Cardiovascular Disorders and Rheumatic Disease

Alexandra Villa-Forte* and Brian F. Mandell

Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, Ohio, United States

A B S T R A C T

Cardiovascular disease is a common and under-recognized problem in patients with systemic rheumatic conditions. Patients may present with disease associated heart involvement at the time of diagnosis or later in the course of the illness. The manifestations vary by disease, and all structures in the heart can be affected and may result in significant morbidity and mortality. Manifestations of cardiac disease in these patients range from subclinical to severe and may require aggressive immunosuppressive therapy. Early recognition is important for prompt institution of appropriate therapy. Treatment of disease associated cardiac involvement is based on severity of disease with more severe manifestations often requiring a combination of corticosteroid and cytotoxic agent. Premature atherosclerosis has been increasingly recognized in patients with systemic lupus erythematosus and rheumatoid arthritis and may result in premature coronary death when compared to the general population. Aggressive control of systemic inflammation in these diseases may result in a reduction in the risk of ischemic heart disease. Although aggressive treatment of the primary rheumatic disease has been associated with an improvement in mortality rates, specific guidelines for prevention of ischemic heart disease in this group of patients have not been formulated and recommendations at this time include aggressive control and monitoring of traditional risk factors.

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Trastornos cardiovasculares y enfermedad reumática

R E S U M E N

La enfermedad cardiovascular es un problema frecuente e insuficientemente reconocido en pacientes con trastornos reumáticos sistémicos. Los pacientes pueden presentar una enfermedad asociada a afección cardiaca en el momento del diagnóstico o en una fase posterior del curso de la enfermedad. Las manifestaciones varían según la enfermedad de que se trate, y todas las estructuras del corazón pueden verse afectadas y pueden causar morbilidad y mortalidad importantes. Las manifestaciones de la enfermedad cardiaca en estos pacientes van de subclínicas a graves y pueden requerir un tratamiento inmunosupresor agresivo. La detección temprana es importante para instaurar con rapidez un tratamiento apropiado. El tratamiento de la afección cardiaca asociada a la enfermedad se basa en la gravedad; las manifestaciones más graves requieren a menudo un tratamiento combinado con corticoides y fármacos citotóxicos. Se ha identificado de manera creciente aterosclerosis prematura en los pacientes con lupus eritematoso sistémico y artritis reumatoide, lo que puede conducir a una muerte coronaria prematura respecto a la población general. Un control agresivo de la inflamación sistémica en estas enfermedades puede conducir a reducir el riesgo de cardiopatía isquémica. Aunque el tratamiento agresivo de la enfermedad reumática primaria se ha asociado a una reducción de las tasas de mortalidad, no se han formulado directrices específicas para la prevención de la cardiopatía isquémica en este grupo de pacientes y las recomendaciones actuales incluyen el control agresivo y el seguimiento de los factores de riesgo tradicionales.

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INTRODUCTION

Systemic rheumatic diseases are autoimmune inflammatory conditions with multi-organ involvement, frequently involving the blood vessels and the heart. Cardiac disease may occur in patients with an established diagnosis of a rheumatologic disorder or may be the initial presentation in patients with no prior diagnosis. The cardiologist may be the first specialist to evaluate patients with underlying rheumatic diseases who present with initial symptoms related to the heart. Cardiac involvement in rheumatic diseases can range from asymptomatic or mild to severe or life-threatening; and is a significant cause of morbidity and mortality in these patients. Patients may not present with overt clinical cardiac symptoms making the diagnosis of heart disease more difficult.

* Corresponding author: Department of Cardiovascular Disorders and Rheumatic Disease, Cleveland Clinic, 9500 Euclid Ave / A50, Cleveland, Ohio 44195, United States.

E-mail address: villaa@ccf.org (A. Villa-Forte).

In addition to causing myocardial, valvular, pericardial and conduction system abnormalities, rheumatologic disorders have been associated with premature atherosclerosis leading to ischemic heart disease at a young age. The increased risk for coronary events cannot be solely attributed to traditional cardiovascular (CV) risk factors and may be a result of chronic systemic inflammation from the rheumatic disease. The prevalence and relevance of ischemic heart disease have further increased due to advances in therapy, which results in increased life expectancy in patients with rheumatic diseases. The cardiac manifestations of specific rheumatic diseases more commonly associated with heart disease will be addressed here.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an inflammatory multisystem disease associated with immune complex deposition, production of autoantibodies, and various laboratory abnormalities and clinical features. Patients may present with virtually any organ-system involvement including arthritis, glomerulonephritis, skin rashes, serositis, and neurological symptoms. Frequent laboratory abnormalities include anemia, thrombocytopenia, leucopenia or lymphopenia. Patients with SLE may have positive antiphospholipid antibodies (APLAs), which predispose to arterial and venous thrombosis, pulmonary hypertension, valvular dysfunction, and/or miscarriage.

