Large vessel vasculitides

Caroline Gordon

What's new?

- New imaging techniques, particularly for giant cell arteritis
- New treatments, particularly for Takayasu's arteritis
- More information about the systems that can be affected by giant cell arteritis

Abstract

Giant cell arteritis (GCA) and Takayasu's arteritis are distinct diseases associated with granulomatous large vessel vasculitis. They present with constitutional symptoms such as fatigue, anorexia, weight loss and fever. In addition, there are specific symptoms related to inflammation and ischaemia in the territory of the affected vessels. In giant cell arteritis which usually occurs in people over age 50 the extracranial arteries are most often involved. In Takayasu's arteritis, which usually occurs in people under age 40, the aorta and its branches are the main sites affected. Ischaemia or aneurysm formation are responsible for the clinical features. Polymyalgia rheumatica (PMR) is a clinical syndrome that may precede GCA. As with GCA and Takayasu's arteritis there is a high acute phase response but there is no diagnostic test. In GCA and Takayasu's arteritis the diagnosis is confirmed by biopsy and angiography respectively. In PMR the classical limb girdle pain, stiffness and constitutional upset respond dramatically to low dose steroids. For GCA and Takayasu's arteritis, high dose steroids are required to prevent permanent damage, and cytotoxic agents may need to be considered.

Keywords arteritis; vasculitis; giant cell; Takayasu's; Polymyalgia rheumatica; angiography; imaging; steroids; cytotoxics biopsy; acute phase response; large vessel; vasculitides

The most important large vessel vasculitides are giant cell arteritis (GCA) and Takayasu's arteritis. These are similar but distinct idiopathic diseases characterized by constitutional symptoms with raised inflammatory markers in the blood and underlying granulomatous large vessel vasculitis. The two conditions are distinguished predominantly by the nature of the vessels involved and the resultant clinical presentation. Polymyalgia rheumatica (PMR) is a syndrome that may precede GCA. There is clinical and histological overlap between these two conditions, which can be considered opposite ends of a disease spectrum, but their management differs and thus they are discussed separately in this contribution.[1]

Pathology – both GCA and Takayasu's arteritis are associated with panarteritis of large and medium vessels involving lymphocytes, macrophages and multinucleate giant cells. The inflammation starts with infiltration of the adventitia and progresses inwards, involving the media and resulting in extensive fragmentation of the internal elastic lamina. Intimal proliferation is found but fibrinoid necrosis is uncommon. Healing with replacement of elastic tissue by fibrosis, obliteration of the vasa vasorum and irregular thickening of the intima occurs particularly in Takayasu's arteritis. This can result in stenosis, dilatation and/or aneurysm formation. Recanalization of occluded vessels is common.

Differential diagnosis – distinguishing GCA from simple PMR can be difficult because the conditions overlap and can coexist.[2,3] Focal symptoms and signs suggesting vessel ischaemia in association with nonspecific PMR features and a high acute phase response strongly suggest GCA and the need for high-dose corticosteroids to prevent irreversible ischaemic damage. Distinguishing GCA from Takayasu's arteritis is helped by differences in age group affected and expression of disease. GCA is usually more corticosteroid responsive and has a less protracted course than Takayasu's arteritis. Other differential diagnoses are listed in Table 1.

Polymyalgia rheumatica

PMR most commonly develops in 60–70-year-olds, but it may present from the age of 45 years onwards. The prevalence is about 1/2000 in the over-50s and more than 1/100 in the elderly. The incidence is just over 8/10,000 person years in the UK.[4] It is twice as common in women as in men. GCA has been found in

Differential diagnosis of polymyalgia rheumatica, giant cell arteritis and Takayasu's arteritis

Differential diagnosis	Distinguishing features
• Other vasculitis (e.g. polyarteritis nodosa, Wegener's granulomatosis)	Vessel involvement (size, site) and histology
• Malignancy, including myeloproliferative disorders	Prominent weight loss and poor corticosteroid response
• Infection (e.g. endocarditis, tuberculosis)	Prominent fever and positive cultures
• Polymyositis	Raised creatine kinase and abnormal electromyography
• Inflammatory arthritis (e.g. rheumatoid arthritis)	Prominent (symmetrical) synovitis and abnormal radiography
• Arteriosclerosis	Lack of acute phase response

Table 1

Caroline Gordon *MA MD FRCP is Reader and Consultant in Rheumatology at the University of Birmingham, Sandwell and West Birmingham Hospitals NHS Trust and the University Hospital Birmingham Foundation NHS Trust, Birmingham, UK.* *Competing interests: none declared.*

about 15% of cases. No underlying cause has been identified for the remainder.

Clinical features

PMR is a clinical syndrome characterized by symmetrical pain and stiffness in the shoulder and pelvic girdles associated with constitutional upset that responds dramatically to corticosteroid therapy.

