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treatment of inflammatory myopathies. Nat Rev Rheumatol, 7, 297–306. 19.11.6 Large vessel vasculitis Raashid Luqmani and Cristina Ponte ESSENTIALS Large vessel vasculitis describes a group of primary vasculitides pre- dominantly affecting the aorta and its major branches: its two main types are giant cell arteritis and Takayasu arteritis, but overlap con- ditions are increasing recognized, including isolated aortitis in older patients. Giant cell arteritis Characterized by granulomatous inflammation that penetrates all layers of the wall of medium and (often) large muscular arteries, in particular the superficial temporal artery. Almost exclusively affects patients aged above 50 years, typically white Caucasians. Clinical features—the usual presentation is with unaccustomed headache, often accompanied by systemic symptoms and in associ- ation with a significant acute phase response. Visual loss is a feared complication. The temporal artery pulses can be reduced or absent, and there may be local tenderness. Around 40–50% of patients have symptoms typical of polymyalgia rheumatica. Investigation—Patients should be seen in a rapid access service where a temporal artery ultrasound or biopsy should be performed as soon as the diagnosis is suspected. Management—prednisolone at an initial dose of 40–60 mg/ day, or pulsed intravenous methylprednisolone for patients with visual symptoms. Steroid dose is slowly reduced

after remission is achieved, typically over two to three years. Tocilizumab has recently proven to be an effective steroid-sparing agent. Takayasu arteritis A chronic granulomatous vasculitis characterized by stenosis, occlu- sion, and aneurysm of large elastic arteries, mainly the aorta and its branches, which particularly affects young women, predominantly in Asian, Middle Eastern, and South American countries. Clinical presentation—the acute stage features nonspecific systemic symptoms. In the chronic stage symptoms depend on the anatom- ical location of the vascular lesions, with typical complaints relating to ischaemic claudication of the limbs and pain in large arteries. The commonest physical findings are weak or absent peripheral pulses and/or bruits, or asymmetrical systolic blood pressure measure- ments in the arms or legs. Diagnosis—most patients are diagnosed long after the disease has become established, usually based on angiograms obtained with magnetic resonance or computed tomography angiography. Treatment—is with standard immunosuppressive agents (typically methotrexate) combined with prednisolone. In severe disease there is a role for chemotherapy with cyclophosphamide. Inhibition of interleukin-6 is a promising new treatment option with less toxicity. Surgical bypass graft procedures may be required if the disease is not well controlled. Introduction Large vessel vasculitis is a term used to describe a group of pri- mary vasculitides predominantly affecting the aorta and its major branches. The two major subtypes of large vessel vasculitis are giant cell arteritis and Takayasu arteritis, which have distinctive fea- tures. Giant cell arteritis occurs predominantly in white European women aged above 50 years while Takayasu arteritis affects women below 40 years from the Middle East and Asia. However, there are many similarities between giant cell arteritis and Takayasu arter- itis, particularly in pathogenic mechanisms, histopathology, and clinical manifestations related to large vessel involvement. It re- mains unclear whether giant cell arteritis and Takayasu arteritis are distinct entities or represent different phenotypes of the same disease. The spectrum of large vessel vasculitis encompasses other rare conditions such as isolated aortitis and periaortitis (with or without associated IgG4-related disease), aortitis of Cogan’s syndrome, re- lapsing polychondritis and Behçet´s disease with large vessel in- volvement. Moreover, giant cell arteritis is often associated with polymyalgia rheumatica (PMR), an immune-mediated inflamma- tory condition characterized by shoulder and/or hip girdle pain and morning stiffness, which may also be also considered to be a clinical subtype of large vessel vasculitis. Giant cell arteritis Epidemiology Giant cell arteritis occurs almost exclusively in patients aged over 50 years at the time of diagnosis. It increases with age and peaks in those aged between 70 and 79. Females are affected two to three times more often than males. It occurs predominantly in northern latitudes, mainly affecting white Caucasians; it is very rare in black and Asian races. The highest annual incidence rates have been re- ported in northern Europe and northern United States (>18/100 000 in individuals older than 50 years). Aetiology The aetiology of giant cell arteritis remains unknown, but genetic susceptibility and environmental risks factors play a role in the de- velopment of the disease.

19.11.6 Large vessel vasculitis 4547 The HLA-DRB1*04 allele, expressed in 60% of giant cell arter- itis patients, and polymorphisms of several genes, such as the ones encoding the intercellular adhesion molecule-1 (ICAM-1) and the vascular endothelial growth factor (VEGF), have been associ- ated with increased susceptibility to giant cell arteritis or severity of manifestations. Cyclic patterns and fluctuations in the incidence of giant cell ar- teritis associated with epidemics of Mycoplasma pneumonia, parvo- virus B19 and Chlamydia pneumoniae have been described, but the significance of these observations is unclear. In addition, histo- logical examination of temporal artery biopsy specimens to detect viral DNA of parvovirus B19 or herpesvirus have been negative