The disease prevalence is 15 to 50/100 000 people in the United States and 90% of the patients are women. SLE is more common in blacks and younger patients, but can occur at any age. The diagnosis of SLE is based on clinical and laboratory features. Over 95% of patients with SLE have a positive antinuclear antibody (ANA); however, an isolated finding of a positive ANA is not diagnostic of SLE. Anti–double-stranded DNA is more specific for SLE but with lower sensitivity, occurring in only 50% to 70% of patients, more frequently in the presence of glomerulonephritis. Lupus can be induced by certain medications and both idiopathic and drug-induced lupus can have cardiac manifestations.

Cardiac involvement is common and a significant cause of morbidity and mortality in SLE patients. Its prevalence, if specifically sought, has been estimated to be more than 50%. However, prevalence varies significantly depending on disease definitions and whether asymptomatic disease is included or not. All heart structures can be affected by SLE.[1]

Pericarditis is the most common CV manifestation in SLE. Large series have found clinical or echocardiographic features of pericarditis in 20% to 50% of patients and autopsy series have demonstrated pericardial involvement in more than 60% of patients.[2] Pericarditis is commonly associated with chest pain; however, patients may present with asymptomatic pericardial effusions. Effusions are usually mild and although moderate to large effusions may occur, major complications such as cardiac tamponade are rare in patients without renal failure. In the setting of renal failure, it may be difficult to distinguish pericarditis due to uremia from SLE. Constrictive pericarditis is also rarely seen in SLE. Pericardial fluid is typically an exudate with neutrophil predominance, elevated protein level, and low or normal glucose concentration. The fluid has similar characteristics of those seen in bacterial pericarditis, and infection must therefore be excluded.

Myocarditis is infrequent in SLE, including in autopsy series. Subclinical involvement with detection of myocardial dysfunction by echocardiography is much more common than overt clinical manifestations.[3] Myocardial dysfunction in lupus is usually multifactorial due to some combination of ischemic heart disease, hypertension, renal failure and valvular disease. Patients with peripheral skeletal myositis are reported to be at increased risk for myocarditis. Impaired systolic function and wall motion abnormalities associated with myocarditis may be reversible by immunosuppressive treatment and control of SLE activity. Endomyocardial biopsy for diagnosis of cardiomyopathy in SLE shows small foci of myocardial fibrosis, sparse interstitial mononuclear cell infiltrates, and occasional myocyte necrosis with immune complex and complement deposition. However, biopsy is rarely diagnostic of lupus. Since patients with SLE are commonly treated with hydroxychloroquine, cardiomyopathy induced by this drug should be considered, and biopsy may demonstrate a vacuolar myopathy. However, patients on chronic therapy with this drug may exhibit myocyte changes due to drug exposure, not indicating overt toxicity.

Endocarditis in SLE although reported as a frequent cardiac manifestation, is far more common in autopsy studies than clinical practice. Nonbacterial vegetations (Libman-Sacks) are reported in 15% to 60% of patients in autopsy studies. Echocardiographic studies have reported wide ranging prevalence of valvular abnormalities, reflecting different inclusion criteria and imaging techniques. Studies using transesophageal echocardiogram have shown valvular abnormalities in over 50% of patients, varying from non-specific mild valvular thickening to nodules and large vegetations that may cause serious valvular dysfunction.[4] Vegetations are more frequent in the mitral valve but any valve may be affected. They are usually localized on the atrial side of the mitral valve and the arterial side of the aortic valve. Complications from endocarditis are infrequent with vegetations rarely causing embolic events. Valvular lesions may develop, resolve, persist or worsen independent of disease activity; fibrosis may result in valvular regurgitation. Valve damage and fenestration may occur.

Several studies have demonstrated an association of valvular disease in the presence of APLA, whether the patient has SLE or not.[5] Formal guidelines for prophylaxis with antibiotics for SLE patients with valvular vegetations are not available. However, given that severe regurgitation may increase the risk of bacterial endocarditis, antibiotic prophylaxis should be considered for SLE patients undergoing high-risk procedures.

Arrhythmias, often sinus tachycardia, may frequently accompany myocarditis or pericarditis. Patients who present with arrhythmias or conduction defects should be evaluated for the presence of myocarditis. Sinus tachycardia can be seen in patients with active SLE in the absence of cardiac disease and it usually resolves with treatment of SLE. Other causes of tachycardia to consider include pulmonary embolism and infections. Although isolated conductions defects are very rare in adult patients with SLE, infants born to mothers with positive anti-Ro or anti-La

antibodies independent of the diagnosis of SLE, have an increased incidence of congenital complete atrioventricular (AV) block. The transplacental passage of these autoantibodies to the fetus may cause myocardial inflammation and fibrosis of the conduction system.[6] Fetuses of all women with positive antibodies should be followed with serial echocardiography during pregnancy to detect conduction abnormalities.

