Circulation

IN DEPTH

Medium- and Large-Vessel Vasculitis

ABSTRACT: Systemic vasculitides are multisystem blood vessel disorders, which are defined by the size of the vessel predominantly affected, namely small, medium, or large vessels. The term "large vessel" relates to the aorta and its major branches; "medium vessel" refers to the main visceral arteries and veins and their initial branches. The most common causes of large-vessel vasculitis are giant cell arteritis and Takayasu arteritis, and those of medium-vessel arteritis are polyarteritis nodosa and Kawasaki disease. However, there is some overlap, and arteries of any size can potentially be involved in any of the 3 main categories of dominant vessel involvement. In addition to multisystem vasculitides, other forms of vasculitis have been defined, including single-organ vasculitis (eg, isolated aortitis). Prompt identification of vasculitides is important because they are associated with an increased risk of mortality. Left undiagnosed or mismanaged, these conditions may result in serious adverse outcomes that might otherwise have been avoided or minimized. The ethnic and regional differences in the incidence, prevalence, and clinical characteristics of patients with vasculitis should be recognized. Because the clinical presentation of vasculitis is highly variable, the cardiovascular clinician must have a high index of suspicion to establish a reliable and prompt diagnosis. This article reviews the pathophysiology, epidemiology, diagnostic strategies, and management of vasculitis.

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Systemic vasculitides are multisystem blood vessels disorders, which are defined by the size of the vessel predominantly affected: small, medium, or large, or variable-sized vessels. The Chapel Hill International Consensus Conferences of 1994 and 2012 defined and standardized the nomenclature of systemic vasculitides[1] (Table 1). The term "large vessel" relates to the aorta and its major branches; "medium vessel" refers to the main visceral arteries and veins and their initial branches; and "small vessel" refers to arterioles, capillaries, intraparenchymal arteries, venules, and some veins. However, arteries of any size can potentially be involved in any of the 3 main categories of dominant vessel involvement.

LARGE-VESSEL VASCULITIS

Giant cell arteritis (GCA) and Takayasu arteritis (TA) are the 2 main forms of large-vessel vasculitis. In large-vessel vasculitis, arterial Doppler ultrasound, angio–magnetic resonance imaging (MRI), angio–computed tomography (CT), and

Key Words: giant cell arteritis ■ Kawasaki disease ■ polyarteritis nodosa ■ Takayasu ■ vasculitis

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Table 1. Large- and Medium-Vessel Vasculitis Classification According to the 2012 International Chapel Hill Consensus Conference

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Variable vessel vasculitis
Behçet's disease
Cogan syndrome
Single-organ vasculitis
Isolated aortitis
Vasculitis associated with probable etiology
Infectious aortitis: syphilis-associated aortitis; mycobacterial aortitis; suppurative/mycotic infectious aortitis
Aortitis associated with rheumatologic disease: IgG4-related disease; antineutrophil cytoplasmic antibody–associated vasculitis; spondyloarthritis; Erdheim-Chester disease; relapsing polychondritis; sarcoidosis

Classification from Jennette et al.[1]

18F-fluorodeoxyglucose positron emission tomography are used to detect structural lesions and vascular inflammation (Figures 1 through 3).

Giant Cell Arteritis

Epidemiology

In the US population, GCA is the most frequent primary vasculitis, with an incidence of 18 cases per 100 000 among residents of Olmsted County, Minnesota.[2] The overall age- and sex-adjusted prevalence rate of GCA in the United States was 204 per 100 000 individuals ≥50 years of age.[3] A north-south gradient in the incidence of GCA was seen in Europe, with high rates in Sweden and Norway (generally >20 new cases of GCA per year per 100 000 individuals 50 years of age and older) and a lower incidence in Southern Europe (annual incidence rate of 10 cases per 100 000 people 50 years of age and older in northwestern Spain). The incidence of GCA has been described as lower in Hispanic, Latin American, Asian, and Black populations. However, a recent study suggest that GCA occurs at a similar rate in White and Black patients.[4] Several studies have shown a higher incidence of GCA in women, in particular in the 70- to 79-year-old age group. The lifetime risk of developing GCA is estimated at 1% for women and 0.5% for men in the United States.[5] The GCA prevalence rate is reported at 304 per 100 000 in women and 91 per 100 000 in men.[3] As the population throughout the world continues to age, an increased prevalence of the disease should be expected.

Pathophysiology

A strong association with human leukocyte antigen (HLA)–DRB*04 alleles was found. Studies also indicate gene polymorphisms located outside the major histocompatibility complex region, such as PTPN22, NOS2, ERAP1, REL, and PRKQC, involved in inflammatory responses, may also account for the increased risk of GCA.[6]

The pathophysiology of GCA is still incompletely understood. After dendritic cell activation, $CD4^+$ T lymphocytes, also known as T helper 1 cells, produce interferon-γ and modulate macrophage activation and functions, and T helper 17 cells produce interleukin (IL)–17, which can induce proinflammatory cytokine production such as IL-1, IL-6, and tumor necrosis factor (TNF)–α. Particular Toll-like receptors induce a distinct type of vessel inflammation. Toll-like receptor 4 ligands cause transmural panarteritis, and Toll-like receptor 5 ligands promote adventitial perivasculitis.[7] Questions remain about the nature of the antigens triggering dendritic cell activation and the mechanisms underlying vascular remodeling.

Clinical Presentation

Cranial artery involvement and constitutional symptoms in patients >50 years of age are the usual presentation of GCA. Features of polymyalgia rheumatica occur in 40% to 60% of patients with GCA at diagnosis. The main cranial manifestations of GCA are headache, jaw claudication, and scalp tenderness. Concentrations of acute phase proteins, especially C-reactive protein, are increased in >95% of cases.

An estimated 15% of patients with GCA experience ophthalmologic complications, especially anterior ischemic optic neuropathy, because of arteritic involvement of the short posterior ciliary arteries that supply the optic nerve head, with the remainder composed mainly of retinal blindness caused by central retinal artery involvement.[8] Visual loss is painless, partial or complete, and unilateral or bilateral; once established, it is irreversible. It may be preceded by fleeting visual blurring with exercise, amaurosis fugax, or diplopia; however, it commonly occurs without warning and may be the presenting symptom.

Other ischemic complications of GCA include transient ischemic attack and stroke. GCA-associated strokes are reported in 2% to 7% of patients[9] and are the leading cause of mortality. The causes of stroke in GCA are multifactorial and include hypercoagulability, accelerated atherosclerosis, and direct endothelial damage by arteritis. The conjunction of headache with vertebral and basilar artery involvement in elderly adults is suggestive of stroke associated with GCA. Strokes are typically observed in the period of clinically active disease, between the onset of symptoms of GCA and the first month after the initiation

