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VALVULAR HEART DISEASE

CASE REPORT: CLINICAL CASE

Aortic Regurgitation and Rheumatoid Arthritis

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ABSTRACT

Rheumatoid cardiac nodules are a rare finding in patients with seropositive rheumatoid arthritis. They infrequently become symptomatic but can present as valvular insufficiency. A 53-year-old man with rheumatoid arthritis was found to have worsening aortic insufficiency. Echocardiography revealed nodular densities on the valve, consistent with rheumatoid nodules, causing significant regurgitation. (JACC Case Rep. 2024;29:102671) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 53-year-old Hispanic man with a history of seropositive erosive rheumatoid arthritis (RA), 40 pack-year smoking history, and mild aortic insufficiency presented to the emergency department with subacute altered mental status on a background of several months' history of weight loss and progressive shortness of breath. The patient reported a 50-lb weight loss over a 3-month period and had been experiencing diffuse "soreness" throughout his body. In the emergency department, the patient was febrile to 39.1 °C then hypothermic to 33 °C, hypotensive (blood pressure 108/54 mm Hg), and bradycardic with heart rates in the 50 to 60 beats/min range (**Figure 1**). He received 2 L of intravenous fluids; warming was instituted with a Bair Hugger (3M). Physical examination demonstrated tenderness and swelling of bilateral metacarpophalangeal joints, a left knee effusion, and bilateral ankle tenderness with edema. Laboratory results revealed pancytopenia and neutropenia with a white blood cell count of 2.5×10^3/uL and absolute neutrophil count of 0.2×10^3/uL, platelet count of 93×10^3/uL, and hemoglobin of 10.6 g/dL with mean corpuscular volume of 78 fL. Brain imaging was unremarkable. Chest radiograph and computed tomography chest showed cavitary lung lesion in the left upper lobe (**Figure 2**), hepatosplenomegaly, and multifocal lymphadenopathy. The patient was admitted for work-up and management of neutropenic fever.

TAKE-HOME MESSAGES

- In patients with seropositive RA and aortic insufficiency, include rheumatoid nodules as a potential etiology.
- Although patients with autoimmune diseases are often immunocompromised, distinction between vegetation and other valvular masses can be made based on location and mobility.

PAST MEDICAL HISTORY

The patient was first diagnosed with RA at 38 years of age. He presented with symmetrical polyarthritis describing bilateral feet, knee, ankle, hand, and wrist pain along with morning stiffness for 45 minutes.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

RA = rheumatoid arthritis

T-LGL = large granular lymphocytic leukemia

TTE = transthoracic echocardiography

Bloodwork revealed an antinuclear antibody 640 U/mL (speckled pattern), DNA <10 U/mL, erythrocyte sedimentation rate 52 and rheumatoid factor 306 IU/mL, and positive anticyclic citrullinated peptide immunoglobulin G antibody at >250 U/mL. Hand/wrist radiographs showed symmetrical juxta-articular osteoporosis suggestive of early RA. Feet radiographs showed erosion of the right fifth metatarsophalangeal. He was diagnosed with seropositive RA and started on methotrexate with folic acid which he was continued on for approximately 3 years until he developed bilateral carpal tunnel syndrome and tenosynovitis of the hands and wrists. Etanercept was then added with good response. He was continued on etanercept and methotrexate but was intermittently noncompliant. Methotrexate was ultimately held given issues with follow-up. The patient was lost to follow-up until ~2 years prior to presentation when he was only taking ibuprofen. Etanercept was restarted; however, 4 months prior to admission he stopped taking etanercept due to "feeling unwell."

DIFFERENTIAL DIAGNOSIS

This patient presented with a combination of fevers, pancytopenia, hepatosplenomegaly, and cavitary lung lesion. Given the patient's history of seropositive RA with new cytopenia and hepatosplenomegaly, both Felty syndrome and large granular lymphocytic leukemia (T-LGL) were considered. Fevers in an patient who is immunocompromised raised concern for infection, including endocarditis. Within this diagnostic framework, the lung nodule could represent an autoimmune process such as an RA nodule with cavitation, Sjogren disease, or sarcoidosis. Given his smoking history, primary lung malignancy was also considered.