or inconsistent. Histopathology In giant cell arteritis, the inflammation is most commonly seen in medium size arteries originating from the aortic arch, particularly in temporal, vertebral, ophthalmic, and posterior ciliary arteries. It typically affects the arteries focally and segmentally, leading to so- called ‘skip lesions’, where areas of vasculitic lesions juxtapose areas of normal artery. Histologically, it is characterized by transmural infiltration of mononuclear cells (T cells and macrophages) with fragmentation of the internal elastic lamina. Eosinophils may also be seen, but poly- morphonuclear leukocytes are rare. Giant cells are present in over half the cases, typically at the intima–media junction (Fig. 19.11.6.1). The endothelium is sometimes hyperplastic and thrombosis may be present in sites of active inflammation at the vessel lumen. Over time, the elastic smooth muscle layer of the media is replaced by noncontractile fibrous tissue. In some cases, inflammation is confined to the vasa vasorum or/and to the peri-adventitial small vessels. Compared to pa- tients with more widespread inflammatory change, patients with isolated peri-advential inflammation have less constitutional and cranial symptoms, although the frequency of visual manifest- ations is the same. Patients with isolated vasa vasorum inflam- mation have similar clinical features to patients with transmural inflammation. Pathogenesis The earliest inciting event in the pathogenesis of giant cell arteritis is likely to be activation of resident dendritic cells within the adventitia by Toll-like receptors in response to an unknown stimulus or stimuli. Activated dendritic cells produce proinflammatory cytokines, such as interleukin-18 (IL-18) and IL-6, which recruit and locally activate T cells, particularly T helper subsets 1 and 17 (Th1 and Th17). Th1 cells secrete interferon-γ (IFN-γ) and IL-2. IFN-γ activates macrophages in the adventitia (which secrete IL-1, IL-6 and TGFβ) and in the intima–media junction to form giant cells and to produce matrix metalloproteinases, leading to arterial injury. Repair mech- anisms are activated with the secretion of platelet-derived growth factor (PDGF), which stimulates intimal proliferation, and VEGF, which stimulates neoangiogenesis. The combination of these de- structive and repair mechanisms leads to internal elastic lamina degradation and luminal narrowing or occlusion, resulting in symp- toms of ischaemia. IFN-γ production is relatively steroid resistant in giant cell arteritis. Th17 cells produce IL-17, which appears relevant in early disease, but its production is rapidly suppressed by gluco- corticoid treatment. Clinical manifestations The onset of giant cell arteritis is usually gradual, although in some cases it may start suddenly. Most patients present with constitutional symptoms, such as malaise, fatigue, anorexia, and weight loss. Fever can also be present, usually at low grade (between 37ºC and 38ºC). Table 19.11.6.1 summarizes the published frequencies for the most
Fig. 19.11.6.1 Histopathological features of giant cell arteritis. Cross-sectional view (H&E staining) of a temporal artery in a patient with giant cell arteritis, showing a lymphocytic infiltrate (green arrows), multinucleate giant cells (yellow arrows), intimal hyperplasia and lumen narrowing (red arrow). Image provided courtesy of the TABUL study group.

section 19 Rheumatological disorders 4548 common clinical manifestations in giant cell arteritis, highlighting the differences between patients with more prominent inflamma- tion of the cranial vasculature and of the extracranial arteries. Cranial manifestations The most common manifestations of giant cell arteritis relate to its predilection for the cranial branches of the external carotid artery, particularly the temporal artery (Table 19.11.6.2). New onset of head pain (rather than headache) is the most common symptom and it is typically felt over the temporal regions, although generalized or occipital pain may also occur. The temporal arteries may be tender on palpation, thickened or swollen, and pulses may be diminished or absent. Scalp tenderness may be present, which is usually noticed when patients touch, comb, or brush their hair. Rarely, scalp necrosis occurs due to occlusion of the branches of the scalp arteries. Jaw claudication is the most

