Cardiac Manifestations of Seronegative Spondyloarthropathy in a Human Leukocyte Antigen B27–Positive African American Woman: A Case Report With Literature Review

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INTRODUCTION

The seronegative spondyloarthropathies (SSAs) are a group of chronic rheumatologic diseases primarily involving the axial skeleton that are strongly associated with the human leukocyte antigen B27 (HLA-B27) gene and are relatively uncommon in the African American population. Inflammatory back and peripheral joint pain are typical of these diseases, with extraskeletal sites of involvement including the eyes, skin, and genitourinary tract. The cardiovascular sequelae are encountered less frequently but are an important cause of morbidity and mortality. We present the case of an HLA-B27-positive African American female with the cardiac manifestations of SSA including conduction system, aortic, and mitral valve involvement.

CASE PRESENTATION

A 52-year-old African American woman presented with symptoms of syncope and dyspnea of a month's duration. Exertional and nonexertional syncopal episodes were noted with no associated prodromal symptoms. Dyspnea also occurred both at rest and with exertion.

Her medical history was notable for chronic back pain and idiopathic retroperitoneal fibrosis (IRPF) diagnosed following biopsy of a retroperitoneal mass 15 years prior.

On initial evaluation, her blood pressure was 124/61 mmHg, pulse rate 53 bpm, and respiratory rate 18 breaths per minute. Oxygen saturation was 94% on room air. Cardiac examination revealed a left parasternal heave with a grade 2/6 apical holosystolic murmur. There was neither elevation of the jugular venous pulse nor pitting edema of the lower extremities.

Brain natriuretic peptide was elevated at 1,596 pg/mL (normal, <100 pg/mL). Basic metabolic panel and troponin I were within normal limits.

Electrocardiogram showed complete heart block with a junctional escape rhythm, rate of 53 bpm, and diffuse T wave inversions (Figure 1). A dual-chamber permanent pacemaker was subsequently placed.

Transthoracic echocardiography (TTE) demonstrated severe mitral regurgitation with severe dilation of left atrium and a hyperechoic region in the intervalvular fibrosa (13 mm thick) extending to the base of the mitral valve leaflet, inferior interatrial, and interventricular septum. An area of echogenicity was also noted on the short-axis views of the trileaflet aortic valve. Left ventricular ejection fraction was 60%-65% (Figures 2-5, Videos 1 and 2).

Transesophageal echocardiography (TEE) was subsequently performed. The aortic valvular annulus, commissures, and the subaortic area appeared echogenic and homogenously thickened. There was a central coaptation defect of the aortic valve with moderate aortic regurgitation. Severely thickened and immobile anterior mitral valve leaflet with severe mitral regurgitation was also demonstrated. Three-dimensional images showed thickening at the base of the anterior mitral leaflet, a subaortic bump (Figures 6-8, Videos 3-6).

A contrast chest computed tomography (CT) scan showed new development of circumferential soft tissue thickening surrounding the aortic outflow tract to the level of the valve and thickening of both left atrial and left ventricle (Figures 9 and 10). Coronary angiogram showed normal epicardial coronary arteries.

With a known history of IRPF, a unifying systemic infiltrative process was suspected. Serologic testing for autoimmune disease was negative for anti-scleroderma antibody (anti-SCL 70), antinuclear antibody, rheumatoid factor, and filarial IgG4 antibody. Her erythrocyte sedimentation rate (ESR) was notably elevated at 57 mm/hour (normal, 0-23 mm/hour) with similar elevations in C-reactive protein (CRP) at 48 mg/L (normal, <2.6 mg/L), complement C4 at 47 mg/dL (normal, 12-36 mg/dL), and complement C3 at 242 mg/dL (normal, 90-170 mg/dL). Serum HLA-B27 was positive.

Symptomatic improvement was achieved with intravenous diuresis and she was started on oral furosemide at discharge with a plan for further outpatient workup.

DISCUSSION

HLA-B27 positivity is relatively uncommon, with an estimated prevalence of about 6.1% in the United States.[1] It is particularly rare in the African American population, with previous estimates from the 1970s reporting positivity in 2% to 4% of individuals.[2] A more recent study was unable to accurately quantify prevalence due to an insufficient number of HLA-B27-positive individuals in this ethnic group.[1] Our patient has this rare HLA-B27 positivity in an African American.

