Inflammatory and Connective Tissue Disorders of the Aorta

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Giant Cell Arteritis

Giant cell arteritis (GCA) is a chronic systemic vasculitis that preferentially affects large- and medium-sized arteries with well-developed wall layers and adventitial vasa vasorum [1]. The vasculitis is characterized by granulomatous involvement of the aorta and main branches in which inflammation leads to luminal occlusion, stenosis, and marked disruption in the vascular wall integrity and distal blood flow [2]. Intimal hyperplasia occurs sporadically along the length of the muscular arteries which causes stenosis and occlusion, resulting in a variety of ischemic complications [3]. Conversely, when the aorta is affected, the inflammatory process leads to dilation and aneurysm formation with a predilection for the thoracic aorta [3, 4]. GCA is well known to occur in close association with polymyalgia rheumatica (PMR), and these two syndromes are commonly observed together.

Epidemiology

Giant cell arteritis is the most common of the large-vessel vasculitides (Fig. 16.1) and occurs almost exclusively in the elderly. Patients are typically over 50 years of age, with peak incidence between age 70 and 80 years. Like most other rheumatologic conditions, women are more often affected than men and account for approximately 65 to 75% of patients diagnosed with GCA [1]. The highest frequencies have been reported in populations of Scandinavian and Northern European descent. The annual incidence of GCA in Olmsted County, Minnesota, is 17 per 100,000 persons over the age of 50, which is similar to that reported in Scandinavian countries [1, 6]. In Southern Europe and the Mediterranean, incidence rates are fewer than 10 per 100,000 persons over 50 years of age [1, 3, 7]. There are very few reported cases of GCA in patients of Latino, Asian, Middle Eastern, and African American descent [7]. This high degree of variability among population-based cohorts suggests there may be a genetic predisposition in certain populations. The overall mortality rate in patients with GCA and PMR is similar to that expected in general populations of the same age and sex [7].

Polymyalgia rheumatica has a similar age, sex, and genetic distribution as giant cell arteritis, and diagnostic criteria for both syndromes include age greater than 50 years [8–11]. Despite the many similarities between the two syndromes, the prevalence of PMR is 1 per 133 persons over the age of 50 years [6, 8].

Large-vessel involvement in GCA is likely underestimated in the literature, in part due to the frequent delay in diagnosis and lack of typical cranial symptoms. The prevalence of aortic impairment in GCA is estimated to occur in 10–25% of cases, though this data is based primarily on retrospective reports [7, 12, 13]. A population-based study from Olmsted County, Minnesota, found that patients with GCA were 17.3 times more likely to develop a thoracic aortic aneurysm and 2.4 times more likely to develop an abdominal aortic aneurysm compared to the age- and sex-matched population [14]. There do not appear to be any reliable predictive factors for aortic involvement in GCA; however, arterial hypertension, persistent chronic inflammatory response, and frequent relapses may be associated with increased risk for aneurysm formation [14, 15].

Diagnosis

The American College of Rheumatology has established diagnostic criteria and treatment guidelines for giant cell arteritis, and these have been adapted in the most recent

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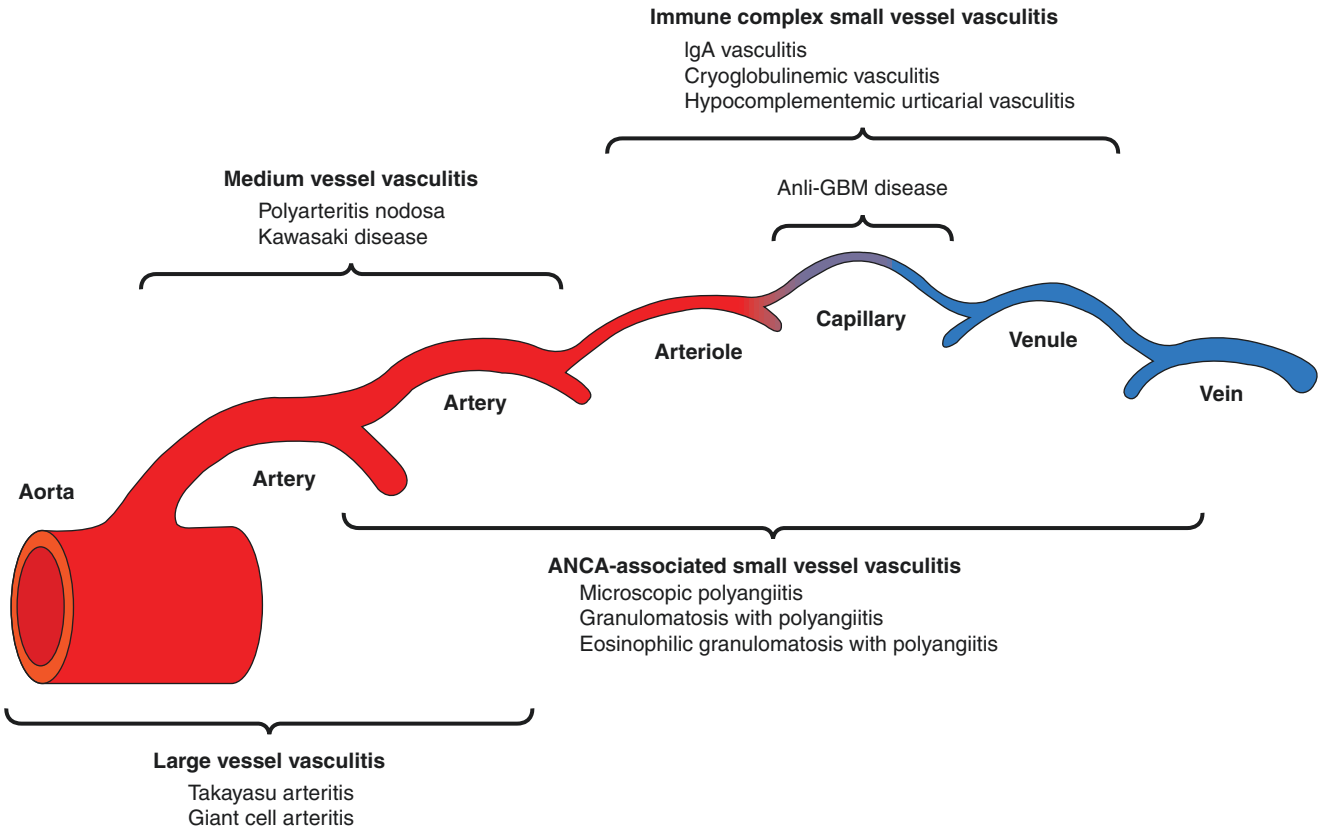

Fig. 16.1 Anatomic distribution of vessel involvement in large-, medium-, and small-vessel vasculitis. (From: Jenette et al. [5]. Reprinted with permission)

American College of Cardiology Foundation/American Heart Association guidelines for the management of thoracic aortic disease [10, 16, 17].

American College of Rheumatology Diagnostic Criteria for Giant Cell Arteritis

Must meet at least 3 criteria.

Age of disease onset ≥50 years
New-onset headache
Temporal artery with decreased pulsation or tenderness to palpation
Elevated ESR > 50 mm/hr. in the first hour of testing (Westergren method)
Biopsy evidence of vasculitis
Predominance of mononuclear cell infiltration and granulomatous inflammation, usually with multinucleated giant cells

Solomon et al. [4]

The diagnosis of GCA is considered on the basis of medical history, clinical evaluation, laboratory, and imaging studies and is confirmed based on histological findings. Three or more criteria confer a sensitivity and specificity over 90% for the disease [10].

Clinical Features

The clinical presentation of giant cell arteritis is variable and widespread, reflecting the truly systemic nature of this disease. The disease course is typically subacute, though isolated aortic disease may be asymptomatic for many months to even years. Patients may manifest with variable ischemic symptoms such as new-onset localized headache, acute ischemic optic neuropathy (resulting in blindness) and other visual changes, jaw claudication, or symptoms of upper extremity claudication; others may have a more silent and indolent course with constitutional symptoms of fever, fatigue, weight loss, and anorexia [1, 7, 10]. On physical exam, the frontal or parietal branches of the superficial temporal arteries may be thickened, nodular, and tender, and pulses may be decreased or absent [7, 8, 18].

Aortic aneurysm, dissection, and large artery stenosis of the upper extremities tend to occur late in the history of the disease but may actually be smoldering long after inflammatory markers return to baseline and therapy is tapered [12]. Aortic arch syndrome is a reported feature of severe GCA, in which arteritis spreads to the subclavian and axillary vessels [3, 19]. Bruits may be heard on auscultation over the carotid, subclavian, axillary, and brachial arteries, and pulses may be absent or diminished [8]. These features mimic the presentation of Takayasu arteritis, and further imaging studies are needed to distinguish the two diseases in the absence of typical cranial symptoms. Aortic aneurysm is often found incidentally or during workup for symptoms of chest pain, new diastolic murmur, or diastolic dysfunction. The thoracic aorta, particularly the ascending aorta, is affected more often than the abdominal aorta in GCA. Aortic dissection and/or rupture can occur during times of subclinical and clinical aortitis, and patients should be monitored even after successful completion of therapy [13].

Approximately 30–50% of patients with GCA report symptoms of PMR simultaneously or in isolation of the diagnosis of GCA [3, 7, 8]. PMR is an autoimmune syndrome that causes inflammation of the bursas and periarticular structures of the shoulder and pelvic girdle in a symmetrical distribution. Patients with PMR typically report acute onset of profound aching and morning stiffness in proximal muscle groups [4]. Patients may report symptoms of PMR before, at the time of, or after the diagnosis of GCA. Symptoms of PMR are also likely to be reported when glucocorticoid treatment for GCA is being tapered [4].

Laboratory Testing

Laboratory analysis is important in the workup of patients with suspected GCA. Infection and malignancy should be rooled out in patients presenting with fever of unknown origin, weight loss, and other nonspecific symptoms. Serum laboratory testing may show a normochromic anemia (anemia of chronic disease), decreased serum albumin, and elevated hepatic enzymes [3, 7, 20]. The characteristic laboratory findings in patients with GCA are a markedly elevated erythrocyte sedimentation rate (ESR) and concomitantly high C-reactive protein (CRP). The ESR can reach 100 mm/hour; however, a less striking elevation should not deter from the diagnosis of GCA. Response to therapy is often guided by the decrease of ESR and CRP levels, and suspicion for relapse can be monitored if these levels increase. Some studies also suggest that elevations in serum interleukin (IL)-6 concentrations correlate with clinical disease activity in GCA [21–23]. However, the clinical utility of following this biomarker has yet to be determined, and IL-6 assays are not routinely available.

Additional antibodies such as rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies (ANCA) are usually negative [8].

Histopathology

The temporal artery biopsy remains the gold standard diagnostic modality for GCA. Biopsy of an artery with the presence of an inflammatory infiltrate within the adventitia and media along with fragmentation of the elastic lamina, with or without giant cells, is consistent with GCA. There may also be features of panarteritis with an inflammatory infiltrate composed of lymphomononuclear cells, neutrophils, and eosinophils, but without giant cells [2]. The sensitivity of a positive temporal artery biopsy ranges from 70% to more than 90%, though it is not 100% specific [7]. Thus, the diagnosis of GCA should be made in the context of clinical and laboratory findings as well. Temporal arteries are frequently not involved in patients with predominantly large-vessel involvement, and the diagnosis should not be excluded with absent cranial features. These findings suggest that there may be two phenotypes of the same disease process [8]. As such, large-vessel biopsies are not routinely feasible, and diagnosis is made based on the presence of laboratory abnormalities and vascular imaging features. The inflammatory pattern in affected arteries is intermittent rather than continuous, thus creating an additional challenge with obtaining an affected biopsy specimen [8].

The pathogenesis of giant cell arteritis is a T cell-mediated process in which T cells enter the artery through the vasa vasorum, undergo clonal expansion, and are stimulated to produce interferon-γ, IL-17, and IL-21 [8]. Cytokine production within the arterial wall activates inflammatory and endothelial cells, vascular smooth muscle cells, and fibroblasts [4]. This process results in the formation of giant cells and ultimately granulomatous infiltrates [8, 24]. Macrophages also produce matrix metalloproteinases, vascular endothelial growth factor, and platelet-derived growth factor that promote remodeling of the arterial wall and destruction of the internal elastic lamina [4, 24]. The primary immunologic injury occurs within the adventitia of the affected segment, whereas the majority of tissue damage occurs within the media-intima junction [25]. This inflammation and remodeling result in intimal hyperplasia and obstruction of the lumen, which gives rise to the ischemic complications observed in GCA [4, 8, 24]. The mechanism is slightly different within the aorta as stenosis is not a feature. Rather, ectasia and circumferential thickening of the aortic wall are consistent with large vessel GCA [12].