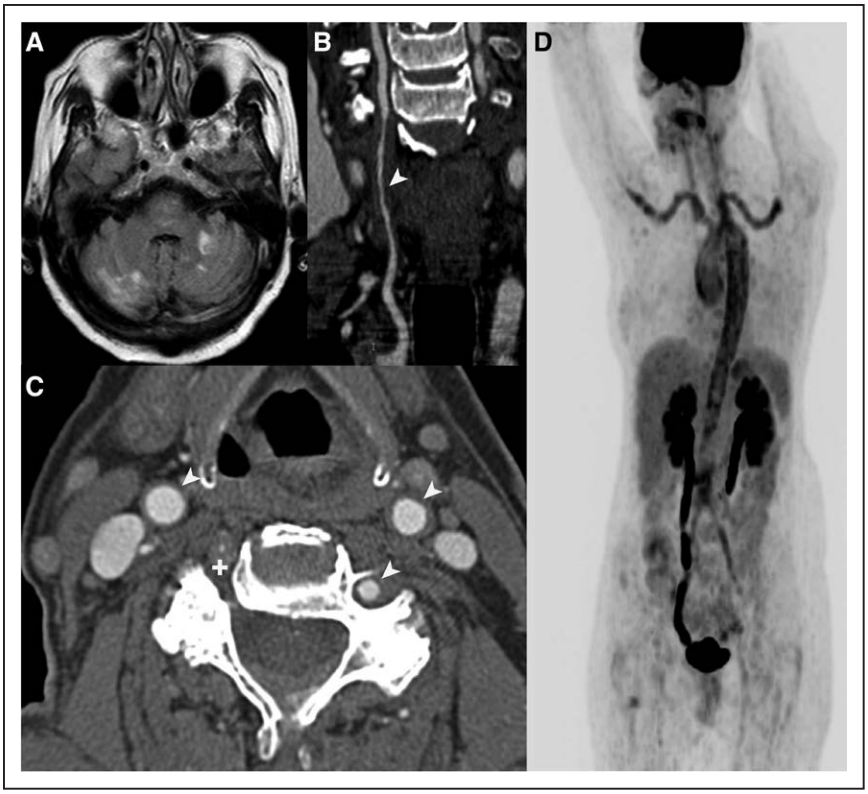

Figure 1. Imaging of large-vessel involvement in giant cell arteritis.
Patient with biopsy proven giant cell arteritis revealed by cerebellous stroke related to inflammatory stenosis of vertebral arteries (**A** through **C**). **A,** Cerebral magnetic resonance imaging showing abnormal hyperintense areas (MRI FLAIR sequences) in the cerebellum. Angio–computed tomography showing long stenosis of the right vertebral artery (**B**) and thickening of the arterial wall of both carotid arteries and the left vertebral artery (arrow) and subocclusive stenosis of the right vertebral artery (cross) (**C**). **D,** FDG-PET fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanner showing intense 18F-fluorodeoxyglucose uptake of bilateral carotid arteries, bilateral subclavian arteries, the entire aorta, and the iliac bifurcation in another biopsy-proven patient with giant cell arteritis.

of steroid therapy.[10] The most frequent symptoms associated with GCA are headache and visual impairment. Brain MRI angiography shows ischemic lesions involving vertebral or basilar arteries in most cases,[11] but internal carotid arteries may also be affected.[9,10] In contrast, atherosclerosis-related strokes involve vertebrobasilar arteries in <20% of cases. Intracranial cerebral artery involvement with cerebral vasculitis on diffusion-weighted brain MRI sequences may occur in GCA. Although involvement of the intracranial arteries is rare in GCA, it can lead to severe neurological complications, such as multiple territory cerebrovascular accidents, multi-infarct dementia, and death.

The major risk of large-vessel involvement in GCA is the development of aorta aneurysm or dissection, which can affect up to 30% of patients.[12,13] Compared with the general population, patients with GCA have a 2-fold higher risk of developing an aortic aneurysm.[14] Aortic involvement can precede cranial symptoms, be associated with cranial symptoms, or occur after the diagnosis of cranial GCA. GCA appears to have a predilection for the thoracic aorta and subclavian and axillary arteries. In contrast with TA, subclavian and axillary diseases seem to cluster symmetrically in GCA.

The prevalence of upper- and lower-extremity vasculitis related to GCA was estimated to be 26% and 18%, respectively. Arterial involvement in patients with GCA with upper-extremity vasculitis is distributed mainly in the subclavian, axillary, and brachial arteries.[15] Raynaud phenomenon is described in up to 24% of patients with GCA-related upper-extremity vasculitis. Lower extremity vasculitis includes mainly the internal iliac artery, the common femoral artery, and the superficial femoral artery.[15]

Diagnosis

GCA is classified according to the American College of Rheumatology 1990 criteria, which require the presence of 3 or more of the following: (1) age at onset ≥50 years; (2) new-onset headache; (3) temporal artery abnormality, such as tenderness to palpation or decreased pulsation; (4) erythrocyte sedimentation rate ≥50 mm/h; and (5) abnormal artery biopsy showing vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cell infiltrates.[16] However, with advances in vascular imaging, it has become clear that GCA is a systemic disease that extends beyond the superficial temporal arteries and can cause manifestations including large-artery stenosis or aortic involvement (aortitis, aneurysm formation, or dissection).[17,18] Temporal artery biopsy with mononuclear cell infiltrate or granulomatous inflammation remains the accepted standard for diagnosis. Although it is highly specific, the sensitivity of temporal artery biopsy has decreased over time, highlighting the fact that many patients with GCA are diagnosed without histological evidence.[19] Vascular imaging is increasingly incorporated into the diagnostic assessment of GCA and identifies clinical subsets of patients based on involvement of temporal and extracranial arteries. Temporal artery ultrasound showing a hypoechoic circumferential halo sign is a useful diagnostic

tool in GCA (68% sensitivity and 91% specificity). In addition to its diagnostic role, temporal arteritis halo correlated positively with systemic inflammation and might be associated with the presence of ischemic features in newly diagnosed GCA.[20] Large-vessel imaging has become an increasingly common form of diagnostic assessment and clinical evaluation in GCA. Large-vessel involvement was evidenced in 27% to 67% by angiography,[12,13] 83% by 18F-fluorodeoxyglucose positron emission tomography imaging,[21] and 100% by autopsy.[22] Classic cranial GCA symptoms may be clinically absent or, if present, may occur significantly less often in patients with large-vessel GCA. In addition, large-vessel GCA may have a stronger female predominance and a younger age of disease onset in comparison with cranial GCA (Table 2).

Management

High-dose glucocorticoid therapy (40–60 mg/d of a prednisone equivalent) should be initiated immediately for induction of remission in active GCA. In patients with GCA with ischemic visual manifestations, the standard initial glucocorticoid dose is usually 1 mg/kg/d (possibly preceded by intravenous methylprednisolone daily for up to 3 consecutive days). Once the disease is controlled, glucocorticoid dose tapering is recommended to a target dose of 15 to 20 mg/d within 2 to 3 months and to 5 mg/d after 1 year.[23] Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of glucocorticoid-related adverse effects or complications) using tocilizumab. Methotrexate may be used as an alternative.[23] Tocilizumab (anti–IL-6 receptor) was approved for GCA by US and European regulatory authorities in 2017 on the basis of the results of 2 randomized control trials that added 1 year of tocilizumab, or placebo, to tapering glucocorticoid therapy.[24] A single small trial significantly favored abatacept (recombinant fusion protein comprising the extracellular domain of human cytotoxic T-lymphocyte antigen 4 and a fragment of the Fc domain of human IgG1) over placebo for time to relapse.[25] A post hoc analysis to compare the proportion of patients in remission at 12 months did not show a significant difference between the treatment arms. Abatacept is currently not approved for the treatment of GCA. The biologics on trial included Janus kinase inhibitors inhibitor targeting (URL: http://www.clinicaltrials.gov. Unique identifier: NCT03725202), anti-IL17 (URL: http://www.clinicaltrials.gov. Unique identifier: NCT03765788), and strategies blocking vascular remodeling.

Antiplatelet therapy is used largely for the treatment of GCA, although there is no evidence for its usefulness. In case of aortitis, monitoring of vascular lesions with ultrasound of the supra-aortic trunks and angio-CT or -MRI for the aorta is recommended.

Table 2. Giant Cell Arteritis With or Without Large Vessel Involvement

Variable	With large-vessel involvement	Without large-vessel involvement
Mean age at diagnosis, y	65–68	74–75
Female sex, %	74–80	64–72
General symptoms, %	31–68	27–42
Cranial symptoms, %	41–68	83–93
Headache, %	32–56	65–79
Jaw claudication, %	20–23	45–67
Ophthalmologic involvement, %	5–10	45–53
Polymyalgia rheumatica, %	21–27	30–43
Positive temporal arteritis biopsy, %	52–56	67–84
Steroid-sparing agents use, %	28–52	5–18
Relapse, %	39	44
Aortic dilatation, %	14–21	5–7

Data from Muratore et al[17] and de Boysson et al.[18]

Takayasu Arteritis

Epidemiology

TA was first described in Japan, and the highest incidence is observed in Asia, although the disease can be found in every ethnic group. In the Far East, its prevalence may increase to 40 cases per 1 000 000 people.[26] In the United States, TA is a rare vasculitis with an estimated incidence of 2 to 3 cases per million people per year.[27] It is not known why TA predominantly affects women, with a female-to-male ratio ranging from 5 to 12. Data suggest that male patients with TA have a higher frequency of hypertension and abdominal aorta involvement.[28]

Pathophysiology

HLA-B*52 is the only gene that shows an association with TA beyond ethnicity. Of note, HLA-B*52 has been shown to be associated with TA in the Turkish population,[29] as well as in Thai and Korean populations, where the allele frequency of HLA-B*52 is 0.7 to 3.2% and 2.8%, respectively. A study involving Turkish and North American–European patients has identified and confirmed 2 independent susceptibility loci in the HLA region: HLA-B/MICA and HLA-DQB1/HLA-DRB1.

