactic osteoporosis treatment with calcium, vitamin D and a bisphosphonate. Low dose aspirin was also commenced. The dose of prednisone was tapered a little over the next month as inflammatory markers decreased (ESR 25 mm/hr, CRP 2 mg/L) and the haemoglobin normalised (135 g/L).

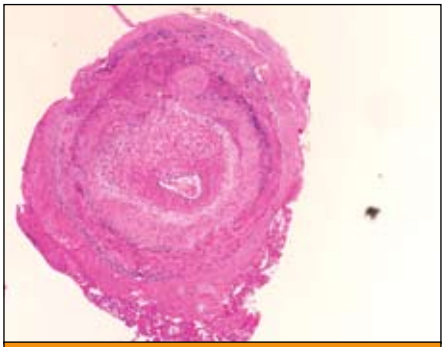

Figure 1. Right sided temporal artery (H&E stain) showing mild mixed inflammatory infiltrate with mixture of multinucleated giant cells, lymphocytes and plump histiocytes. Narrowed arterial lumen due to thickened myxo-oedematous change
Photo courtesy Dr Geoff Watson, Royal Prince Alfred Hospital, Pathology Department

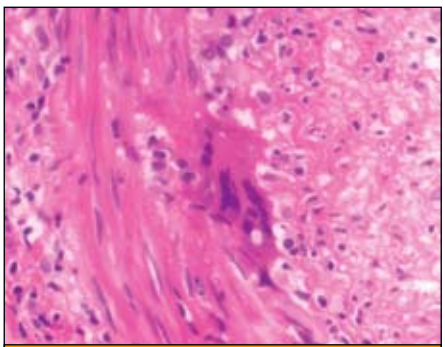

Figure 2. Enlarged view of a multinucleated giant cell
Photo courtesy Dr Geoff Watson, Royal Prince Alfred Hospital, Pathology Department

Discussion

Giant cell arteritis (GCA) is the most common vasculitis in western countries.[1] It almost exclusively develops in patients over 50 years of age, and is more common in women.[2] It is a chronic vasculitis of medium to large size vessels with classic symptoms being headache, jaw claudication, visual disturbance or symptoms of polymyalgia rheumatica. However, as in this case, some patients will have no classic symptoms. The ESR is usually significantly raised (>50 mm/hr), however, it has been reported that about 5% of patients with active GCA have a normal ESR[3]. This case highlights the need to consider GCA in a patient over 50 years of age with anaemia in the context of high inflammatory markers who is otherwise reasonably well.

The initial primary concern in this case was to exclude underlying malignancy given the family history, mild weight loss, anaemia, and high inflammatory markers. An ESR exceeding 100 mm/hr is significant in any age group, with a 90% predictive value for serious underlying disease[4] and should not be ignored. The differential diagnosis of a patient with significantly raised ESR is broad and summarised in *Table 2*.

Although the classification criteria formulated by the American College of Rheumatology (*Table 1*) has been used in clinical practice, many patients present with nonspecific symptoms that do not fulfil the set criteria.[5,6] Diagnosis is often overlooked and delayed in the absence of these so-called classic symptoms.[7] Twenty-five years ago, Strachan et al[8] proposed a clinical classification of GCA to improve the awareness of the diversity of this condition. Apart from the 'classic GCA', they described the concept of 'masked GCA'.This latter group was subdivided into the:

- anaemic group (patients with anaemia as the sole presenting feature)
- malignant or cachectic group (patients with wasting, weight loss and a 'tumour-like' presentation)
- febrile group (patients with pyrexia of unknown origin)
- aneurysmal group (patients with aortic regurgitation or ruptured aortic aneurysm), and
- occlusive group (patients who present with stroke, intermittent claudication or myocardial ischaemia).

Therefore maintenance of a high index of clinical suspicion is essential to institute prompt adequate treatment, especially in atypical cases.

Complications

One of the most devastating complications of GCA is visual loss – GCA is a sight threatening medical emergency and requires prompt recognition and treatment in order to avoid devastating ophthalmic consequences. The true incidence of ocular involvement in GCA (*Table 3*) is poorly defined, with varying reported ranges between 14 and 70%.[9,10] However, if visual loss occurs it is often irreversible. Amaurosis fugax is an important early visual symptom of GCA and signifies impending blindness. It can occur in as many as 31% of patients with GCA[11] and is commonly caused by transient ischaemia of the optic nerve head.

