

ENDOCARDITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Endocarditis is one of the most prevalent forms of cardiac involvement in patients with lupus, as it considered as a life-threatening complication.

The aim of this study is to determine particularities of endocarditis in patients with lupus and to look for distinguishing features between infectious or immunological origin. A retrospective study was conducted on patients with lupus presenting endocarditis. Lupus diagnosed according to the American College of Rheumatology criteria. The diagnosis of endocarditis was made based on the modified Duke criteria.

The present case report studies seven cases of endocarditis. Six of these patients are women, and the other one is a man. They are aged meanly of 29.4 years (extremes: 20-36). Fever was present in all the cases with a new cardiac murmur in six cases and a modification of its intensity in one instance. The biologic inflammatory syndrome was present in six cases. A cardiac ultrasound performed in six cases made the diagnosis of endocarditis which involved the left heart valves in five cases and the right heart valves in one instance. Valvular insufficiency was identified in six patients. The valve involvement was mitral in two cases, mitral-aortic in two others, aortic in the fifth one and tricuspid in the sixth one. Endocarditis was infectious in 4 cases, thanks to positive blood culture. The germs identified were gram-negative bacilli in two cases, the anaerobic organism in one instance and gram-positive cocci in one instance. *Candida albicans* was isolated in one case.

Libman-Sacks endocarditis was objectified in three cases. A combination of Libman-Sacks endocarditis with infectious endocarditis was diagnosed in one instance. The treatment consisted of antibiotics in four cases with surgery in two cases. The outcome was favorable in five cases and fatal in the two others.

Endocarditis in lupus can be infectious or Libman-Sacks endocarditis. These two conditions share several clinical features. The only distinctive argument remains positive blood culture. The treatment should be initiated as early as possible to limit the valve damage and improve the outcome.

KEYWORDS: Systemic lupus erythematosus, infectious endocarditis, Libman-Sacks endocarditis

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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory, multi-system autoimmune disease of unknown etiology. It has a large

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clinical polymorphism and its symptoms vary in severity. Cardiovascular, renal manifestations, and infectious complications are the major factors that determine the prognosis as well as functional life. Valvular disease is one of the most prevalent forms of cardiac involvement in patients with SLE. It is a relatively common cause of morbidity [1]. The valve lesions can be either Libman-Sacks endocarditis or infective endocarditis which is characterized by a particularly severe clinical presentation due to its occurrence in an immunocompromised ground [2, 3]. Libman-Sacks endocarditis remains a diagnosis of exclusion with infective endocarditis because of their several similarities in clinical presentation [4]. Seven cases of endocarditis complicating SLE whether infective or Libman-Sacks are reported.

Case reports

In this report, seven patients, 6 women, and one man, with a mean age of 29.4 years were followed in our department for SLE. All our patients met the criteria of the American College of Rheumatology for SLE due to the presence of four or more of the 11 criteria. The diagnosis of infectious endocarditis was made according to the Modified Duke criteria. Endocarditis identified at diagnosis of SLE in four cases.

The features of the patients showed in Tables 1 and 2. Patient 1 initially presented a nephrotic syndrome. The diagnosis of lupus was made since she also had a malar rash with arthritis and an abnormal antinuclear antibody (ANA) titer. Treatment consisted of prednisone at a dose of 1.5 mg/kg/day. She later presented fever with tachycardia, polypnea, and modification of the cardiac murmur. The laboratory tests showed hyperleukocytosis (white blood cells (WBC) at 27000/mm³) with a CRP level of 100 mg/l. Echocardiography showed a large mobile aortic vegetation associated with severe aortic insufficiency. Blood cultures isolated a coagulase-negative staphylococcus. Despite an appropriate antibiotic treatment, she died in septic shock. Patient 2 presented a combination of Libman-Sacks endocarditis and infective endocarditis. Diagnosis of lupus was made one year before since she presented arthritis with malar rash, proteinuria, hematuria and abnormal ANA titer. She was hospitalized later for a weakness associated with exertional dyspnea and a mitral cardiac murmur. On-going treatment consisted of prednisone (5mg/day) and chloroquine (300mg/day). Cardiac ultrasound showed a slightly thickened mitral valve with mitral regurgitation grade 2-3. She first received prednisone at a dose of 1.5 mg/kg per day. Five days later, she developed a fever with pericardial friction and modification of the cardiac murmur. At biology, CRP level was 90mg/l with an elevated WBC count of 12100/mm³. Blood culture isolated enterobacteria. Echocardiography showed the presence of vegetation over the mitral valve about 0.8 cm. She was treated with appropriate antibiotics (Ceftriaxone, Ofloxacin). Rapid apyrexia marked evolution with no vegetation on cardiac ultrasound control. Patient 3 had a fever with a mitral cardiac murmur. Routine investigations showed a CRP level of 20mg/l with WBC count of 6000/mm³. Cardiac ultrasound showed mitral and aortic insufficiency grade 2 with mitro-aortic diffuse valvular thickening without vegetation. She initially received antibiotics. However, blood cultures were negative, and she developed arthritis with persistent fever. Diagnosis of Libman-Sacks endocarditis then retained since she also had an abnormal titer of both ANA and antibody to double-stranded DNA antigen (anti-dsDNA). She was treated with prednisone (1mg/kg/day) leading to apyrexia and a good clinical outcome. Patient 4 presented a fever with cardiac murmur and arthritis.