The pathology of TA is characterized by the involvement of all arterial layers (ie, panarteritis) with a variable inflammatory infiltrate including acute exudative, chronic, and granulomatous inflammation, situated mainly in the media and adventitia, whereas hyperplasia and neovascularization are observed in the intimal layer.[30] Inflammatory lesions in TA eventually evolve to fibrosis in the arterial wall.[30] There are pathological features that may help to distinguish between TA and

GCA. Aortic wall thickness is generally greater in TA than in GCA. In addition, GCA is more commonly associated with inflammation that is most severe in the inner media, and GCA is not as often associated with the severe adventitial scarring seen in TA. Compact granulomas are more commonly seen in TA than in GCA.[31]

Clinical Presentation

Clinical presentations of TA vary from vascular symptoms attributable to arteritis (pulseless stage) to nonspecific constitutional or inflammatory symptoms, arthralgia and myalgia, episcleritis, and cutaneous involvement without clinical or radiographic evidence of arterial occlusive disease (prepulseless stage). TA may be associated with other inflammatory diseases, such as sarcoidosis, spondyloarthritis, or Crohn disease (Table 3).

TA is the leading cause of aortitis in young subjects. The aorta can be involved along its entire length, and although any of its branches can be involved, the most commonly affected are the subclavian and common carotid arteries. Although the most frequent pattern of disease varies geographically, stenotic lesions predominate (found in >90% of patients), whereas aneurysms are reported in ≈25%.[32] Compared with GCA, the carotid, renal, and mesenteric arteries are more frequently affected in TA. In a large cohort study, 50% of patients with TA relapsed and experienced a vascular complication at 10 years.[33] The cumulative incidence of aneurysm at 10 years is estimated to be 7%.[34] Progressive disease course, thoracic aorta involvement, and retinopathy are associated with vascular complications. The presence of 2 of these factors defines patients at high risk for death and vascular complications. In the high-risk TA group, the 5-year incidence of death and vascular complications is 48.5%, compared with 21.6% in those with low risk.[35]

Table 3. Differences Between Giant Cell Arteritis and Takayasu Arteritis

Variable	Giant cell arteritis	Takayasu arteritis
Demographics		
Mean age at diagnosis, y*	69–75	27–36
Female sex, %*	67–79	61–91
Geographic origin	White	Asia and Maghreb
Genetics	HLA-DRB1*04	HLA-B52
Associated manifestations		
Erythema nodosa	…	Yes
Episcleritis	…	Yes
Ischemic optic neuropathy	Yes	…
Ischemic retinopathy	…	Yes
Associated diseases	Polymyalgia rheumatica	Inflammatory bowel disease, sarcoidosis, ankylosing spondylitis
Large vessel involvement, %†	45–80	100
Subclavian arteries, %	39–54	69–71
Axillary arteries, %	39–54	10–20
Carotid arteries, %	17–27	37–57
Iliofemoral arteries, %	13–47	16–20

HLA indicates human leukocyte antigen.

*Data from Comarmond et al[33], Gonzalez-Gay et al,[94] Subramanyan et al,[95] Maksimowicz-McKinnon et al,[96] Jain et al,[97] and Salvarani et al.[98]

†Data from Comarmond et al[33], Grayson et al,[99] and de Boysson et al.[100]

The occurrence of stroke and transitory ischemic attack is estimated to be between 10% and 20%.[33] Stroke or transitory ischemic attack may be the first signs of the disease and are independently associated with vascular complications and death in patients with large-vessel vasculitis.[34] Silent cerebral infarction is also reported. Neurological symptoms include headache, dizziness, syncope, convulsions, and visual disturbances. The underlying mechanisms of ischemic strokes in TA remain unclear. Embolism, occlusion secondary to arterial thrombosis, and vasculitis of hemodynamic origin have been suspected. Stroke is more likely ischemic than hemorrhagic. The steno-occlusive lesions are more willingly observed in the carotid than the vertebrobasilar territories.[36] Hemorrhagic strokes are related to hypertension and occur more specifically in patients with TA with steno-occlusive lesions of the abdominal aorta and renal arteries.[36] Recanalization by collateral vessels is frequently seen on angiography. Supra-aortic trunk involvement may also manifest with syncope, headaches, seizures, carotidynia, visual loss, and subclavian steal syndrome.

Renal involvement in TA is frequent, primarily because of renal artery stenosis, which leads to renovascular hypertension. The renal artery involvement is often bilateral and frequently ostial and proximal, usually with coexistent stenosis of the perirenal aorta. Renovascular dilatative and aneurysmal lesions are rare. Renal artery stenosis will result in activation of the renin-angiotensin-aldosterone system, which, in turn, leads to hypertension through vasoconstriction and retention of sodium and water. New-onset hypertension occurs in 30% to 45% of patients with TA,[33] among whom 20% to 30% and 5% have imaging evidence of renal artery stenosis and occlusion, respectively. The prevalence of renal artery involvement varies and seems to be closely related to ethnicity, with a higher prevalence in Asians.[37] Kidney vascular involvement worsens the progression of the disease, and the estimated glomerular filtration rate significantly decreases as the severity of renal artery stenosis increases.[37] Less than 10% of patients with TA will develop end-stage renal disease.[33] Although end-stage renal disease is 1 of the major complications of TA, hemodialysis induction can be difficult because of several factors, including insufficient arterial flow for vascular access, difficulty in determining blood

pressure, and hemodynamic instability during hemodialysis because of TA-associated cardiovascular complications. Heart failure and pulmonary hypertension are significantly more prevalent among patients with renal artery involvement.[37]

Ischemic retinopathy may occur in 14% of patients with TA because of compromise of the internal carotid circulation with central retinal hypoperfusion.[38] Patients may also present with hypertensive retinopathy, mostly attributed to renovascular chronic systemic hypertension caused by renal artery occlusion.

Cardiovascular complications, including heart failure, pulmonary hypertension, myocardial infarction, and ruptured aortic aneurysm are the major causes of morbidity and mortality in TA.[35] Late gadolinium enhancement using cardiac MRI was identified in 27% of patients with TA[39] and a typical pattern of myocardial infarction in 20% of cases.[40] Comarmond et al reported that the prevalence of myocardial ischemia was 5 times greater in TA compared with healthy controls.[40]

Coronary artery involvement is detected in ≈10% of patients with TA.[33,41] This consists mostly of stenosis or occlusion of the coronary ostia. There are 3 types of coronary abnormalities: type 1, stenosis or occlusion of the coronary ostia and the proximal segments of the coronary arteries; type 2, diffuse or focal coronary arteritis, which can extend diffusely to all epicardial branches or can involve focal segments; and type 3, coronary aneurysms.[42] Type 1 lesions are more frequent.

Aortic regurgitation secondary to dilation of the aortic root[43] occurs in 5% to 55% of patients. Mitral and tricuspid insufficiency may also occur. Valvular insufficiency is mild in most cases.[43]

Intermittent claudication resulting from TA is much more common in the upper extremities than in the lower extremities. Types III, IV, and V of TA involve the abdominal aorta and may cause abdominal aortic coarctation, resulting in renovascular hypertension, intermittent claudication, or both. Intermittent claudication accounted for 15% of patients in a retrospective series of 272 patients.[44] Raynaud phenomenon is reported in 5% to 14% of cases of TA.