Coronary arteritis, resulting in cardiac ischemia, occurs rarely in patients with SLE and is difficult to diagnose with certainty unless by pathologic examination. Patients with SLE have an increased risk of atherosclerotic cardiovascular disease (ASCVD), which is far more common in SLE than coronary arteritis. The tempo and pattern of disease progression documented by repeat catheterization may also be useful to strongly suggest arteritis instead of more routine ASCVD. Other causes of acute coronary syndromes in SLE include coronary thrombosis associated with the presence of APLAS. In the Helsinki Heart Study, APLA levels were an independent predictor of coronary artery disease (CAD).[7] Aortitis with associated valvular regurgitation can occur rarely in SLE.[8]

Pulmonary artery hypertension (PAH) is common, but usually mild, in SLE and its manifestations are similar to idiopathic pulmonary hypertension.[9] Clinically significant PAH is less common and patients may be asymptomatic at the time of diagnosis by echocardiography. In SLE patients, PAH can be associated with intimal hyperplasia and medial thickening and, rarely, pulmonary arteritis. Patients should be evaluated for secondary pulmonary hypertension caused by recurrent thromboembolic disease, especially in the presence of APLAS.

There is no single treatment for SLE. Treatment is selected based on the type and severity of clinical manifestations and are managed on an individual basis. Life- or organ function-threatening disease is treated with high-dose corticosteroids (CS) and other immunosuppressive medications, including cyclophosphamide, azathioprine, mycophenolate mofetil or methotrexate.

Treatment of any heart disease in SLE depends on its severity. Mild cases of pericarditis without hemodynamic compromise may be treated with nonsteroidal anti-inflammatory drugs (NSAID) therapy, if there is no contraindication. Corticosteroids are used for more severe disease or when there is no response to NSAIDs. There are no data on colchicine for the treatment of pericarditis from SLE, but this agent is more frequently being used for recurrent disease. It must be dosed carefully in the setting of renal dysfunction. Large pericardial effusions may need to be drained if there is hemodynamic compromise. Coronary arteritis, symptomatic myocarditis and valvulitis are usually treated with high-dose CS, with or without adjunctive cyclophosphamide or azathioprine. The surgical indications for valvular disease are not different in SLE. Long-term anticoagulation is necessary in patients with thrombotic syndromes and positive APLAs. This may influence the decision as to replacement valve type. Thrombocytopenia may complicate therapeutic decisions in these patients.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory polyarthritis with a prevalence of 0.5% to 2% in the adult population. The disease is more common in women (2 to 4 times), with its peak onset during their third to fifth decades of life. RA typically presents with a symmetrical polyarthritis involving small and large joints. The diagnosis of RA is based on clinical manifestations. Although approximately 70% of patients have a positive rheumatoid factor (RF), its presence does not confirm the diagnosis of RA as it may be present in healthy individuals and other diseases, including chronic viral hepatitis and bacterial endocarditis. The anti-cyclic citrullinated peptide (anti-CCP) test, adds some specificity to the serologic diagnosis; it is not detected in RF-positive patients with hepatitis C. Both RF and anti-CCP are associated with more severe disease and extra-articular manifestations in patients with RA.

Cardiac involvement in RA includes pericarditis, valvulitis, myocarditis and an increased prevalence of atherosclerotic coronary heart disease. The pericardium is affected in approximately 40% of patients, with pericarditis being the most frequent cardiac manifestation in RA.[10] Pericarditis is most commonly detected by echocardiography and at autopsy, as it is usually asymptomatic. It is seen more frequently in patients with rheumatoid nodules and a positive RF. A chronic, clinically silent pericardial effusion is more common than acute symptomatic pericarditis.[11] The electrocardiogram (ECG) is usually normal in patients with chronic pericardial disease, but may show characteristic changes in acute pericarditis. Patients with pericardial effusion frequently have associated pleural effusions. Constrictive pericarditis is not common but can occur; it must be distinguished from restrictive cardiomyopathy, a rare complication of secondary amyloidosis in patients with longstanding RA.[12]

Chronic pericarditis may rarely result in pericardial calcification. The pericardial fluid in RA is similar to pleural fluid; variable leukocyte counts ranging from scant to more than 30 000/mm³, generally with a neutrophil predominance. High protein levels, low glucose levels and low complement are usually seen. Immune complexes and RF may be present in the fluid, but their presence does not confirm that the pericarditis is caused by RA.

Myocardial disease in RA is rare and typically does not cause clinical symptoms. However, RA is associated with an increased risk of congestive heart failure (CHF). Whether the underlying pathophysiology is related to subtle inflammatory myocardial disease or ischemic heart disease is unknown. Granulomatous nodules may be seen in the myocardium pathology, and cause conduction block, but this is exceedingly rare.[13]

Secondary amyloidosis is rare in rheumatoid disease, but can cause cardiomyopathy and AV block. Abnormalities in the conduction system have been described and, once established, may not reverse with treatment for RA.