It is unclear why some regions of the artery are spared and why some vascular branches are unaffected in GCA. There

appears to be a tissue tropism despite the systemic involvement of GCA. This is likely reflective of subtle differences in the microanatomy of certain regions of the arterial tree and possibly the territorial distribution of dendritic cells; however, the exact mechanism is poorly understood [19, 26]. The vessels most typically affected include the external carotid branches of the aorta, particularly the superficial temporal and occipital arteries; ophthalmic, posterior ciliary arteries; vertebral, distal subclavian, axillary arteries; as well as the thoracic aorta. Lower extremity vasculitis and involvement of the abdominal aorta is less common; intracranial, coronary, and mesenteric arteries are essentially spared [1, 3, 4, 19].

Imaging Findings

Imaging is an important component to the diagnosis and management of patients with GCA. Patients with classical cranial manifestations or biopsy-proven GCA should be screened for large-vessel disease. Likewise, aortic involvement should be considered in patients with disease relapse or persistently elevated inflammatory markers, fever of unknown origin, or upper extremity claudication symptoms. Different radiological methods have been useful in identifying the presence of aortitis and assessing response to treatment.

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) of the aortic arch and its branches are useful imaging techniques in the evaluation of patients with GCA (Fig. 16.2). These techniques are helpful in assessing the extent of arterial involvement in patients with biopsy-proven GCA and also to monitor vascular lesions for signs of progression [28]. Inflammatory activity is observed as delayed enhancement of the arterial wall due to leaky micro vessels. However, vessel wall edema is not always associated with disease activity or the development of new lesions and should not solely influence treatment decisions. Traditional magnetic resonance imaging (MRI) is sensitive and specific for the detection of stenosis, occlusions, dilations, and aneurysms and adds information about the presence of vessel wall thickness, edema, and mural wall abnormalities that together are suggestive of aortic wall inflammation [29].

Conventional angiography used to be the reference standard for the diagnosis of large-vessel vasculitis, though now is seldom used for diagnostic purposes due to the availability of noninvasive imaging techniques. Arteriography shows long, regular, smooth-walled stenosis in GCA, as well as occlusions and/or dilations; however, this technique is not helpful for the early diagnosis of vasculitis [28]. Aortic angiography is now reserved primarily for the planning of revascularization procedures [4].

The use of positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) has demonstrated use in the evaluation of large vessels and detection of GCA in the medium and large vessels. Increased uptake of 18F-FDG by hypermetabolic cells within blood vessels is suggestive of inflammation and can be helpful in detecting early disease before the development of structural lesions. This functional imaging technique is also useful in monitoring disease activity over time and response to treatment [30, 31]. When combined with CT, this imaging technique can demonstrate functional lesions and structure simultaneously. However, FDG is taken up by all hypermetabolic cells and currently cannot distinguish vasculitis from other inflammatory lesions such as atherosclerotic changes in vessel walls. The sensitivity and specificity of 18F-FDG PET with CT has yet to be established and is not yet a cost-effective method for diagnosing and monitoring GCA. There are several limitations of using PET and PET-CT for the long-term monitoring of patients with GCA, and further studies are needed to validate criteria for disease activity in large-vessel vasculitis.

The role of imaging studies in both short- and long-term follow-up has been insufficiently defined. Many authors suggest annual chest radiographs in patients with GCA at time of diagnosis and then for several years following remission in order to detect dilation of the thoracic aorta. Others suggest increased screening for abdominal aortic aneurysm. These recommendations are based on a proposed algorithm for the early detection of aneurysms in GCA, but remains to be validated [31, 32].

Treatment

Treatment of giant cell arteritis is currently based on European Leage Against Rheumatism (EULAR) guidelines and adapted for all large-vessel vasculidities. High-dose glucocorticoids are the mainstay treatment for inducing remission in patients with GCA and should be started at 1 mg/kg per day, maximum 60 mg oral prednisone per day. For patients with cranial GCA and visual symptoms, 3 days of pulse IV methylprednisolone is recommended in order to prevent irreversible vision loss [16]. Symptoms tend to resolve quickly once corticosteroid therapy is initiated; fever, headache, and PMR symptoms usually improve within days. Ischemic symptoms and claudication may take considerably longer to resolve. The inflammatory response usually returns to normal within 2–4 weeks, as evident by the decrease of ESR and CRP; however, the ESR and CRP are imperfect markers of disease activity in GCA and should not be used as sole predictors of response to therapy [33]. Corticosteroids should then be gradually tapered once there is clinical improvement and the ESR has returned to normal values. Treatment duration is highly variable, with majority of patients able to discontinue corticosteroid therapy within 1–2 years.

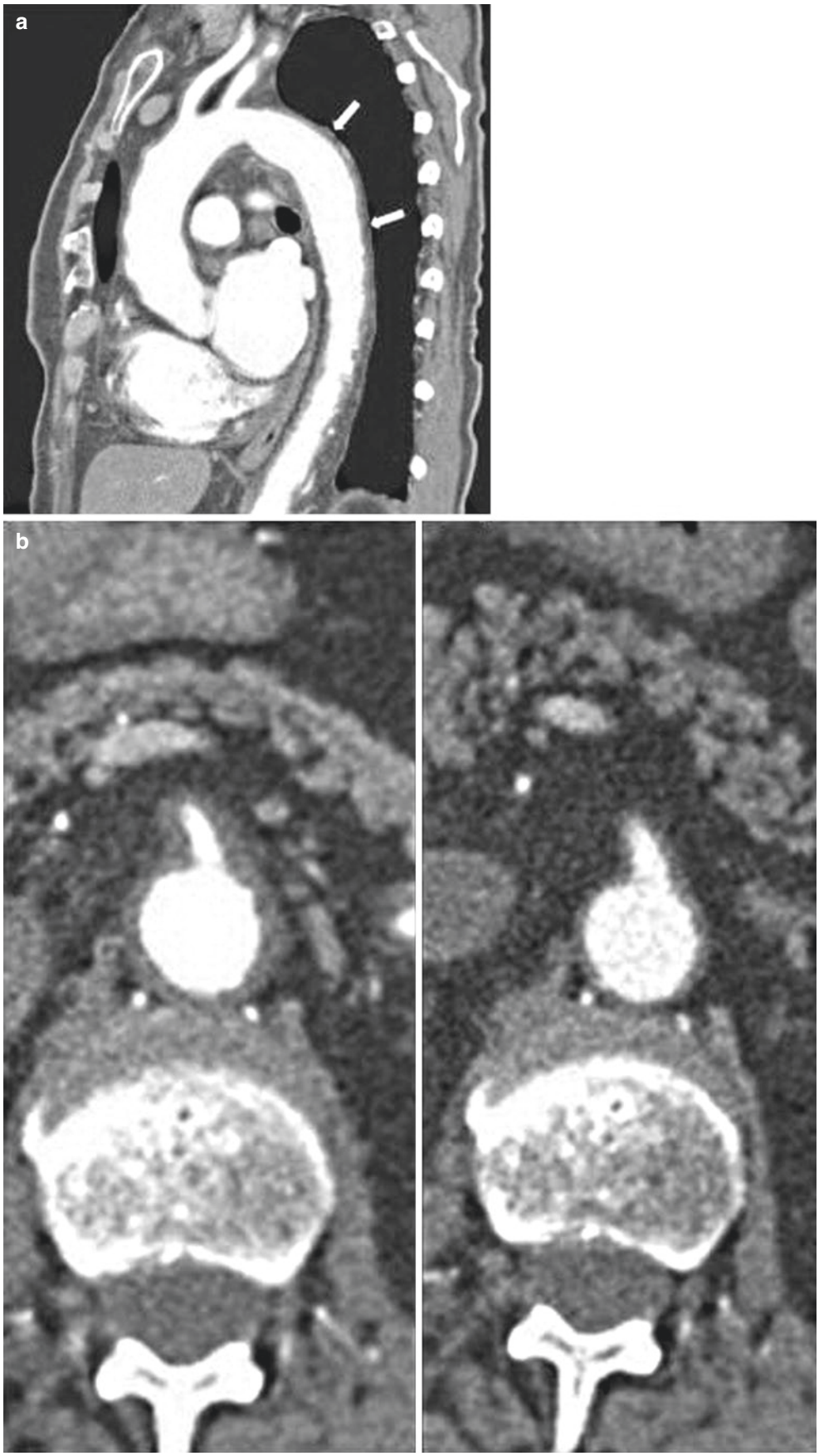

Fig. 16.2 CT angiogram of a patient with GCA and involvement of the aorta. (**a**) Sagittal image demonstrating thickened arterial walls, most prominent in the great vessels and throughout the entire descending thoracic aorta. (**b**) Arterial wall thickening extended into the upper abdominal aorta and superior mesenteric artery before (left) and after (right) treatment with corticosteroids. (From: Warrington and Cooper [27]. Reprinted with permission)

Some patients with GCA may tolerate complete discontinuation of corticosteroids and achieve remission. However, approximately 40–50% of patients experience relapse during corticosteroid tapering and require return to a higher dose. Recurrence of the disease after complete withdrawal of corticosteroid therapy is estimated to occur in 20–30% of patients and is most commonly seen within the first year after steroid discontinuation [34]. There have been several studies looking at the efficacy of methotrexate as a steroid-sparing option, though results are conflicting [34]. Tocilizumab, an IL-6 inhibitor, has recently been approved as a steroid-sparing agent and is the first biologic to be indicated for the treatment of GCA [23, 35].

There is little data on the long-term evolution of large artery involvement in GCA. Population-based studies from Minnesota and northern Spain demonstrated that median time from diagnosis of GCA to diagnosis of thoracic and abdominal aortic aneurysm was 10.9 years and 6.3 years, respectively [3, 36]. This may suggest that patients with large artery involvement may have subclinical disease that continues to smolder long after their initial disease manifestations were treated. Patients with aortic aneurysms between 3 and 5 cm in diameter which are enlarging in the context of elevated inflammatory markers (ESR and CRP) should receive high-dose glucocorticoids as well, though there is no data on the use of pulse-dose steroids [33].

The use of low-dose aspirin is recommended in patients with GCA and has been shown to reduce the risk of visual loss, transient ischemic attacks, and stroke [16, 33].

Surgical Treatment

There are no validated guidelines regarding surgical repair of aneurysms in patients with GCA; therefore, current consensus is adapted from recommendations of atherosclerosis-related aneurysms. The mortality rate in GCA patients with aortic aneurysm (excluding rupture) is similar compared to patients with aortic aneurysm unrelated to GCA [37]. Surgical intervention should be considered in cases of a symptomatic aneurysm or an ascending aorta ≥5 cm in diameter, descending aorta >6 cm, abdominal aorta >5.5 cm, and any aneurysm that has expanded >0.5 cm within a 6-month period [31]. Revascularization procedures such as stenting or bypass grafting to repair stenosis are rarely required though may be indicated in patients with subclavian artery stenosis [31]. Reports on successful revascularization for limb claudication also noted that restenosis is common, as similarly observed in patients with Takayasu arteritis [31, 38]. If required, surgical procedures should be performed during the quiescent phase of disease, so as to avoid increased complications from high doses of immunosuppression, delayed wound healing, and graft failure.

Follow-Up

The frequency for patient follow-up should be guided by their clinical manifestations and adverse events.

Takayasu Arteritis

Takayasu arteritis (TA) is a chronic vasculitis of unknown etiology that primarily affects the aorta and its main branches [39]. Takayasu arteritis has also been called pulseless disease, occlusive thromboaortopathy, and Martorell syndrome. Descriptions of this condition date back as far as 1803 in Japan and have since been reported throughout the world [40]. Women are affected in 80–90% of cases, and the age of onset is typically during the reproductive years (10–40 years old) [41]. In the United States and Europe, the estimated incidence is 2.6 per million per year, whereas in Japan, there are approximately 150 new cases each year [41].

Pathogenesis

The pathogenesis of Takayasu arteritis is poorly understood, and it is unclear how geographical differences account for the high degree of variability among the prevalence of disease. Inflammation, largely driven by mononuclear cells (predominantly lymphocytes), histiocytes, macrophages, and plasma cells, drives a process of destruction of the elastic lamina and the muscular media of the aorta and its main branches [39]. Giant cells and granulomatous inflammation occurs in the media and adventitia [39]. This destruction of the elastic lamina and media thus leads to aneurismal dilation of the affected segment. The inflammatory stage is propagated by the production of inflammatory cytokines, such as IL-6, IL-1, and RANTES. Intimal proliferation from progressive inflammation contributes to the formation of stenosis as the deposition of smooth muscle cells, mucopolysaccharides, and fibroblasts leads to fibrosis and destruction of the vessel architecture [42, 43]. Over time, dense scarring replaces the adventitia and leads to compromise of the vascular lumen [41].