specific symptom for giant cell ar- teritis, but it is not pathognomonic (amyloidosis or atherosclerosis can also cause this symptom). Inflammation of the facial arteries re- sults in ischaemia of the masseter muscles, which leads to pain when chewing or talking (relieved by rest). If the lingual artery is involved, tongue claudication may occur, although this is a very rare manifest- ation of giant cell arteritis. Ischaemia of the ophthalmic artery and its branches, which supply the optic nerve and eye, is the main cause of the most severe ocular manifestations seen in giant cell arteritis. The most common symptoms are blindness, blurred vision, and diplopia. Visual loss may be partial or complete, in one or both eyes, and it is generally irreversible and pain free. It is mainly due to anterior ischaemic optic neuropathy, caused by occlusion of the posterior ciliary arteries, and frequently preceded by amaurosis fugax (transient visual loss). In the acute phase of anterior ischaemic optic neuropathy fundoscopic examination typically shows a pale optic disc oedema. Less com- monly, visual loss may occur due to posterior ischaemic optic neur- opathy, arterial occlusion of the central retinal artery or cilioretinal vessels, or occipital cortex infarction in the setting of a stroke. Arteritis of the vertebral and basilar arteries can cause transient ischaemic attacks and stroke in up to 7% of patients with giant cell arteritis. Other less common features of cranial giant cell arteritis include audio vestibular dysfunction, dysphagia, cough, sore throat, facial pain, but these rarely occur in isolation. Extracranial manifestations Extracranial involvement in giant cell arteritis, or large vessel giant cell arteritis, has been described in 45–83% of cases, varying ac- cording to the imaging modality used. Patients with large vessel giant cell arteritis may present with claudication, heart murmurs, and arterial bruits or decreased/absent pulses. Upper limbs are more frequently affected than lower limbs, and the thoracic part of the aorta is more commonly involved than the abdominal part. The risk of aortic aneurysms is increased when compared to the gen- eral population (twofold increased risk in the United Kingdom). However, aortic aneurysms are more likely to occur late in the dis- ease course (around 3–4 years after the initial symptoms of giant cell arteritis). Although controversial, both large vessel giant cell ar- teritis and Takayasu arteritis have similar distribution and type of aortic lesions when assessed by magnetic resonance angiography (MRA) (97% stenoses or occlusions, and 3% aneurysms). Giant cell arteritis and polymyalgia rheumatica Polymyalgia rheumatica symptoms occur in about 40–50% of pa- tients with giant cell arteritis during the disease course. They con- sist of aching and/or morning stiffness of the shoulder girdle and/ or hips, typically symmetrical, and accompanied by elevated inflam- matory markers and pathologic ultrasound findings (subdeltoid bursitis, biceps tenosynovitis, glenohumeral synovitis, trochanteric bursitis, and/or hip synovitis). In patients with isolated polymyalgia rheumatica, around 10% will subsequently develop giant cell arter- itis. See Chapter 19.11.11 for further discussion. Table 19.11.6.1 Frequencies for the most common features of giant cell arteritis Clinical manifestations of giant cell arteritis (%) Constitutional symptomsa Weight loss 43% Fever 42% Fatigue 39% Myalgia 39% Arthralgia 30% Cranial manifestations Headache 70–90% Absent /diminished pulses or tenderness of the temporal arteries 30–60% Jaw claudication 40–50% Scalp tenderness 33–50% Visual disturbances (transient or permanent) 20–50% Caused by b: – Anterior ischaemic optic neuropathy 91% – Central retinal artery occlusion 11% – Cilioretinal artery occlusion 10% – Posterior ischaemic optic neuropathy 4% Audio vestibular dysfunction (hearing loss, tinnitus, and vertigo) 5–25% Respiratory symptoms (cough, sore throat, and hoarseness) c.9% Stroke 3–7% Scalp necrosis <5% Tongue necrosis <5% Extracranial manifestations Polymyalgia rheumatica 40–50% Peripheral neuropathy c.14% Large vessel stenosesc 13% Thoracic aorta aneurysm and/or dissectionc 11% Abdominal aorta aneurysm and/or dissectionc 10% Laboratory results in patients with giant cell arteritis (%) Inflammatory markers Elevated ESR and/or elevated CRP 90–95% ESR >50 mm/h 85–90% ESR ≥100 mm/h

30–60% ESR of 40–50 mm/h 10% ESR <40 mm/h 5% Others Anaemia 35–65% Thrombocytosis 30–60% High alkaline phosphatase 30–60% CRP: C-reactive protein, ESR: Elevated erythrocyte sedimentation rate. a Smetana et al. 2002; b Hayreh et al. 2002; c Nuenninghoff et al. 2003.

19.11.6 Large vessel vasculitis 4549 Diagnostic investigations Laboratory tests High inflammatory markers are present at the onset of the disease in most patients with giant cell arteritis. The combination of normal values for both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) makes the diagnosis very unlikely. However, particu- larly in cases of localized disease without constitutional symptoms, ESR and CRP values may be normal. Normochromic-normocytic anaemia, thrombocytosis, high fibrinogen levels, and increased liver enzymes, particularly alkaline phosphatase, have also been described in patients with giant cell arteritis. Temporal artery biopsy For many years temporal artery biopsy has been considered the ‘gold-standard’ test for diagnosing giant cell arteritis but in- creasingly, imaging is replacing it in many hospitals because of its relatively poor sensitivity. It should be performed as soon as possible after the treatment is initiated, preferably within the first 7–10 days. The length of the temporal artery biopsy required is unclear. Segments of at least 0.5–1 cm (post-formalin fixation) are considered acceptable for accurate pathological review. Despite the high specificity of temporal artery biopsy (around 95–100%), it has low sensitivity for diagnosis (about 50%) due to poor sam- pling, delay in organizing the procedure, and the segmented na- ture of the pathological findings. Ultrasound guided biopsy has failed to show improvement in the sensitivity of temporal artery biopsy for diagnosing giant cell arteritis. Temporal artery biopsy should be performed from the most symptomatic site. Bilateral temporal artery biopsy (adding the contralateral temporal artery) may increase diagnostic yield by up to 9–13%, but is not routinely recommended. Imaging Ultrasound has proven to be effective in diagnosing giant cell arter- itis based on the presence of a dark ‘halo’ around the temporal artery wall (Fig. 19.11.6.2). In unequivocal cases it has been suggested that a positive ultrasound may replace histology and this increasing use of imaging as a diagnostic tool is likely to replace biopsies in many hospitals in future. Large vessel giant cell arteritis may be diagnosed by dif- ferent imaging techniques. An ultrasound showing homogeneous hypoechoic wall thickness more than 1.5 mm in the large vessels (e.g. axillary arteries) is compatible with giant cell arteritis; however, this imaging modality cannot assess all deep large vessels, such as thoracic aorta (frequently involved in giant cell arteritis). Magnetic resonance imaging (MRI) and angiography (MRA) are valuable for identifying early signs of vasculitis, particularly oedema and wall thickness, be- fore arterial complications occur; mural contrast enhancement as a result of vascular remodelling can lead to false-positive findings. 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) cannot reliably delineate the vessel wall, but may be more sensitive than MRI in detecting early vascular inflammation. The combination of FDG PET with computed tomography (CT) (FDG PET-CT) improves the identification of anatomic areas and the dif- ferential diagnosis with atherosclerosis. However, it is an expen- sive test with a high radiation dose and still lacks a standardized definition of vascular inflammation based on the intensity of FDG uptake. CT may be useful in assessing large vessel involvement, par- ticularly in deep vessels, but it has a low sensitivity to detect early vessel wall alterations. Diagnosis and classification criteria There are no diagnostic criteria for giant cell arteritis. Classification cri- teria were developed by the American College of Rheumatology (ACR) in 1990 (Table 19.11.6.2). However, they lack inclusion of imaging as a

