Large vessel vasculitides

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Abstract

Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are the two primary large vessel vasculitides. They are idiopathic systemic inflammatory conditions characterized by granulomatous inflammation of large and medium-sized arteries. TA affects a younger age group, predominantly involves the aorta and its main branches, and tends to be a two-phase disease with inflammatory and occlusive stages. In contrast, GCA affects an older age group and classically involves the temporal and other cranial arteries, although it can affect the aorta and its primary branches (large vessel GCA). Constitutional symptoms are a feature of both diseases, and vascular symptoms depend on the pattern of arterial involvement. Temporal artery biopsy and angiography remain the gold standards for diagnosis of GCA and TA, respectively. New imaging modalities are challenging this practice and have the potential to allow early diagnosis and monitoring of disease activity. Treatment has seen major advances over the last decade. With the advent of vigorous immunosuppressive therapy, new biological therapies and intervention with percutaneous transluminal angioplasty supported by stenting, the prognosis of patients with large vessel vasculitis seems likely to improve.

Keywords Angiography; giant cell arteritis; immunosuppression; large vessel vasculitis; MRCP; Takayasu's arteritis

Key points

- The development of visual symptoms in giant cell arteritis (GCA) can signify impending visual loss and is a medical emergency
- GCA and Takayasu's arteritis (TA) can present with constitutional symptoms alone without any localizing symptoms; both diseases should therefore be considered in the differential diagnosis of pyrexia of unknown origin
- With early appropriate imaging, TA can be diagnosed in the pre-stenotic phase
- There is an increasing role for ultrasound in the assessment of patients with suspected GCA. While temporal artery biopsy can remain positive for up to 4 weeks after commencing corticosteroids, ultrasound is likely to be most useful in the first 3 days of corticosteroid therapy
- Biological therapy has an emerging role in the management of refractory/relapsing disease

Introduction

Large vessel vasculitis is characterized by inflammation of the aorta and its major branches. Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are the two primary large vessel vasculitides. Other rheumatic causes of aortitis include seronegative spondyloarthropathies, Behçet's disease and IgG4 related disease.

GCA and TA are systemic inflammatory conditions that share similar histological abnormalities — granulomatous inflammation of large and medium-sized vessels — but differ in age of onset and pattern of vascular structures preferentially involved. GCA (also known as temporal or cranial arteritis) has a predilection for the extracranial branches of the carotid artery, with the temporal arteries frequently affected. TA (also known as pulseless disease or aortic arch disease) predominantly affects the aorta and its main branches, leading to segmental stenoses, occlusion, dilatation and aneurysm formation; coronary and pulmonary arteries can also be affected. GCA is associated with polymyalgia rheumatica (PMR) in 20–50% of cases, and around 15% of PMR patients develop GCA.

Epidemiology

GCA is the most common of the vasculitides. It occurs primarily in people >50 years of age, and the incidence increases with age. It is more common in northern latitudes. The incidence in Europe is reported to be 7–29 per 100,000 in persons >50 years old. It is twice as common in women as men. By contrast, the mean age of onset of TA is 30 years, and it is more common in people of Asian descent. Worldwide and UK annual incidence are estimated at 2.6 and 0.8 cases per million population, respectively. Approximately 80% of patients are women.

The aetiology of GCA and TA is unknown. Both genetic and environmental factors are likely to play a role. Siblings of patients with GCA have a 10-fold increased risk of acquiring the disease. An association with the major histocompatibility complex has been reported for both diseases. No causative infectious agent or toxin has been identified.

Pathogenesis

The pathogenesis of GCA and TA is poorly understood. Cell-mediated autoimmunity plays an important role. The histological appearance is of a focal pan-arteritis. The transmural inflammatory infiltrate is largely composed of lymphocytes, macrophages and multinucleated giant cells, which may be organized into granulomas.

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The cellular infiltrate in TA tends to localize to the adventitia and outer parts of the media. Immune cell access can be via the adventitia and the vasa vasorum vessels. Destruction of the elastic lamina and muscular media can lead to aneurysmal dilation. Ultimately, intimal proliferation and dense scarring can compromise the vascular lumen, resulting in arterial stenosis.

In GCA, the integral role played by vessel wall dendritic cells (DCs) is becoming more evident. DCs are present at the adventitia–media border and normally act as immune sentinels. Toll-like receptors (TLRs) are present on DCs, and their interaction with appropriate TLR ligands such as lipopolysaccharide can trigger DC activation. This can lead to a switch in the functional status of DCs, making them very effective at recruiting, activating and retaining the T cells in the vessel wall, with consequent damage. T helper 1 and 17 CD4+ T cell subsets are especially abundant in the resulting vascular infiltrate. The centre of tissue damage in GCA lies at the internal elastic lamina. Concentric intimal thickening, partly resulting from oedema, narrows the vessel, and luminal thrombosis can occur.