CRP level was 30mg/l. Echocardiography showed the presence of mitral vegetation about 0.5 cm. She was treated with antibiotics, but blood cultures remained negative without clinical improvement. The diagnosis of lupus was then made since she also had malar rash, leucopenia and an abnormal ANA titer with probably Libman-Sacks endocarditis. She received prednisone (0.5mg/kg/j), and the results were good. Patient 5 had lupus nephritis complicated by renal failure. Lupus was initially diagnosed according to the presence of malar rash, arthritis, hemolytic anemia, abnormal titers of ANA, anti-dsDNA and antiphospholipid antibody-associated with renal disorders. She was on dialysis using a jugular catheter. She had a fever with a biological inflammatory syndrome (CRP level of 360mg/l, WBC count of 17600/mm³). Chest radiography was normal. She developed a new cardiac murmur. Blood cultures isolated Methicillin-resistant *Staphylococcus aureus*. Cardiac ultrasound showed vegetation on the tricuspid aortic orifice with the presence of a perforation of the left anterior cusp and an abscess on the aorto-mitral trigone with an aortic insufficiency grade 3. She administered antibiotics (Vancomycin, Ceftriaxone) and surgical repair with the replacement of the aortic valve with good results. Thirty months later, she was on peritoneal dialysis for a good left ventricular function at cardiac ultrasound control.

Patient 6 presented a fever with a new cardiac murmur. WBC count was 9200/mm³ with a CRP level of 18mg/l. Blood cultures were negative. The diagnosis of lupus with Libman-Sacks endocarditis was evoked since he also presented malar rash, arthritis, nephrotic syndrome with an abnormal ANA titer. Cardiac ultrasound was not performed initially since it was not available at the time of diagnosis. Treatment consisted of prednisone at a dose of 1.5 mg/Kg per day with a good clinical outcome. Cardiac ultrasound performed later during treatment was normal.

Patient 7 had lupus nephritis leading to end-stage renal failure. She presented an iterative thrombosis of her fistulas related to a deficiency of active protein C, so she dialyzed with a permanent catheter. She presented a fever with a new aortic murmur. CRP level was 453mg/l with WBC count of 18000/mm³. Blood cultures isolated *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Cardiac ultrasound showed tricuspid endocarditis with vegetation on the lateral valve about 0.8 cm. The treatment associated appropriate antibiotics (Imipenem, ciprofloxacin). Evolution was characterized by the persistence of fever. Blood cultures isolated *Candida albicans*. Cardiac ultrasound revealed an increase in the size of vegetation to about 1.5 cm. The antibiotics were changed (amphotericin B, piperacillin, colymycin) and the patient received a surgical cure for the replacement of the tricuspid valve. She died twenty days later after a status epilepticus due to cerebral hemorrhage.

Discussion

Our study shows clinical features of Libman-Sacks endocarditis and also of infectious endocarditis in patients with SLE. This type of endocarditis is sometimes unclear, especially in patients with SLE presenting fever and new cardiac murmur. As the matter of fact, fever was present in all our cases together with a new cardiac murmur in 6 cases and a modification of its intensity in one case. In the cases of Libman-Sacks endocarditis observed in our study, fever can be explained by SLE exacerbation since the diagnosis was made at the onset of the disease.

Since the occurrence of bacterial endocarditis in patients with persistent Libman-Sacks endocarditis is not uncommon, it is

Table 1 Clinical manifestations at diagnosis of lupus.