Fig. 19.11.6.2 Ultrasound of the parietal branch of the right temporal artery (left) and of the left axillary artery (right) in longitudinal view showing a black hypoechoic rim or ‘halo’ (yellow arrows).
Table 19.11.6.2 ACR 1990 classification criteria for giant cell arteritis 1. Age at onset >50 years 2. New onset headache 3. Temporal artery abnormality (tenderness to palpation or decreased pulsation) 4. Increased ESR (>50 mm) 5. Abnormal artery biopsy (showing vasculitis characterized by a predominance of mononuclear infiltration or granulomatous inflammation) The patient is classified as having giant cell arteritis if at least three of these five criteria are present (sensitivity of 93.5% and specificity of 91.2%). Adapted from Hunder GG et al. (1990) The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum, 33(8): 1122–8.

section 19 Rheumatological disorders 4550 criterion, and are not suitable for diagnosis, given they were designed to differentiate giant cell arteritis from other vasculitides, but were not validated to distinguish vasculitic from nonvasculitic diseases. A major multicentre observational study in currently underway to de- velop diagnostic criteria and revise classification criteria for systemic vasculitis in accordance with standards defined by the ACR and the European League Against Rheumatism (EULAR)—The Diagnostic and Classification Criteria for Vasculitis (DCVAS) study. Management Treatment Glucocorticoids Glucocorticoids are the mainstay of treatment in giant cell arter- itis and they should be prescribed immediately after the diagnostic suspicion of giant cell arteritis. In most cases they are able to pro- vide complete symptomatic relief within 24–48 hours. The optimal glucocorticoid dosing regimen is still unclear. Most guidelines recommend an initial dose between 40 mg and 60 mg/day for in- duction of remission and pulsed intravenous methylprednisolone for patients presenting with visual symptoms. Daily dosing has shown to be more effective than alternate day dosing, but single or divided daily doses have comparable results. Glucocorticoid re- duction should occur after resolution of clinical symptoms and la- boratory abnormalities, typically at around 4 weeks of treatment. The tapering regimen is variable and dependent on disease activity, glucocorticoid toxicity, and patient compliance. The British Society for Rheumatology (BSR) has proposed a tapering scheme of 10 mg/ day reduction every 2 weeks down to 20 mg, followed by 2.5 mg/day less every 2–4 weeks down to 10 mg/day and then reduced by 1 mg/ day every 1–2 months until discontinuation. Minor flares occur in about half the patients, usually responding to an increase in prednisolone of 5–10 mg/day. A major flare with visual or neurological symptoms usually results in escalation of glucocorticoid to the original induction dose, together with con- sideration of introducing other immunosuppressive therapy (see ‘Other immunosuppressive therapy’, next). The total duration of glucocorticoid treatment varies. The average time is two to three years, but it may exceed five years, particularly in patients with recurrent disease or in those who develop sec- ondary adrenal insufficiency. Moreover, the burden of high-dose glucocorticoids is considerable, reported in up to 86% of patients at 10-year follow-up, particularly due to posterior subcapsular cataract (41%), bone fractures (38%), infections (31%), hypertension (22%), diabetes mellitus (9%) and gastrointestinal bleeding (4%). Other immunosuppressive therapy Other immunosuppressive treatments have been tried for giant cell arteritis, with the aim of allowing a safer and faster reduction of glucocorticoids. However, results of studies have been conflicting and generally disappointing. A modest reduction in disease relapse and glucocorticoid exposure has been reported with methotrexate. Azathioprine can be used, but evidence supporting its steroid-sparing effect is limited. In small case series, leflunomide has shown to be effective as a steroid-sparing agent in patients with difficult-to-treat giant cell arteritis, but prospective randomized placebo-controlled trials are still necessary to support these findings.