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VIDEO HIGHLIGHTS

Video 1: Parasternal short-axis echocardiographic view showing echodense homogenous thickening of mitral valve.
Video 2: Composite of TTE views.
Video 3: TEE four-chamber view showing thickened aortomitral continuity.
Video 4: TEE long-axis view showing thickened aortomitral continuity.
Video 5: TEE long-axis view showing moderate aortic regurgitation.
Video 6: TEE three-dimensional image of aortic valve.

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val since that time, the occurrence of valvular and cardiac conduction abnormalities has been well documented in SSA, sometimes occurring without preceding arthropathy.[6]

In AS, which is the prototype and most common SSA, these cardiac sequelae are quite common, with Ljung *et al.*[7] finding an arrhythmia and/or valvular heart disease in about 15% of a cohort of AS patients. Aortic regurgitation is the most commonly encountered valvular abnormality, found in 18% of AS patients evaluated with TTE by Klingberg *et al.*[7-9]

The underlying pathogenesis of the valvular disease involves cellular inflammation with accompanying platelet activation/aggregation affecting the aortic root/valve. Fibroblast hyperactivity is a reparative response resulting in intimal proliferation and adventitial thickening. The overall effect is a fibrotic process involving the aortic annulus, cusps, and aortomitral junction resulting in shortened, displaced cusps and dilatation of the aortic root causing aortic regurgitation.[5,8,10] Another common finding is the subaortic bump that results

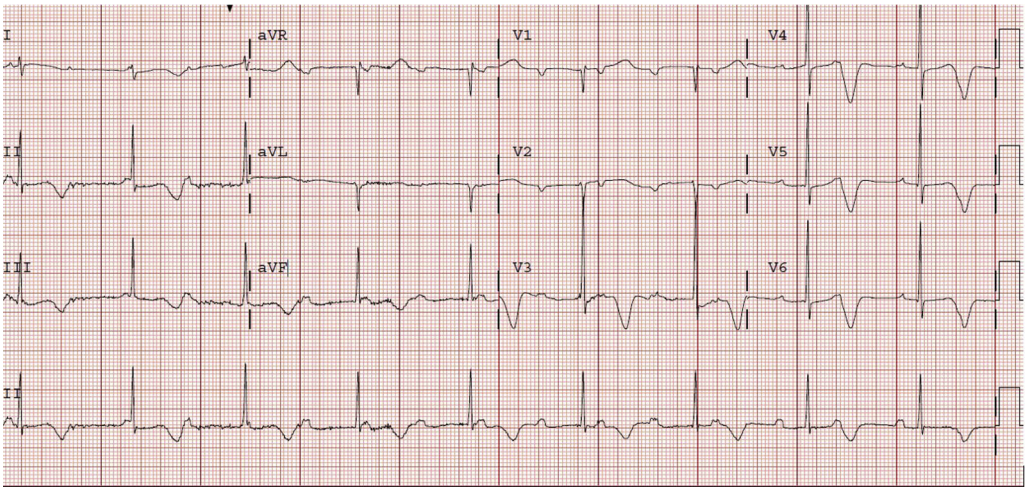

Figure 1 Twelve-lead electrocardiogram demonstrating complete heart block with junctional escape rhythm. Rate = 53 bpm, diffuse T wave inversions.

SSA is an umbrella term for a group of diseases including ankylosing spondylitis (AS), reactive arthritis, and psoriatic arthritis, which have in common a clinical phenotype of inflammatory back and/or peripheral joint pain and enthesitis in addition to a strong association with the HLA-B27 gene.[3] Extra-articular manifestations of the SSA include psoriasis, oral ulcers, recurrent uveitis, colitis, pulmonary fibrosis, atlantoaxial subluxation, and osteoporosis.[3] The prevalence of SSA is estimated to be between 0.6 and 2.4 million in US adults over 25 years of age.[4] Current data specific to the African American population are lacking; prior studies, however, suggest a lower prevalence in this ethnic group compared with European whites.[4]

Diagnosing SSA involves incorporation of clinical, laboratory, and radiologic data as defined in the Assessment of Spondyloarthritis International Society classification criteria. Other commonly used classification criteria include the European Spondylitis Study Group criteria and the Amor criteria.