The trigger that sets off the inflammatory cascade in Takayasu arteritis has yet to be determined. Inflammation is primarily localized to a portion of the thoracic or abdominal aorta, or even the entire vessel. Studies documenting early findings in Takayasu arteritis have observed that the initial vascular lesions tend to occur in the left proximal to middle subclavian artery [43]. As the disease progresses, the left common carotid, vertebral, brachiocephalic, right middle or proximal subclavian artery, right carotid, and aorta can be affected; the abdominal aorta and pulmonary arteries are involved in approximately half of cases [43].

Diagnosis

The clinical features of TA have been well described in a number of cohort studies including patients from all over the world, with a heterogeneous clinical presentation ranging from incidental physical exam findings to catastrophic neurologic events. The diagnostic criteria as outlined by the American College of Rheumatology are as follows:

American College of Rheumatology Diagnostic Criteria for Takayasu Arteritis [44]

- Disease onset ≤40 years
- Claudication
- Blood pressure difference >10 mmHg between the upper extremities
- Decreased brachial artery pressure
- Subclavian or aortic bruit
- Abnormal angiogram showing narrowing or complete occlusion not caused by arteriosclerosis or fibromuscular dysplasia

In a majority of patients, the progression of TA is thought to occur in two distinct phases. The first phase, or the "prepulseless" phase, is characterized by nonspecific constitutional symptoms such as fever, night sweats, malaise, weight loss, arthralgias, and myalgias. Vascular symptoms are rare at presentation. The second phase, or chronic "pulseless" phase, is characterized by vascular insufficiency due to dilation, narrowing, or occlusion of the proximal branches of the aorta [40]. Patients may experience claudication symptoms, chest pain, dyspnea, abdominal pain, or even neurologic symptoms from involvement of the carotid and subclavian arteries that can lead to subclavian steal syndrome [45–48]. Symptoms of congestive heart failure may also be present and indicative of aortic dilation and aortic regurgitation [41]. Due to the chronic nature of the disease, collateral circulation typically develops and can delay the onset of ischemic symptoms.

Physical exam is important in detecting TA because patients rarely look chronically ill. Obtaining blood pressure measurements of all four extremities can reveal a discordance of 10 mmHg or more when stenosis is present. Bruits may be audible over the subclavian, brachial, carotid arteries and abdominal vessels. Aortic regurgitation may also be present. Hypertension develops from stenosis of the renal artery or decreased elasticity of the aorta [45–48]. However, due to stenosis of the arteries of the upper extremities, blood pressure may be difficult to assess. Despite the variability that exists in disease presentation, roughly 20% of patients have a single, self-limited inflammatory episode, while the remaining population has a progressive and relapsing disease course [40, 45, 49].

Laboratory studies most often reveal findings consistent with inflammation, with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). A normochromic normocytic anemia suggestive of anemia of chronic disease and hypoalbuminemia may be present. Autoantibodies associated with other forms of vasculitis, including antinuclear, antineutrophil cytoplasmic, anti-DNA, and antiphospholipid antibodies are not found in TA [42, 43].

Radiographic imaging is an important tool in establishing the diagnosis of TA because arterial biopsy is typically not practical. Historically, the mainstay of diagnosis has been invasive angiography; however, noninvasive imaging such as MRI/MRA and CTA are replacing angiography as the gold standard for diagnosis (Fig. 16.3). The aortic arch and its primary branches tend to demonstrate the most extensive involvement, and lesions appear as smooth-walled, tapered, focal areas with narrowing and dilation along the vessel when observed with contrast-enhanced techniques [50]. Beyond observing luminal stenosis, MRI/MRA and CTA offer information about vessel wall thickness, edema, and contrast enhancement, which can be diagnostic and also useful for monitoring disease activity and response to treatment. The use of 18-FDG PET can also be used to provide valuable information about cellular activity and metabolically active lesions within an inflamed vessel before morphological changes appear on other imaging studies [50]. PET scanning is limited in the ability to provide information regarding wall structure of luminal blood flow, however. At the current time, there is no single best imaging modality for the diagnosis and monitoring of disease activity in patients with Takayasu arteritis, and often, patients will require more than one imaging study to determine changes in their disease course.

Medical Treatment

The goals of medical therapy remain focused at suppressing inflammation in order to arrest the progression of existing lesions as well as prevention of new lesions. Corticosteroids are the first-line drug of choice and work quickly to decrease the acute inflammatory response that causes damage to the vasculature. In approximately 60% of patients, there is a short-term response with the decrease in ESR, improvement in peripheral pulses, and resolution of inflammatory symptoms. However, TA can remain clinically active at a subclinical level when steroids are decreased, and relapse occurs in as many as 50% of patients when steroid therapy is weaned [40, 49]. Historically, steroid-sparing agents such as cyclophospha-

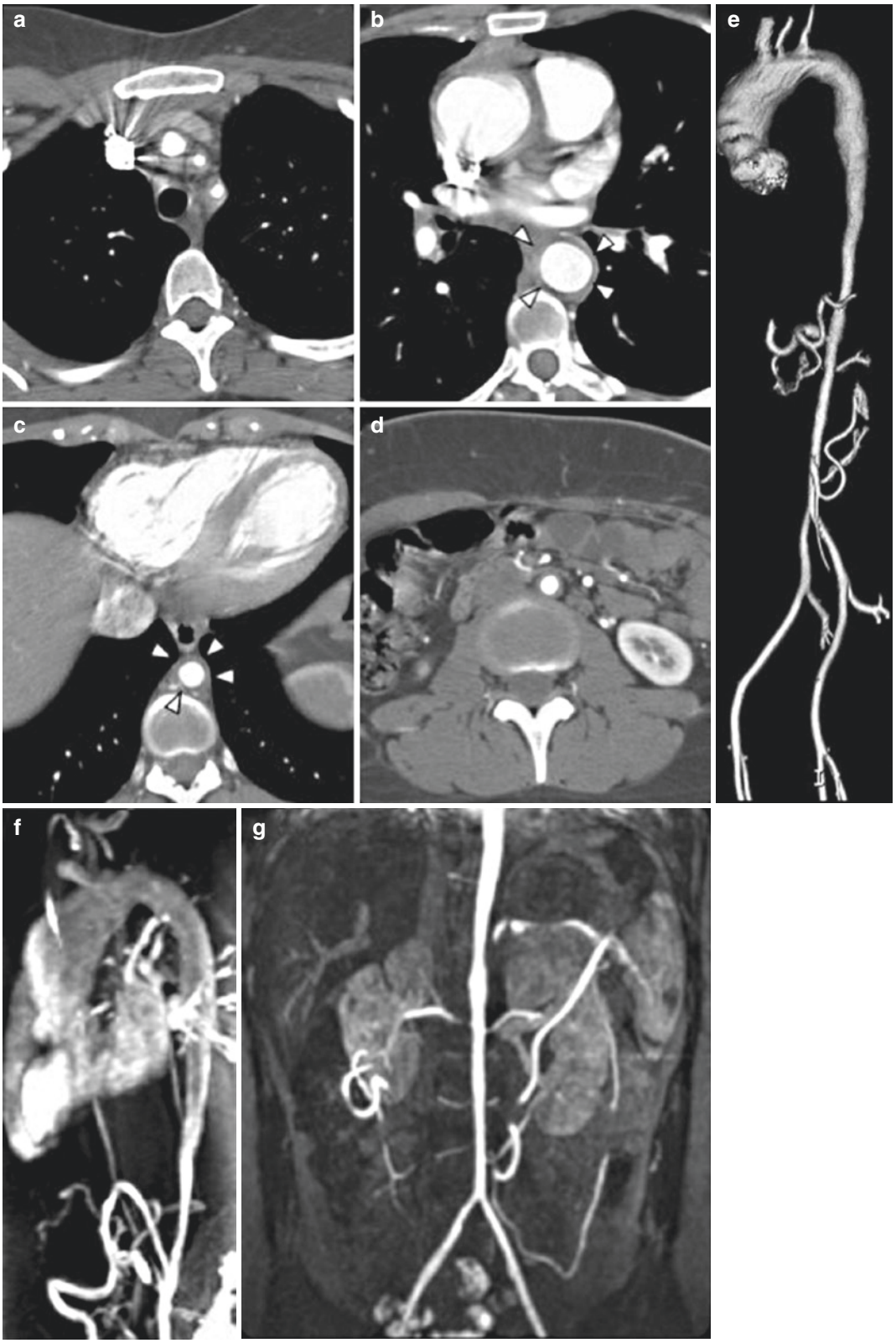

Fig. 16.3 Takayasu arteritis with involvement of the thoracoabdominal aorta and great vessels as shown on contrast-enhanced CT and MR studies, noting the narrowing of the arterial lumen and circumferential soft tissue thickening of the walls of the vessels. (**a**) Narrowing of the left common carotid and left subclavian arteries. (**b**) Mid-descending aorta. (**c**) Aorta just above the diaphragm. (**d**) Infrarenal aorta. (**e**) Volume-rendered image from CT showing the extent of involvement. (**f**) MR sagittal slices of the thoracic aorta. (**g**) MR coronal slices of the abdominal aorta (CT, computed tomographic imaging; MR, magnetic resonance imaging). (From Hiratzka et al. [18]. Reprinted with permission from Elsevier)

mide, azathioprine, methotrexate, and mycophenolate mofetil have been used for patients with disease refractory to steroid therapy; however, data supporting these alternatives has not been reinforced by large randomized controlled clinical trials. Biologic agents such antitumor necrosis factor agents (TNF-alpha inhibitors) such as etanercept and infliximab have been used with some success to achieve sustained remission in several patients once corticosteroids were weaned [51]. Tocilizumab, an interleukin (IL)-6 inhibitor, has also been used to treat patients with TA with some success [52]. There is currently no data to support the duration of treatment required for patients with a diagnosis of TA, but close symptomatic monitoring is important once stenosis is observed because fibrosis eventually replaces the inflammatory lesions and can lead to symptom onset even years after initial diagnosis and treatment.

Surgical Treatment

The diagnosis of TA is often made after stenotic and occlusive lesions have already occurred, and unfortunately, these lesions are not reversible with medical therapy. Surgical intervention to correct the stenosis for symptomatic lesions is often necessary. Surgical indications in patients with TA include secondary hypertension with critical renal artery stenosis, symptomatic claudication limiting activities of daily living, cerebrovascular ischemia or stenosis of greater than three vessels, moderate aortic insufficiency, myocardial ischemia, stenosis of the aortic arch, as well as thoracic aortic aneurysm greater than 5 cm [45, 49, 53, 54]. Surgical intervention is preferred when disease is quiescent in order to decrease the risk of early complications including restenosis, anastomotic failure, thrombosis, bleeding, and infection. There have been higher rates of restenosis observed with endarterectomy, patch angioplasty, and endovascular procedures compared with traditional bypass grafting [45, 49, 53, 54]. Bypass grafting remains the surgical treatment of choice, with an estimated 20-year rate of restenosis estimated between 20% and 30%. The 20-year rate of patients who undergo bypass grafting for TA has a 75% survival [40, 45, 49, 53, 54]. Long-term survival data in patients with TA undergoing aortic valve repair and aortic arch replacement are 76% for 15-year survival and 83% for 10-year survival, respectively [55, 56].

IgG4-Related Disease

IgG4-related disease (IgG4-RD) is an increasingly recognized immune-mediated inflammatory condition that has been shown to affect nearly every organ, including the aorta [57]. The condition is suspected to account for a large proportion of previously unidentified causes of inflammatory thoracic and abdominal aneurysms. Retroperitoneal fibrosis is also one of the major manifestations of IgG4-related disease and can present as a mass compromising the aorta and its branches. IgG4-related disease is characterized by tumefactive lesions, dense lymphoplasmacytic infiltrate with an abundance of IgG4-positive plasma cells, and storiform fibrosis (star-like whirling pattern of cellular infiltrate) [58]. Patients will often have elevated serum IgG4 levels, though this is not an essential diagnostic criterion [58].

IgG4-related disease was first described in the literature as an etiology of autoimmune pancreatitis. Patients with infiltrating pancreatic lesions who underwent biopsy were noted to have specimens that contained large numbers of IgG4-positive plasma cells without concomitant evidence of malignancy [59]. Walker et al. initially described features of inflammatory abdominal aortitis in 1972 as marked thickening of the aneurysm wall, fibrosis of the adjacent retroperitoneum, and rigid adherence of adjacent structures to the anterior aneurysm wall [60]. In 2008, these same features were again described along with an abundance of IgG4-positive plasma cells within the inflammatory infiltrate and lead to the hypothesis that IgG4-related disease could be responsible for a subset of inflammatory abdominal aneurysms [61]. Similar histopathologic features have now been described in virtually every organ system, including the meninges, lymph nodes, lungs, liver, biliary tree, salivary glands, periorbital tissues, kidneys, aorta, breast, prostate, thyroid, pericardium, skin, mediastinum, and retroperitoneum.

