Lupus of the Heart: Case Report and Pathogenesis Review

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Abstract
We present a case of Lupus with cardiac involvement and review the recent understanding of the molecular mechanisms of the disease. A young woman presented with seizures, sudden right sided painful loss of vision and ulcers on the feet. On examination there was pansystolic murmur suggestive of mitral regurgitation and transesophageal echocardiography showed the presence of large sessile mass over the base of anterior leaflet on the left atrial side suggestive of Libman-Sacks endocarditis. In a young female with manifestations of multiple organ system failure, with cardiac murmurs, we should beware of Libman-Sacks endocarditis. Transesophageal echocardiography is an important tool for early diagnosis and prompt treatment. Recent concepts of SLE pathogenesis centered around Apoptosis and NETosis help to understand the cardiovascular manifestations of this disorder.

LEARNING OBJECTIVE
Patients with Libmann Sacks endocarditis can be diagnosed by 2D-Echo. The key pathogenesis of SLE may be NETosis and aberrant apoptosis.

INTRODUCTION
SLE is a multiorgan autoimmune disease with episodes of flaring up of the diseases at periodic intervals. Among the systems affected, cardiovascular diseases are the major cause of death in SLE [1]. We present a case of SLE with cardiac involvement and review the cardiac manifestations of SLE in modern day practice and the recent concepts of the molecular mechanisms of the disease.

CASE PRESENTATION
A 21 year old woman presented with sudden right sided painful loss of vision and non-healing ulcers on both feet. She had a history of seizures 6 months back and imaging showed hydrocephalus due to aqueductal stenosis. She had a history of malar rash on sun exposure, tingling and numbness of hands on exposure to cold temperatures and small joint pains of both hands. Cardiac examination revealed a pansystolic murmur. Transesophageal Echocardiography [TEE] showed severe mitral regurgitation with a large sessile mass over the base of anterior leaflet on the left atrial side suggestive of Libman Sacks endocarditis (Figure 1). Apart from elevated serum anti-nuclear antibodies [ANA=32 IU/ml], blood and urine biochemical investigations were normal. She was diagnosed by SLE [SLICC criteria]. SLEDAI score was 26 (seizure – 8, visual disturbance – 8, vasculitis – 8, rash - 2). She is responding well to treatment with oral prednisolone and wound care.

DISCUSSION
Our patient presented with seizures and MRI showed hydrocephalus due to aqueductal stenosis. Hydrocephalus is infrequent in SLE and it is proposed that the immune complex deposits within the arachnoid villi impair CSF flow causing hydrocephalus [2]. It increases the intracranial tension precipitating seizures. Sudden right sided painful loss of vision and ulcers on feet are due to vasculitis characteristic of SLE. Our patient was diagnosed before cardiac failure and she recovered with aggressive treatment.

Early TEE helped in prompt diagnosis and treatment of the cardiac lesion in our patient. Bai et al. [3] and Gerldine [4] reported cases of SLE with endocarditis being monitored by Transesophageal echocardiography (TEE). A Head to head comparison study [5] of TEE vs Transthoracic echocardiography showed that Libman-Sacks endocarditis was more commonly detected by TEE than by TTE with TTE having a only 63% sensitivity and 58% specificity. The subsequent review by Roldan, the principal investigator [6] on the role of echocardiography in SLE conclude that the potential advantages of earlier and accurate diagnosis of Libman-Sacks endocarditis by TEE should be recognised and utilised by clinicians.
The pathogenesis of SLE has been discussed exhaustively in many reports and now it is possible to describe it with deeper understanding. The traditional view that immune complexes containing autoantigens and autoantibodies activate complement and inflammatory injury to tissues cannot account for all of the clinical observations [7]. Additional models have been proposed.

Abharrant apoptosis

SLE is characterised by aberrant apoptosis and decreased removal of apoptotic cells (Figure 2A). During apoptosis, Myeloid dendritic cells (MDC) take up the apoptotic blebs. The MDCs stimulate autoreactive T helper cells which inturn induce the formation of autoantibodies by B cells. These antichromatin autoantibodies bind with the chromatin from the apoptotic blebs to form deposits of immune complexes on basal membranes. MDCs also stimulate plasmacytoid dendritic cells to produce IFN-α which further confagrates the inflammation. Thus abnormal apoptosis plays an important role in immune complex deposition and the subsequent organ damage seen in SLE.