Retrospective studies have demonstrated benefit in the use of more intense immunosuppression using cyclophosphamide for steroid-resistant patients who have failed either methotrexate or azathioprine. TNF inhibitors have been used in patients with giant cell arteritis, but with disappointing results. Beneficial effects of tocilizumab, a monoclonal IL-6 receptor blocker, have been described in several small case series of giant cell arteritis. A multicentre, randomized, double-blind, placebo-controlled trial designed to formally evaluate the ability of tocilizumab in maintaining disease remission has re- cently been published demonstrating the efficacy and safety of tocilizumab as a steroid-sparing agent after 52 weeks. Other biologic treatments have been studied for giant cell arteritis with promising results (e.g. abatacept and ustekinumab). Better understanding of the biology of giant cell arteritis should lead to the identification of more targets for more specific intervention in future. Adjuvant therapy In the absence of contraindications, low-dose aspirin (75–150 mg/ day) should be considered in all patients with giant cell arteritis. Although there are no randomized controlled trials evaluating its use as an adjuvant treatment, two retrospective studies have sug- gested that low-dose aspirin reduces the risk of visual loss and stroke in patients with giant cell arteritis. Bone protection with calcium, vitamin D supplements and bisphosphonates as well as gastrointes- tinal protection with proton pump inhibitors are recommended in all patients with giant cell arteritis. Disease monitoring There are still no validated tools or biomarkers to assess treat- ment response in giant cell arteritis. Although in clinical practice CRP and ESR are the most commonly used inflammatory markers for this purpose, they do not consistently reflect disease activity. Preliminary analyses of circulating pentraxin 3 (PTX3), VEGF, IL-6, and antibodies against ferritin have suggested promise as potential predictors of disease activity. However, further studies with larger numbers of patients and longer follow-up are warranted to assess the value and feasibility of their routine use. Imaging has an important role for monitoring giant cell arteritis. Using ultrasound scans, the presence of halo correlates with ischaemic symptoms. Moreover, it has been reported that the halo size decreases with glucocorticoid therapy, suggesting that ultrasound may be a simple but powerful tool to assess disease activity. In large vessel giant cell arteritis, MRI, positron emission tomography, and ultrasound are the preferable imaging modalities for monitoring response to treatment. Screening for aortic aneurysms is advisable at least every 2 years by chest radio- graph, echocardiography, positron emission tomography, or MRI. The optimal frequency for patients' routine care should be guided by clinical symptoms, serum markers, and imaging; however, after dis- ease remission, regular review is advisable for the first year. Prognosis The prognosis of giant cell arteritis is generally favourable. Some studies have found an overall life expectancy similar to the gen- eral population, while others have described a slight increase in mortality, mostly due to cardiovascular events (stroke, myocardial infarction, dissections, and rupture of aneurysms). Glucocorticoid-related adverse events have been reported in 86% of patients at 10-year follow-up and are also related to an increase in mortality. Patients with large vessel giant cell arteritis have a higher incidence

19.11.6 Large vessel vasculitis 4551 of disease relapses and cumulative steroid doses when compared to patients with cranial giant cell arteritis. Takayasu arteritis Epidemiology The annual incidence of Takayasu arteritis is extremely low is most populations studied, around 1–3 per million. It occurs predomin- antly in Asian populations, although patients with Takayasu arter- itis have increasingly been recognized in other regions, such as the United States, Europe, and South America. It has a female predom- inance of 8–9:1 affecting adults and children, with the peak inci- dence occurring in the third decade of life. Aetiology The aetiology of Takayasu arteritis is

unknown. Geographic differ- ences in the incidence and patterns of vascular involvement sug- gest that genetics and environmental risks factors may play a role in the development of the disease. Mycobacterium tuberculosis, hepatitis B, and herpes virus have been inconsistently implicated as triggers of Takayasu arteritis. In addition, there have been several reports of HLA associations across multiple ethnicities, particularly HLA-B*52 (and to a lesser extent HLA-B*67 in Japanese patients). Identification of susceptibility loci in IL6, FCGR2A/ FCGR2A, RPS9/LILRB3, and an intergenic locus on chromosome 21q22 have also been found in Takayasu arteritis. Histopathology The pathologic features seen in Takayasu arteritis are almost indistinguishable from the ones found in giant cell arteritis. Inflammation is more common in the aorta and its major branches. Typically two distinct phases may coexist in the disease: an acute inflammatory phase and a chronic phase characterized by intimal hyperplasia and fibrosis of the tunica media and intima. Aortic wall thickness is often greater in Takayasu arteritis than in giant cell ar- teritis. Moreover, severe adventitial scarring and compact granu- lomas are more frequently seen in Takayasu arteritis than in giant cell arteritis. Pathogenesis The pathologic process of Takayasu arteritis remains poorly under- stood. Just as in giant cell arteritis, the interaction between dendritic cells and lymphocytes may contribute to the immune-mediated re- sponse seen in Takayasu arteritis. A potential target is a 65-kD heat shock protein (HSP-65), which is highly expressed in the media and vasa vasorum. Infiltration with γδ T cells, cytotoxic T lymphocytes, T helper cells, natural killer cells, and macrophages occurs in pa- tients with Takayasu arteritis. There is a release of proinflammatory cytokines, such as IFN-γ, TNFα, IL-1, and IL-6, and matrix metalloproteinases, leading to arterial wall damage. Patients with Takayasu arteritis have been reported to have higher expression of IFN-γ than patients with giant cell arteritis, which may explain the increased rates of stenosis and occlusion in Takayasu arteritis. Interestingly, the Th1-FN γ axis is steroid sensitive in Takayasu ar- teritis, as opposed to giant cell arteritis. Circulating anti-endothelial cell antibodies (AECA) have been inconsistently found in patients with Takayasu arteritis. They may be involved in the pathogenesis of Takayasu arteritis by activation of the endothelial cells. Clinical manifestations Patients with Takayasu arteritis typically have a heterogeneous clin- ical presentation; however, a tri-phasic pattern of disease progres- sion has been described with a potential overlap between stages: Phase 1: Pre-pulseless period, characterized mostly by constitu- tional features, such as fatigue, low-grade fever, weight loss, arth- ralgia, and myalgia. Phase 2: Vascular inflammation predominates, characterized by vessel pain and tenderness. Phase 3: Inflammation has settled, but bruits and signs of ischaemia persist as consequences of previous disease activity. The diagnosis of Takayasu arteritis is often delayed for a substan- tial period of time (months to years). In up to 20% of cases, the diag- nosis is only made due to incidental findings, such as unexplained high inflammatory markers, unequal arm blood pressures, or bruits. Geographical differences have been reported in the vascular in- volvement of the disease: the aortic arch and its branches are the most frequently affected vessels in Japanese patients, as opposed to Indian patients where the abdominal aorta is more commonly in- volved. Lower limbs are also less affected than upper limbs. Table 19.11.6.3 summarizes the published frequencies for the most common clinical features of Takayasu arteritis. Table 19.11.6.3 Frequencies of the most common features of Takayasu arteritisa Clinical manifestations of Takayasu arteritis (%) Constitutional symptoms Fatigue 26–56% Arthralgia 5–39% Myalgia 15–30% Fever 9–27% Weight loss 2–25% Vascular manifestations Absent or diminished pulses 60–88% Asymmetric blood pressure 47–81% Bruits 62–80% Hypertension 35–77% Claudication 38–70% Carotidynia 14–32% Other manifestations Headache 26–57% Dizziness 24–50% Palpitations 9–37% Visual disturbances 5–34% Cutaneous manifestations (e.g. erythema nodosum, pyoderma gangrenosum, purpura) 3–28% Exertional dyspnoea 20–27%