Epidemiology

The epidemiology of IgG4-related disease is inadequately described in the literature, and there are very few population-based studies that describe the disease in detail. There has traditionally been a lack of definition of IgG4-related disease in literature prior to the current decade, and nomenclature as well as the understanding of the disease process continues to evolve [62]. A Finnish retrospective case-control study estimated an incidence of retroperitoneal fibrosis to be 1 per 1,000,000 person-years, although this figure is likely to increase as recognition of the disease evolves [63]. The majority of patients diagnosed with IgG4-related disease are men over the age of 50 years, though disease severity appears to affect men and women similarly [62]. Recent literature suggests that approximately 2–15% of abdominal aortic aneurysms are inflammatory in nature and approximately 1–6% of those inflammatory aneurysms are estimated to be IgG4-related [64].

Diagnostic Criteria

The diagnosis of IgG4-related disease is made primarily on the basis of characteristic histopathological features and the presence of elevated IgG4-positive plasma cells within the tissue. The number of IgG4-positive plasma cells per high-power field that is consistent with a diagnosis of IgG4-related disease varies from tissue to tissue [65]. The presence of a dense lymphocytic infiltrate, storiform fibrosis, and obliterative phlebitis classically represents IgG4-related disease [65]. The formation of a mass may be the predominant feature in some patients, and in others, a plaque-like infiltrate may predominate [66]. The inflammatory infiltrate is composed of B and T lymphocytes, and plasma cells are often in abundance [58, 65]. Eosinophils and scattered macrophages are also present in the infiltrate. The storiform pattern of fibrosis mimics the spokes of a cartwheel with spindle cells that radiate from the center and is typically found within the lymphocytic infiltrate [65]. Greater than 50 IgG4-positive plasma cells in a biopsy sample of the aorta is highly suggestive of IgG4-related disease; likewise, a biopsy of a retroperitoneal mass with greater than 30 IgG4-positive plasma cells is consistent with the diagnosis [65]. IgG4-positive plasma cells should be distributed throughout the infiltrate, rather than being clustered in isolation. The inflammatory process of aortic disease predominantly appears as marked enlargement of the adventitia with inflammatory cells intermixed with irregular fibrotic areas; other features include sclerosing inflammation within the media with disruption of elastic fibers and scattered eosinophils [61, 66, 67]. Despite disruption of the media and aneurysm formation, rupture occurs less frequently than other forms of aortitis, likely due to the thickened arterial wall [68]. This pattern of inflammation differs from the erosive and exudative changes with predominant neutrophilic infiltration within the intima and media, as seen with atherosclerotic disease [61]. Necrotizing forms of arteritis are not typically seen and if present should raise suspicion for the diagnosis of IgG4-related disease [65]. Granulomatous formation is also unusual [58]. Chronic lesions may appear as dense fibrosis with little inflammatory infiltrate, which often makes the diagnosis of IgG4-related disease challenging [66]. Serum levels of IgG4 are elevated in approximately 60% of patients with biopsy-proven IgG4-related disease; however, the degree of elevation of IgG4 immunoglobulins does not correlate with disease activity [62, 65]. The presence of elevated serum IgG4 levels alone is not recommended to make a diagnosis of IgG4-related disease and monitoring serum levels can be helpful to follow in response to treatment if they are positive at time of diagnosis [62].

Clinical Presentation

IgG4-related disease typically presents subacutely, and symptoms are largely related to the organ or organ systems involved. Patients rarely have a fever or feel constitutionally ill. There may be subtle findings on laboratory evaluation, but inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often normal [62]. Along with the tumefactive lesions, many patients with IgG4-related disease have features of atopy, eczema, asthma, and low-grade eosinophilia [68]. The mass-like lesions observed with IgG4-related disease are typically discovered incidentally on radiographic studies or diagnosed via biopsy specimens. Patients may have disease that is confined to one organ; others may present with symptoms related to multiorgan dysfunction [58].

Retroperitoneal fibrosis is typically discovered as an inflammatory mass involving the abdominal aorta, the kidneys, or the ureters and may present as vague abdominal or flank pain, back pain, urinary retention with hydronephrosis, edema of the lower extremities, or lower extremity claudication symptoms [57, 58, 62, 64]. Aortic aneurysms are often discovered during routine screening or found incidentally on chest radiography. Aneurysm formation occurs frequently along the aortic arch and less likely results in dissection at this location [64, 67, 69]. Several large case series estimated that approximately 4% of aortic root replacements had histopathological features consistent with IgG4-related disease [65, 70, 71]. IgG4-related disease should be considered in patients with aortitis of unclear etiology, particularly if involvement occurs along the ascending or abdominal segments of the aorta.

Imaging findings vary considerably from one organ to another. Radiographic features are often nonspecific and do not provide reliable distinction between IgG4-related disease and malignancy. Arterial lesions are highly reflective of sclerosing inflammation located predominantly in the adventitia [67]. Image findings include homogeneous and circumferential wall thickening with enhancement in the late phases after contrast administration on contrast-enhanced computed tomography [67]. Calcification is not a typical finding and should raise suspicion for an alternative diagnosis if observed in abundance. Affected segments of the aorta vary in length. Retroperitoneal IgG4-related disease can appear as a soft tissue density infiltrating the retroperitoneal space and encasing the aorta, often leading to compression, but not invasion [67]. The mass may also encompass the ureter and contribute to hydronephrosis or appear as a fat density in the pelvis and paravertebral area with compression of the iliac arteries [67]. It is not possible to distinguish IgG4-related disease from malignancy based on radiographic features alone, and further investigation is warranted when a retroperitoneal mass is observed.

Pathophysiology

The pathogenesis of IgG4-related disease is poorly understood. Proposed mechanisms have been supported for pathways related to genetic predisposition of human leukocyte antigen (HLA) serotypes among Asian populations in particular; also, mechanisms related to molecular mimicry and response to infectious agents have been suggested [58]. Autoimmune responses are suspected as well, though there has yet to be a specific autoantigen target identified [58]. It is also not clear if the role of IgG4 antibodies is pathogenic or acts as a response to an immunogenic process. The inflammatory cascade is perpetuated by IL-4, IL-5, IL-10, and IL-13, as well as tumor-necosis factor-β (TGF-β) [59]. These cytokines become overexpressed through an immune response dominated by type 2 helper T (Th2) cells. CD4+ cytotoxic T cells are also increased in the peripheral blood and within fibrotic masses, suggesting that these cells play a dynamic role in the disease process [62]. The inflammatory response created by upregulated cytokines and continuous antigen presentation by B cells and plasmablasts leads to eosinophilia, elevated IgG4 and IgE production, and the initiation of immune-mediated destruction of the involved tissue [58, 62]. Inflammatory cells infiltrate the target organ and lead to structural damage and tumefactive enlargement at the affected site. Epithelial damage occurs as tissue infiltration progresses and leads to immune complex deposition within the vessel walls [57]. Lymphocytes and plasma cells invade the walls of the venous channel and extend into the lumen, which contributes to obliterative phlebitis [62, 66].

Treatment and Management

The optimal treatment for IgG4-RD has yet to be determined. Current literature supports the approach established in the 2015 International Consensus Guidance statement on the management and treatment of IgG4-related disease [69]. This consensus is based upon observational data, including case reports and small case series [72]. There are few case reports about the treatment of extrapancreatic IgG4-related disease, and little is known regarding follow-up and long-term management, specifically in patients with aortitis [73]. Glucocorticoids are the first-line treatment for patients with active, previously untreated IgG4-RD. Most patients respond to glucocorticoids within several weeks, with symptomatic relief, reduction in the size of masses or organ enlargement, and improvement in organ function [72]. Serum levels of IgG4 can be helpful to monitor response to therapy if quantities were elevated at time of diagnosis, though serum levels have not shown to correlate with disease severity [62, 65]. Patients with aortitis may not have a measurable clinical response and thus will need to be monitored via repeat imaging to follow treatment response. Those patients who respond poorly to glucocorticoids may have disease that has progressed toward advanced fibrosis with little active inflammatory infiltrate; however, there is not a defined method for identifying these patients [73]. Patients should be monitored closely for side effects due to glucocorticoid therapy as well, specifically hypertension and glucose intolerance, as these comorbidities can contribute to increased morbidity in patients with IgG4-related disease.

Some patients may relapse following an initial induction course of corticosteroid therapy, and retreatment with glucocorticoids is warranted. In this event, consideration to use a steroid-sparing agent for maintenance therapy is recommended [62, 72, 73]. Azathioprine, methotrexate, and mycophenolate mofetil have been used as glucocorticoid-sparing agents in an attempt to maintain remission following initial treatment with glucocorticoids, though their efficacy has not been tested in controlled clinical trials [62, 72, 73]. These disease-modifying antirheumatic drugs (DMARDs) have not been shown to be effective in inducing remission on their own, and overall length of therapy once remission is achieved is unknown. There are also several case series, including an open-label pilot study, advocating for the role of rituximab, a CD-20 monoclonal antibody that targets B cells, as treatment for IgG4-related disease [62, 73, 74]. Results are promising, but follow-up data is lacking.

Data regarding the prognosis and appropriate follow-up for patients with IgG4-related disease has yet to be defined, specifically for aortic disease. Imaging is recommended to follow aneurysm diameter and growth, as well as mass size in respect to retroperitoneal fibrosis. Untreated IgG4-related disease often progresses from an inflammatory lymphoplasmacytic infiltrate to extensive fibrosis, though the timing of this transition is not well understood [58]. The mortality rate for patients with IgG4-related disease is estimated to be similar to the general population of the same age and sex demographics; there is little data reported regarding long-term follow-up of patients with IgG4-RD [62].

Behçet's Disease

Behçet's disease is a chronic inflammatory condition characterized by recurrent oral and genital ulcers, skin lesions, and ocular disease. The gastrointestinal tract, central nervous system, and vascular system can also be involved, and patients may report symptoms of arthritis as well. Unlike other forms of vasculitis, Behçet's disease is known to affect blood vessels of all sizes including large, medium, and small arteries, as well as veins. Mucocutaneous, articular, and ocular manifestations are often more severe in the early phase of the disease and may

be presenting features that aid in the diagnosis [75, 76]. However, central nervous system and vascular features tend to present later in the disease course, even up to 10 years following diagnosis, and can contribute to significant morbidity and mortality in patients with this disease [75].

Epidemiology

Behçet's disease primarily affects young men and women between the ages 20 and 40 years. There is a higher prevalence reported in countries along the Ancient Silk Road, particularly the Mediterranean, Asia, and the Middle East [77]. The vast majority of epidemiological information is obtained from case registries and population studies conducted in Turkey and the Middle and Far East. The prevalence of Behçet's disease in Turkey is reported as 80–421 cases per 100,000 compared to 5.2 per 100,000 in the United States [77]. In areas where Behçet's is more common, the disease affects men and women equally, though it appears to be more severe in young males [78]. The onset of Behçet's disease is rare in children and the elderly [77].

Clinical Manifestations

Patients diagnosed with Behçet's disease often present initially with complaints of recurrent and painful oral and genital ulcers. Other clinical features are variable among individuals and populations and can range in severity. Patients can also have cutaneous lesions such as palpable purpura, erythema nodosum, pathergy, and constitutional symptoms including fever, malaise, and weight loss [76]. Ocular disease can vary from uveitis to retinal vasculitis and optic neuritis. Features of pulmonary, gastrointestinal, and renal disease have also been described in patients with Behçet's disease [76].

Diagnostic Criteria for Behçet's Syndrome [79]

Recurrent oral ulcerations.

- At least three aphthous or herpetiform in 12 consecutive months

And at least two of the following:

- Recurrent genital ulcerations
- Skin lesions – erythema nodosum-like lesions, papulopustular-like, pseudo folliculitis, acneiform nodules
- Eye lesions – anterior or posterior uveitis, retinal vasculitis
- Positive pathergy test

Common laboratory findings included elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and an abnormal leukocyte count. There are no specific antibodies or laboratory tests associated with Behçet's disease, and diagnosis is made on the basis of clinical findings in the absence of other systemic diseases.

Vascular involvement in Behçet's disease is one of the leading causes of morbidity and mortality, particularly involvement of the arterial circulation. Vascular complications have been reported to occur in up to one-third of patients with Behçet's disease and range in severity and degree of systemic involvement [75, 80]. The most common manifestations are thrombophlebitis, arterial and venous occlusions, aneurysms and varices [81, 82]. Vascular disease is typically more severe in younger patients and more common in males [75, 80, 83]. The majority of lesions affect the venous system, though involvement of a major artery is estimated to occur in 1.5–2.2% of patients [81, 84]. The aorta, both thoracic and abdominal, and the pulmonary, femoral, and popliteal arteries are the most frequent locations of aneurysm formation [85]. Involvement of visceral vessels and coronary arteries is rare. Atherosclerosis does not appear to occur at an accelerated rate in Behçet's disease, and plaque disruption is not noted to be a component of the thromboembolic phenomenon observed with arterial occlusions [75].