Ecocardiographic and autopsy studies show evidence of valvular disease in about 30% of patients with RA. These are usually of no clinical or hemodynamic significance. Mitral regurgitation may be more common in RA patients as compared to control population. Although rare, aortic root abnormalities, including aortitis have been reported in association with RA.[14]

Coronary vasculitis is an extremely rare complication of RA; but patients with RA have an increased risk of CAD and premature death from atherosclerotic disease. Although currently unsupported by adequate evidence, it is reasonable to consider longstanding RA as an intermediate risk factor in assessing preoperative risk, similar to patients with renal insufficiency in the American Heart Association guidelines.

Mild pericarditis in patients with RA is initially treated with NSAIDs. However, since most of the heart manifestations may be related to active RA, effective control of disease activity with intensification of systemic immunosuppressed therapy may be the most effective therapy. Patients with hemodynamic compromise or recurrent pericardial effusions may need pericardiocentesis and/or a pericardial window. There are no data on colchicine therapy in RA pericarditis.

The current therapeutic approach with aggressive use of disease-modifying drugs as soon as the diagnosis of RA is established may be associated with a reduction of systemic manifestations, including heart disease. Traditional disease-modifying antirheumatic drugs may be used as monotherapy or in combination and include agents such as methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. Tumor necrosis factor (TNF) inhibitors are extremely effective agents, although cost and the unknown long-term effects of therapy have prevented the use of these agents as first line therapy for most patients. The use of high-dose infliximab in patients with severe CHF and RA has been associated with heart failure and increased cardiac mortality.[15] The data available do not clearly preclude the use of anti- TNF agents in patients with mild and controlled CHF, but warrant increased vigilance. There are data that aggressive control of the systemic inflammation of RA with methotrexate or anti-TNF agents may reduce CV morbidity.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease that commonly affects the entire spine and the sacroiliac joints. Large peripheral arthritis, tendonitis and enthesitis are commonly seen in patients with AS and unlike in RA, involvement tends to be asymmetrical. The prevalence of AS is approximately 0.5% to 1% in whites and it is rare in black populations.

AS is one of the diseases included in the group of spondyloarthropathies, these conditions share many clinical features and a high prevalence of the HLA-B27 antigen. Although the great majority of Caucasian patients with AS have the HLA-B27 (90%-95%), most individuals who carry this gene do not have the disease, and therefore gene typing should not be a routine diagnostic test. Presence of the gene predisposes to anterior uveitis and cardiac conduction disease and perhaps proximal aortitis. Patients may express extra skeletal B27-associated cardiac and other complications without overt rheumatic disease.[16]

Aortic root, valvular disease and conduction abnormalities are the most important manifestations of cardiac involvement in AS. The myocardium and rarely, the pericardium can also be affected. Pericarditis, although reported, is rare in AS.

Aortic disease and aortic regurgitation have been well recognized in AS. Autopsy and echocardiographic studies reveal disease that ranges from mild aortic wall thickening without clinical consequences to rapid heart function deterioration due to acute severe aortic regurgitation. The aortic root thickening occurs from intimal proliferation and adventitial scarring. Aortic root disease has been reported in up to 100% of AS patients who had aortic regurgitation in an autopsy series.[17] Characteristic findings include proximal aortitis with thickening and decreased elasticity of the aortic root, with subsequent dilation. Aortic valve thickening was predominantly manifested as nodularities affecting the cusps (72%).

Echocardiographic studies have shown aortic valve thickening and mitral valve thickening in 40% to 50% of patients. The severity of aortic root disease is associated with the patient's age and duration of AS. However, an electrocardiographic and transthoracic echocardiographic study of 100 Swiss men with AS of more than 15 years duration has shown no significant increase in valvular or conduction disease.[18]

Cardiac conduction abnormalities have been found in up to one third of patients with AS. Atrioventricular conduction block may initially be intermittent, but tends to progress. Complete heart block may be seen in 1% to 9% of patients with AS. Conduction abnormalities seem to be related to the presence of HLA-B27, occurring in the absence of skeletal manifestations. It is more common in male patients, and as many as 20% of men with permanent pacemakers may have the HLA-B27 gene. In women with permanent pacemakers, the frequency of the gene was not increased.[16]

Electrophysiologic studies have indicated that the most common level of block is in the AV node itself, not within or below the bundle of His.[16] Atrial fibrillation may also occur more commonly than expected in patients with the HLA-B27 gene.

For many years, AS was treated with NSAIDs and physical therapy with marginal benefit and continuous progression of disease. Methotrexate and sulfasalazine have also been used with improvement of peripheral joint involvement but no effect on spinal disease.

The B27 extra-articular manifestations, including cardiac disease are treated, as needed, with CS and/or surgery. The use of anti-TNF agents (i.e. etanercept, infliximab, adalimumab) in AS has been associated with remarkable clinical efficacy. They have not been well studied in the treatment of extra-articular manifestations, but it is possible that better control of inflammation in AS may be beneficial in preventing CV disease. As noted before, the use of these agents in patients with severe heart failure warrants close monitoring.