INVESTIGATIONS

Pathology of the lung mass revealed showed lymphoplasmacytic infiltrate and organizing pneumonia. A bone marrow biopsy showed a hypercellular bone marrow. Transthoracic echocardiography (TTE) showed moderate to severe aortic regurgitation (**Figure 3**). Given valvular insufficiency and concern for infectious endocarditis, a transesophageal echocardiogram (TEE) was obtained (**Figure 4**). TEE showed a trileaflet aortic valve without vegetation. There were echobright rounded nodular densities noted at the commissures (Video 1). The most prominent nodule was between the non- and right coronary cusp. The right coronary cusp was especially thickened and retracted and likely responsible for distorting the jet of regurgitation. The aortic regurgitation was categorized as moderate. When these changes were compared with a TTE performed 2 years prior (**Figure 5**), the aortic valve changes had worsened. Nodular changes on the prior TTE were noted only on the right coronary cusp and aortic regurgitation was at most mild.

FIGURE 1 Electrocardiogram Showing Sinus Rhythm

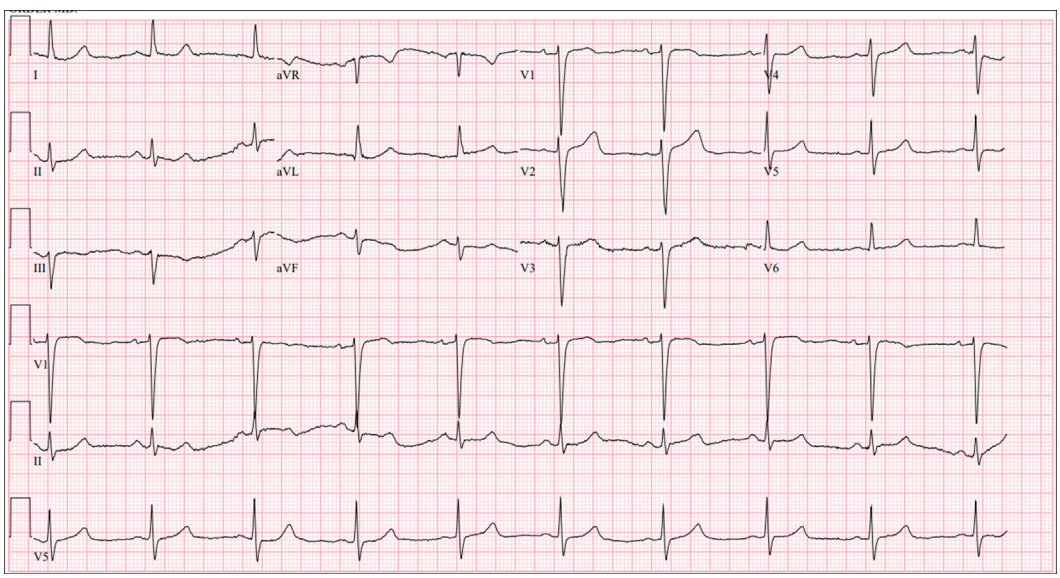
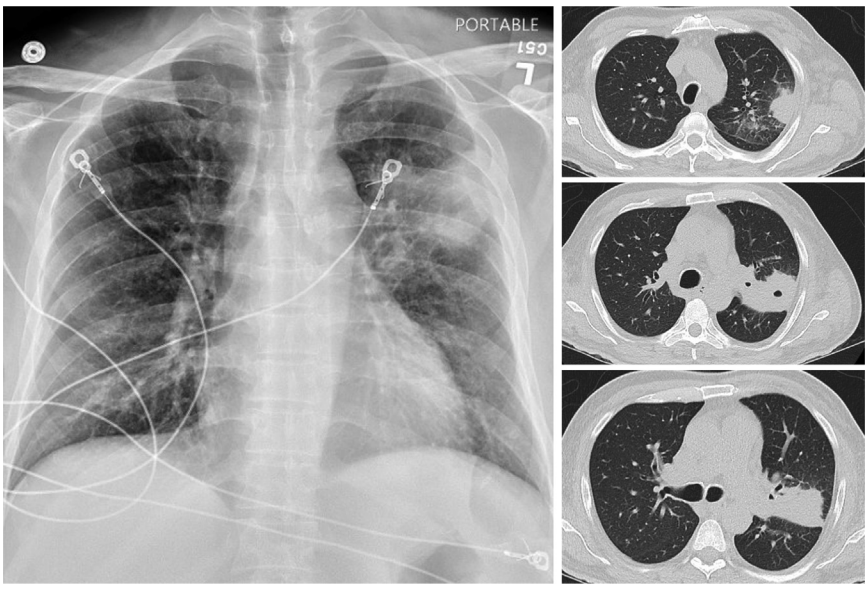
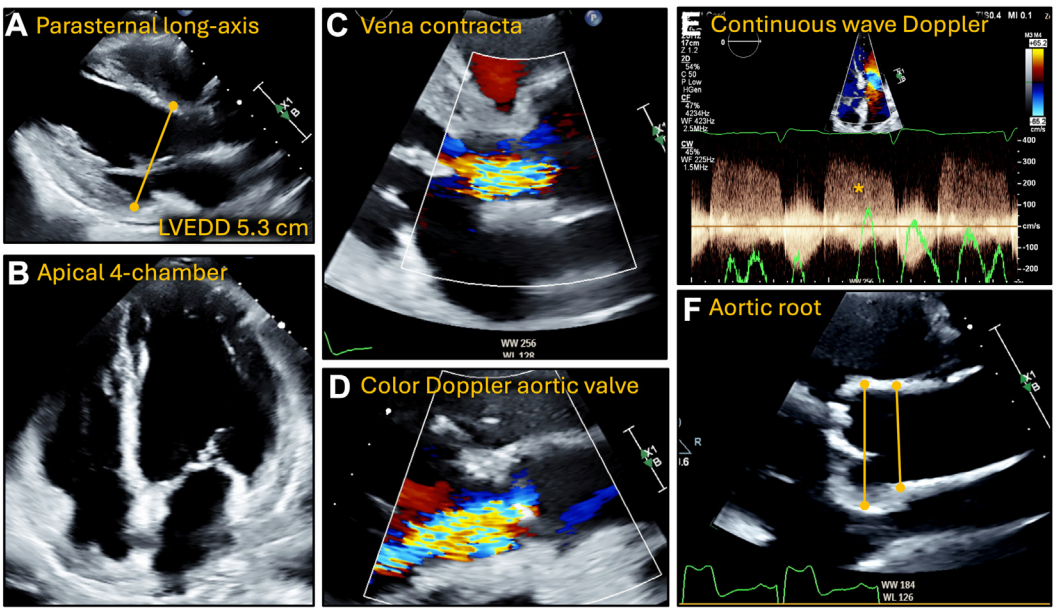