Pathogenesis

The underlying cause of Behçet's disease is unknown. Similar to other autoimmune conditions, Behçet's disease may represent abnormal immune activity triggered by exposure to an unknown agent, possibly infectious, in patients with a genetic predisposition [86]. Genetic and environmental factors are suspected to contribute to increased risk of developing the disease, although the exact contribution of influences is unknown. The most frequent genetic association is with human leukocyte antigen (HLA)-B51, which has been studied in several ethnic groups [87]. Other possible mechanisms of disease include formation of immune complexes and autoantibodies to an unknown antigen, and vascular endothelial activation and hypercoagulability [86]. Once the trigger is initiated, there is evidence of altered innate immune function, abnormal cellular immunity, and upregulation of inflammatory cytokines; antibody and immune complex formation; and neutrophil activation [78]. These mechanisms lead to a complex relapsing and remitting chronic inflammatory state.

Microscopic examination of affected vessels demonstrates an inflammatory arteritis with obliteration of the vasa vasorum [85]. This process results in dilation and unstable aneurysm formation. There is lymphocyte invasion of the media that leads to perivascular degeneration and destruction

of the elastic fibers [80, 82, 85]. As the vessel structure weakens, erythrocytes extravasate and contribute to further endothelial destruction. Fibrosis results with destruction of the intima. Life-threatening dissection can occur as a result of this inflammatory cascade and rapid destruction of the vessel wall. Aortic aneurysms are at an increased risk for rupture regardless of size in patients with Behçet's disease [80].

Endothelial damage and vascular inflammation also lead to thrombus formation and occlusion within both the venous and arterial circulation. This occurs as endothelium-dependent flow-mediated dilation is reduced and inflammatory cytokines are increased in the circulation [88, 89]. Thrombosis is more common with venous disease and has been reported to cause occlusion of the superior and inferior vena cava [76].

Management

The results of surgical management are mixed; however, endovascular repair remains the preferred management for patients with life-threatening disease. The most common complications following repair of the primary lesion are recurrent graft occlusions and pseudoaneurysm formation [80]. Patients with a primary aortic aneurysm often need repeat operations to correct anastomotic aneurysms, graft thrombosis, ulceration, or aortoenteric fistula formation [82]. Ideally, surgery would be performed following the period of acute inflammation, though this is not practical in the event of an acute rupture. Iscan et al. documented a cohort of 20 patients with Behçet's disease and aortitis was found in 14 patients in the form of ascending, thoracic, abdominal, and infrarenal aneurysms [80]. Many patients had more than one aneurysm and multiple other organ systems affected. Seventy-nine percent of patients had aneurysms occurring along the abdominal aorta, and six of those patients presented with ruptured aneurysm [80]. It is not uncommon for pseudoaneurysm formation to occur at the site of angiography puncture [80]. This creates a challenge for operative repair and also monitoring of disease burden via conventional angiography; thus, less invasive methods of imaging the vasculature is recommended. Additional complications, such as suture line dehiscence, aortoenteric fistula formation, graft occlusion, and thromboembolic events, enhance the morbidity and mortality of affected patients [80].

Medical management is also paramount in patients with Behçet's disease, as the syndrome involves systemic inflammation. Symptoms are generally recurrent and relapse is common. Consensus regarding treatment is based on small clinical trials and case reports, with very few follow-up studies available. In 2008, the European League Against Rheumatism (EULAR) published recommendations for the treatment of Behçet's disease and guidelines for each of the major organ systems involved [90]. Treatment for aortic disease has been extrapolated from reports of successful use of immunosuppressive therapy in patients with pulmonary artery aneurysms and other forms of large-vessel vasculitis [90]. The combination of cyclophosphamide and high-dose corticosteroids has improved the survival of patients with pulmonary artery disease, and a similar treatment approach is applied to large-vessel disease [91]. In a retrospective review of 25 patients with large-vessel arterial disease, glucocorticoids plus additional immunosuppression with azathioprine or cyclosporine were more effective than glucocorticoids alone for the treatment of pre- and postoperative inflammation [92]. The role of tumor necrosis factor alpha (TNF-α) inhibitors in the setting of vascular disease is not known [90]. There is general consensus that patients should be maintained on immunosuppression for several years following diagnosis given the high rate of the disease relapse [90]. The optimal duration of treatment is unclear. The use of anticoagulation to prevent thrombus formation, particularly in the postoperative period, is also controversial, as the risk of fatal bleeding is of concern following aortic aneurysm repair [90, 93].

There are no formal recommendations regarding screening patients with Behçet's disease for arterial involvement. The clinician should have high suspicion for aortic involvement in patients who present with concerning symptoms of chest pain, abdominal pain, or back pain. Most experts recommend screening patients for pseudoaneurysms with duplex ultrasound, contrast computed tomography (CTA), or magnetic resonance angiography (MRA) [93, 94]. The role of CT and MRI in evaluating and monitoring vascular changes in Behçet's disease has not been fully evaluated. There is some controversy with differentiating true and false aneurysms of the aorta and pulmonary arteries by CT scan [94]. The optimal surgical techniques are also highly variable due to an increased risk for postoperative complications resulting from the systemic vasculitis but also from concomitant glucocorticoid treatment.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease of the axial skeleton and is one of several diseases within the greater family of spondyloarthropathies. Ankylosing spondylitis is largely a clinical diagnosis and can vary based on specific findings present on medical history, physical exam, radiographic imaging, and laboratory evaluation. Other inflammatory conditions with similar features that also involve the axial skeleton include psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy. The hallmark feature of ankylosing spondylitis is enthesitis, or inflammation around the sites of ligament insertion into

bone. This is most evident in the sacroiliac joints and spine, leading to radiographic evidence of acute sacroiliitis and potentially sclerosis [95]. Inflammation is also found within large tendons, peripheral joints, and the digits [95]. Extra-articular manifestations include anterior uveitis, cardiovascular disease, and aortitis with predilection for the ascending and abdominal aorta [95, 96]. Ankylosing spondylitis is strongly associated with the human leukocyte antigen (HLA)-B27 gene [96].

Aortitis

Aortic disease in patients with ankylosing spondylitis was first described in the 1970s when Bulkley et al. illustrated features of aortic regurgitation characterized by annulus dilatation, thickening of the aortic cusps, and inward folding of the free margins of the leaflets, that occurred in the absence of a stenotic lesion [97]. These findings are known as lone aortic regurgitation and are strongly associated with the presence of HLA-B27 [98, 99]. Aortic distensibility measurements have demonstrated less elasticity in the aortic root of patients with ankylosing spondylitis compared to healthy controls; this feature likely reflects a sclerosing inflammatory process that preferentially targets the aortic root and aortic cusps [100].

The fibrotic process that occurs at the annulus can also extend into the left atrium and lead to damage of the anterior leaflet of the mitral valve, which can induce mitral regurgitation and thus lead to conduction defects [101]. Classic histopathologic findings include proliferation of the intimal cells of the aorta, focal inflammation of the media with destruction of elastic tissue and fibrosis, and fibrous thickening of the adventitia [96, 97, 102]. This inflammatory process also contributes to narrowing of the vasa vasorum and infiltration of the vascular wall with lymphocytes and plasma cells [97]. There have been case reports of abdominal and thoracic aneurysm formation in patients with ankylosing spondylitis, though these complications are rare [103–106]. Specimens of abdominal aneurysms have shown hyalinization of the connective tissue, lymphocytic infiltrate, abundant calcification, and obliteration of elastic fibers within the vessel wall [106].

Clinical Presentation and Diagnosis

The diagnosis of ankylosing spondylitis is based on the recognition of clinical, laboratory, and radiographic image findings consistent with inflammatory sacroiliitis [107]. Current diagnostic suggestions are adapted from the 2013 Assessment of SpondyloArthritis International Society (ASAS). The modified algorithm has a sensitivity and specificity of 75–80% for axial disease among European patients with back pain longer than 3 months but less than 2 years and age of onset less than 45 years of age [108]. The algorithm includes the presence of sacroiliitis on X-ray, presence of inflammatory back pain, enthesitis, dactylitis, uveitis, positive family history, irritable bowel disease (IBD), psoriasis, asymmetrical arthritis, positive response to nonsteroidal anti-inflammatory disease, and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) [108]. Increased recognition of symptoms, early diagnosis, and the widespread use of disease-modifying antirheumatic drugs (DMARDs) and biologic therapy have led to fewer long-term complications, including aortitis and cardiovascular disease [109].

The clinical presentation of aortitis in patients with ankylosing spondylitis is variable and likely underestimated in the literature. Findings are often diagnosed incidentally, and symptoms do not become clinically significant until late in the disease course [102]. The spectrum of aortic involvement includes chronic hemodynamically stable disease with resultant fibrosis of the aortic root, to acute manifestations marked by a new diastolic murmur or symptoms of rapidly progressive diastolic dysfunction from involvement of the aortic valve [102, 110]. The exact prevalence of aortitis is unknown. The prevalence of aortic valve disease is estimated between 4% and 10%, with the latter noted in patients with disease duration greater than 30 years [110]. Epidemiological data is lacking, and limited case series reporting aortic involvement in patients with ankylosing spondylitis lack genetic and geographical diversity.

Despite reports that patients with ankylosing spondylitis are at increased risk for aortitis and aortic disease compared to age- and sex-matched healthy populations, there are no current guidelines for routine screening and monitoring of aortic involvement. The overall risk of aortic disease appears to directly correlate with increased disease duration and uncontrolled systemic inflammation. Small case series have demonstrated the use of transesophageal echocardiography as a method for detecting and monitoring ascending aortic disease in patients with ankylosing spondylitis; however, regular screening has not been standardized [102, 110]. Current recommendations from the ASAS and European League Against Rheumatism (EULAR) indicate that patients with ankylosing spondylitis should have appropriate cardiovascular screening based on national guidelines and aggressive suppression of the inflammatory process in order to decrease cardiovascular morbidity even further [111].

Management

Treatment course for patients with ankylosing spondylitis is based on the presence or absence of sacroiliac involvement (axial disease) and uveitis, as well as changes in disease course [111]. There are no specific therapeutic

recommendations or interventions for aortitis. Conventional surgical procedures for the repair of aortic aneurysms and valvular insufficiency are recommended [102]. Routime medical therapy for ankylosing spondylitis includes non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDS), tumor necrosis factor -alpha antagonists (TNF-inhibitors), and the anti-interleukin (IL)-17A monoclonal antibody secukinumab [109]. Clinical trials are currently investigating the efficacy of several other monoclonal antibodies as potential therapy for ankylosing spondylitis, and data will be emerging with respect to the use of biosimilar medications. Unfortunately, patients with severe disease, including complications involving the aorta, are excluded from clinical trial data [109].

Other Systemic Inflammatory Diseases with Involvement of the Aorta

Inflammatory aortitis should be considered in any patient who presents with acute aortic insufficiency, occlusive arterial disease, aortic aneurysm, or dissection without other associated risk factors [109]. Although aortic involvement has been reported in a number of systemic inflammatory diseases, the most common include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Cogan syndrome. These disease will be discussed briefly, as current treatment with the use of disease modifying antirhematic drugs (DMARDS) and biologic therapy has significantly altered the course of these diseases and the prevalence of vascular complications is decreasing.

Aortitis diagnosed in association with rheumatoid arthritis has been reported in a number of case series dating back to before the 1980s. The largest of these series included ten patients between the years of 1959 and 1985, in which nine patients were reported to have seropositive disease rheumatoid arthritis with severe extra-articular manifestations [113]. Seven of the patients (70%) had clinically significant rheumatoid vasculitis; three died as a direct result of aortitis; and four suffered fatal myocardial infarctions [113]. These complications are rare, though they continue to be of clinical concern because vascular disease can be potentially fatal. Patients will typically have severe, long-standing disease with high degrees of chronic systemic inflammation. Asymptomatic aortic regurgitation is far more common in patients with RA and has been reported in as high as 30% of patients with a confirmed diagnosis [114].