The association between cardiac disease and SSA can be traced back to at least the 1970s when Bulkley and Roberts[5] described autopsy findings in patients with aortic regurgitation and AS. In the inter-

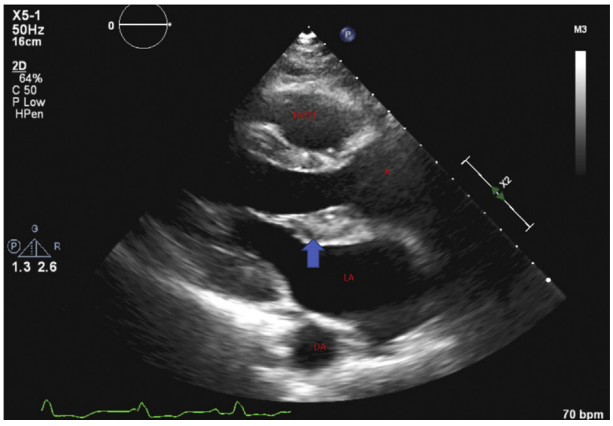

Figure 2 Parasternal long-axis echocardiographic view showing homogenous thickening of aortic valvular annulus, commissures, subaortic area. and mitral valve (*arrow*). *A*, Aorta; *DA*, descending aorta; *LA*, left atrium; *RVOT*, right ventricular outflow tract.

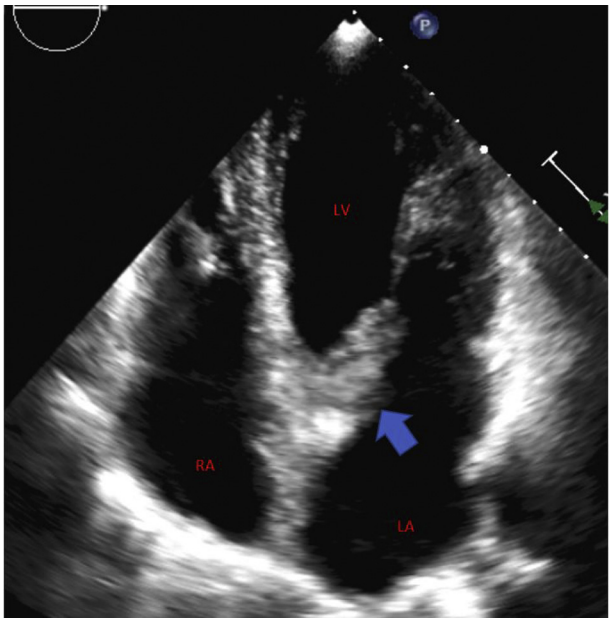

Figure 3 Four-chamber echocardiographic view showing homogenous thickening of valvular apparatus (*arrow*). *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium.

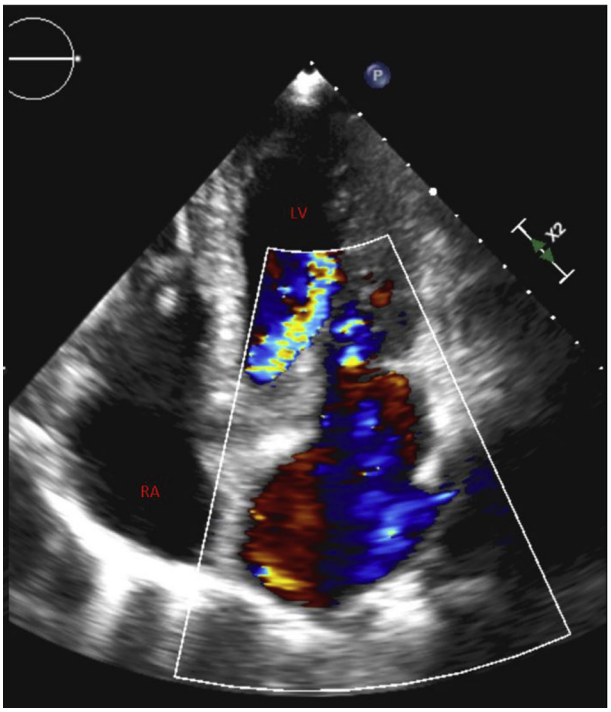

Figure 4 Four-chamber echocardiographic view with color Doppler indicating moderate aortic regurgitation and severe mitral regurgitation. *LV*, Left ventricle; *RA*, right atrium.

from the extension of the fibrosis into the aortomitral junction.[8] The anterior mitral cusp may also be involved in this inflammatory process, producing mitral regurgitation as seen in our patient, although this is less common.[11] The exact trigger for this inflammatory process and preferential involvement of the left heart valves is unclear.[8]