Diagnosis

Different sets of classification criteria of TA[45,46] have been proposed. The first criteria set for diagnosing TA was developed by Ishikawa and included 1 mandatory age criterion (< 40 years), along with 3 major (2 imaging and 1 clinical) and 10 minor (2 clinical, 1 laboratory, and 7 imaging) criteria.[45] This set of criteria was subsequently optimized by Sharma et al in 1996 and consists of 3 major criteria, including left or right midsubclavian artery lesions and characteristic signs and symptoms of at least 1 month duration, and 10 minor criteria: a high erythrocyte sedimentation rate, carotid artery tenderness (carotidynia), hypertension, aortic regurgitation or annuloaortic ectasia, pulmonary artery lesion, left midcommon carotid lesion, distal brachiocephalic trunk lesion, descending thoracic aorta lesion, abdominal aorta lesion, and coronary artery lesion. The presence of 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria suggests a high probability of TA.[46] A frequently used set of criteria for TA is the American College of Rheumatology 1990 classification criteria,[47] which include age at disease onset <40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference >10 mm Hg in systolic blood pressure between arms, bruit over subclavian arteries or aorta, and arteriogram abnormality. The problems related to these criteria stem from the restrictive criteria of age, new vascular imaging procedures, and the noninclusion of coronary and pulmonary arterial involvement. An angiographic classification that considers arterial locations distinguishes between 6 types: (1) type I, involving the aortic arch; (2) type IIa, affecting the ascending aorta, aortic arch, and its branches; (3) type IIb, involving the ascending aorta, aortic arch and its branches, and the descending thoracic aorta; (4) type III, affecting the descending thoracic aorta, abdominal aorta, or the renal arteries; (5) type IV, involving the abdominal aorta or renal arteries; and (6) type V, which combines type IIb and type IV.[48]

Management

Glucocorticoid therapy is the mainstay for induction of remission in TA, but relapses are frequent. Nonbiological disease-modifying agents (eg, methotrexate) are usually given in combination with glucocorticoids in patients with TA.[23] Tocilizumab or TNF inhibitors can be considered in case of relapsing or refractory disease despite conventional disease-modifying antirheumatic drug therapy.[49] One randomized control trial in a small cohort of patients with TA failed to meet the primary end point but suggests that tocilizumab may be favored over placebo for time to relapse of TA without new safety concerns.[50] Antiplatelet therapy is largely used for the treatment of TA, although there is no evidence for its usefulness.

Elective endovascular interventions or reconstructive surgery should be performed in patients with major vascular complications in phases of stable remission.[51] However, arterial vessel dissection, large aneurysm, or critical vascular ischemia requires urgent referral to a vascular team. Regular follow-up and monitoring of disease activity is recommended, primarily based on symptoms, clinical findings, ESR/CRP (erythrocyte sedimentation rate/C reactive protein) levels, and vascular imaging.

Other Causes of Aortitis

Aortitis is a group of disorders characterized by inflammation of the aorta and diagnosed by imaging of the entire aorta or histopathology when available.

Angio-CT, which uses iodinated contrast material, may demonstrate thickening of the aortic wall, usually regular, circumferential, and >2 mm. In addition, angio-CT allows an accurate assessment of stenotic lesions of the aorta or large arteries, most common in TA, as well as the presence and extent of aortic aneurysms or thrombus. Angio-MRI with gadolinium contrast enhancement may find vessel wall edema, enhancement, or wall thickening.[52] 18F-fluorodeoxyglucose positron emission tomography may be particularly useful when combined with traditional cross-sectional imaging modalities.[53] 18F-fluorodeoxyglucose positron emission tomography may demonstrate uptake of fluorodeoxy-D glucose in the arterial wall even before visible anatomic arterial changes occur.[54]

Aortitis contributes to significant morbidity and mortality through the development of aortic aneurysm, aortic wall rupture, aortic acute dissection, or thrombotic luminal obstruction. The most common causes of aortitis are GCA and TA, although it is also associated with several other rheumatologic diseases, such as Behçet's disease (BD), IgG4-related disease, and antineutrophil cytoplasmic antibodies-associated vasculitis.

Noninfectious aortitis is defined as an inflammatory process involving 1 or more layers of the aortic wall in which the inflammation cannot be accounted for by some other process, such as atherosclerosis or infection. If the inflammation is limited to the adventitia, then the term "periaortitis" is often used. In studies involving primarily the thoracic aorta, noninfectious aortitis has been reported to involve from 2% to 16% of aortic resections. A granulomatous/giant cell pattern is the most common pattern of inflammation in aortitis.

Isolated Aortitis

The term "isolated aortitis" was included in the Chapel Hill classification under the category of single-organ vasculitis.[1] Aortitis is identified either pathologically or radiologically in the absence of clinical evidence of systemic vasculitis. Two thirds of patients present with proximal aortitis. Over time, 45% of patients with isolated aortitis develop new vascular lesions, and 40% require further vascular surgery.[55]

IgG4-Related Disease

IgG4-related disease is a recently recognized disease that may be associated with aortitis or periaortitis. IgG4-related disease is characterized by elevated serum levels of IgG4 and histopathologic findings. The abdominal aorta is the most frequently affected arterial site, and 1% to 5% of abdominal aortic aneurysms are estimated to be IgG4-related disease. IgG4-related disease can either result in lymphoplasmacytic aortitis or be restricted to the adventitia, as in periaortitis. The principal histopathologic findings are lymphoplasmacytic infiltration, lymphoid follicle formation, obliterative adventitial phlebitis, and fibrosis, which may have a storiform pattern. International consensus guidelines for the pathological diagnosis of IgG4-related aortitis/periaortitis require the presence of lymphoplasmacytic aortitis/periaortitis, with >50 IgG4$^+$ plasma cells per 400× high-power field, and an IgG4/IgG ratio >50% when counting the 3 high-power fields with the highest degree of IgG4 positivity.[56]

Relapsing Polychondritis

Relapsing polychondritis causes destruction of the ear and nasal cartilage as well as scleritis. The aorta can rarely be involved, particularly the ascending aorta. The most frequent aortic lesion in relapsing polychondritis is aortic insufficiency (occurring in 4% to 9% of patients). The medial elastic tissue is destroyed and replaced by vascular granulation tissue and focal necrosis. Neutrophil leukocyte aggregates forming microabscesses may be present in the media and intima.

Granulomatosis With Polyangiitis

Large-vessel involvement with aortic aneurysm or dissection has been occasionally reported in granulomatosis with polyangiitis. Both the thoracic and abdominal aortas may be involved, and some cases present on imaging as primarily periaortitis. Histologically, there is granulomatous inflammation of the media and adventitia, with geographic necrosis surrounded by palisading histiocytes and scattered giant cells admixed with neutrophils.

Infectious Aortitis

Infectious aortitis (*Staphylococcus*, *Salmonella*, *Streptococcus pneumoniae*, and other non-*Salmonella* Gram-negative bacilli, mycobacteria, and syphilis) represents a rare cause of aortitis in industrialized nations.

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa (PAN) and Kawasaki disease (KD) are the major variants[1] (Figure 4). The onset of inflammation in medium size vasculitis is more acute than the onset of inflammation in large-vessel vasculitis.