SYSTEMIC SCLEROSIS

Systemic sclerosis (SS) or scleroderma is a multisystem disease characterized by vasculopathy and tissue fibrosis. Microvascular occlusive disease is a result of intimal proliferation with progressing fibrosis in combination with vasospasm phenomenon. Although early lesions may show lymphocytic inflammation, this is a non-vasculitic ischemic process linked to predominant fibrosis of the skin and other target organs. Raynaud's phenomenon usually precedes skin involvement and ultimately occurs in more than 90% of patients, suggesting an initial and critical role of vascular dysfunction. The disease is divided into limited cutaneous variants and the diffuse cutaneous/systemic form.

Scleroderma is a rare disease with an estimated incidence of 0.6 to 19 per million of the general population per year. There is an increased prevalence in certain populations, such as the Choctaw native americans. The average age of onset is between 45 and 65 years. Children are infrequently affected. Among younger individuals, there is a female predominance of approximately 7:1 versus 3:1 for entire scleroderma cohorts.

Over 90% of patients are ANA-positive in SS and in CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), the limited variant of the disease.

Cardiac manifestations in SS vary from clinically silent involvement to overt signs of heart disease that can be associated with increased morbidity and mortality. Involvement usually occurs late in the disease course.[19]

Pericardial involvement although common in SS, is usually clinically asymptomatic. Fibrinous pericarditis has been observed in up to 70% of patients at autopsy.[20] Two echocardiography studies reported small pericardial effusions in 14% of 77 patients and none of 106 patients.[21,22] Large effusions rarely occur, and are a poor prognostic sign. Pericardial effusions may also be a result of uremia in patients with renal disease.

Myocardial dysfunction in SS may have multiple causes including pulmonary and renal disease and hypertension. True primary myocardial disease in SS is more common in patients with

diffuse disease and/or peripheral skeletal myositis. An autopsy study reported focal areas of contraction band necrosis and fibrosis.[23] The severity of the lesions was unrelated to concomitant pulmonary and systemic hypertension. These findings could be a result of intermittent ischemia caused by vasospasm of the intramyocardial arteries.

Angiographic studies have demonstrated normal epicardial coronary arteries in patients with segmental wall motion abnormalities suggesting that microvascular disease with vascular spasm could be involved in the pathogenesis of myocardial dysfunction. Approximately 80% of SS and 65% of CREST patients have fixed perfusion defects on scintigraphic imaging. Right ventricular wall motion abnormalities can be abnormal in SS in patients without PAH, and the same underlying process of microvascular disease may be the cause.[24]

Conduction abnormalities are frequently seen in the ECG with most patients being asymptomatic. Premature ventricular contractions are the most common arrhythmia in SS. Abnormalities can be found throughout the conduction system, with more than 60% of patients having ventricular ectopy. Patients with symptomatic conduction defects have worse prognosis and may be prone to sudden death.[19] SS is a cause of a "pseudoinfarction" pattern on ECG. The risk of CHF and cardiac sudden death is increased in patients with coexistent skeletal myositis. Primary valvular disease is not common.

PAH is one of the most serious clinical manifestations in SS and CREST syndrome. It may result from intrinsic pulmonary artery disease or from interstitial fibrosis in patients with SS.[25] Patients should undergo periodic echocardiography to screen for asymptomatic PAH, and if suspected by echocardiography, should be confirmed and quantified by hemodynamic catheterization.

At present, there is no proven effective treatment to limit the progression of SS. Treatment management is targeted to control symptoms. There is no role for long-term or high doses of CS in SS; its use may precipitate renal crisis and therefore should be avoided. Renal crisis is a complication in SS that may be associated with minimal or severe hypertension, rapidly rising serum creatinine, microangiopathy, thrombocytopenia, and left ventricular failure. The main treatment objective is rapid control of blood pressure with angiotensin-converting enzyme inhibitors, and other antihypertensive medications added as needed. Corticosteroids should not be used.[26]

A few cardiac complications such as myositis and pericarditis with effusions may require CS therapy, which should be cautiously used because of the risk of inducing renal crisis. Conduction disease and arrhythmias are treated as they would be in patients without SS. Vasodilator therapy with calcium channel blockers, prostacyclin or endothelin antagonist may be associated with initial improvement, however failure of treatment later in the disease is usually the result of fixed obliterative lesions.

VASCULITIS

The primary systemic vasculitides are inflammatory conditions of unknown etiology. They are commonly classified based on the vessel size and the pattern of organ involvement.

Vasculitides more commonly associated with CV disease (CVD) include giant cell arteritis (GCA), Takayasu arteritis (TA), polyarteritis nodosa (PAN), and Churg-Strauss syndrome (CSS). Although primary cardiac involvement is not common in Wegener's granulomatosis and the disease will not be discussed in this review, rare cases of conduction disease and clinical

pericarditis have been noted, and accelerated atherosclerosis may occur in these patients, compared with people matched for age, gender, and conventional risk factors.[27,28]

Takayasu Arteritis

TA is an idiopathic large-vessel granulomatous vasculitis that affects the aorta and its major branches. TA is rare with an estimated prevalence of 2.6/1 000 000 persons in the United States and 1.26/1 000 000 in northern Europe. The disease is more common in Japan where has been reported in 1 in every 3000 autopsies.[29] TA is more frequent in young women (6 to 10:1).