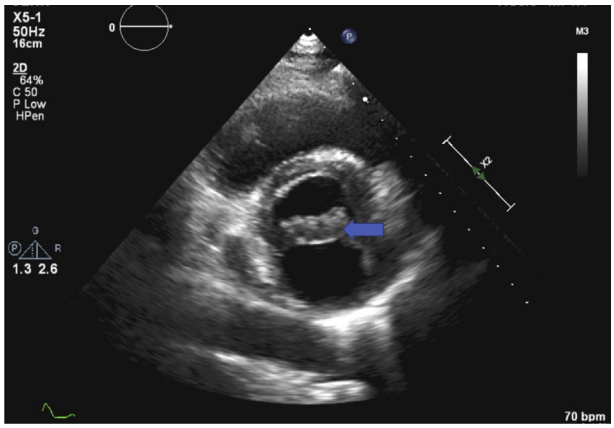

Figure 5 Parasternal short-axis echocardiographic view showing echodense homogenous thickening of mitral valve (*arrow*).

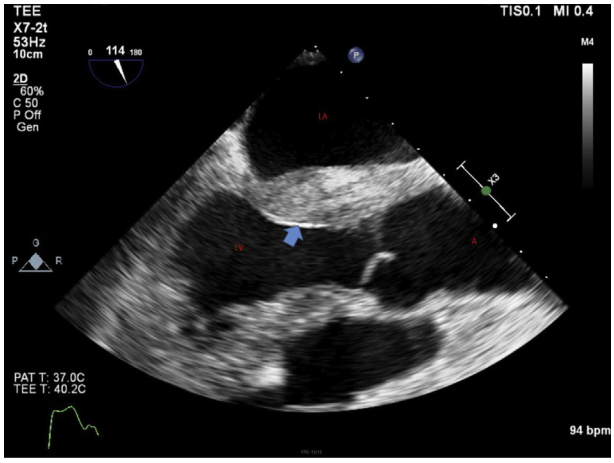

Figure 6 Long-axis TEE view showing thickened aortomitral continuity (*arrow*). *A*, Aorta; *LA*, left atrium; *LV*, left ventricle.

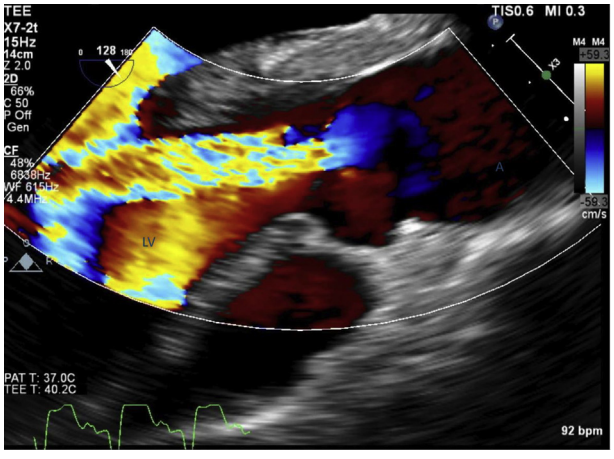

Figure 7 Long-axis TEE view with color Doppler showing moderate aortic regurgitation. *A*, Aorta; *LV*, left ventricle.

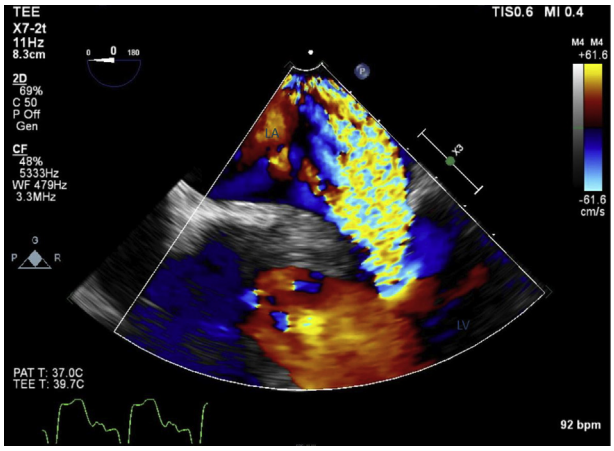

Figure 8 Four-chamber TEE view with color Doppler showing severe mitral regurgitation. *LA*, Left atrium; *LV*, left ventricle.

