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ANA-NEGATIVE LUPUS PRESENTING WITH HEART FAILURE AND SEVERE VALVULAR DYSFUNCTION: CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Antinuclear antibody (ANA) negative lupus is an important subset of the systemic lupus erythematosus (SLE) disease spectrum. Since the introduction of human cell line for ANA assay, the occurrence of true ANA-negative SLE has been a rare clinical phenomenon. The nature of cardiac involvement in ANA-negative SLE is not well understood, although any cardiac involvement, including valvular dysfunction, should be considered as a presenting manifestation of SLE irrespective of serology status. Early recognition and intervention appears to be associated with decreased morbidity.

The following report describes our first case of ANA-negative SLE with an initial presentation of severe cardiac valvular dysfunction and heart failure. It also characterizes the spectrum of disease severity in ANA-negative SLE and demonstrates how aggressive SLE therapy can improve cardiac disease.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of autoimmune origin that can affect all organs of the body.[1] The diagnosis of SLE often depends on both clinical criteria and the presence of serological markers such as antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) antibody. When these markers are absent yet other supportive criteria are met, the term "seronegative" SLE is given. Despite the diagnostic challenge associated with seronegative disease, these patients appear to have clinical manifestations similar to their seropositive counterparts.[2] Cardiac dysfunction including valvulitis has been well-described in the seropositive population, but such description is lacking in the seronegative SLE cohort. In this report, we present a case of severe multivalvular insufficiency with heart failure as the initial presentation of seronegative SLE in a young woman.

Case Presentation

A previously healthy 26-year-old woman presented with 1 month of productive cough with clear sputum, shortness of breath, nonbilious emesis, and nonbloody diarrhea. She also noted a 10-pound weight loss, myalgia, and decreased urine output. The patient initially presented to her primary care physician and was treated empirically for acute bronchitis with antibiotics. She obtained only minimal relief and subsequently presented to the emergency department for further evaluation. At the time of presentation, the patient was afebrile with stable blood pressure. Cardiac auscultation was significant for 3/6 systolic murmurs heard best at the apex and right midsternal border, respectively. The remainder of the examination revealed bibasilar rales, abdominal distension, and bilateral pitting edema of the lower extremities. Laboratory studies were significant for white blood cell count 15.2 K/uL, hemoglobin 9.1 g/dL, potassium 6.2 mmol/L, blood urea nitrogen 200 mg/dL, creatinine 31.2 mg/dL, aspartate transaminase 389 U/L, alanine aminotransferase 486 U/L, lipase 4228 U/L, creatine kinase 2289 U/L, troponin 0.105 ng/mL, and B-type natriuretic peptide 4995 pg/mL. The urinalysis revealed significant proteinuria with red blood cells and leukocytes. Blood cultures drawn on two occasions were negative. Serologies for rare serologic causes of endocarditis were not drawn because of lack of risk factors or exposure. Chest X-ray showed bilateral lower lobar patchy opacifications concerning for pneumonia. The patient was treated empirically with antibiotics and underwent hemodialysis for acidosis, uremia, and volume overload. A transthoracic echocardiogram (TTE) revealed mildly dilated left ventricle with moderately depressed ejection fraction (35%-40%) and severe tricuspid and mitral regurgitation (Figure 1). Renal ultrasound demonstrated small kidneys bilaterally with increased echogenicity.

Based on the patient's complex clinical presentation and multiorgan involvement including left ventricular (LV) failure with valvular dysfunction, acute renal failure, pancreatitis, and transaminitis, the suspicion for SLE was high. Yet, ANA serologies were repeatedly negative as were serology results for anti-dsDNA, anti-Smith, and antiphospholipid antibodies. However, the patient's serology result for anti-SSA/Ro came back positive. Due to the unclear etiology of her renal failure and the equivocal autoimmune serology panel, a percutaneous needle biopsy of the right kidney was performed. Biopsy results were consistent with lupus nephritis, showing full house staining (positive) glomerular deposits of IgG and C3 (Figure 2). The patient was started on steroids and hydroxychloroquine for SLE as well as beta-blockers and showed significant improvement in her symptoms. At her 10-month follow-up visit, the patient's symptoms were significantly improved, and repeated TTE showed an LV ejection fraction of 60%, with moderate mitral regurgitation and mild to moderate tricuspid regurgitation. Valvular thickening had also improved.

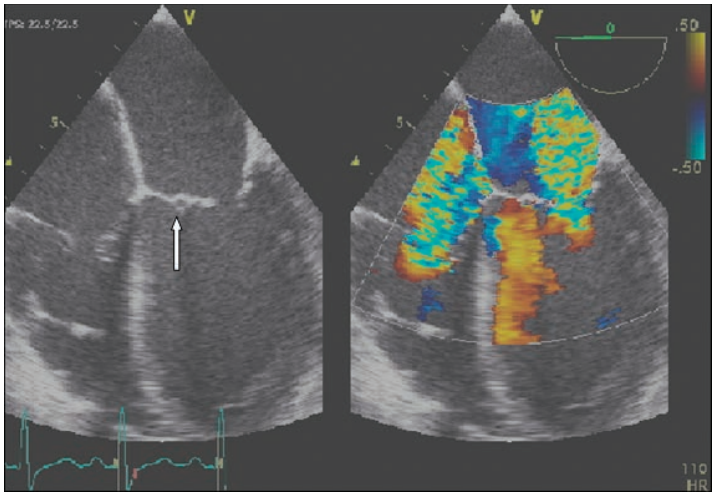

Figure 1. Transesophageal echocardiogram shows significant mitral and tricuspid regurgitation. Arrow points to thickened anterior mitral leaflet.