Patients with TA may develop arterial stenosis and or aneurysms. Stenoses occur 3 to 4 times more often than aneurysms which are more commonly seen in the aortic root. Claudication of the extremities is the most common symptom, and bruits, blood pressure, or pulse asymmetries are the most common signs in TA. Hypertension usually results from renal artery stenosis, but can also be caused by suprarenal aortic stenosis or a chronically damaged aorta. Cardiac, renal, and central nervous system vascular complications cause most severe morbidity and mortality.[30,31]

The diagnosis of TA is based on symptoms of claudication, ischemia, or the finding of hypertension, blood pressure and/or pulse asymmetries in young individuals in combination with vascular imaging abnormalities. If vascular surgery is needed, histopathologic abnormalities may support the diagnosis and permit accurate assessment of local disease activity.

Constitutional symptoms occur in about 50% and may indicate active disease. An elevated erythrocyte sedimentation rate (ESR) further suggests the presence of active disease. Many patients without symptoms may still have progressive disease and as many as 50% may have normal ESR. Active disease in these patients is difficult to determine and is suggested by the presence of new vascular abnormalities in imaging studies and/or the presence of inflammatory changes in specimens obtained during bypass surgical procedures.

Cardiac complications in TA result more commonly from aortic aneurysm leading to aortic regurgitation and inadequately treated hypertension. Coronary artery vasculitis is not common with angiographic or autopsy studies showing an incidence of 5% to 15%. Lesions are more frequently seen in ostial or proximal regions.[30–32]

Echocardiography studies suggest that left ventricular systolic dysfunction caused by myocarditis may affect approximately 18% of patients.[33]

Almost all patients with TA improve when treated with high doses of CS; relapses are common with tapering of CS therapy. CS-resistant or relapsing patients may respond to the addition of cyclophosphamide or methotrexate. Chronic immunosuppressive therapy is frequently necessary because of relapses. Preliminary studies have shown that treatment with anti-TNF inhibitors may dramatically improve or control the disease in patients with TA who have relapsed during tapering of steroid therapy.[34,35]

Other important aspect in TA is the distinction between inflammatory lesions and damage. Clinical features may be a result of morbidity such as fibrotic fixed stenosis, aneurysms and thrombosed vessels in patients without active disease. These patients may require surgical intervention because of clinical deterioration.

Hypertension affects approximately 40% to 90% of patients. One problem in monitoring these patients relates to not knowing whether blood pressure recordings in an extremity

accurately reflect aortic root pressure. Because over 90% of patients have stenotic lesions and the most common site of stenosis is the subclavian and innominate arteries, blood pressure in one or both arms may underestimate pressure in the aorta. Elevated aortic root pressure increases the risks of hypertensive complications. Intravascular pressure recordings during angiographic procedures should be compared to the blood pressure in the extremities obtained at the same time; this should be considered and planned ahead of any anticipated angiographic studies.

In the absence of contraindications, patients should have the entire aorta and its primary branches evaluated in vascular imaging studies. Magnetic resonance angiography does not allow measurement of intravascular pressures, but it is frequently used to diagnose and monitor vascular lesions avoiding the need for repeated catheter-guided angiography.

Surgical correction of clinically significant lesions is sometimes needed, especially in the setting of renal artery stenosis and hypertension. In about 20% of patients, aortic root involvement may lead to valvular insufficiency, angina, and CHF. Severe or progressive changes may require aortic surgery, with or without valve replacement. Severe symptomatic stenoses of subclavian and carotid vessels should be treated by grafts that originate from the aortic root. Grafts originated from an arch vessel may be lost because of new stenosis in an initially normal subclavian or carotid artery. A graft from the ascending aorta is more likely to be functional long-term because the ascending aorta in TA essentially never becomes stenotic. Angioplasty and intravascular stents frequently result in restenosis, hence bypass is preferred whenever feasible. However, even high flow surgically placed grafts are at increased risk of premature closure. Vascular biopsy specimens for histopathologic evaluation should be obtained in all surgeries to help determining disease activity.

Giant Cell Arteritis

GCA affects a population older than 50 years (mean age of 74 years). GCA is more common in northern latitudes. In Iceland and Denmark, the prevalence is 27 and 21/100 000, respectively, in the group older than 50 years.

The most characteristic features of GCA are new onset of atypical and often severe headaches, scalp and temporal artery tenderness, acute visual loss, polymyalgia rheumatica, and jaw pain. The finding of a high ESR supports the clinical diagnosis of GCA, but is not specific and may not be present even in patients with biopsy proven GCA. The yield of positive temporal artery biopsies is about 50% to 80%, depending on the clinical pattern of disease.