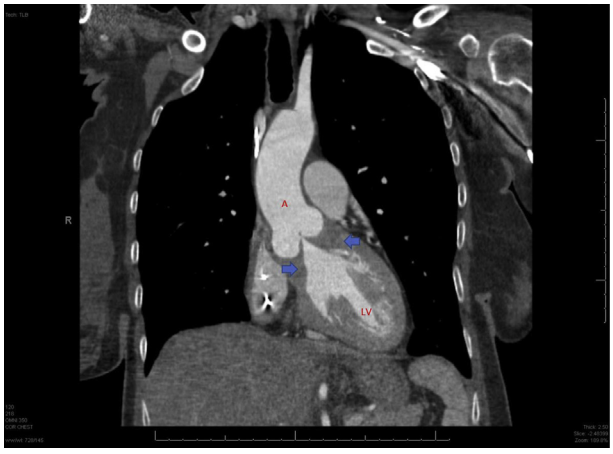

Figure 9 CT scan of chest in coronal view demonstrating circumferential soft tissue thickening surrounding the aortic outflow tract (*arrows*). *A*, Aorta; *LV*, left ventricle.

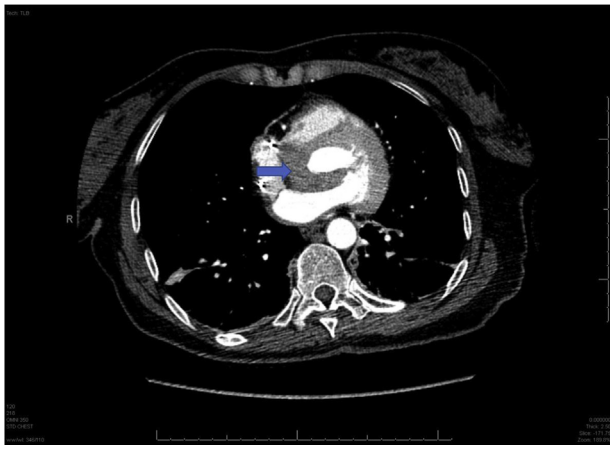

Figure 10 CT scan of chest in axial view images demonstrating soft tissue prominence around the left atrium and left ventricular myocardial thickening (*arrow*).

The duration of SSA and patient age have been shown to correlate with the severity of aortic root disease and valvular dysfunction.[8-10] Less well defined is the association between the activity of SSA and the valvular disease. Some degree of correlation is expected due to the similarity of the tendon-like fibrous attachments of the aortic cusps to entheses.[8,9] Studies, however, suggest a lack of correlation, with reasons postulated including different antigens being responsible for cardiovascular and skeletal inflammation. In addition, inflammatory markers commonly used in monitoring disease activity such as ESR and CRP do not correlate well with clinical activity.[12]

Conduction system disease is the most commonly encountered cardiac complication in SSA, with about 33% of a cohort of patients with AS having some form of conduction disturbance in one study, and these conduction disturbances may precede the valvular manifestations.[13] There are two main factors that are thought to be contributors to the development of conduction system disease—inflammation/fibrosis involving the membranous portion of the interventricular septum and inflammatory damage to the arterial supply of the atrioventricular node.[14] There is again no definitive association between the markers of disease activity in SSA (including ESR and CRP) and the development of conduction system disease. Duration of SSA may, however, play a role.[14,15]

CONCLUSION

Our case highlights the importance of recognizing the association between HLA-B27-associated SSA and serious cardiovascular complications. It is noteworthy to point out that with our patient's history of chronic back pain, which had been ongoing for at least 10 years (attributed to IRPF and treated empirically with prednisone and ibuprofen), HLA-B27 positivity, and elevated CRP, she meets the Assessment of Spondyloarthritis International Society criteria for axial spondyloarthritis. This diagnosis provides a logical explanation for her valvular and cardiac conduction diseases. These complications can occur shortly after presentation; however, the risk of developing valvular insufficiency or conduction disorders persist even several years from diagnosis.[10]

It is therefore imperative for clinicians to maintain a high index of suspicion for these cardiac manifestations of SSA, which have been termed HLA-B27-associated cardiac syndrome, including a low threshold for cardiovascular testing for seemingly trivial symptoms, as earlier identification may result in more favorable outcomes.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2019.05.001.

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