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Cardiac involvement in systemic lupus erythematosus

Cardiac diseases are common in patients with systemic *lupus erythematosus* (SLE) and constitute the third cause of death in this disease after infections and kidney disorders (1). Cardiac abnormalities (pericardial, myocardial, valvular and/or coronary artery diseases) are noted in over 50 percent of SLE individuals (2). Valvular disease – most often mitral regurgitation, usually hemodynamically insignificant is met in approximately 75 percent (2), pericardial disease, usually a clinically silent effusion – in up to 55 percent (2), myocardial dysfunction – in up to 78 percent (2) and coronary artery disease – in up to 16 percent of patients (3).

The frequency of cardiac involvement estimated by transthoracic echocardiography amounts 34% (4), by transoesophageal echocardiography – 46–61% (4) and in autopsy 65–100% (2).

Heart problems in SLE include: 1) pericarditis, 2) valvular disease, 3) coronary artery disease, 4) myocarditis, 5) pulmonary hypertension.

Pericarditis is the most common manifestation. It is subclinical in 2/3 of patients and is present in 1/3 of SLE subjects with active disease (5). 30% of SLE patients develop pericardial effusion, causing retrosternal or precardial pain, dry cough, dyspnoea, subfebrile state or fever, myalgias and artralgias. At presentation pericardial rub, the rise in ESR and CRP values as well as an increase in troponins' concentrations are detected. In ECG generalised ST segment elevation and T wave reversion are present (in contrast to local changes typical of myocardial infarction). Echocardiography is essential in quick assessment of pericardial morphology and its haemodynamic sequels. Pericardial effusion in SLE is usualy about 10 mm thick, serous, acidic, with low or normal glucose and high protein content, slightly elevated leucocytosis (< 5000 WBC/ml), lymphocytes, few macrophages, low complement and detectable antinuclear antibodies (ANA). It may contain LE cells. The pericardium may reveal foci of inflammatory lesions with immune complexes and predominant of mononuclear cells, but scaring may be the primary finding in healed disease.

Heart tamponade is a condition of haemodynamic disturbances due to increased pericardial fluid pressure. It presents with dyspnoea in vertical body position, decreased effort tolerance, cough, syncope and the classic Beck's triad of symptoms: hypotension, silent heart sounds and overfilling of jugular veins. Chest X-ray reveals heart enlargement without pulmonary haemostasis, echocardiography – pericardial fluid (the "dancing heart" sign), diastolic right atrium retraction and inferior caval vein enlargement.

Pericardiocenthesis is a life-saving treatment. Large effusions, suggestive of tamponade or constrictive pericarditis are rare in SLE, however (5). Purulent pericarditis may occur in an immunosuppressed debilitated patient (6). Pericardiocentesis may be indicated to exclude potentially life-threatening causes of pericarditis, such as infections (e.g. tuberculosis), or neoplastic pericarditis or to drain the fluid in case of tamponade. In the absence of fever or a documented infection that could predispose to purulent pericarditis, we do not routinely perform diagnostic pericardiocentesis in patients with SLE pericarditis unless the symptoms persist despite treatment.

The course of pericarditis in SLE is benign in the majority of patients. Symptomatic pericarditis often responds to a nonsteroidal antiinflammatory drug (NSAIDs) (2). Patients who do not tolerate or do not respond to NSAIDs can be treated with prednisolone (0.5 do 1 mg/kg per day in divided doses). Sometimes triamcynolone injections given into pericardial cavity are applied, as well.

Colchicine may reduce the risk of recurrence of idiopathic pericarditis. Its effectiveness in SLE patients is uncertain. The use of cholchicine can be warranted in cases nonresponsive to NSAIDs and/or glucocorticoids.

Percutaneous drainage under echocardiographic guidance is effective in treatment of cardiac tamponade. Surgical drainage is rarely needed, but can be necessary loculated effusions (7).

Valvular disease – systolic marmurs, usually due to aortic and mitral valve disturbances, have been noted in 16 to 44 percent of SLE patients (2). Structural valvular disease is its most common cause (8), but one must keep in mind that anaemia, fever, tachycardia and cardiomegaly can induce functional murmurs, as well. Mitral valve involvement, usually asymptomatic, accompanied with mild to moderate regurgitant marmur is the most common (9). Mitral valve prolapse appears to be more frequent in lupus than in general population (25 percent of cases versus 9 percent of control in one study (9). Diastolic murmurs have been noted in 1–3% of patients (2). They often reflect aortic insufficiency, which occasionally requires valve replacement.