Polyarteritis Nodosa

Epidemiology and Pathophysiology

PAN is becoming a rare disease. PAN is a systemic disease, although there is a limited form of the disease called cutaneous PAN. The reduction in the incidence of PAN may be related to the decrease in hepatitis B virus (HBV) infection achieved by widespread vaccination.[57] Moreover, other systemic necrotizing vasculitides (ie, antineutrophil cytoplasmic antibodies-associated vasculitis, cryoglobulinemic vasculitis) are recognized as distinct entities because of increased awareness and improved diagnostic techniques. In the past, systemic necrotizing vasculitis was generally considered as PAN or related variants. The annual incidence of PAN currently ranges from 0 to 1.6 cases per million inhabitants in European countries,[58] and its prevalence is ≈31 cases per million.[59] PAN affects patients of

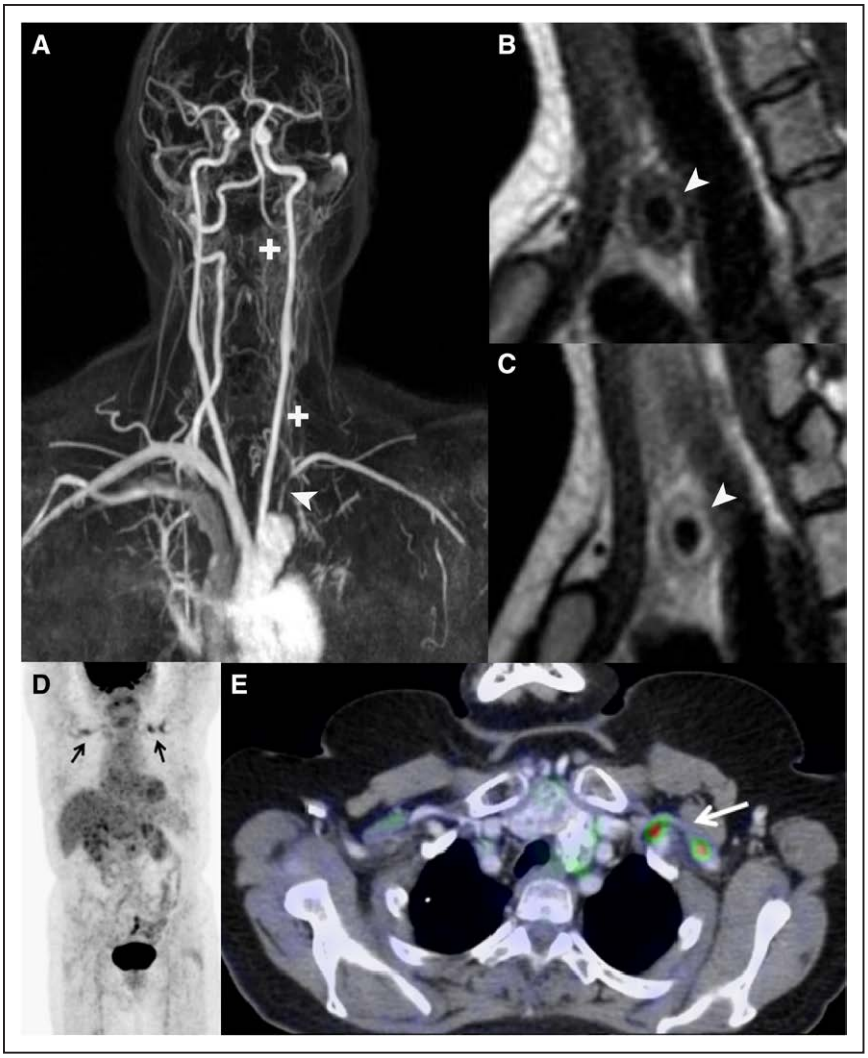

Figure 2. Imaging of Takayasu arteritis. Three-dimensional magnetic resonance imaging (MRI) angiography showing left subclavian artery subocclusion (arrow) and left vertebral artery occlusion from V1 to V3 segments (crosses). Left V4 is perfuse by collateral supply through the right vertebral artery with basilar trunk (**A**). Sagittal T1 without contrast (**B**) and with contrast (**C**) revealing thickening and enhancement of left subclavian artery, suggestive of active disease. **D,** FDG-PET fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanner showing 18F-fluorodeoxyglucose uptake of bilateral subclavian arteries (black arrows) in another patient with Takayasu arteritis. **E,** Intense 18F-fluorodeoxyglucose uptake of left subclavian artery (white arrow).

any sex or ethnic background. The peak incidence occurs in the fifth or sixth decade of life.[58,59] Before vaccination against HBV was available, more than one third of adults with PAN were infected by HBV. At present, <5% of patients with PAN are HBV-infected in developed countries.[59] The most widely implicated mechanism is the development of lesions induced by immune complexes.

Deficiency of adenosine deaminase 2 (DADA2) is the first monogenic vasculitis syndrome caused by loss-of-function homozygous or compound heterozygous mutations in the cat eye syndrome chromosome region 1 gene. DADA2 usually manifests in childhood, with 77% of reported patients consulting before the age of 10 years. The mean age at molecular analysis is 16.5 years (range, 1 to 35 years). The marked reduction of both plasma levels and enzymatic activity of adenosine deaminase 2 detected in affected patients with respect to healthy donors[60,61] confirmed the hypothesis that the causative mutation determines the loss of function of the protein.

Clinical Presentation

PAN is a necrotizing vasculitis that manifests by weight loss, fever, asthenia, peripheral neuropathy, renal involvement, musculoskeletal involvement, gastrointestinal tract involvement, cutaneous lesions, hypertension, or heart failure. Peripheral neuropathy is often the most frequent and earliest symptom of PAN. Raynaud phenomenon is described in 20% of cases. In severe forms, digital vasculitis may lead to digital ischemia or necrosis, reported in 6% of cases.[57]

The kidney is the most commonly affected visceral organ in PAN. Its prevalence ranges from 26% to 44%. Patients may develop hematuria, moderate proteinuria, slowly progressive renal failure, and hypertension. The underlying mechanism of kidney damage is vasculitis of the renal and interlobar arteries, resulting in microaneurysm formation, tissue infarction, or hematomas. Of patients with PAN, 15% have serum creatinine levels >140 µmol/L, and kidney microaneurysms or stenoses are present in 66% of cases.[57] New-onset hypertension occurs in 30% to 40% of cases and is more prevalent in patients with HBV-related PAN.[57] Spontaneous renal hemorrhage or rupture is a rare complication and is typically unilateral.

Cardiovascular manifestations are reported in 25% of cases. Cardiac involvement is represented by

cardiomyopathy vasculitis or pericarditis. Heart failure, affecting the left ventricle more frequently than the right, is the predominant symptom and may be attributed to specific coronary arteritis or disseminated myocardial arteriolar infarcts but also to hypertension or renal involvement. Schrader et al autopsied 36 patients with PAN, 50% of whom had evidence of coronary arteritis, and 8% had large infarcts.[62]

Neurological symptoms of PAN-related central nervous system involvement are variable and depend on the territory affected. Their onset can be acute (eg, stroke or seizures) or more chronic and insidious, such as headaches or encephalopathic symptoms (cognitive and vigilance disorders or psychiatric manifestations). Motor deficits are common. MRI is essential and may show ischemic disseminated lesions of different ages, which are suggestive of vasculitis.[63] Meningeal tissues, as well as the parenchyma, can be gadolinium enhanced. Hemorrhagic lesions can be observed within acute ischemic lesions. In addition to microaneurysms, which occur more frequently in PAN, multiple arterial segmental and focal stenoses and occlusions are other typical vasculitis findings in cerebral angiography. Microaneurysm formations are frequent in medium-sized vessels of patients with PAN, although they are more rarely reported in brain vessels.[63] Patients with DADA2 and early-onset PAN present with strokes in more than 50% of cases. Central nervous system events are predominantly multiple acute or chronic ischemic lacunar infarcts located in the deep-brain nuclei or the brain stem, sparing the subcortical white matter.[61] Hemorrhagic events seem to be a part of the clinical spectrum, although they occurred more frequently in patients taking aspirin or warfarin.

DADA2 is characterized mainly by early-onset PAN, chronic or recurrent systemic inflammation with fever and elevation of acute phase reactants, usually associated with strokes, hypogammaglobulinemia, cytopenia and skin manifestations, such as livedo reticularis, Raynaud phenomenon, ulcerative lesions, digital necrosis.[60,61] In most patients, neurological involvement affecting both the peripheral and central nervous systems has been described. The severity of the central nervous system involvement is rather variable. In some patients, transitory ischemic attack has been described, whereas others developed an ischemic or hemorrhagic stroke. The neuropathy ranges from transient mononeuritis to permanent polyneuropathy. Most patients have gastrointestinal manifestations, such as abdominal pain, weight loss, hepatomegaly, splenomegaly, portal hypertension, bowel perforation, or stenosis.