Large-vessel vasculitis is frequently observed in autopsy studies of patients with GCA. It may be the first manifestation of the disease. GCA may cause clinically evident aortitis in at least 15% of cases and can also involve the primary branches of the aorta, especially the subclavian arteries.[36,37] Patients with GCA usually present with similar large-vessel involvement as seen in TA. Among older adults with inflammatory large-vessel disease, the same clinical evaluation and precautions must be applied in GCA as in patients with TA, such as the need to identify an extremity that provides a reliable blood pressure equivalent to aortic root pressure and follow-up monitoring for new bruits, pulse, and blood pressure asymmetry.

Patients with GCA are more than 17 times more likely than age-matched controls to have thoracic aortic aneurysms and about 2.5 times more likely than age-matched controls to have abdominal aortic aneurysms. Thoracic aortic dissection in GCA is associated with markedly increased mortality.[38] The presence of large-vessel disease, including aortic aneurysms, in older adults with GCA is not always caused by atherosclerosis and pathologic specimens should always be obtained when surgical procedures are necessary. GCA can also involve leg vessels and cause leg claudication.

Approximately half of patients with GCA have cardiac disease. Myocardial infarction caused by GCA is rare or may be under diagnosed as histopathology is not usually obtained from coronary arteries in older patients. A review of 72 cases with histopathologic documentation included 18 deaths directly attributable to GCA. Of the 18 deaths, the causes were aortic aneurysm rupture in 6, aortic dissection in 6, stroke in 3 and myocardial infarction in 3.[39]

Treatment with CS is the most effective therapy for GCA and often eliminates symptoms within 1 week. Cytotoxic and other immunosuppressive agents, including anti-TNF agents, have not proved efficacious in controlled trials. Several studies have demonstrated that the use of low-dose acetylsalicylic acid reduces cranial ischemic events (blindness and stroke) three- to fourfold compared with patients who had not received such therapy; in the absence of contraindications, all patients with GCA should receive low-dose acetylsalicylic acid.[40,41]

Polyarteritis Nodosa

PAN is a nongranulomatous disease of only medium-sized arteries. The older PAN literature included patients with both PAN and microscopic polyangiitis (MPA), a disease that is defined by the presence of small-vessel vasculitis. Since the Chapel Hill Consensus Conference (CHCC) on Nomenclature, cases of non-granulomatous vasculitis with glomerulonephritis (renal capillaritis) and pulmonary infiltrates (alveolitis or capillaritis) are considered MPA and not PAN.[42] Because of that, it is difficult to know the exact incidence of PAN but it is a rare disease, with an annual incidence of less than 1/100 000. There is no gender predominance and although individuals of any age can be affected, incidence peaks between 40 and 60 years. PAN has been associated with hepatitis B, and less commonly with hepatitis C infection.

Any organ system can be involved. However, according to the CHCC guidelines, features resulting from small vessel (capillary or venule) disease, such as palpable purpura, pulmonary infiltrates or hemorrhage and glomerulonephritis are not associated with PAN. In contrast, these findings occur in MPA.

PAN would more typically include deep skin inflammatory changes that may cause painful nodules, infarction and gangrene, peripheral neuropathy, renal infarction, hypertension, pulmonary infarctions, and cardiac disease. Markers of poor prognosis include ischemia or infarction of critical organs (brain, intestine, kidneys, and heart).[43]

Although clinically apparent heart disease may only affect less than one third of cases, necropsy studies may reveal medium-sized vessel vasculitis more frequently, in up to 75% of patients. The most common clinical manifestation associated with the CV system is hypertension, most frequently caused by renal artery involvement. Angina and myocardial infarct may occur in the setting of absent or mild atherosclerotic disease suggesting the presence of coronary arteritis. Angiography is useful to make this diagnosis. Congestive heart failure may be a result of myocardial infarcts from vasculitis but may also be a complication from hypertension. Left ventricular hypertrophy is usually associated with the presence of hypertension. Pericarditis is not a common clinical manifestation. It was rarely observed in one necropsy study, where only 2 out of 66 patients

had evidence of acute pericarditis. Pericardial effusions were not seen in that study.

Evaluation of prognostic factors in PAN revealed a poorer survival in patients with cardiac disease. The 5-year survival for those with cardiac or renal involvement was 38% versus 78% for those without their involvement.[43]

CS is the main therapy in PAN; not all patients with PAN require the addition of adjunctive immunosuppressive agent (cyclophosphamide, methotrexate, or azathioprine) to the CS. In the setting of critical organ disease, including cardiac disease, cytotoxic agents are indicated.

Churg-Strauss Syndrome

CSS is a very rare systemic small-vessel granulomatous vasculitis that typically includes a history of asthma, eosinophilia, pulmonary infiltrates, upper airway inflammation, and variable renal, neurologic, cutaneous, and cardiac involvement. Histopathologic observations from involved organs reveal eosinophilic tissue infiltration, granuloma, and vasculitis.