	Age/gender	Symptoms	Biology	Immunology	Renal histology
Case 1	25/F	Arthritis, MR, Pt, Ht, cardiac murmur	SR=55, creat=123 $\mu\text{mol/l}$, Pt=6g/24h, NS	ANA=1/512	Active diffuse global LN
Case 2	31/F	Arthritis, MR, Pt, Ht, cardiac murmur	SR=70, YG=22g/l, Pt=1.3g/24h	ANA=1/6400, CH50<10U/ml	diffuse global LN with fibrosis
Case 3	24/F	Fever, Arthritis, weakness, cardiac murmur	SR=100, Hb=7.6g/dl	ANA+, anti-DNA+	diffuse global LN
Case 4	34/F	Arthritis, fever, cardiac murmur	HB=7g/dl, WBC=2200 elts/mm ³ , YG=21g/l, creat=80 $\mu\text{mol/l}$	ANA=1/800	
Case 5	28/F	MR, arthritis	PT=2.48g/24h, creat=856 $\mu\text{mol/l}$	ANA= 1/800, anti-DNA+, antiphospholipid+	Extracapillary glomerulonephritis with fibrosis
Case 6	20/M	Fever, MR, arthritis, RS, Pt, Ht, cardiac murmur	SR=120, Pt=3g/24h, NS, YG=21g/l, creat=264 $\mu\text{mol/l}$	ANA=1/1600	diffuse global LN with membranous LN
Case 7	16/F	MR, arthritis, photosensitivity, oral ulcer, psychiatric impairment	Pt=1.6g/24h, creat=75 $\mu\text{mol/l}$	ANA=1/1600, anti-DNA+	Active focal LN with membranous LN
MR: malar rash, NS: nephrotic syndrome, RS: raynaud syndrome, Pt: proteinuria, Ht: hematuria, SR: sedimentation rate, creat: creatinine, YG: gammaglobuline, ANA: antinuclearantibodies, CH50: hemolytic complement, anti-DNA+: positive anti-DNAantibodies, antiphospholipid+: positive antiphospholipid antibodies, WBC: white blood cells, Hb: hemoglobin, elts: elements, LN: lupus nephritis					

Table 2 Patient's data at diagnosis of endocarditis.

	Symptoms	Biology	Cardiac ultrasound	Blood culture	Treatment	Outcome
Case 1	Fever, chest pain	SR=100, WBC=27000, CRP=100mg/l	AV, AI	Coagulase negative staphylococcus	Oxacillin, Genta, CS:1mg/kg/day	Death (septic shock)
Case 2	Fever, modification of intensity of CM	SR=58, WBC=12100, CRP=90mg/l	MV (0.8cm)	Serratia	Ceftriaxone, ofloxacin, CS:10mg/day	Recovery
Case 3	Fever, CM, cardiac failure	SR=100, Hb=7.6g/dl, CRP=20mg/l, WBC=6000	Valvular thickening, MI, AI	Neg	CS:1mg/kg/day	Recovery
Case 4	Fever, arthralgia	SR=101, WBC=2200, CRP=30mg/l	MV (0.5cm)	Neg	CS:0.5mg/kg/day	Recovery
Case 5	Fever, weakness, CM	WBC= 17600, CRP=360mg/l	AV, AI, TP	Staphylococcus aureus meti-R	Vanco, ceftriaxone, CS:10mg/day, aortic VR	Recovery
Case 6	Fever, CM, arthralgia	SR=120, WBC=9200, CRP=18mg/l		Neg	CS:1.5mg/kg/day	Recovery
Case 7	Fever, CM	CRP=453mg/l, procacitonin=2,9ng/ml, WBC=18000	Vegetation on PV (1.5cm)	Pseudomonas, klebsiella pneumonia, candida albicans	Fosfo, piperacilin, amphotericin B, tricuspid VR	Death
AI: aortic insufficiency, MI: mitral insufficiency, AV: Aortic vegetation, MV: Mitral vegetation, PV: pulmonary valve, TP: tricuspid perforation, PC: procacitonin, SR: sedimentation rate, WBC: white blood cells, CRP: C-reactive protein, CM: cardiac murmur, meti-R: meticillin resistant, CS: corticosteroids, Neg: negative, genta: gentamycin, vanco: vancomycin, fosfo: fosfomycin, piperacilin: piperacillin, colimycin: colimycin, amphotericin B: amphotericin B, VR: valvular replacement						

mandatory to differentiate these two conditions, as the management and treatment are relatively different [5]. Modified Duke Criteria utilizing pathologic and clinical criteria can be useful in helping differentiate infective endocarditis and Libman-Sacks endocarditis [6].