Transesophageal echocardiography, which is more sensitive than transthoracic echocardiography, was used to determine the frequency, clinical course and complications of valvular disease. Thickening of the leaflets was most common occurring in 51 percent of patients (8). Valvular vegetations were present in 43 percent, valvular regurgitation in 28 percent, valvular stenosis in 3 percent (8). Symptoms and signs follow the occurrence of fibrosis and shortening of tendinous chords. Treatment is operative in 1–9 % of patients. Serious complications comprise cerebral stroke in 13% of patients and peripheral embolism, heart failure, endocarditis and death (altogether in 22% of cases (8).

Our routine practice is to perform cardiac auscultation at most visits, followed by echocardiography for the evaluation of significant or changing murmurs or changing cardiac function.

Some studies have suggested an association between the valvular disease and antiphospholipid antibodies (8, 10), other reports have not confirmed the relationship between antiphospholipid antibodies and cardiac disease (9, 11).

Verrucous endocarditis – Libman-Sacks endocarditis is a common complication of SLE. It has been associated with antiphospholipid antibodies in 12 percent of patients (12), but not all studies (13).

The verrucae are usually localised near the valve edge and consist of immune complexes, mononuclear cells, hematoxylin bodies and fibrin and platelet thrombi. The mitral, aortic and tricuspid valves are more often involved (2). Healing usually leads to fibrosis, scarring, and, in some cases, calcification. If the verrucal lesions are extensive, the healing process can produce valve deformity leading to mitral or aortic regurgitation.

Verrucous endocarditis is typically asymptomatic. However, the verrucae can fragment and produce systemic emboli causing myocardial infarction or stroke. Infectious endocarditis can develop on already damaged valves, as well (13). Blood cultures and echocardiography should be performed whenever fever and a new marmur are noted in a patient with SLE (13). The usefulness of echocardiography in patients with regurgitant marmurs without fever, embolic events, or symptoms of heart failure is uncertain. There is the suggestion one does not perform screening echocardiography in the absence of symptoms or physical findings suggestive of valvular heart disease. High prevalence of valvular heart disease in SLE warrants antibiotic prophylaxis in selected patients undergoing procedures associated with a risk of bacteriemia (such as dental care) (14).

Glucocorticoid and/or cytotoxic therapy have no effect upon valvular lesions (13). In the absence of infective endocarditis, antiplatelet or anticoagulation therapy should be considered in individuals

with vegetation or significant valvular thickening. Valve replacement surgery or valvuloplasty may be necessary for some patients who develop severe mitral or aortic valvular insufficiency, or, rarely for those with symptomatic stenotic lesions.

Myocarditis is an uncommon, often asymptomatic manifestation of SLE observed in 8 to 25 percent of patients (15). Global hypokinesis as an echocardiographic indication of myocarditis is present in approximately 6 percent of cases (16). Only 10% of affected individuals present with fever, weakness, palpitations, tachycardia disproportional to body temperature, dyspnoe and chest pain (16).

Myocarditis should be suspected in resting tachycardia disproportionate to body temperature, electrocardiographic (e.g. as ST and T wave) abnormalities and unexplained cardiomegaly. The last one can be associated with symptoms and signs of congestive heart failure, conduction abnormalities, and/or arrythmias (16). Echocardiography may reveal abnormalities in both systolic and diastolic function of the left ventricle.

Acute myocarditis may accompany other manifestations of acute SLE, particularly the pericarditis. Among many causes of cardiomyopathy, drug use (e.g. cyclophosphamide, antimalarials, phenothiazines) or comorbid disorders (e.g. uremia or postpartum cardiomyopathy) should be excluded. Myocardial biopsy may be needed to distinguish active myocarditis from fibrosis and other causes of cardiomyopathy (2). Histologic examination reveals infiltration of the myocardium with mononuclear cells. Inflammation may lead to fibrosis that may be manifested clinically as dilated cardiomyopathy.

Treatment of lupus myocarditis has not been assessed in controlled trials. Improvement in systolic function has been noted in some patients treated with glucocorticoids, other immunosuppressants (e.g. cyclophosphamide, azathioprine), or intravenous immunoglobulin (16). There is the suggestion that acute *lupus myocarditis* be treated initially with high dose glucocorticoids (methylprednisolone 1000 mg intravenously daily for three days followed by 1 mg/kg per day in divided doses) plus usual therapy for heart failure if present (16). Cardiomyopathy with fibrosis is usually resistant to steroids and/or immunosuppressive drugs.