Syncope 16–19% Raynaud’s phenomenon 11–15% Stroke 3–10% Laboratory results in patients with Takayasu arteritis (%) Elevated erythrocyte sedimentation rate 50–83% Elevated C-reactive protein 51–60% a Data based on the clinical characteristics of 125 patients from China (Cong et al. 2010); 248 patients from Turkey (Bicakcigil et al. 2009); 108 patients from Korea (Park et al. 2005); 106 patients from India (Jain et al. 1996); and 60 patients from North America (Kerr et al. 1994).

section 19 Rheumatological disorders 4552 Diagnostic investigations Unlike giant cell arteritis, vessel biopsies are rarely obtainable in Takayasu arteritis. The diagnosis is mostly based on the combination of clinical features, high inflammatory markers, and the presence of characteristic arterial lesions on imaging. Laboratory tests Inflammatory markers are typically high at the onset of Takayasu ar- teritis, just as they are in giant cell arteritis. The ESR has been reported to be more commonly elevated than CRP. Normochromic-normocytic anaemia, thrombocytosis, and hypergammaglobulinaemia are also very frequent. AECA do not seem to have any value in the diagnosis of Takayasu arteritis. Imaging A clinical suspicion of Takayasu arteritis should prompt imaging examination of the arterial tree. Although conventional angiog- raphy is still the gold-standard for diagnosing Takayasu arteritis, it is an invasive procedure and is not able to detect wall thickness or oedema, thus it is not useful for early diagnosis. Vessel stenosis is the most common arteriographic finding, present in more than 80% of patients at the time of diagnosis; aneurysms may be present, but typ- ically occur later in the disease course. Other imaging modalities have shown high sensitivity and spe- cificity for the diagnosis of Takayasu arteritis (compared with con-ventional angiography): 98% and 93% respectively for computed tomography angiography (CTA) as shown in Fig. 19.11.6.3 and both 100% for magnetic resonance angiography. positron emission tom- ography-scans may be more sensitive than MRI in detecting vessel inflammation and are a suitable whole-body screening method for diagnosing early Takayasu arteritis, especially in cases with nonspecific presenting symptoms, where the differential diag- nosis is wide (Fig. 19.11.6.4). Ultrasound has been reported to be more sensitive than MRI in assessing the common carotid ar-teries. It can be used to evaluate the involvement of other vessels, such as the axillary and subclavian arteries. It has the disadvantage of being extremely operator dependent and not being able to access the thoracic aorta. Diagnosis and classification criteria In 1988, Ishikawa proposed a set of diagnostic criteria for Takayasu arteritis based on the age of disease presentation, clinical signs and symptoms, laboratory findings, and angiographic abnormal- ities. However, these criteria restricted the age of the disease onset (<40 years) and were only tested in 96 Japanese patients (and 12 controls with other aortic diseases), not taking into account the geographical differences in patterns of vascular involvement. These criteria were subsequently modified by Sharma in 1995 with the re- moval of the obligatory criteria of age and adjustment in the other clinical and angiographic criteria (Table 19.11.6.4). They were tested in 106 Indian and 79 Japanese patients with angiographic- ally proven Takayasu arteritis and showed a sensitivity of 92.5% and specificity of 95%. Classification criteria for Takayasu arteritis were developed in 1990 by ACR, essentially with the aim of identifying a homogeneous group of patients to include in epidemiologic studies and clinical trials (Table 19.11.6.5). Both the existing diagnostic and classification criteria do not include newer imaging modalities, such as CTA, magnetic resonance angiography, positron emission tom- ography, or ultrasound. The DCVAS study is underway to update these criteria.
Fig. 19.11.6.3 Computed tomography angiogram of the chest with intravenous iodinated contrast of a patient with Takayasu arteritis in axial view (left) and sagittal view (right) showing concentric wall thickening of the distal aspect of the aortic arch and the descending thoracic aorta (yellow arrows).