Systemic lupus erythematosus is associated with a number of cardiovascular complications; however, aortic involvement has rarely been reported [112]. While uncommon, patients with SLE and aortic involvement shared common risk factors of early onset of disease, long-term corticosteroid therapy, and significant arterial hypertension [115–118]. Interestingly, histopathologic examination of the arterial walls of patients with aortic involvement revealed distinct medial degeneration (similar to that seen in Marfan syndrome) rather than an inflammatory cellular infiltrate [116]. These findings suggest that long-term corticosteroid use and mechanical forces over time lead to aneurysm formation and instability within the vessel wall [115–117]. The prognosis in lupus patients with dissecting aortic aneurysm is grim, given that chronic corticosteroid use leads to weakening of distal segments of the aorta, thus making surgical repair and wound healing difficult [116]. Among the reported cases of SLE-related aortitis, there appears to be a predilection for the ascending aorta [115–118]. Echocardiography can be a reliable method for monitoring patients with SLE and the aforementioned risk factors for potential fatal aortic dissection [115–118].

Cogan syndrome is a systemic inflammatory disease that primarily affects young adults and involves the eyes and inner ear [119]. Aortitis with valvular insufficiency has been reported to occur at any time during the disease course and has an estimated prevalence of up to 10% of those diagnosed with Cogan syndrome [120, 121]. While aortic involvement is common, it is the association with ostial coronary artery disease that substantiates the recommendation for invasive coronary angiography in patients with Cogan syndrome and aortic involvement [119]. Acute aortitis may be life-threatening and often asymptomatic. Radiographic imaging of the aorta and its branches should be pursued in patients diagnosed with Cogan syndrome at the time of diagnosis and throughout the disease course [122]. Successful surgical treatment of both coronary artery disease and valvular regurgitation with conventional surgical techniques has been reported with good success [121, 123].

Marfan Syndrome

Marfan syndrome (MFS) is one of the most common inherited systemic disorders of connective tissue and results from mutations in the extracellular matrix protein fibrillin 1. Cardinal manifestations include proximal aortic aneurysm and disorders of the aortic root, dislocation of the ocular lens, and various musculoskeletal abnormalities such as excess linear growth of long bones and joint laxity [124].

The incidence of Marfan syndrome in the general population is estimated between 2 and 3 cases per 10,000 individuals [124, 125]. Marfan syndrome is most often inherited in an autosomal dominant respect with complete penetrance and variable expression. The majority of cases are caused by mutations in the FBN1 gene [123]. In as many as 25% of cases, a sporadic mutation leads to syndrome features, though the genetic history of the disorder is still being stud-

ied [126]. Other genes that have been linked to Marfanoid phenotypes include FBN2, TGFBR1, and TGFNR 2 [126].

Pathophysiology

The FBN1 gene is responsible for encoding fibrillin-1 monomers, which are an important glycoprotein component of the extracellular matrix and also function to preserve the synthesis and maintenance of elastic fibers. The production of abnormal fibrillin-1 monomers disrupts the formation of fibrillin-1 multimers and thereby the formation of structurally normal microfibrils. These microfibrils normally serve as the substrate for elastin within the aorta and other connective tissues [127]. More recently, a second genetic mutation has been identified and termed Marfan syndrome type 2 (MFS2), which is caused by a mutation in the gene that encodes the transforming growth factor beta type II receptor (TGFBR2) [128]. Mutation of this gene results in decreased and disordered incorporation of fibrillin into the connective tissue matrix [129]. Disruption of these structural protein components in the extracellular matrix leads to weakening of the vessel walls, and predisposes to dilatation and aneurysm formation. This dilatation, usually beginning at the level of the sinuses of Valsalva and extending into the ascending aorta, is thought to be secondary to the shear forces experienced by the aorta at these anatomic segments [125].

Clinical Manifestations

Marfan syndrome is known to be associated with a number of cardiovascular complications, particularly with the cardiac valves. Thickening of the atrioventricular valves can lead to prolapse and regurgitation, which may then progress to overt heart failure. This phenomenon is the leading cause of morbidity and mortality in younger individuals diagnosed with MFS. Mitral valve prolapse (MVP) is the most prevalent valvular abnormality in MFS, and is observed in 35–100% of patients [124]. Aortic insufficiency typically presents later in life in 15–44% of affected individuals, secondary to progressive dilatation of the aortic root [124]. Aortic dilatation is already present in 50% of those affected with MFS during childhood and is known to be a progressive phenomenon, in such that the severity of disease is directly proportional to the degree of dilatation and the length of the affected segment [125]. Dilatation is often greatest at the aortic root, which portends to a more favorable prognosis than if the dilation extends to involve the aortic arch [130]. Aortic aneurysm and dissection remain the most feared and life-threatening manifestations of MFS and should be ruled out in any patient with characteristic features of disease presenting with chest pain. There is an increased incidence of dissection with increasing aortic diameter and a family history of dissection, which makes lifelong monitoring for aortic disease a necessity in patients with MFS [124, 125].

Management

Routine monitoring of aortic dilation is essential for management of individuals with MFS. Current recommendations suggest baseline imaging with TTE, CT, or MRI, followed by repeat imaging within 6 months to assess rate of change (Fig. 16.4) [125, 131]. If the vessel wall is stable and less than 4.5 cm in diameter, annual screening thereafter is acceptable. TTE reliably allows for serial measurement of the proximal aorta, and CT and MRI offer the additional benefit of imaging the more distal segments of the aorta. More frequent monitoring is recommended if aortic diameter is approaching the threshold for surgical intervention (5 cm) or exhibits rapid growth (>0.5 cm per year) [125].

Beta-blocker therapy has been the cornerstone of medical therapy to decrease the rate of progression of aortic dilatation in patients with MFS, although this is not clearly defined by the small amount of data available [125, 132]. There are conflicting opinions within international societies, as the most recent American Heart Association (AHA) guidelines recommend the use of beta-blocker therapy in patients with MFS, while the European Society of Cardiology does not. Additional therapies have been investigated within the last decade, including the role of angiotensin-II receptor blockers (ARBs), for their role in inhibiting the TGF-β receptor. Brooke et al. demonstrated that the use of ARBs showed a significantly lower rate of progression of aortic dilatation once therapy was initiated in one study of a small cohort of pediatric patients [133]. The largest study to date by Lacro et al. monitored more than 600 children and young adults with MFS over a 3-year period and compared the use of losartan to atenolol and followed the rate of aortic dilation between groups. This study demonstrated no statistically significant difference between the two groups, and both groups showed a clear decrease in the aortic root Z scores [132].

Patients with Marfan syndrome should also be counseled regarding lifestyle modifications due to the increased risk for aortic dissection. Affected individuals should avoid contact sports and strenuous exercise that can lead to additional mechanical stress on the aorta. Additionally, women with MFS should be cautioned against pregnancy if the aortic diameter is greater than 4 cm, due to an increased risk for dissection [125]. Women with aortic dilation should be followed with serial TTEs and continued on beta-blocker therapy during pregnancy [125].

In terms of surgical management for patients with aortic involvement, elective repair is recommended when diameter is

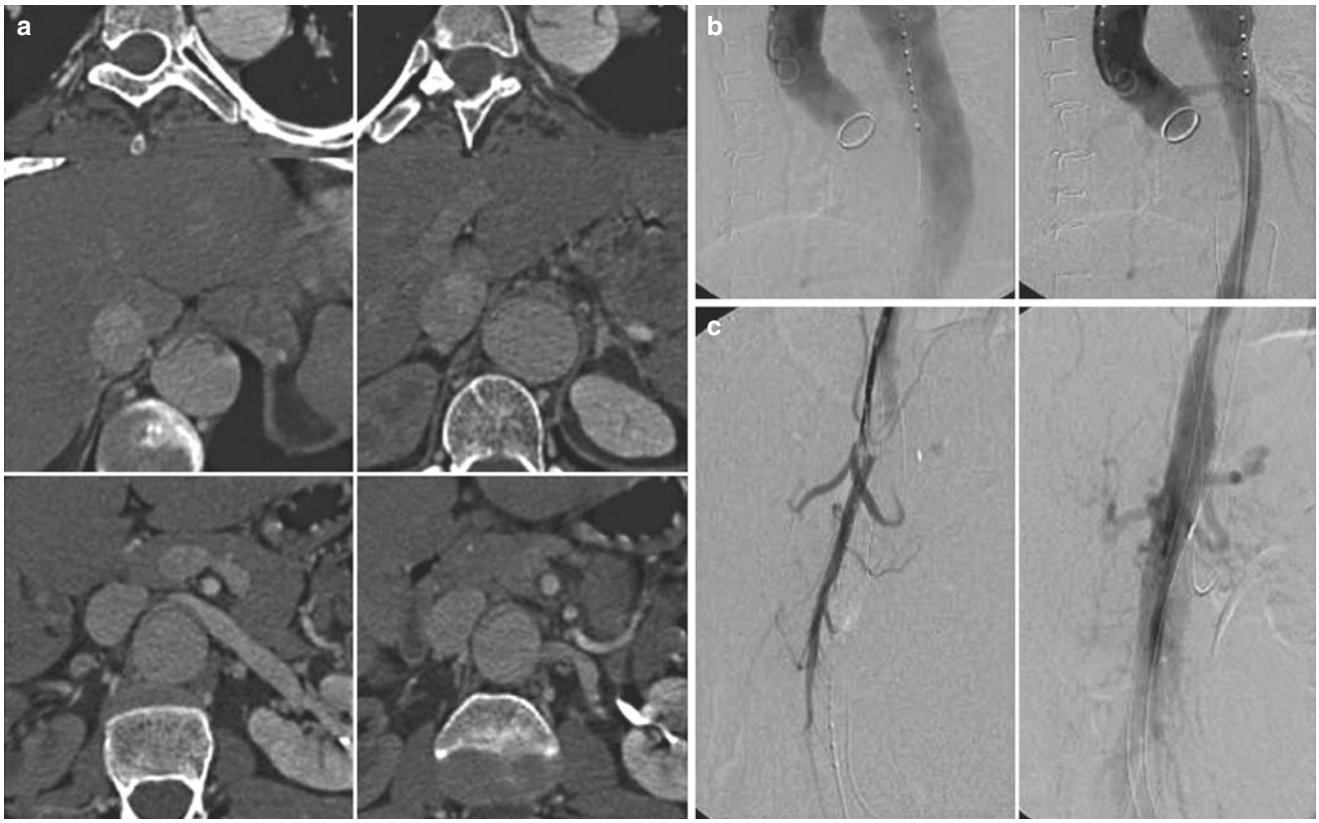

Fig. 16.4 Stent graft treatment in a 27-year-old with Marfan syndrome and newly diagnosed symptomatic type B aortic dissection. (**a**) Selected images from the CT scan showing type B dissection with a large proximal entry tear and true lumen collapse distally. True lumen is obliterated at the level of the abdominal aortic branch vessels, and the left kidney is supplied by false lumen and appears well perfused. (**b**) Aortograms before and after implantation of a stent graft. (**c**) Abdominal aortograms before and after stent graft placement. (From: Cherry and Dake [131]. Reprinted with permission from Elsevier)

≥5 cm, rate of growth is >0.5 cm per year, there is a family history of aortic dissection at a diameter <5 cm, or there is significant aortic insufficiency [125]. Gott et al. published a large case series that compared 30-day mortality rate in elective versus emergent aortic aneurysm repair and reported nearly a tenfold decrease in mortality favoring elective repair [134]. Surgical technique has evolved since first pioneered by Bentall, and currently, valve-sparing procedures are the method of choice when appropriate [135]. Valve-sparing surgery greatly decreases the risk of valve thrombosis and anticoagulation-related morbidity [135]. When compared to composite graft replacement, valve-sparing surgery demonstrated a lower mortality immediately postoperative and at 5 years, as well as decreased rates of both thrombotic and bleeding complications [134]. Despite the many advances in endovascular therapies for the treatment of vascular disease, open repair remains the treatment of choice in patients with MFS. Endovascular repair should be reserved for individuals with MFS and previous aortic replacement if complicated by distal dissection or false aneurysm, as mortality risk is estimated to be 33% with repeat open repair in this patient population [135].