Discussion

SLE was once thought to be a relatively homogeneous autoimmune disease. However, our understanding has changed as this is now understood to represent a heterogeneous spectrum of disease that includes ANA-negative or seronegative lupus.[3] ANA-negative lupus was originally described in the 1970s.[4] Interestingly, these reports were later minimized following the discovery that many of the negative-ANA results were due to the use of mouse tissue substrate.[5] After human cell lines replaced the ANA mouse assay, there was a significant fall in the reporting of ANA-negative lupus. Currently accepted serological markers in the diagnostic criteria for SLE include ANA, anti-dsDNA, anti-Smith, and antiphospholipid antibodies. Our patient had a confirmed negative ANA serology, negative anti-dsDNA antibody, and negative antiphospholipid antibodies. In the past decade, further serological classifications have identified other autoantibodies associated with SLE and other rheumatic diseases with variable sensitivity and specificity. Reichlin et al. found that nearly all patients with ANA-negative SLE were actually positive for anti-Ro/SSA autoantibody, as was the case in our patient.[3,6]

The first cases of cardiac valve involvement in patients with SLE were described in the early decades of the 20th century.[7] Valvular disease in the setting of lupus includes leaflet thickening, noninfective vegetation (marantic endocarditis), regurgitation, and stenosis. Review of the literature reveals no prior reports of ANA-negative SLE presenting with either severe multivalvular insufficiency or decompensated heart failure. The majority of cardiac involvement in seropositive SLE appears to be subclinical. Significant valvular dysfunction in symptomatic patients with lupus has been estimated to be approximately 3% to 4%.[8] However, in large autopsy studies of patients with known SLE, valvular involvement has been as high as 59%. Of these cases, aortic insufficiency appeared to be the most common manifestation.[9] Interestingly, over the last two decades, several studies have implicated the importance of antiphospholipid antibodies in the pathogenesis of valvular disease in SLE although the exact pathogenesis remains unclear.[7]

To our knowledge, this case represents the first report to describe cardiac involvement as the initial presentation of SLE with negative serologic studies. Our patient's valvular disease and left ventricular systolic dysfunction also improved with aggressive SLE therapies. This improvement occurred despite limitations in the use of traditional cardiac agents such as angiotensin-converting-enzyme inhibitors due to her profound renal impairment. Prior reports had described variable responses to aggressive therapy in patients with seropositive SLE cardiac disease.[10] This patient's successful response may indicate a distinct susceptibility of cardiac disease to antirheumatologic therapies in this SLE subset.

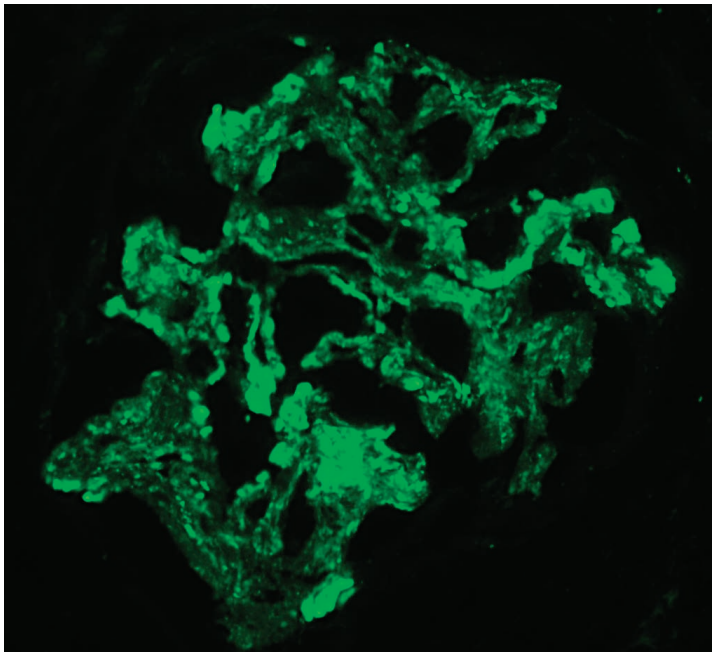

Figure 2. Immunofluorescent study shows mesangial and peripheral deposition of IgG and global or segmental deposits of immunoglobulin IgG, IgM, C3, C4, C1q, kappa light chain, and lambda light chain in both peripheral and mesangial locations (x40).

Conclusion

ANA-negative SLE is a rare but important subset of the SLE disease spectrum. Cardiac involvement, including valvular dysfunction, should be considered as a presenting manifestation of SLE irrespective of serology status. Early recognition and intervention appears to be associated with decreased morbidity.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords: ANA-negative lupus, heart failure, valvular dysfunction

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