Coronary artery disease (CAD). Chest pain in SLE is usually of musculoskeletal or pleural origin, yet SLE increases the risk of early atherosclerosis and coronary artery disease even 50-fold in women in the 3rd and 4th decade of life, especially treated with corticosteroids (CS) or exposed to classical cardiovascular risk factors (17). CAD is present in 8.3% of SLE patients with long-lasting disease, treated with CS (18). Symptomatic coronary artery disease has been described in 2 to 45 percent of SLE patients (17, 18) and can lead to acute myocardial infarction in young women (17,18). Angina or myocardial infarction are usually due to atherosclerosis, yet the rare causes can be thrombosis in an angiographically normal coronary artery (19), coronary vasculitis or arterial emboli.

Coronary disease leading to angina, myocardial infarction, heart failure, and death, is becoming an increasing problem, particularly in the patient with long-standing SLE treated with glucocorticoids (17). Atherosclerotic plaques in the carotid arteries, suggesting the presence of similar lesions in the coronary arteries, are found in a higher proportion of patients with SLE than age and gender matched controls (17).

Factors responsible for premature coronary disease in patients with SLE are incompletely understood and include increased frequency of both – traditional risk factors, such as hypertension, hyperlipidemia, obesity or diabetes (20) and others – such as CS treatment which causes overweight, hyperlipidemia and diabetes itself. The increased risk of stroke, myocardial infarction, angina, and death in patients with SLE is not exclusively due to traditional risk factors (21). Nevertheless, attention to modifiable risk factors such as hypertension, hyperlipidemia, cigarettes smoking, obesity, diabetes and sedentary lifestyle is important (22).

The use of glucocorticoids (which can cause or exacerbate hyperlipidemia, diabetes and obesity) has been suggested to be a risk factor for CAD in patients with SLE (23). Patients who receive higher doses of glucocorticoids are more likely to have more active and severe disease (22).

Other suggested risk factors for coronary artery disease in patients with SLE include: elevated plasma homocysteine levels (22), chronic nephritis (24), low serum levels of C3 (25), elevated levels of antibodies to dsDNA (25), antiphospholipid antibodies (22) (which promote thrombosis) and increassed oxydative stress (26).

It has been proposed that autoimmune vascular injury in SLE may predispose to atherosclerotic plaque formation via a number of possible mechanisms (22): The deposition of immune complexes stimulates the accumulation of cholesterol in the plaque. Antibodies to oxidized low density lipoprotein help concentrate these atherogenic particles in the vessel wall macrophages. Vascular endothelium dysfunction, platelet hyperactivity, impaired fibrinolysis, elevation of triglyceride levels due to auto-antibodies to lipoprotein lipase, complement activation and disturbed activation of transforming growth factor beta–1 also can play a role.

Another possible contributor to accelerated atherosclerosis is decreased compliance of central vessels (27). This may produce increased shear stress, predisposing to endothelial damage and platelet activation.

Patients with SLE should be made aware of the importance of risk factor reduction. Patients with lupus should be advised to stop smoking, exercise, achieve a body mass index of 25 kg/m^2, and follow measures designed to improve lipid profiles (3). Hydroxychloroquine should be used in preference to prednisone, whenever possible and aspirin should be prescribed for its antiplatelet properties (22).

Hypertension is an important risk factor in SLE (23). For patients with hypertension there is recommended aggressive therapy, like that for patients with diabetes or chronic kidney disease, aiming for a goal blood pressure <130/80 mm Hg. The choice of an antihypertensive regimen depends in part upon coexisting disorders. As examples, nifedipine for patients with the Raynaud phenomenon and an angiotensin converting enzyme inhibitor for those with renal disease. Glucocorticoids may contribute to hypertension and diabetes, so the steroid dosage should be reduced, if possible. Symptomatic coronary artery disease should be treated as in patients without lupus.

Conduction defects, which may represent a sequel of active or past myocarditis have been noted in 34 to 70 percent of patients with SLE (15). First-degree heart block is often transient, higher degrees of heart block and arrhythmias (such as atrial fibrillation) are unusual in adults. Autopsy studies have revealed focal inflammatory cell infiltrates or, more often, fibrous scarring of the conduction system.