Diagnosis

The diagnosis of PAN theoretically requires histological proof showing segmental fibrinoid necrosis of medium-sized vessels. However, the diagnosis can be based on a combination of clinical, immunologic, and radiological findings. Antineutrophil cytoplasmic antibodies negativity and angiographic features are useful for diagnosis. Angiographic findings, including microaneurysms (ie, 1- to 5-mm diameter), ectasia, or occlusive disease in celiomesenteric and renal arteries (Figure 3), are present in ≈40% to 90% of patients at the time that clinical symptoms appear.

Management

PAN treatment is essentially based on therapeutics already prescribed for other vasculitides. For non–HBV-PAN,

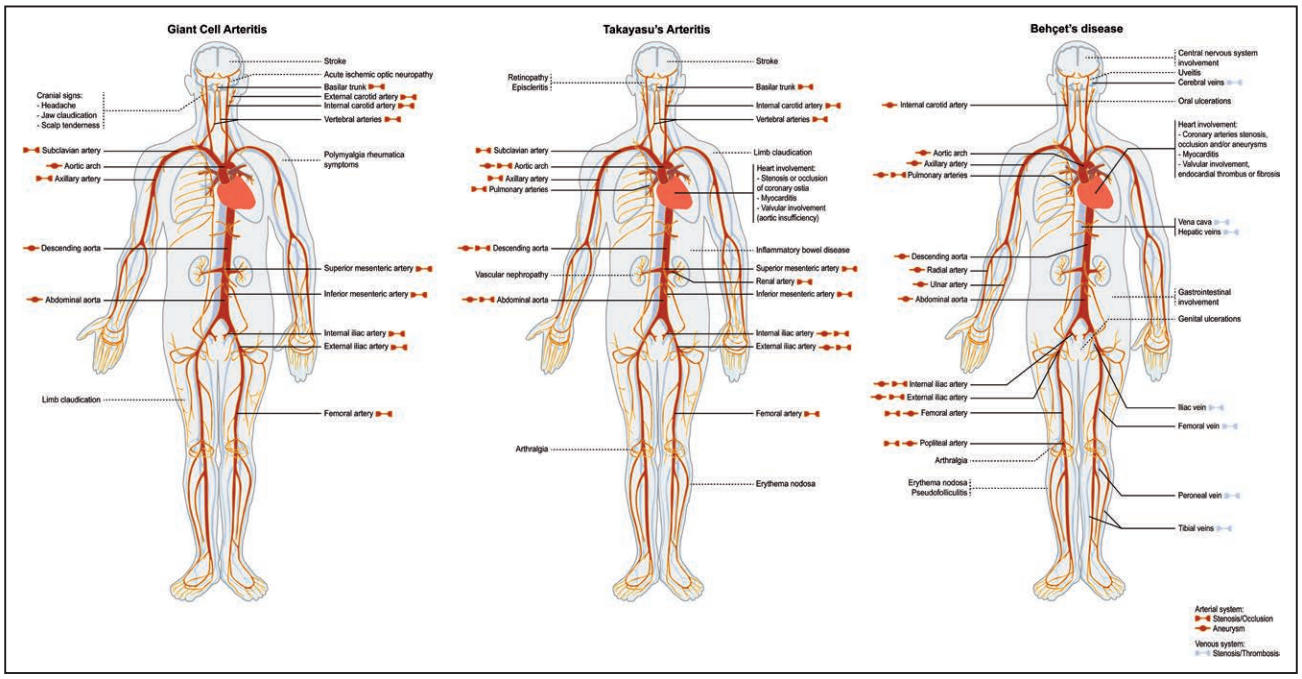

Figure 3. Representative pattern of predominant vascular and organ lesions in large-vessel vasculitis.

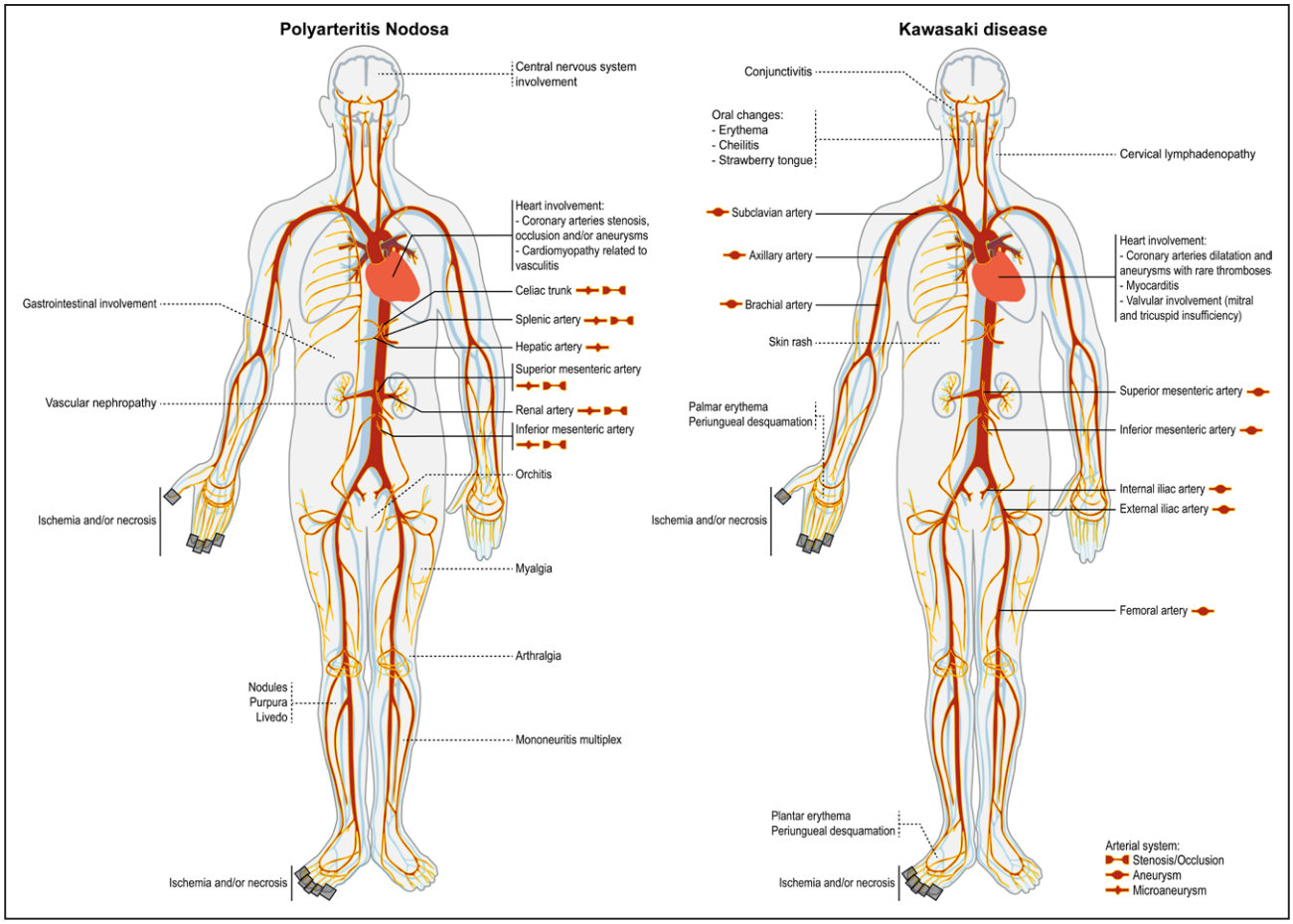

Figure 4. **Representative pattern of predominant vascular and organ lesions in medium-vessel vasculitis.**

treatment remains based on corticosteroids and immunosuppressants, and for HBV-PAN, antiviral agents are used in combination with plasma exchanges and initial corticosteroids to rapidly control the most severe PAN manifestations during the first weeks of overt vasculitis.