Musculoskeletal pain is diffuse and there may be associated muscle tenderness, though this is less marked than in inflammatory myositis. Early-morning stiffness may be so profound that the patient cannot get out of bed, but there is no true muscle weakness in the initial stages. It may be difficult to assess muscle strength, however, because of the pain in the muscles and periarticular structures such as tendons, bursae and joint capsules. If muscle atrophy develops, shoulder movements may be limited in chronic cases. Synovitis of the peripheral joints is rare, usually mild and transient. More severe synovitis usually indicates an alternative diagnosis such as rheumatoid arthritis, that may also present with marked systemic upset.

Constitutional symptoms are common and include profound fatigue, anorexia, weight loss and low-grade fever. Depression may develop, usually as a reaction to the severe pain, stiffness and malaise that limit physical activities. It is important to exclude infection and malignancy (which may also present with such nonspecific symptoms), particularly in patients who do not respond to corticosteroids.

Investigations

Confirmation of the diagnosis is not possible because PMR is a clinical syndrome and there is no diagnostic test. The most typical findings are raised ESR, C-reactive protein (CRP) and viscosity. Creatine kinase and other muscle enzymes are normal, as are electromyography and muscle biopsies, in contrast with inflammatory myositis. Raised liver enzymes (specifically alkaline phosphatase and γ-glutamyltransferase) reflect the acute phase response.

Assessment of disease activity involves measurement of one of the acute phase reactants (usually ESR, CRP or plasma viscosity). CRP is occasionally elevated in the presence of a normal ESR, and usually changes more quickly with disease activity and therapy than the other markers of the acute phase response. Mild hypochromic or normochromic, normocytic anaemia is common. This anaemia and abnormal liver function tests resolve as ESR/CRP settles with corticosteroid therapy.

Management

PMR responds poorly to non-steroidal anti-inflammatory drugs but very quickly to oral corticosteroids such as prednisolone, 15–20 mg daily. Higher doses are not required unless there are features of GCA (see below). Treatment is usually required for 2–3 years but may be necessary for longer.

The prednisolone dose should be reduced in small decrements (1–5 mg/day) every 2–4 weeks such that the symptoms remain under control and CRP/ESR is within the normal range. It is unwise to reduce the corticosteroid dose in the presence of an elevated (particularly an increasing) acute phase reaction, because this usually heralds an exacerbation of disease. Prednisolone can usually be reduced to 10 mg daily by 3 months and should be maintained at this dose for a further 3 months. The dose should then be reduced by 1 mg/day each month to the lowest dose that prevents recurrence of symptoms of the disease or an increase in CRP/ESR. It is difficult to predict this dose because of considerable variation between patients, but about 0.1 mg/kg/day is often the lowest tolerated dose in the first 2 years after diagnosis. Thereafter, it may be possible to gradually withdraw cortico-steroids completely at a rate of 1 mg/day each month. Some patients require low doses (e.g. prednisolone, 2–5 mg/day) for several more years. Addition of corticosteroid-sparing agents such as azathioprine, 1–2 mg/kg/day, or methotrexate, 7.5–15 mg once per week, may facilitate corticosteroid reduction but seldom enables complete discontinuation in patients with persistent disease.

Giant cell arteritis

GCA is uncommon before the age of 50 years. The worldwide incidence is about 1/50,000/year and the disease is about four times more common in women than in men.

Clinical features

The symptoms and signs of GCA result from the combination of inflammation and ischaemia in the territory of the affected vessels. The extracranial arteries, which have internal and external elastic laminae, are typically involved; intracranial vessels are seldom involved.[2]

Unilateral throbbing headache is the most common feature. It usually occurs in the temporal area (temporal arteritis), but is sometimes occipital (vertebrobasilar arteritis) or diffuse. The headache usually starts suddenly and can be constant or intermittent. The pain is so severe that it may disturb sleep. It is often associated with scalp tenderness overlying the affected arteries, which may be thickened and nodular with reduced or absent pulsation.

Facial pain and claudication of the jaw muscles may occur on chewing or prolonged speaking.

Visual symptoms (Figure 1) are caused by occlusion of orbital or ocular arteries and present with partial or complete visual loss in one or both eyes or, less commonly, diplopia. The visual loss is sudden, painless and usually permanent. Transient monocular visual loss (amaurosis fugax) may occur initially with changes in posture and may precede complete visual loss.

Other neurological symptoms include vertigo, hearing loss and ataxia caused by involvement of the vertebrobasilar system. Less commonly, vasculitis in the vasa nervorum causes mononeuropathy or mononeuritis multiplex.

Involvement of large vessels such as the aorta and its branches, especially the subclavian and axillaryarteries, occurs in over 25% of patients.[5] Aortic involvement presents in a manner similar to Takayasu's arteritis, with aortic arch syndrome, absent pulses and arm claudication. Thoracic or abdominal aortic aneurysms may be found and can present as life-threatening acute aortic dissection early or late in the disease. Hypertension and cardiac disease are rare.

Nonspecific symptoms of inflammatory disease (e.g. fever, malaise, weight loss) are common. Other symptoms of PMR such as limb girdle pain and early-morning stiffness (see above) occur in about 50% of patients. PMR may precede the more