NETosis

Neutropenia is a feature of SLE [8]. The dying neutrophils release neutrophil extracellular traps (NETs). This process called NETosis, contributes autoantigens [9] (Figure 2B).These autoantigens stimulate the excess production of SLE-related autoantibodies, including antibodies against nucleosomes and double stranded DNA (dsDNA) [10].

HMGB1

1. The chromatin of apoptotic cells is tightly attached to the proinflammatory mediator high mobility group box protein 1 (HMGB1). HMGB1-containing nucleosomes from apoptotic cells induce Secretion of interleukin (IL) 1beta, IL-6, IL-10, and tumor necrosis factor (TNF) alpha in macrophages.

2. Expression of costimulatory molecules in dendritic cells (DC).

3. Toll-like receptor (TLR) 2-dependent action in anti-dsDNA and antihistone IgG antibodies.

These mechanisms activate antigen presenting cells against nucleosomes and dsDNA [11] (Figure 3).

With these pathogenetic mechanisms in view, cardiac manifestation can be appreciated in a new light. Cardiovascular manifestations of SLE include pericarditis, myocarditis, endocarditis, conduction disturbances [1], coronary artery disease and hypertension.

Even as 40% of SLE patients have pericardial effusion detected by echocardiography [1], only 25% patients have any symptoms. Granular deposition of immune complexes is seen in pericarditis of SLE [1]. This immune complex deposition may be due to abharrant apoptosis and NETosis.

Acute pericarditis appears as a typical precordial or substernal chest pain aggravated by supine position, other features include fever, tachycardia and decreased heart sounds; examination may reveal a pericardial rub. Transient elevation of ST segment or mild T-wave changes are characteristic findings in ECG. Echocardiography can reveal mild effusion or thickening of pericardial layers [1].

NSAIDS [Non-steroidal anti-inflammatory drugs] and/or corticosteroids are used treatment in mild pericarditis. IV corticosteroids are used in more severe cases or if cardiac tamponade is present. In patients with recurring pericarditis antimetabolites like methotrexate or immunosuppressants like mycophenolate mofetil or azathioprine are useful [1].

Myocarditis is the characteristic feature of myocardial involvement in SLE [1]. It occurs in 0 to 8% cases. Fine granular immune complexes deposition [due to abharrant apoptosis and NETosis] in the perivascular tissues are seen in lupus myocarditis.

Signs and symptoms of myocarditis include shortness of breath, tachycardia and arrhythmias. Ventricular dysfunction and dilated cardiomyopathy are late features of the disease [1].

Echocardiography might show global or segmental hypokinesia. T2 weighted MR imaging of myocardium shows abnormal relaxation times in SLE myocarditis [12]. Myocarditis is treated with high-dose steroids. Azathioprine or intravenous immunoglobulins (IVIG) may also be used.

Endocarditis: Valvular involvement is common in SLE. The mitral valve, the aortic valve, the pulmonary valve and the tricuspid valve are affected in SLE in descending order of frequency. The commonest finding in valvular SLE is of a mid-systolic murmur. Echocardiography can diagnose characteristic lighman sack’s lesion of SLE endocarditis [13]. Pathologically, the primary lesion consists of endothelial cells, Anitschow myocytes and inflammatory mononuclear cells in the valve ring and pocket.

SLE also involves the cardiovascular system in the form of atherosclerosis and its complications like CAD or stroke [14]. Atherosclerosis itself can cause hypertension in SLE patients, but hypertension in SLE is predominantly due to renal disease or steroid therapy [13].

In summary, in a young female with manifestations of multiple organ system failure, with cardiac murmurs, Libman-Sacks endocarditis is a definite possibility. Optimal treatment...
Recent studies show that immune complex mediated damage to the connective tissue in SLE patients is instigated by aberrant apoptosis and NETosis. These underlying mechanisms also contribute to diffuse destruction producing the various cardiovascular manifestations like pericarditis, myocarditis, endocarditis, CAD and hypertension in SLE patients. Immunosuppressive therapy remains the chief modality of treatment in almost all these cardiovascular complications of the disease.

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REFERENCES