In DADA2, the first-line treatment consists of TNF inhibitors and is effective in controlling inflammation and in preserving vascular integrity.[64] Hematopoietic stem cell transplantation has been successful in a group of patients presenting with hematologic manifestations.[65]

Kawasaki Disease

Epidemiology

KD is a worldwide illness with varying incidence rates. The highest incidence is in East Asia, with an annual rate of 80 to 308.0 per 100 000 children <5 years.[66,67] In the United States and in countries with predominantly non-Asian populations, the usual annual rate is 10 to 20 per 100 000 in children <5 years old.[68] KD has a striking age distribution, with 80% of cases occurring in children <5 years old and 50% in those <2 years old. KD occurs seasonally, with winter peaks in Japan and a winter-spring predominance in the United States and many other temperate areas. The male-to-female ratio of patients with KD is ≈1.5:1.[66,68] More recently, in the context of the coronavirus disease 2019 (COVID-19) pandemic, several studies have reported outbreaks of KD-like disease. The monthly incidence was estimated to be 30-fold higher than that observed for KD across the previous 5 years in Italy.[69]

Pathophysiology

Several susceptibility genes (ITPKC, CASP3, FCGR2A, BLK, CD40, and HLA class II) have been shown to have an association with KD.

The seasonality of KD is highly suggestive of viral etiology.[68] Innate immune system activation of signaling pathways related to IL-1, IL-6, and TNF is an early event in KD. Seven to 9 days after onset, an influx of neutrophils and lymphocytes is observed, along with destruction of the internal elastic lamina and fibroblastic proliferation. Inflammatory infiltrates in the arterial wall can lead, in more severe cases, to loss of structural integrity, resulting in dilation and aneurysm formation. Within weeks to months, the active inflammation is replaced by progressive fibrosis and scar formation, which may result in progressive stenosis.

Clinical Presentation

KD is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral nonexudative

conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy.

Coronary arteries are affected in ≈20% of cases, which can lead to myocardial infarction or sudden death.[70] Coronary involvement in systemic vasculitis may manifest with aneurysm formation, thrombosis, or coronary dissection. Thrombus formation within the aneurysm and distal embolization are also possible complications because of the abnormal blood flow inside the aneurysm. The highest risk of thrombi occurs when the diameter of the aneurysm exceeds 5 mm. Panarteritis occurs in the acute phase of KD, and coronary artery aneurysms develop in the subacute phase. During the chronic phase, these aneurysms will undergo regression or remodeling. Coronary artery abnormalities during the acute illness range from dilation only to aneurysms of various numbers, sizes, and characteristics, with the involvement occurring first in proximal segments and then extending distally.[71] The most common locations of aneurysms are at the bifurcation of the left main coronary artery and in the proximal right coronary artery. Serial echocardiographic studies in acute KD show that coronary artery dilation may be visible early in the illness, usually in the second and third week of the acute phase. Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms from 25% to 4%.[72,73] Even with treatment in the acute phase of KD with IVIG and aspirin, up to 5% of patients will develop serious and potentially life-threatening cardiac complications. Patients with KD who have persistent coronary artery aneurysm, defined as a Z-score ≥2.5 after 6 weeks (Z-score is the internal dimension of the coronary artery expressed as the number of SD units normalized for body surface area), are considered to be at high risk for long-term arterial damage and will require clinical and imaging follow-up. The risk of thrombotic and stenotic complications is related to aneurysm size. Large or giant aneurysms (≥8 mm in diameter or a Z-score ≥10) are the least likely to resolve.

Myocarditis develops early, and acute left ventricular dysfunction is generally transient and responds readily to anti-inflammatory treatment. The rapid improvement in left ventricular function differs from that observed in other causes of myocarditis. Using gallium citrate Ga-67 scans and technetium-99m–labeled white blood cell scans, myocardial inflammation can be documented in 50% to 70% of patients.[74] Histopathologic analysis of myocarditis in acute-phase KD has demonstrated that myocardial inflammatory changes occur before coronary artery abnormalities and without concurrent ischemic damage.[75] Acute myocardial inflammation is infrequently associated with overt ventricular ectopy.

Valvular dysfunction occurs in 25% of patients regardless of coronary artery involvement and most often involves the mitral and tricuspid valves.[76] Valvular insufficiencies are often observed in the acute phase of KD because of valvulitis or myocarditis-induced myocardial dysfunction.[76] These lesions mostly disappear with the resolution of the acute illness, but a small group of the lesions persists and progresses. There is also late-onset aortic or mitral insufficiency caused by thickening or deformation of fibrosed valves, with the timing ranging from several months to years after the onset of KD. Some of these lesions require valve replacement. The incidence and outcome of valvular diseases in the high-dose-globulin era remain to be elucidated.

Diagnosis

The diagnosis of KD is based on the presence of at least 5 days of fever, and 4 of the 5 principal clinical features, which include (1) changes in extremities (acute phase: erythema of the palms and soles, and edema of the hands and feet; subacute phase: desquamation of the fingers and toes); (2) polymorphous exanthema, primarily involving the trunk and extremities, and accentuation in the groin with early desquamation, diffuse maculopapular eruption, scarlatiniform erythroderma, and erythema multiforme-like; (3) bilateral bulbar conjunctival injection; (4) changes in lips and oral mucosa: erythematous and cracked lips, strawberry tongue, and oral and pharyngeal hyperemia; and (5) cervical lymphadenopathy (>1.5 cm diameter). Patients with at least 5 days of fever but <4 of the principal criteria can be diagnosed with KD when coronary artery abnormalities are detected. Other multiple organs and tissues are inflamed during the acute illness and may cause clinical symptoms, such as arthralgia and arthritis, peripheral facial nerve palsy, hepatitis, or diarrhea.[71] Macrophage activation syndrome rarely occurs and is often associated with IVIG resistance. The clinical features are typically not all present at a single point in time, and it is generally not possible to establish the diagnosis early in the course. The pericardium, myocardium, endocardium including valves, and coronary arteries all may be inflamed. Echocardiography has a high sensitivity and specificity for the detection of abnormalities of the proximal coronary artery segments. Transesophageal echocardiography, angio-CT, and cardiac MRI can be useful for the evaluation of older children and adolescents in whom visualization of the coronary arteries with transthoracic echocardiography is inadequate. Cardiac multidetector computed tomography is a noninvasive technique that is widely considered to be a powerful method for the detection of coronary artery vasculitis. The temporal and spatial resolution of multidetector computed tomography allows imaging of both the lumen and vessel wall, which allows the

diagnosis of coronary artery vasculitis in the context of systemic vasculitis.

Management

Cardiovascular manifestations and complications are the major contributors to morbidity and mortality related to KD, both during the acute illness and in the long term. Severe cardiac complications of KD are overrepresented in males. KD relapse is a rare occurrence, in <3% of patients. All patients diagnosed with KD need to receive anti-inflammatory treatment. IVIG (2 g/kg given as a single intravenous infusion) is the first-line treatment and should be instituted as soon as the diagnosis is established. IVIG reduces the prevalence of coronary artery abnormalities.[72] During the acute phase of KD, acetylsalicylic acid may be used for its anti-inflammatory effects (80 to 100 mg/kg/d in the United States and 30 to 50 mg/kg/d in Japan and Western Europe). However, acetylsalicylic acid does not appear to lower the frequency of development of coronary abnormalities.[77] Adjunctive corticosteroid therapy with IVIG and acetylsalicylic acid may be considered for KD at the highest risk for IVIG resistance (recrudescent or persistent fever at least 36 hours after the end of IVIG infusion).