19.11.6 Large vessel vasculitis 4553 Management The rarity of Takayasu arteritis is a major limitation for random- ized controlled trials; thus therapeutic decisions are often based on observational studies, case series and clinician´s experience. The management of patients with Takayasu arteritis not only in- cludes medical treatment, but also potential surgical intervention. Medical treatment Glucocorticoids Glucocorticoids are the mainstay treatment for Takayasu arteritis. For patients with newly presenting active disease, the European League Against Rheumatism (EULAR) recommends an initial dose of prednisolone of 1 mg/kg/day (maximum 60 mg/day) for at least one month with subsequent gradual tapering. Although never for- mally tested, a lower initial dose of prednisolone can be considered in patients with no signs of ischaemia, especially if they have a high risk of glucocorticoid-related side effects. Fig. 19.11.6.4 FDG PET-CT scan of a patient with Takayasu arteritis showing increased FDG uptake throughout the entire aorta and both subclavian, axillary and carotid arteries (yellow arrows). Table 19.11.6.4 Revised Ishikawa diagnostic criteria for Takayasu arteritis Criteria Definition Major criteria (1) Left mid subclavian artery lesion The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography (2) Right mid subclavian artery lesion The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to orifice determined by angiography (3) Characteristic signs and symptoms (at least 1month duration) Limb claudication, pulselessness or uneven pulse in limbs, undetectable blood pressure or the difference in bilateral limb systolic blood pressure >10 mm Hg, fever, neck pain, transient amaurosis, blurred vision, syncope, palpitations, or dyspnoea Minor criteria (1) High ESR Unexplained persistent ESR >20 mm/h (2) Carotid artery tenderness Unilateral or bilateral carotid arteries tenderness (neck muscle tenderness not included) (3) Hypertension Persistent blood pressure >140/90 mm Hg brachial or >160/90 mm Hg popliteal (4) Aortic regurgitation or dilatation Confirmed by auscultation, doppler ultrasound, or angiography (5) Pulmonary artery lesion Lobar or segmental artery occlusion or presence of stenosis, aneurysm, luminal irregularity, or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography (6) Left mid common carotid lesion Presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography (7) Distal brachiocephalic trunk lesion Presence of the most severe stenosis or occlusion in the distal brachiocephalic trunk artery (8) Descending thoracic aorta lesion Stenosis, dilation, aneurysm, luminal irregularity, or any combination (tortuosity alone not included) (9) Abdominal aorta lesion Stenosis, dilation, aneurysm, luminal irregularity, or any combination (10) Coronary artery lesion Age <30 years, in the absence of risk factors like hyperlipidaemia or diabetes mellitus (documented on angiography) The presence of two major or one major and two minor criteria or four minor criteria suggests a high probability of Takayasu arteritis. Adapted from Sharma BK et al. (1996) Diagnostic criteria for Takayasu arteritis. Int J Cardiol, 54 Suppl: S127–33, copyright 1996, with permission from Elsevier. Table 19.11.6.5 ACR 1990 classification criteria for Takayasu arteritis

1. Age <40 years old
2. Claudication of extremities
3. Decreased brachial arterial pulse
4. BP difference >10 mm Hg in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta

6. Arteriogram abnormality (narrowing or occlusion of the aorta, its proximal branches, or large arteries in the proximal upper or lower extremities) The patient is classified as having Takayasu arteritis if at least three of these six criteria are present (sensitivity of 90.5% and specificity of 97.8%). Adapted from Arend WP et al. (1990) The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum, 33(8): 1129–1134.

section 19 Rheumatological disorders 4554 Other immunosuppressive therapy Other immunosuppressive therapy is considered in patients who relapse or are unable to tolerate corticosteroids. Based on evi- dence from small open-label studies, methotrexate is the first drug of choice, followed by azathioprine. Recent evidence sup- ports mycophenolate mofetil and leflunomide as steroid-sparing agents. Cyclophosphamide is reserved for severe life or vital organ threatening conditions. Biological agents have been suc- cessfully used to induce remission in refractory Takayasu arter- itis, particularly tocilizumab and TNF inhibitors (etanercept and infliximab). B cell depletion with rituximab has also shown some benefit. Adjuvant therapy All patients should be prescribed low-dose aspirin (75–150 mg/ day) and supplementation with calcium and vitamin D. Additional prophylaxis of osteoporosis with bisphosphonates should be con- sidered in accordance with local guidelines. Surgical treatment Revascularization procedures (e.g. angioplasty, stenting or bypass surgery) are indicated in patients with severe stenosis. They should be performed in the quiescent phase of the disease and in experi- enced centres. Endovascular interventions have higher rates of re- stenosis than surgical reconstructions, but may be appropriate in selected patients with limited lesions. Disease monitoring All patients with Takayasu arteritis need long-term monitoring due to its progressive and relapsing nature. Unfortunately, as in giant cell arteritis, there are no valid biomarkers for assessing treatment response and diagnosing relapse. Takayasu arteritis is therefore currently monitored based on the patients' symp- toms and signs (e.g. presence of new bruits or diminished/ab- sent pulses), serum inflammatory markers (ESR and CRP) and imaging (preferably magnetic resonance angiography or positron emission tomography; still limited evidence on ultra- sound). Other potential serum markers to assess disease ac- tivity have been investigated (AECA, circulating endothelial cells, antibodies against ferritin, VEGF, IL-6, IL-8, IL-18, matrix metalloproteinase-9, and adipokines), but with inconclusive re- sults. High levels of plasma PTX-3 have recently been detected in the serum of patients with active disease, but further confirma- tory studies are warranted. The most frequently used criteria in clinical studies to define 'ac- tive disease' in Takayasu arteritis were set by Kerr et al. in 1994 (Table 19.11.6.6). The Indian Takayasu Activity Score (ITAS2010) is a validated tool for disease assessment in Takayasu arter- itis (Table 19.11.6.7), derived from the Birmingham Vasculitis Activity Score—BVAS (a validated tool to evaluate disease activity in small and medium-vessel vasculitis). However, more evidence is required of its value in accurately differentiating disease activity from damage. Prognosis The prognosis of Takayasu arteritis varies according to different studies. It is highly dependent on the type and severity of the ex- isting vascular lesions and adverse effects of immunosuppression. Long-term survival rates are around 80% to 90%, decreasing to 66% in cases of major Takayasu arteritis disease complications such as hypertension, retinopathy, or vascular aneurysms. Disease relapses have been reported in up to 96% of cases, with 66–84% of patients requiring additional immunosuppression to the standard gluco- corticoid therapy. IgG4-related aortitis and periaortitis Overview IgG4-related disease (IgG4-RD) is a recently recognized fibro- inflammatory condition characterized by tissue infiltration of IgG4-positive plasma cells, fibrosis with a storiform pattern, and a 'tumour-like' swelling of the