FIGURE 2 **Lung Imaging**



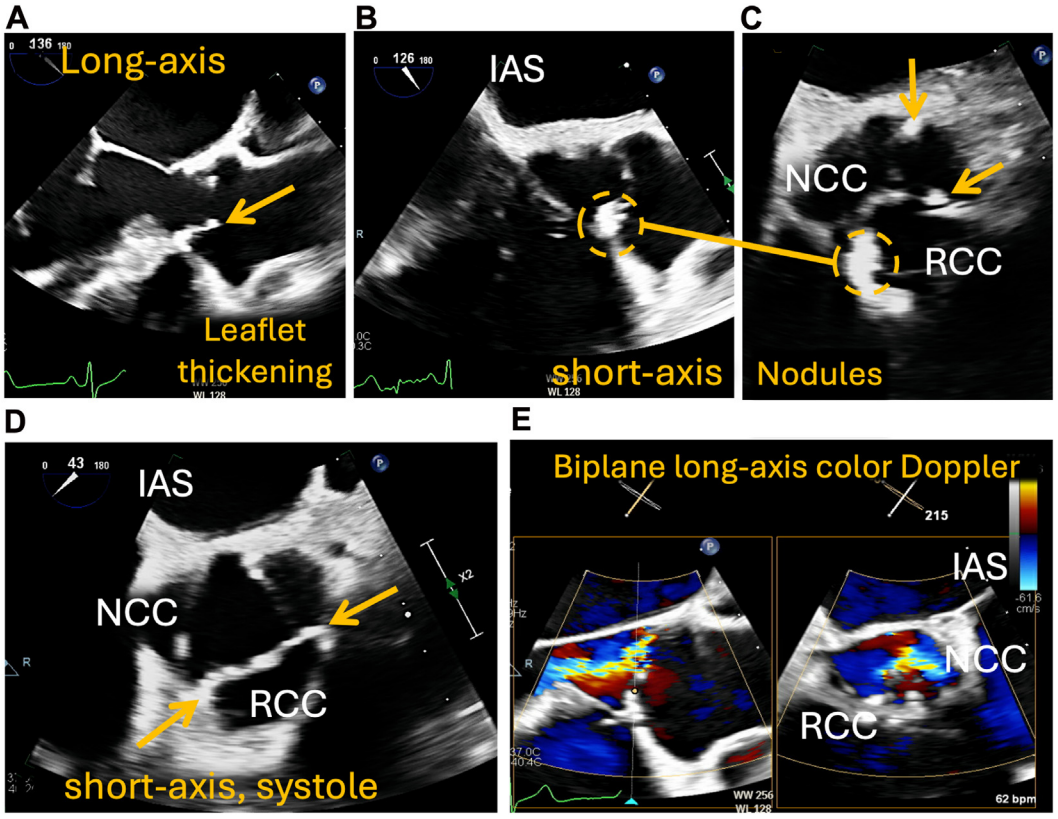
Chest radiograph (right) with cavitary left upper lobe mass. Computed tomography (left) with a 6.4- × 3.6-cm cavitated lung mass and enlarged mediastinal lymph nodes.