In our study, four cases of infectious endocarditis and three cases of Libman-Sacks endocarditis were identified in which the diagnosis was finally retained in front of negative blood culture, extra-cardiac signs of lupus activity and retrospectively after real improvement with steroids.

In two cases, the diagnosis of Libman-Sacks endocarditis was not made initially. Antibiotics were administered at the beginning and then in the absence of improvement; steroids gave to a good outcome.

Some authors have insisted on the importance of certain biological parameters to help distinguish between Libman-Sacks endocarditis and infective endocarditis, such as the white blood cell count, CRP level, and antiphospholipid antibody level [4, 7, 8].

As a matter of fact, the white blood cell count should be low during a lupus flare and the CRP would be elevated in infection and eventually low in SLE. Meanwhile, being a sensitive marker of inflammation, CRP can also be high in SLE, which is an inflammatory disease. In fact, it has been noted that CRP levels are higher in lupus patients versus controls [9]. In our patients, it was found that CRP level was high in all the cases, but it was greater in those with infective endocarditis. However, the white blood cell count was high in only patients with infective endocarditis. Moderate to high level of antiphospholipid antibody is suggestive of SLE since infection could not significantly raise the antiphospholipid antibody titers [10]. Libman-Sacks endocarditis is associated with antiphospholipid antibodies in about 50% of cases [11]. Several studies have found an association between antiphospholipid antibodies and the presence of valvular dysfunction [1, 12]. However, in our study, antiphospholipid antibodies were found in only one case which doesn't have Libman-Sacks endocarditis.

Valvular involvement is common in SLE [7]. Diffuse valvular thickening is the most common abnormality which involves either the mitral or the aortic valve [7]. Libman-Sacks vegetations are noninfective verrucous vegetations that develop mainly on the mitral valve [5]. They can also be seen on the endocardium surface. A transesophageal echocardiogram is the most useful method to detect valvular lesions [1, 13]. In our cases, cardiac ultrasound detected vegetations without the need for a transesophageal echocardiogram.

Libman-Sacks endocarditis seems to have a better prognosis in our study. In fact, recovery was noted in all cases. Infective endocarditis is a complex disease [14, 15] whose diagnosis is based primarily on the echocardiographic findings and the microbiological status [16].

Blood cultures are positive in about 85% of patients. However, the occurrence of culture negative endocarditis rises to about 10% in most surgical series [17]. All our reported cases of infective endocarditis had positive blood cultures.

In the last years, changes in epidemiology and microbiology of infective endocarditis have been seen. In developed countries, infective endocarditis is now affecting older patients and those with no previously known valve disease [16]. Immuno-compromised patients are also at risk of developing this disease. Compared to the general population, patients with SLE have an increased prevalence of functionally impaired cardiac valves

due to the presence of Libman-Sacks lesions which may make these patients face the risk of developing infective endocarditis [2, 3].

Nowadays, there is also an increase in the number of cases of infective endocarditis caused by staphylococci [18]. In our series, staphylococcus was isolated in 2 cases, enterobacteria in one case and the fourth case three germs were identified (enterobacteria, Gram-negative bacilli, and Candida).

Only about 5% of patients with catheter sepsis were found to have infectious endocarditis, which is due to staphylococcal organisms [18]. Iatrogenic endocarditis most often occurs in patients undergoing chronic hemodialysis with many staphylococcal bacteremia and who may also have sclerotic valves [18]. Indeed, in our study, we reported two cases of haemodialyzed patients with a permanent catheter that might be the cause of the infectious endocarditis.

Mortality associated with infectious endocarditis is reported to be 20% during the initial hospitalization and 20% to 30% during the first year. Gram-negative bacillus and fungal endocarditis bear a mortality exceeding 50% [18]. In fact, evolution was fatal in the only case in our study with fungal endocarditis.

The mortality risk of surgical valve replacement is higher in patients with SLE and especially in patients under immunosuppressive regimen [19]. In fact, among the two patients who underwent surgery in our study, death occurred in the subject receiving high doses of steroids.

Conclusion

Valvular damage in SLE patients is often under diagnosed. Their investigation is thus desirable for early treatment. The diagnosis of Libman-Sacks endocarditis remains difficult to distinguish from infective endocarditis. A positive bacteriological survey remains the main distinctive feature between these two conditions.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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