Treatment

The recognised drug to treat GCA is systemic corticosteroids which suppress the inflammatory response and minimise the ischaemic complications of the disease. Controversy remains on the optimal starting dose of systemic steroids, route of administration, and duration of therapy. A reasonable guideline is to start with a dose of 1 mg/kg/day of prednisone. Response is usually rapid with improvement in both symptoms and blood parameters. In patients with visual symptoms or life threatening vasculitis, intravenous methylprednisolone pulses may be more appropriate.[12] Although GCA should always be confirmed by a temporal artery biopsy,[13] treatment should not be delayed and instituted if there is any suspicion of GCA.

The use of steroid sparing agents such as methotrexate, azathioprine, cyclophosphamide and cyclosporin may be useful in reducing the side effects of steroids. However, due to a paucity of data there are currently no conclusive recommendations.[14,15] Individual treatment regimens are formulated on the basis of clinical presentation, severity of symptoms, patient

Table 1. The American College of Rheumatology criteria for diagnosis of GCA[6]

Three of the following criteria must to be met for patients to be classified as having the disease:

- Age at onset ≥50 years
- New onset of localised headache
- Temporal artery tenderness or decreased pulsation
- ESR ≥50 mm/hr (by the Westergren method)
- Positive temporal artery biopsy (showing vasculitis characterised by predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells)

Table 2. Differential diagnosis for patient with anaemia and ESR >100

- Infection – including mycobacterium tuberculosis
- Malignancy
- Connective tissue disease
- Systemic vasculitides
- Sarcoidosis
- Amyloidosis

Table 3. Ocular manifestations of GCA

- Eye pain
- Amaurosis fugax
- Diplopia (ocular motor ischemia)
- Irreversible visual loss (anterior ischaemic optic neuropathy, central retinal artery occlusion, ischaemic choroidopathy)
- Visual hallucinations

response to treatment, and the development of adverse side effects.

Several studies have also shown the presence of reactive thrombocytosis in GCA[10] that has led to the presumptive role of aspirin to prevent visual loss and other ischaemic lesions. Although there is some evidence that low dose aspirin can reduce cranial ischaemic symptoms,[16] further studies are required to validate this theory.

Summary of important points

- GCA should be considered in patients over 50 years of age with anaemia and raised inflammatory markers.
- The concept of 'masked GCA' is useful in picking up nonclassic presentations of GCA.
- An ESR >100 mm/hr is always clinically significant.
- Prednisone should be commenced at 1 mg/kg/day as soon as GCA is suspected.
- Do not delay treatment to obtain a temporal artery biopsy.

Conflict of interest: none declared.

References

1. Gonzalez-Gay MA, Garcia-Porrua C. Epidemiology of the vasculitides. Rheum Dis Clin North Am 2001;27:729–49.
2. Calvo-Romero JM. Giant cell arteritis. Postgrad Med J 2003;79:511–15.
3. Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population based study. Arthritis Rheum 2001;45:140–5.
4. Brigden M. The erythrocyte sedimentation rate. Still a helpful test when used judiciously. Postgrad Med 1998;103:257–62.
5. Nordborg E, Nordborg C. Giant cell arteritis: strategies in diagnosis and treatment. Curr Opin Rheumatol 2004;16:25–30.
6. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology. Criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
7. Desmet GD, Knockaert DC, Bobbaers HJ. Temporal arteritis: the silent presentation and delay in diagnosis. J Int Med 1990;227:237–40.
8. Strachan RW, How J, Bewsher PD. Masked giant cell arteritis. Lancet 1980;194–6.
9. Hayreh SS, Podhajsky PA, Zimmerman B: Ocular manifestations of giant cell arteritis. Am J Ophthalmol 1998;125:509–20.
10. Gonza´lez-Gay MA, Garcı´a-Porru´a C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore) 2000;79:283–92.
11. Hayreh SS, Zimmerman B. Management of giant cell arteritis. Our 27 year clinical study: new light on old controversies. Ophthalmologica 2003;217:239–59.
12. Chan CC, Paine M, O'Day J. Steroid management in giant cell arteritis. Br J Ophthalmol 2001;89:1061–4.
13. Hall S, Hunder GG. Is temporal artery biopsy prudent? Mayo Clin Proc 1984;59:793–6.
14. Hoffman GS. A multicentre, randomised, double blind, placebo controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309–18.
15. Jover JA, Hernandez-Garcia C. Combined treatment of giant cell arteritis with methotrexate and prednisone. A randomised, double blind, placebo controlled trial. Ann Intern Med 2001;134:106–14.
16. Nesher G, Berkun Y. Low dose aspirin and prevention of cranial ischaemic complications in giant cell arteritis. Arthritis Rheum 2004;50:1332–7.
17 Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990; 33:1122–8.

afp **CORRESPONDENCE** email: afp@racgp.org.au