Clinical features of giant cell arteritis

The symptoms and signs of GCA can be classified into subgroups (see below). Onset is usually insidious, the condition developing gradually over several weeks. Diagnostic criteria for GCA were issued by the American College of Rheumatology (ACR) in 1990 (Table 1). The sensitivity and specificity of these criteria have been questioned, especially when the diagnosis is made on clinical criteria without performing temporal artery biopsy (TAB).

Cranial vessel involvement: headache and scalp pain are the most common symptoms, occurring in 50–70% of patients. Persistent temporal or, less commonly, occipital headache is typical. Patients can have difficulty combing their hair, or have discomfort lying on a pillow. Rarely, scalp necrosis can occur. Jaw and tongue claudication are highly specific symptoms of GCA. Tongue gangrene has been reported. Examination may reveal prominent, tender, pulseless temporal arteries, although these vessels can feel normal.

Visual loss is the most common serious consequence, occurring in up to 20% of patients. It is often preceded by premonitory visual symptoms, such as blurring, amaurosis fugax, hemianopia and diplopia. Visual symptoms can occur in isolation, making diagnosis challenging. The presence of visual symptoms should be considered a medical emergency as prompt treatment can prevent the development of irreversible visual loss. If the condition is left untreated, the second eye can become affected within days. Ocular manifestations vary according to the pattern of arterial branch involvement. Anterior ischaemic optic neuropathy is the most common lesion resulting from involvement of the posterior ciliary arteries, branches of the ophthalmic artery that supply the optic nerve head. Retinal changes are uncommon because occlusion of the central retinal artery or its branches is rare.

Neurological complications are relatively rare. The internal carotid and vertebral arteries can be involved, leading to strokes, seizures, vertigo, cerebral dysfunction and depression (the latter either disease-related or a response to the illness). Involvement of the intracranial arteries is unusual.

Large vessel involvement: large vessel GCA usually involves the aorta and its main branches and is often subclinical, as is apparent from fluorodeoxyglucose positron emission tomography (^{18}FDG PET). It is clinically detectable in only 10–15% of patients with GCA. Clinical findings include arm claudication, absent or decreased pulses and bruits over the involved arteries. Involvement of the coronary, mesenteric and other visceral arteries is rare. Renal vasculitis is unusual.

Constitutional symptoms: many patients experience lethargy, malaise, low-grade fever and weight loss. A small subset of patients present with fever and systemic upset without any localizing symptoms.

Musculoskeletal symptoms: around half of all patients exhibit symptoms of PMR with pain and stiffness affecting the shoulder and pelvic girdles. A small subgroup of patients have a peripheral non-erosive arthritis predominantly affecting the knees, wrists and metacarpophalangeal joints.

American College of Rheumatology classification criteria for giant cell arteritis

- Age at disease onset ≥50 years
- New-onset localized headache
- Temporal artery tenderness or decreased pulsation
- ESR ≥50 mm/1st hour
- Abnormal artery biopsy characterized by mononuclear infiltration or granulomatous inflammation

The presence of three or more criteria yields a diagnostic sensitivity of 93.5% and specificity of 91.2%, according to: 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.
ESR, erythrocyte sedimentation rate.

Table 1

Clinical features of Takayasu's arteritis

TA typically progresses through an inflammatory phase, in which systemic symptoms predominate, to a phase of vascular occlusion, when ischaemic symptoms develop. Approximately 20% of patients are asymptomatic. A delay in diagnosis is typical in early pre-stenotic disease because of the lack of classical signs, and physicians should have a high degree of suspicion in young patients with undefined systemic inflammatory symptoms. Table 2 outlines the ACR classification criteria for TA. These favour diagnosis of established stenotic disease and are not helpful in detecting early pre-stenotic TA.

Constitutional symptoms: fatigue, malaise, weight loss, arthralgia, myalgia and low-grade fever are all common in the early phase of TA.

Vascular features: limb claudication commonly develops with disease progression. Absent or diminished pulses in limb vessels are the hallmark of TA. A systolic blood pressure difference (>10 mmHg) between the arms is a discriminatory finding. Unilateral tenderness of the carotid artery close to the bifurcation (carotidynia) should be sought. Hypertension is present in most