Ehlers-Danlos

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders that results from mutations in the genes responsible for the formation of the extracellular matrix. These mutations create loss of structural integrity of virtually all tissues throughout the body. The syndrome is characterized by features of joint hypermobility, skin extensibility, and tissue fragility. EDS is a rare condition, with a prevalence of 1 per 10,000–20,000 births [136]. Table 16.1 lists the Villefranche classification of EDS and associated genetic mutations [136]. The vascular subtype, formerly type IV, is an autosomal dominant condition with 100% phenotype penetrance. The genetic mutation involved in vascular EDS occurs within the COL3A1 gene and results in structural defects of the pro α1 (III) chain of collagen type III. Mutations result in decreased thermal stability of the collagen network and abnormalities in procollagen production and apoptosis [138]. Type III collagen is an essential structural component of blood vessels, particularly arteries, as well as other connective tissues [139]. The abnormalities in collagen

Table 16.1 Villefranche Classification

New (former name)	Genetic defect	Protein defect	Inheritance pattern
Classical type (I and II)	COL5A1	Collagen V	Autosomal dominant
	COL5A2		
	COL1A1	Pro α(I) and pro α2(I) chains of procollagen I	Autosomal dominant
	COL1A2		Autosomal dominant or recessive
Hypermobility type (III)	TNX	Tenascin X	Autosomal dominant
Vascular type (IV)	COL3A1	Collagen III	Autosomal dominant
Ocular-scoliotic types (VIa/VIb)	PLOD1/unknown	Decreased PLOD1 enzyme activity/unknown	Autosomal recessive/unknown
Arthrochalasic types (VIIa/VIIb)	COL1A1/COL1A2	Prevent cleavage of N-propeptides	Autosomal dominant
Dermatosparactic type (VIIc)	ADAM-TS2	Deficient in procollagen I N-terminal proteinase	Autosomal recessive
Other forms			
X-linked (type V)			X-linked recessive
Periodontotic (VIII)			Autosomal dominant
Fibronectin deficient (X)	TNX	Tenascin X	Autosomal dominant
Unspecified			

From Germain and Herrera-Guzman [137]. Reprinted with permission from Elsevier

production and function can thus lead to spontaneous rupture of large- and medium-sized arteries, including the aorta. The abdominal aorta and its branches, the vessels of the aortic arch, and the large arteries of the limbs are the most vulnerable and prone to rupture [140]. Vascular EDS comprises roughly 4% of all EDS subtypes, and of those patients affected, approximately 80% of individuals are estimated to experience a vascular event by the age of 40 [138, 139, 141].

Pathogenesis

There have been 29 types of collagen identified in the human body, and each type provides unique structural support to the extracellular matrix of tissues including the skin, bones, liver, vascular system, muscles, and so on. Collagen surrounds the smooth muscle cells and the elastic lamellae, and together with elastin, create the tensile strength and stiffness of the aorta [142]. Over 90% of collagen is comprised of types I, II, III, and IV. Type I is the most abundant [142]. Type III is structurally similar to type I and contributes support to the skin, bones, and arteries. The aorta and its main branches are composed of type I and III collagen (as well as types IV, V, VI, and VII) [137]. Type III collagen specifically increases the overall flexibility of the aortic wall. Defects in the processing of procollagen III lead to vascular wall weakness and instability. In the normal aorta, type I and III collagen form the architecture of the intima, media, and adventitia layers. The concentration of type III collagen is particularly increased in the adventitia throughout the entire length of the aorta [137]. The endothelial and smooth muscle basement membranes are primarily composed of types I, III, IV, and V collagen [137]. Collagen also plays a critical role in vessel wall repair and regeneration, and the absence or altered composition of specific collage fibrils can result in impaired restoration of the vessel architecture.

The distribution of collagen is important in the flexibility and extensibility of the vascular system, and most specifically the aorta. Nonlinear elasticity is one of the most important mechanical features of the aorta and is dependent upon the ideal collagen and elastin structural motif [137]. The extracellular matrix of the aorta also varies slightly along the length of the vessel to accommodate for physiological changes in mechanical stress. The ascending aorta is dominated by type I, III, and IV collagen within the intima and media layers, whereas type I and IV collagen are distributed throughout the intima and media layers of the descending thoracic aorta [142]. The abdominal aorta is composed of type I and IV collagen within the intima and media, and type III collagen is heavily distributed in the adventitia layer [142]. The ratio of type I to type III collagen is also important in the pathophysiology of aneurysm development and vessel strength. In 1987, Menashi et al. demonstrated that a subgroup of patients with a significant family history of aortic aneurysm had decreased amounts of type III collagen in the media compared to the control group without aortic aneurysms [143]. This finding is consistent with features that are observed in patients with vascular EDS, as type III collagen is the main structural defect that contributes to abnormal wall structure of the aorta and thus increased incidence of aortic aneurysm formation.

Diagnostic Criteria for Vascular Ehlers-Danlos (Type IV) [142]

Major Criteria:

- Family history of vascular Ehlers-Danlos
- Arterial rupture
- Intestinal rupture
- Uterine rupture during pregnancy

Minor Criteria:

- Thin translucent skin
- Extensive scars and hyperpigmentation over bony prominences and skin
- Easy bruising
- Characteristic facies
- Acrogeria (aged appearance to the extremities)
- Hypermobility of small joints
- Tendon or muscle rupture
- Early-onset varicose veins
- Arteriovenous carotid-cavernous sinus fistula
- Pneumothorax or pneumohemothorax
- Mitral valve prolapse
- Club foot
- Chronic joint dislocations/subluxations
- Congenital dislocation of hips
- Gingival recession

Clinical Manifestation and Diagnosis

The diagnosis of vascular EDS is made on the basis of specific clinical criteria shown below:
The combination of two major criteria is highly specific for the condition, and the presence of one or more minor criteria supports the diagnosis of EDS [136]. Unlike other forms of EDS, skin and joint hyperextensibility is not often associated with vascular disease. Further biochemical and genetic testing to assess for abnormalities in procollagen production and the identification of the COL3A1 gene mutation are necessary to confirm the diagnosis of vascular EDS [138, 139, 141].

Individuals with vascular EDS are at risk for spontaneous vascular rupture, gastrointestinal perforation, or other organ rupture. Approximately 70% of patients with vascular EDS present with hemorrhagic shock, acute abdomen, retroperitoneal hemorrhage, or uterine rupture at the time of delivery [138]. Patients typically present with a major arterial or gastrointestinal event by the third decade of life, and the overall life expectancy of individuals with vascular EDS is 45 years old [144]. Stroke is an uncommon manifestation; however, there have been case reports of intracranial aneurysm rupture, spontaneous carotid-cavernous sinus fistulae formation, and cervical artery aneurysm [144]. Mitral valve prolapse and spontaneous coronary artery dissection in patients with EDS have also been reported but are rare events [144]. Individuals with primarily the hypermobility subtypes of EDS appear to have a higher incidence of aortic root dilatation, which is not a common feature of vascular EDS [145].

Management

There are currently no specific medical interventions shown to decrease mortality of patients with vascular EDS and no standardized protocols for monitoring patients with EDS. Morbidity can be somewhat modified by educating the affected individual about specific risk factors unique to vascular EDS. All patients should be offered genetic counseling and counseling regarding lifestyle modifications, including strict blood pressure control to avoid hypertension, avoidance of strenuous physical activity and contact sports (to limit sheering stress on the vasculature system and abdominal organs), and counseling about pregnancy and the risk of uterine rupture [139–141]. Patients are recommended to avoid GI endoscopies and should also avoid the use of antiplatelet therapy due to the increased risk of bleeding [140]. Ong et al. reported results from a multicenter, open-labeled, randomized trial in which celiprolol, a selective β1 antagonist with partial β2 agonist activity, was compared to no treatment in 53 patients with a clinical diagnosis of vascular EDS [146], results demonstrated a decreased incidence of arterial rupture and dissection in patients over a 4-year period compared to the control group [146]. Celiprolol (along with other selective β1-antagonists) has been shown to suppress the expression of transforming growth factor-β (TGF-β) in damaged vessels, which further reduces matrix remodeling [140]. Patients should be followed with noninvasive imaging to monitor for the development of asymptomatic aneurysms and dissections via echocardiogram, CT angiography (CTA), or MR angiography (MRA), and should have baseline imaging done at time of diagnosis [147] (Fig. 16.5). Patients with vascular EDS should be evaluated for cardiac valvular and vascular disease, as well as aortic dilation. Several experts recommend that patients are monitored with noninvasive imaging every 3–6 months [144, 145, 149].

Surgical procedures are challenging in patients with vascular EDS, as patients have an increased risk of complications from elective surgery and arteriography. The main concerns include life-threatening hemorrhage, anastomotic failure/disruption, poor wound healing, and wound dehiscence [140]. Surgical repair of affected vessels should be reserved for those presenting with imminent life-threatening

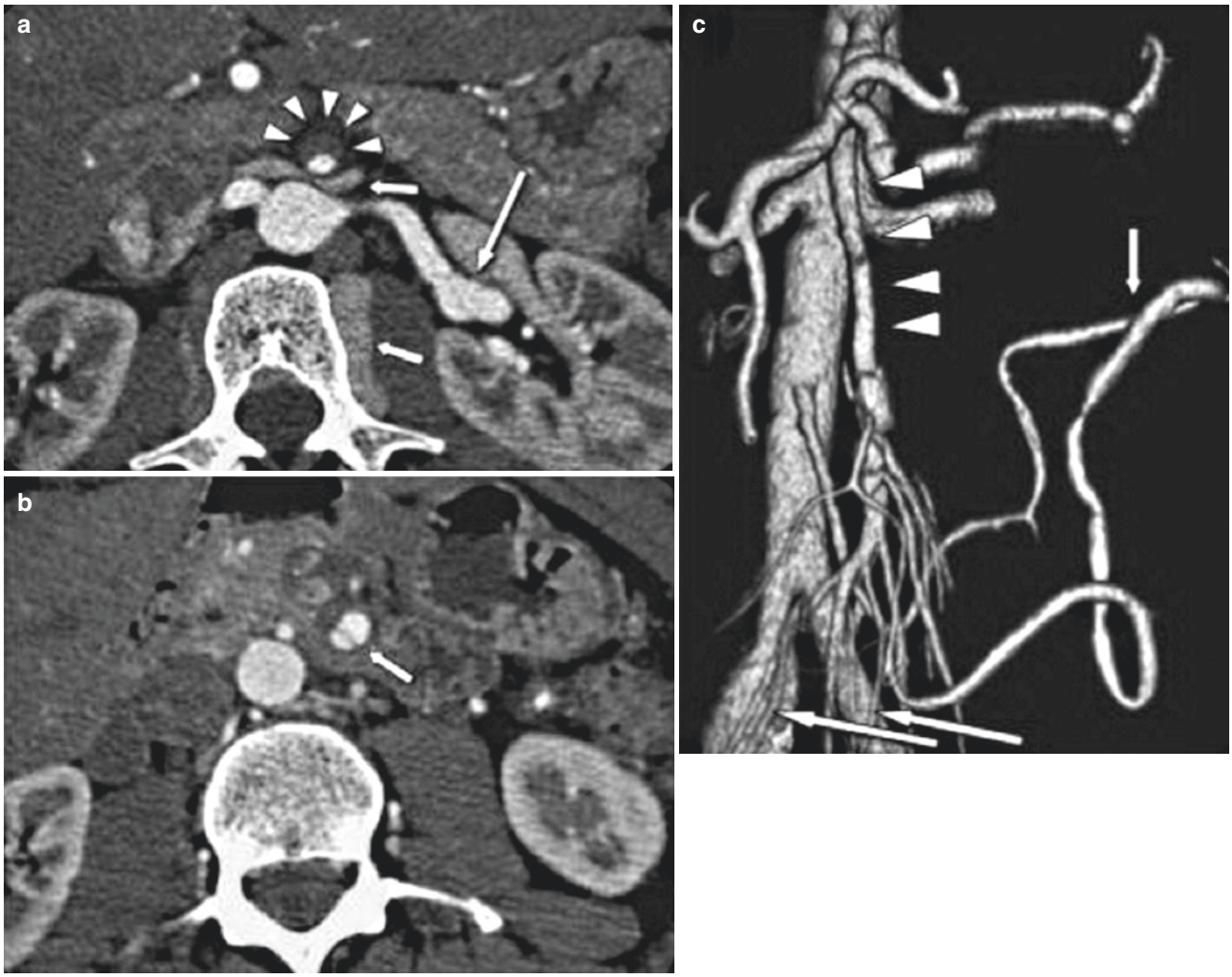

Fig. 16.5 CT angiogram revealing the dissecting aneurysm of the superior mesenteric artery (SMA) in a patient with type IV EDS. (**a**) Pictures show a thrombus occluding the false lumen of the proximal superior mesenteric artery [arrow heads], left renal artery aneurysm [long arrow], azygo-lumbar venous arch ectasia and "nutcracker" sign of the SMA (short arrows). (**b**) Intimal flap of the distal SMA aneurysm. (**c**) 3D reconstruction, straight aspect of the SMA with missing proximal branches (arrow heads), a well-developed Drummond arcade (short arrow), and bi-iliac aneurysms (long arrow). (From Nourissat et al. [148]. Reprinted with permission from Elsevier)

bleeding or vascular rupture. When surgical intervention is necessary, special consideration/attention to technique is imperative, including gentle handling of all tissues, use of balloon occlusion or of protected arterial clamps, tensionless anastomosis with pledgeted sutures, and application of Dacron or Teflon cuffs to cover the anastomosis [150]. Endovascular approaches are preferred if arterial or venous embolization is achievable [150].