Approximately 10% to 20% of patients do not respond to initial IVIG. In IVIG-resistant patients (recrudescent or persistent fever at least 36 hours after the end of their IVIG infusion), a second IVIG infusion of 2 g/kg with or without corticosteroids is most frequently used.[78] Infliximab (anti–TNF-α, single 5 mg/kg infusion) is an alternative to a second IVIG infusion. Compared with a second infusion of IVIG, infliximab may reduce hospitalization and fever duration, but coronary artery outcomes and adverse events seem equivalent.[79] Alternative treatments in highly refractory patients included cyclosporine, monoclonal antibody therapy such as anakinra (recombinant IL-1β receptor antagonist), or plasma exchanges.[71]

The major long-term risks for patients with KD with coronary artery aneurysms are thrombosis within the aneurysm or coronary stenosis, either of which can result in myocardial ischemia. Patients with KD who have coronary artery aneurysms persisting after 6 weeks should remain on long-term low-dose aspirin. Risk stratification for long-term management is based on maximal coronary artery luminal dimensions (normalized as Z-scores). Patients with KD with persistent coronary artery aneurysm, defined as a Z-score ≥2.5 after 6 weeks, require lifelong clinical and imaging follow-up.

Thromboangiitis Obliterans (Buerger Disease)

Thromboangiitis obliterans is a segmental inflammatory arteritis that involves small- to medium-sized arteries and veins of the extremities.[80] Thromboangiitis obliterans mainly affects young patients with tobacco exposure who present with ischemic ulcers, pain at rest, claudication, and cool extremities, but also migratory thrombophlebitis and Raynaud phenomenon.[80] Distal arterial occlusions can ultimately lead to limb amputation in 34% of patients within 15 years from diagnosis.[81] In a retrospective series of 224 patients, 76% had lower limb claudication, and 36% and 30% had lower- or upper-extremity ischemic ulcerations, respectively.[81] The cornerstone of treatment is tobacco cessation. Complete abstinence is crucial because a reduction in tobacco exposure does not prevent progressive tissue necrosis and limb loss. In addition, prostacyclin analogs improve ulcer healing, pain, and amputation-free survival.

VARIABLE-VESSEL VASCULITIS

Behçet's disease

Epidemiology

BD affects young people and is a systemic vasculitis of arterial and venous vessels of any size. Data suggest large geographic variations in the frequency of BD, with prevalence rates of 20 to 420/100 000 inhabitants for Turkey,[82] 1.5 to 15.9 for southern Europe, and 0.3 to 4.9 for northern Europe. In North America, the prevalence of BD has recently been estimated at 5.2 cases/100 000 individuals.[83] Population-based studies of immigrants or migrant populations consistently indicate that migrants from areas of high BD prevalence remain at high risk for BD, which may even be close to the prevalence observed in their countries of origin.[84] Young men have the worse prognosis. BD occurs mainly between 18 and 40 years. Some pediatric-onset cases have been reported. After 55 years, the onset of BD is exceptional, and the diagnosis has to be made cautiously.

Carrying the HLA-B51 suballele confers a relative risk of 5.8 of developing BD. HLA-B51 does not seem to be correlated with the prognosis of the disease.[85] Studies have identified associations with genome-wide significance (in the IL23R-IL12RB2, IL10, STAT4, CCR1-CCR3, KLRC4, ERAP1, TNFAIP3, and FUT2 loci).[86]

Clinical Presentation

Clinical manifestations of BD include oral ulcerations, genital ulcerations, joint involvement, skin manifestations (pseudofolliculitis and erythema nodosum), uveitis, and cardiovascular and neurological manifestations.

The frequency of arterial involvement in BD ranges from 2.2% to 18%, with marked male predominance. Arterial involvement can be found in any peripheral artery, particularly in the femoral artery, popliteal artery, iliac artery, and abdominal aorta.[87,88] Large artery involvement may result in both aneurysmal dilatation and,

less commonly, stenosis or arterial occlusion. The clinical presentation of aneurysms varies widely from an asymptomatic to pulsatile mass, back pain, painful mass, hematoma, intermittent claudication, gangrene of the forefoot, or fever.[87,88] Multiple aneurysms can be seen in peripheral arteries. Loss of peripheral pulses may occur in patients with arterial occlusion of the extremities.[87]

Aortic inflammatory involvement during BD is more frequent in young men. The vascular inflammation may complicate single or multiple localized aneurysms (Figure 3). Rupture of aorta or pulmonary artery aneurysms are the main causes of death.

Cardiac involvement is reported in 6% of patients with BD, mostly in men with associated vascular involvement.[89] BD cardiomyopathy can be related to primary myocardial disease, disturbance of the coronary microcirculation, or the presence of silent ischemia. Myocardial manifestations include cardiac arrhythmias and, rarely, myocarditis. Ventricular tachycardia and fibrillation have been reported. A systematic Doppler tissue echocardiography study found a higher proportion of diastolic dysfunction in patients with BD when compared with control subjects.[90] The outcome of cardiac involvement in BD is poor, accounting for 15% of deaths.[89]

Coronary artery lesions occur in 5% of patients with BD and are more frequent in men.[89] They manifest through chest pain, angina pectoris, or acute myocardial infarction. Coronary lesions are usually proximal and may lead to ischemic cardiomyopathy or ventricular aneurysm. Lesions of the coronary arteries include stenosis, occlusion, and pseudoaneurysm, with or without myocardial infarction. They may also complicate a coronary angiography as a result of a pathergy reaction.

Mitral and, less frequently, aortic valvular insufficiency have been observed in patients with BD.[89] Valvulitis has been reported, with valve leaflets covered by fibrin with necrosis and massive growth of granulation tissue.[91] Cardiac thrombi in BD are mainly located in the right atrium and ventricle and rarely in other sites of the endocardium.[89] Endomyocardial fibrosis is a rare complication of BD and is likely the sequela of vasculitis involving the endocardium or myocardium.[89]

Diagnosis

As there is no pathognomonic test for BD, the diagnosis is based on clinical manifestations. Because HLA-B51 is present in ≈59% of BD cases and 29% of healthy controls, it would not constitute a diagnostic test. Mucocutaneous lesions are the hallmark of BD. In 1990, the International Study Group's diagnostic/classification criteria proposed a set of diagnostic criteria for BD, including recurrent oral aphthosis (mandatory criterion) associated with at least 2 of the following criteria: (1) genital ulceration, (2) skin lesion, (3) uveitis, and (4) pathergy test positivity.[92] In 2014, the new International Criteria for Behçet's Disease included both vascular and neurological features, and assigned more points for the presence of oral or genital aphthosis and ocular findings.[93]

Management

Treatment of BD depends on the organs involved. Oral ulcerations, which are the hallmark manifestations of BD, should be first treated by symptomatic topical therapy and colchicine (1 to 2 mg/d). In refractory cases or intolerance to colchicine, apremilast or thalidomide are interesting alternatives. For severe manifestations (ie, neurological or major vessel involvement), the use of glucocorticoid and disease-modifying antirheumatic drugs (eg, azathioprine or cyclophosphamide) is mandatory. Biological agents, including mainly anti-TNF, were proved effective in retrospective studies.

Cogan Syndrome

Cogan syndrome is a rare disease with ≈300 cases published in the literature. It is characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis affecting vessels of any size, aortitis, aortic aneurysms, and aortic and mitral valvulitis. Aortitis occurs in up to 10% of cases of Cogan syndrome. The aortitis usually affects the ascending aorta and the arch and is usually caused by inflammation with a mixed inflammatory pattern. It affects young adults, and no sex or ethnic predominance has been identified.

CONCLUSIONS

Prompt identification of vasculitides is important because they are associated with an increased risk of mortality. Despite recent randomized controlled trials with biological agents, management of medium- and large-vessel vasculitis depends on observational studies. Well-designed controlled trials using validated outcome measures, standardization of disease assessment, and identification of reliable biological markers that could guide the choice of targeted therapies are important unmet needs. Strategies using biologics aiming at lowering glucocorticoid doses for induction therapy and reducing cumulative glucocorticoid doses are underway. The ultimate goal is to achieve the best cost-benefit and efficiency-tolerance balance.

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Disclosures

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