Congenital heart block may be a part of the neonatal lupus associated with the presence of anti-Ro/SSA or anti-La/SSB antibodies in infants whose mothers suffer from SLE, Sjögren's syndrome, an undifferentiated autoimmune disorder, or are asymptomatic. The risk of complete heart block (in utero or neonatal) complicating pregnancy in women with anti-Ro or ant-La antibodies amounts 1 to 7 percent (15).

Pulmonary hypertension – means an increase in pulmonary artery pressure > 25 mm Hg at rest or > 30 mm Hg at effort. It occurs in 7% of SLE patients. Its possible mechanism is endothelial dysfunction and intimal proliferation in small pulmonary arteries together with an imbalance between vasiconstrictive and vasodilating substances. Patients with mild pulmonary hypertension, a less common complication of lupus, are also more likely to have antiphospholipid antibodies (28). Symptoms and signs comprise dyspnoe, decreased effort tolerance and right ventricular heart failure.

Venous thrombosis. The reported incidence of venous thrombosis in patients with SLE was approximately 10 percent (29). Thrombosis can occur in any vessel due to vasculitid or the presence of antiphospholipid antibodies. It usually involves lower extremities, but can also affect the renal veins and inferior vena cava. Pulmonary embolism is rare. Risk factors for venous thrombosis include antiphospholipoid antibodies, the use of oral contraceptives (particularly in association with smoking cigarettes, older age, and glucocorticoid used (29). Degenerative vascular changes are caused by immune complexes and post-steroid hyperlipidemia.

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SUMMARY

The estimated incidence of cardiac manifestation of SLE (valvular, pericardial, myocardial and coronary heart disease) is about 50 percent. Pericarditis is the most common manifestation. The course of pericarditis in SLE is benign in the majority of patients. Symptomatic pericarditis responds to NSAIDs or prednisolone. Valvular disease, most often valve thickening, less frequently vegetations or stenotic lesions are found in echocardiography. Nonbacterial thrombotic endocarditis – Libman-Sachs disease may occur in patients with SLE in the presence or absence of antiphospholipid antibodies. Differential diagnosis must include bacterial endocarditis. In case of SLE patients with no symptoms of heart failure, no unexplained fever, emboli, or new heart marmur, screening echocardiography in search of valvular heart disease should not be recommended. Myocarditis is an uncommon, often asymptomatic manifestation of SLE, only 10% of affected individuals present with fever, weakness, palpitations, tachycardia and chest pain. Coronary artery disease occurs even 50-fold more often in women in the 3rd and 4th decade of life. Coronary disease leading to angina, myocardial infarction, heart failure, and death, is becoming an increasing problem, particularly in the patient with long-standing SLE treated with glucocorticoids.

Zmiany w sercu u chorych na toczeń rumieniowaty układowy

W TRU zmiany w sercu (zajęcie zastawek, zapalenie osierdzia, zapalenie mięśnia serca, choroba wieńcowa) występują szacunkowo w 50%. Najczęstszą manifestacją jest zapalenie osierdzia, o łagodnym przebiegu u większości chorych. Zapalenie osierdzia ustępuje po zastosowaniu NLPZ lub kortykosteroidów. Zmiany na zastawkach to przeważnie ich pogrubienia, rzadziej wegetacje lub zwężenia ujść widoczne w echokardiografii. Zapalenie Libman-Sachsa występuje u chorych na TRU z obecnością lub bez przeciwciał antyfosfolipidowych. Należy wykluczyć w rozpoznaniu różnicowym bakteryjne zapalenie wsierdzia. Pacjenci, u których nie ma objawów niewydolności krążenia, gorączek, zatorów lub nowych szmerów w sercu, nie wymagają badania echokardiograficznego serca. Rzadko występuje zapalenie mięśnia serca i tylko u 10% chorych stwierdza się objawy kliniczne, jak gorączka, osłabienie, bicie serca, przyspieszona czynność serca i ból w klatce piersiowej. Choroba wieńcowa nawet 50 razy częściej występuje u kobiet w trzeciej i czwartej dekadzie życia. Bóle za mostkiem, zawał mięśnia serca, niewydolność krążenia i śmierć stają się narastającym problemem, zwłaszcza u chorych z długo trwającym TRU, leczonych kortykosteroidami.