FIGURE 3 **Transthoracic Imaging**



(A and B) Transthoracic echocardiography on admission. (C and D) There was moderate to severe aortic regurgitation. The pressure half-time (E) was not consistent with severe aortic insufficiency. (E) The density of the regurgitation jet (*) was less than the density of forward flow. The aortic root was not dilated suggesting that the etiology of aortic insufficiency was valvular (F). LVEDD = left ventricular end-diastolic dimension.

FIGURE 4 Transesophageal Echocardiography



(A) On long-axis transthoracic echocardiography views, the right coronary cusp was thickened (arrow). (B, C, D) Nodules are seen (arrows). (B and C) The largest nodule is located adjacent to the right coronary leaflet (circles). The jet of regurgitation is eccentric (E). IAS = interatrial septum; NCC = noncoronary cusp; RCC = right coronary cusp.

The patient had an infectious work-up including hepatitis A, B, and C, HIV, cytomegalovirus, Epstein-Barr virus, Streptococcus pneumoniae, *Legionella* species, acid-fast bacillus, QuantiFERON gold, *Aspergillus* species, *Histoplasma* species, and syphilis, along with blood cultures. These studies were negative. Blastomyces antibodies resulted positively; however, confirmatory immunodiffusion testing was negative. Bartonella immunoglobulin G was positive at 1:2048 with a falsely positive Q fever antibody screen. After discharge, molecular studies performed on the bone marrow returned positive for T-LGL.

MANAGEMENT

The patient was started on broad-spectrum antibiotics on presentation; however, he continued to have cyclic fevers throughout his hospital course. Given recurrent fevers of unknown origin, he was treated for *Bartonella henselae* infection with 14 days of rifampin and doxycycline. His fevers finally abated with administration of granulocyte colony-stimulating factor and prednisone. He was ultimately started on methotrexate for T-LGL.

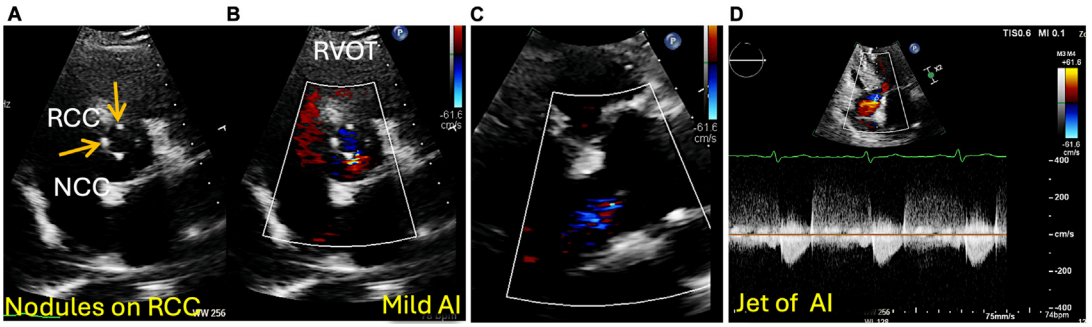
OUTCOME AND FOLLOW-UP

In the outpatient setting, the patient remains on methotrexate with the possibility to restart etanercept in the future. He will continue to follow-up with cardiology for surveillance of his aortic valve.