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an inherited group of connective tissue disorders that results from genetic alterations in type I collagen. The condition results in a wide range of phenotypic expression and features, most of which are inherited in an autosomal dominant manner; autosomal recessive mutations as well as de novo mutations have also been reported [151]. There are eight classic types of OI, ranging from clinically silent to mutations that are incompatible with life. All phenotypes of OI have some degree of vascular involvement, as type I collagen is a major structural protein of the aorta and its branches.

OI has an estimated incidence of approximately 1 in 20,000 births, and the severity of disease presentation depends largely on the expression of the genetic mutation [152]. Milder forms of OI lead to decreased amounts of normal type I collagen, while the more severe forms result from the complete absence of type I collagen [153]. Given this genetic variability, the clinical manifestations vary substan-

tially within families. There is variable expression of the classic features, including blue sclera, abnormal dental development (dentinogenesis imperfecta), hyperlaxity if ligaments and skin, hearing impairment, and abnormal development and structure of bones [154]. Other features involve abnormalities in the development of the respiratory system and decreased muscle tone of peripheral muscles [154].

Pathogenesis

Osteogenesis imperfecta is caused by mutations of the COL1A1 or COL1A2 genes, which leads to defects in the alpha-1 and alpha-2 chains of type I collagen. These defects are predominantly autosomal dominant [151]. Type I collagen fibers are polymers of tropocollagen molecules, each of which is a triple helix that contains portions of one alpha-2 chain and two alpha-1 polypeptide chains [151]. Type I collagen is an important structural protein, integral to the composition of bone and numerous connective tissues [151]. Elastin and collagen (types I and III) are the primary load-bearing elements in aortic tissue. Type I and III collagen make up 80–90% of the collagen present in the aorta and are the major constituents of the intimal, medial, and adventitial layers [155]. Deficiencies in both elastin and type I and III collagen have been well described in the literature, as predisposing to aneurysm formation.

While diagnosis of OI is made based on the observation of clinical signs and symptoms as previously described, there is no direct serologic test for the diagnosis of OI. Individuals may have nonspecific lab abnormalities indicative of bone and mineral metabolism, such as elevated alkaline phosphatase and hypercalciuria [156].

Little data exists on the prevalence of cardiovascular complications in patients with the varying forms of OI, and most patterns are drawn from small case series. Numerous cardiovascular complications have been reported in individuals with OI, including aneurysms or dissection that can present in nearly any vascular territory. Valvular heart disease including aortic valve insuficiency and mitral valve prolapse are common most commonly AI and MVP [157]. Patients with OI present a similar clinical challenge to those with EDS given the increased tissue friability, increased bleeding risk, and theoretical potential for late pseudoaneurysm development and should therefore be managed in a similar fashion.

Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) was first described in 1844 by Paget and is now one of the most common cardiac congenital anomalies. The estimated prevalence of BAV ranges from 0.5% to 2% in the general population, with a male predominance of 3:1 [158, 159]. The exact mechanism of embryologic development that leads to bicuspid valve formation is not entirely understood. Over half of patients with BAV have additional congenital cardiovascular malformations, including anomalous coronary artery variants, atrial septal defect, ventricular septal defect, patent ductus arteriosus, supravalvular aortic stenosis (William's syndrome), obstructing left heart lesions (Shone's syndrome), and aortic wall abnormalities including coarctation (with or without Turner's syndrome), dilation, or dissection [158]. BAV is an important clinical challenge to physicians due to the significant number of associated conditions, early development of valvular lesions, and increased risk of endocarditis. Complications are common in adulthood, and therefore, the burden of disease related to BAV is more significant than any other congenital cardiac lesion.

Genetics and Pathogenesis

BAV shows a strong familial predisposition. Approximatley 10–14% of first-degree relatives will have BAV as well [158]. Inheritance is thought to follow a multifactorial and occasionally autosomal dominant pattern, with evidence of incomplete penetrance and variable expression [158, 160]. There is general consensus that individuals with BAV have an accelerated loss of the aortic media, low fibrillin content, and increased matrix metalloproteinase 2 activity, which leads to loss of elastic tissue and predisposition to aortic root dilatation [158, 160]. Interestingly, in smaller studies, the prevalence of aortic root dilatation in first-degree relatives of individuals with BAV, who have morphologically normal tricuspid aortic valves, has been reported as high as 32% [161]. In these studies, it was found that both patients with BAV and their first-degree relatives with dilated aortic roots were found to have a lower aortic distensibility and higher aortic stiffness index as compared to control subjects [161].

Clinical Presentation and Diagnosis

The diagnosis of BAV can be difficult as the majority of patients may have a normal physical exam and are clinically asymptomatic until the development of valvular disease. Symptoms of aortic stenosis, aortic insufficiency, and infectious endocarditis can incidentally lead to the identification of BAV. A systolic ejection murmur may be present on physical exam. Chest radiography may reveal cardiomegaly in the setting of chronic AI, aortic dilation, rib notching if coarctation is present, or aortic valve calcification [162].

Transthoracic echocardiography (TTE) is usually diagnostic for BAV. Chan et al. reported a sensitivity and specificity of 92% and 96%, respectively, for identifying bicuspid

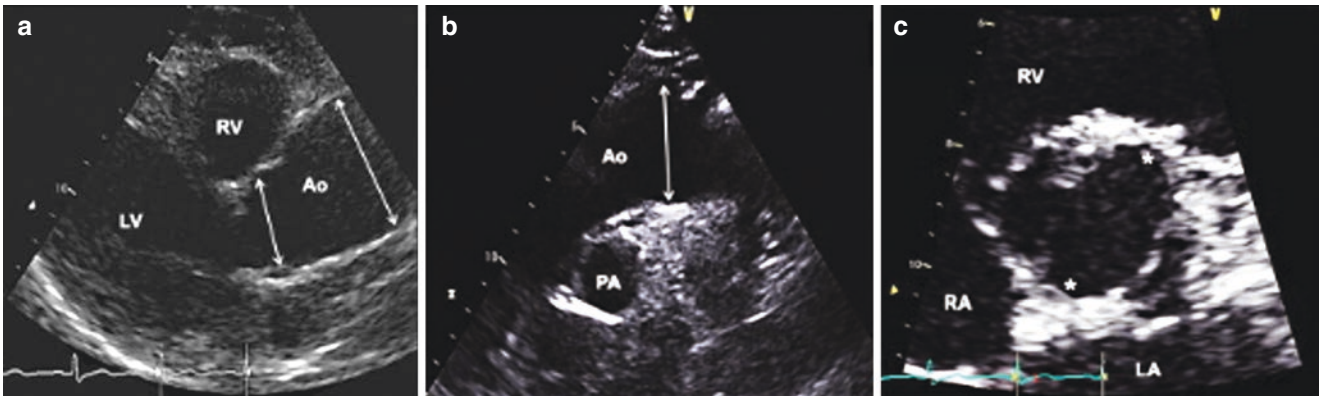

Fig. 16.6 Transthoracic echocardiogram of a 60-year-old woman with bicuspid aortic valve. Images show (**a**) parasternal long axis view showing aortic aneurysm with dilated root measuring 3.6 cm (first arrow from the left) and mid-tubular ascending aorta measuring 4.7 cm (second arrow from the left). (**b**) Suprasternal view showing mildly dilated proximal arch measuring 3.6 cm. (**c**) Parasternal short axis view through the aortic valve in systole showing two commissures (asterisks) with nonright fusion. RV right ventricle, LV left ventricle, Ao aorta, RA right atrium, LA left atrium, PA pulmonary artery. (From: Michelena et al. [165]. Reprinted with permission from Elsevier)

valve when adequate echocardiographic images are obtained [163]. Espinal et al. published a series of 710 patients and demonstrated improved diagnostic accuracy using transesophageal echocardiography (TEE), especially when using multiplane analysis. Transesophageal echocardiography is also superior for the assessment of the aortic root as well as for aortic dissection [164]. MRI and CT imaging have very high sensitivity and specificity for identifying cardiac valve structural abnormlaities and have the advantage of providing additional information about other associated anomalies as well as the extent of aortic involvement [158, 160] (Fig. 16.6).

Management

The management of bicuspid aortic valve is multifactorial and may require several important lifestyle modifications to prevent future complications. Patients should be educated regarding the risk of valvular lesion progression, the risk of infective endocarditis, as well as the potential for aortic aneurysm and dissection. Aortic stenosis in patients with BAV has been shown to progress more rapidly with a projected increase in gradient of 27 mmHg per decade and requires surgical replacement on average of 5 years earlier than individuals with normal tricuspid aortic valve stenosis [166, 167]. Aortic insufficiency secondary to BAV has been reported to be 1.5–3% and may occur in isolation or in association with aortic root dilatation, coarctation, or infective endocarditis [168–172]. BAV has been reported in as high as 25–54% of cases of aortic valve endocarditis, despite the overall decrease in cases of infective endocarditis in developed countries [173–175]. Good oral hygiene should be recommended for patients with BAV; however, current American College of Cardiology and American Heart Association guidelines do not recommend antibiotic prophylaxis for patients with BAV [176].

The most common abnormality in patients with BAV is aortic dilatation, with a prevalence of 20–84% [159]. Aortic dilatation begins in childhood in patients with BAV and increases throughout life at a higher rate than that of individuals with tricuspid aortic valves [177]. Originally thought to be secondary to long-standing effects of shear wall stress from abnormal flow dynamics, more recent investigation supports evidence of underlying structural abnormalities at the cellular level [178]. Dilatation can occur in the absence of valve dysfunction and typically involves the aortic root, ascending aorta, and occasionally the arch. The most feared complication is aortic dissection. While the exact incidence is controversial, some sources estimate that aortic dissection occurs 5–10 times more frequently in patients with BAV, and at a younger age on average, than those with structurally normal aortic valves [158, 160].

Screening and Follow-Up

The American College of Cardiology and the American Heart Association have several recommendations regarding the management of patients with bicuspid aortic valves. All first-degree relatives of patients with known BAV should undergo transthoracic echocardiography (Class 1, LOE C) [176]. Patents with known BAV should have both the aortic root and ascending thoracic aorta evaluated for evidence of aortic dilatation (Class 1, LOE: B) [176]. Serial transthoracic echocardiograms should be performed annually if there is presence of significant valve lesions or aortic root ≥40 mm; if neither abnormality is present, then patients can undergo screening every 2 years [179, 180]. Patients with BAV remain at risk for development of aortic root

dilation even after aortic valve replacement and should have continued surveillance following surgical correction [158, 160].

Treatment

The treatment approach for patients with bicuspid aortic valve should entail a combination of blood pressure control, lifestyle modification, and serial monitoring for the development of severe valvular dysfunction. In most cases, indications for aortic valve replacement are similar to those for patients with degenerative tricuspid aortic valve disease. If significant valvular disease is present during childhood or young adulthood, valvuloplasty remains the procedure of choice. In the adult patient, calcification of the valve and comorbid conditions makes valve replacement the preferred approach. Approximately 30% of adults who undergo aortic valve surgery will also require aortic root replacement secondary to ascending aortic aneurysm [181, 182]. Indications for resection of aortic aneurysm in patients with BAV are shown below. Surgical options include replacement of the supracoronary ascending aorta with a graft, replacement of the root and ascending aorta with reimplantation of the coronary arteries (Bentall procedure), and valve-sparing replacement. The Bentall procedure has the advantage of avoiding re-operation and lower rate of aortic complications, which make this technique the ideal procedure for young patients [158, 160].

Indications for Resection of Aneurysm Involving the Ascending Aorta in Patients with BAV [158, 160]

- Aortic diameter >5.0–5.5 cm
- Aortic ratio >1.5 or 1.4 in women planning to become pregnant
- Annual growth rate >3–5 mm
- Symptomatic aneurysm
- Large sinus of Valsalva aneurysm
- Patients undergoing valvular surgery for BAV with aortic diameter >4–5 cm or ration >1.4

Special Considerations

Women with BAV should be counseled regarding the risk of physiological and hemodynamic changes that occur during pregnancy which can lead to deterioration and rapid symptoms of congestive heart failure. Females with BAV and significant dilation >45 mm should be counseled against pregnancy [179].

Exercise restrictions for individuals with severe AS or AI and dilated aortic root with BAV are no different than those for patients with structurally normal aortic valves and thoracic aortic disease, with some caveats [176]. Patients with aortic diseases, in general, should be counseled on exercise. Aerobic exercise is typically encouraged. Some have advocated a treadmill exercise stress test to evaluate the blood pressure response to aerobic exercise. Heavy lifting or those activities resulting in significant strain or use of the Valsalva maneuver should be avoided. Isometric activities can cause an increase in the mean arterial pressure, and consequently a significant rise in central aortic pressure with a theoretical increased risk for aortic dissection or rupture. This phenomenon is observed with the Valsalva maneuver also. Therefore, strenuous labor and routine heavy lifting should be avoided in those with an ascending aortic aneurysm [176].

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