organs. Elevated serum concentra- tions of IgG4 (>135 mg/dl) are present in 60% to 70% of patients. It can affect any organ system and involve one or multiple organs simultaneously. It has been frequently described in the pancreas, biliary tree, and gallbladder, major salivary glands, periorbital tis- sues, lymph nodes, lungs, kidneys, retroperitoneum, and aorta. Although reports of the disease are worldwide, its true epidemiology is still unknown. Unusually for an inflammatory disease, it appears to mainly affect men above 50 years of age with a male-to-female ratio around 4–6:1 (except for the variant involving head and neck where the ratio is around 1:1). Diagnostic criteria have been developed (Table 19.11.6.8), but in most cases definitive diagnosis requires histological documenta- tion of the organ involved. IgG4-related aortitis and periaortitis Involvement of the aorta and its surrounding tissues has been re- ported in around 9% of cases of IgG4-RD. Up to 75% of cases of patients previously classified as having ‘isolated idiopathic thoracic aortitis’ due to incidental histological findings of vas- cular inflammation following repair of thoracic aortic aneur- ysms/dissections are now known to have IgG4-RD. In addition, a subset of patients diagnosed with the so-called ‘inflamma- tory abdominal aortic aneurysm’ or ‘periaortitis’ (abdominal aortic aneurysms with severe atherosclerosis that contain more chronic inflammation and scarring in the adventitia than typical atherosclerotic aneurysms) have IgG4-RD. Moreover, IgG4-RD accounts for most cases of ‘idiopathic retroperitoneal fibrosis’ or Ormond’s disease, which may affect the periaortic region. Treatment of IgG4-RD with aortic or periaortic involvement is with high-dose of glucocorticosteroids. In steroid-dependent cases, azathioprine, methotrexate, mycophenolate mofetil, or rituximab have been used. Table 19.11.6.6 Criteria for active disease in patients with Takayasu arteritisa 1. Constitutional features, such as fever, musculoskeletal (no other cause identified) 2. Elevated ESR 3. Features of vascular ischaemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain (carotidynia), asymmetric blood pressure in either upper or lower limbs (or both) 4. Typical angiographic features a New onset or worsening of two or more features indicates ‘active disease’ Adapted from Kerr GS et al. (1994) Takayasu Arteritis. Ann Intern Med, 120(11): 919–929.

19.11.6 Large vessel vasculitis 4555 Table 19.11.6.7 ITAS2010—Indian Takayasu Activity Score Tick box only if abnormality is present and new or worse within the past 3 months Tick box only if abnormality is ascribed to current, active vasculitis

1. SYSTEMIC
2. RENAL None □ None □ Malaise/Wt. Loss >2 kg ∘ Hypertension (Diastolic >90 mm Hg) ● Myalgia/Arthralgia/Arthritis ∘ Hypertension (Systolic >140 mm Hg) ∘ Headache ∘
3. ABDOMEN
4. NERVOUS SYSTEM None □ None □ Severe Abdominal Pain ∘ Stroke ●
5. GENITOURINARY SYSTEM Seizures (not hypertensive) ∘ None □ Syncope ∘ Abortions ∘ Vertigo/dizziness ∘
6. CARDIOVASCULAR SYSTEM R L 6a. Bruits None □ Carotid ∘ ∘ Subclavian ∘ ∘ Bruits (see 6a) ● Renal ∘ ∘ 6b. Pulse and BP Inequality Pulse Inequality (See 6 b) ● Present ∘ 6c. Pulse Loss New Loss of Pulses (See 6c) ● Carotid ∘ ∘ Subclavian ∘ ∘ Claudication (See 6d) ● Brachial ∘ ∘ Radial ∘ ∘ Carotidodynia ● Femoral ∘ ∘ Popliteal ∘ ∘ Posterior Tibial ∘ ∘ Aortic Incompetence ∘ Dorsalis Pedis ∘ ∘ Myocardial Infarct/Angina ∘ 6d. Claudication Cardiomyopathy/cardiac failure ∘ Arm ∘ Leg ∘ Physician Global Assessment ESR_____ CRP_____ Active Grumbling or persistent Inactive New Imaging Y/N? If Y—specify _____ Scoring ITAS2010: Add all scores (see glossary) Item scores □ = 0 ∘ = 1 ● = 2 Scoring ITAS. A including acute phase response: For ESR,

score ITAS plus: 0 for ESR <20; 1 for ESR 21–39; 2 for ESR 40–59; and 3 for ESR >60 mm For CRP score ITAS plus: 0 for CRP <5; 1 for CRP 6–10; 2 for CRP 11–20; and 3 for CRP >20 mg/dl Adapted from Misra R et al. (2013) Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). Rheumatology (Oxford), 52(10): 1795–1801, by permission of Oxford University Press.

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