DISCUSSION

Roughly, 1% of the global population suffers from RA.[1] The synovial membranes of joints are the predominant target of the autoimmune damage; however, extra-articular manifestations, including cardiac, can also occur.[2] Although the most common cardiac manifestation is pericarditis, patients can also

FIGURE 5 Transthoracic Echocardiogram Performed 2 Years Prior to Current Admission

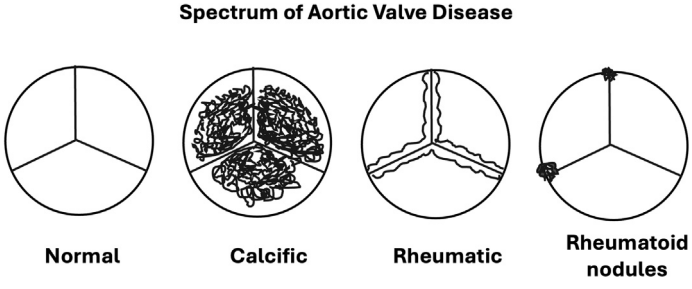


(A) Transthoracic echocardiography 2 years prior showing changes in the right coronary cusp. (B, C, D) Aortic regurgitation is mild. AI = aortic insufficiency; NCC = noncoronary cusp; RCC = right coronary cusp; RVOT = right ventricular outflow tract.

develop coronary vasculitis, diastolic dysfunction, atherosclerosis, and valvular lesions.[2] The main valves reported to be affected are the mitral and aortic valves.[3] In general, joint disease precedes valvular involvement. Typically, the valvular lesions are focal, asymptomatic, and rarely lead to significant valve dysfunction; those that do go on to cause pathology usually result in valve incompetence.[1] Severe aortic insufficiency has been reported.[4] A meta-analysis showed that patients with RA were 4 times more likely to have aortic valve thickening and/or valvular calcification than control patients and were twice as likely to develop aortic insufficiency.[2] Differentiating rheumatoid nodules from vegetation can be made based on the location and mobility of the mass. Vegetations are predominantly associated with the leaflet tips, located on the low-pressure side of the valve, and characterized by independent mobility. Rheumatoid nodules are predominantly located on the midportion and base of the valve leaflets and are immobile[4] (**Figure 6**). There is a growing body of literature to support the use of fluorodeoxyglucose positron emission tomography in the diagnosis of infective endocarditis. Given that the concern for endocarditis was low in this case after TEE was performed, fluorodeoxyglucose positron emission tomography was not pursued.

The proposed mechanism for the development of rheumatoid nodules includes vascular trauma or fibrosis of the valve structures from extra-articular inflammation.[1,2] Surgical pathology may show myxoid degeneration of the valve with fibrosis and leaflet fusion.[5] Ongoing, chronic inflammation in patients with RA is thought to contribute to progressive valvular damage.[6] This patient had been on intermittent treatment for RA for years. In fact, when he initially presented, he was thought to have Felty syndrome, a condition characterized by the triad of RA with destructive joint involvement, neutropenia, and splenomegaly, a condition that has also been

FIGURE 6 Potential Schema for Categorization of Etiologies of Valvular Aortic Insufficiency Including Rheumatoid Nodules



referred to as extreme RA. There is considerable overlap between Felty syndrome and T-LGL, often making it difficult to tell the 2 conditions apart.

Currently, there is no treatment available for asymptomatic cardiac rheumatoid nodules.[5] Invasive approaches for the mitigation of cardiac nodules are indicated only when there is evidence that the nodules are contributing to abnormal cardiac function, rhythm disturbances, or embolic events.[5]

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KEY WORDS aortic insufficiency, rheumatoid arthritis, rheumatoid nodules, valvular disease

APPENDIX For supplemental videos, please see the online version of this paper.