The incidence of CSS is approximately 2.4 cases/1 000 000 persons annually. It may affect any age, with the peak age group being 35 to 50 years old and no gender predominance.

The diagnosis of CSS requires a past or present history of asthma or other types of allergy conditions. In addition, patients have peripheral eosinophilia and clinical manifestations related to specific organ-system involvement. General symptoms of fever, weight loss and fatigue are present in 70% to 100% of cases. Other common clinical features include lung involvement (hemorrhage or infiltrates), peripheral neuropathy, skin lesions, gastrointestinal disease and musculoskeletal symptoms. Renal involvement (glomerulonephritis) is less common but affects at least one third of patients.

The frequency of cardiac disease in CSS varies significantly in different series from 15% to 55% of cases. Cardiac disease in CSS is the major cause of death, accounting for nearly half of all deaths.[44] Most common manifestations include pericarditis, myocarditis, and less frequent, coronary arteritis. Endocarditis is usually not associated with CSS. Congestive heart failure may be severe. It occurs in 15% to 30% of cases. Patients may rapidly develop myocardial dysfunction with heart failure that can be reversible if prompt aggressive treatment is initiated.

Myocardial damage can occur by means of extensive tissue infiltration resulting in fibrosis and/or from coronary or small vessel vasculitis leading to ischemia. Tissue eosinophilic infiltrates are the most common histopathologic findings in biopsies. Epicardial and myocardial granuloma can also be seen. Although vasculitis is described as another mechanism of disease, coronary angiography can be normal, suggesting predominant involvement of smaller vessels.[45]

Treatment with CS usually results in dramatic improvement. In patients with critical organ system involvement, including the heart, pulse intravenous therapy with methylprednisolone in combination with a cytotoxic agent may be indicated.

RISK OF ATHEROSCLEROSIS IN RHEUMATIC DISEASES

Systemic rheumatic diseases have been frequently associated with increased CV morbidity and mortality and accelerated atherosclerosis. The chronic inflammatory state associated with systemic rheumatic diseases may play an important role in the pathogenesis of premature atherosclerosis in these patients.

Patients with RA die prematurely as compared with the general population, mostly due to ASCVD, with a relative risk of at least 2 compared with age-matched normal controls after controlling for traditional atherogenic risk factors.[46–48] Coronary artery atherosclerosis, appears more severe and prevalent in patients with longstanding RA for more than 10 years as compared to those with early disease (<5 years) and control subjects.[49] Increase in the intima-media thickness of the carotid artery was also higher in patients with RA as compared to controls[50]. The cause of increased atherosclerosis in patients with RA is not known, but it is not explained by traditional CV risk factors alone. Increased risk of CAD has been related to longer duration of disease, more severe RA as measured by the use of anti-TNF inhibitors, RF positivity and extra-articular disease.[51,52] Elevated systemic levels of pro-inflammatory cytokines as seen in RA may accelerate the development of atherosclerosis. The presence and severity of coronary calcification has been associated with RA duration, which may be an indication that duration of chronic inflammatory burden is important to determine premature atherosclerosis. Evidence that treatment with methotrexate or anti-TNF inhibitors decreases the risk of CVD further supports that theory.[53,54] Chronic use of CS has been thought in the past to increase atherosclerosis but results have been inconsistent. CS could potentially also decrease the risk for CV complications in RA by controlling inflammation.

Dyslipidemia may precede the development of clinical RA. The disease may be associated with proatherogenic lipid profiles such as low total and high-density lipoprotein (HDL) cholesterol and high triglyceride levels, a pattern that is associated with a more atherogenic low-density lipoprotein particle.[55] HDL in patients with RA may not exert antioxidant activity and thus may not be protective.[56]

Given the limited knowledge about an association between therapy for RA and risk of CAD, aggressive prevention and treatment of traditional risk factors and suppression of systemic inflammation in RA are reasonable goals to decrease risk of CV events.

Premature myocardial infarction in patients with SLE, was observed in 1976 by Urowitz et al.[57] Since then, many studies have demonstrated a significantly increased morbidity and mortality from CVD in SLE. The incidence of CAD in SLE patients has been estimated to be 50-fold higher than in age and gender-matched controls without SLE. In several studies, CVD was the leading cause of death in these patients.[58–60] Studies using scintigraphy, electron beam computerized tomography, and autopsy have shown a high prevalence of subclinical CAD. Myocardial infarction from CAD may occur in young patients with SLE.

As in patients with RA, there is enough evidence to suggest that traditional CV risk factors do not fully account for the increased rate of atherosclerosis in SLE patients and the disease is likely an independent risk factor. Longer duration and more active disease are also associated with increased atherosclerosis in SLE.[61] High triglyceride and lipoprotein (a) levels and nonprotective forms of HDL have been described in patients with SLE.[62] Treatment of SLE patients should not only target disease activity control but also regular screening and aggressive management of traditional risk factors for CVD.

CONFLICTS OF INTEREST

None declared.

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