Quadricuspid Aortic Valve and Rheumatoid Arthritis: A Coincidence or Interconnection

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ABSTRACT: Quadricuspid aortic valve is a very rare congenital anomaly. Its association with rheumatoid arthritis is exceptional with this being the third case reported in the literature. We report a case of a 52 year old female patient with quadricuspid aortic valve type C accompanied by moderate to severe aortic regurgitation and longstanding, advanced form of rheumatoid arthritis. Having refused surgical aortic valve intervention 4 years ago, the patient is currently under a watchful follow-up strategy. The patient received a diagnosis of rheumatoid arthritis over 15 years before and presently has serious deformities in the hands, legs, feet, and spine. In conclusion, quadricuspid aortic valve and rheumatoid arthritis together are extremely rare. While it is possible that this association is coincidental, considering the genetic background of both disorders, there is a potential for them to be interconnected comorbidities. This report is the first to highlight the association between the 2 disorders.

KEYWORDS: Quadricuspid aortiv valve, rheumatoid arthritis, aortic regurgitation

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Introduction

Quadricuspid aortic valve (QAV) is a very rare congenital heart disorder. It's incidence in autopsy series is 0.00028 to 0.00033%,[1] 0.0059 to 0.0065% in transthoracic echocardiography examinations,[2] 0.05 to 1% in surgery settings for patients with aortic regurgitation.[3] Quadricuspid aortic valve in up to one third of cases is associated with other cardiac disorders, such as: atrial septal defect, ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, sinus of Valsalva fistula, mitral valve prolapse, hypertrophic cardiomyopathy, transposition of the great arteries, coronary artery anomalies, and so on.[4,5] No authors described a possible interconnection between QAV and rheumatoid arthritis (RA). However, with thorough literature search we were able to locate only 2 reports of patients with RA and QAV, although a possible association was not emphasized.[6,7] RA, on the other hand, is a systemic disease that can affect multiple organs, including blood vessels, leading to vasculitis.[8] Prevalence of vasculitis in RA ranges from 1 to 5%, while postmortem studies show up to 25% frequency.[9] Vasculitis in RA usually affects small vessels and only rarely involves medium sized arteries. Nonetheless, individuals with RA have been observed to exhibit an increased prevalence of macrovascular disease, potentially linked to the use of steroids.[10,11]

Case Report

We report a case of a 52 year old female patient who was diagnosed 8 years earlier with moderate aortic regurgitation due to QAV. Transesophageal echocardiography (TEE) demonstrated QAV type C, according to Hurwitz and Roberts, with moderate aortic regurgitation. Four years earlier based on the symptoms, mainly dyspnea on physical effort, and echocardiographic findings, patient was referred to Cardio-surgery Department for aortic valve intervention. However she was not prepared to undergo the procedure and refused it at the time. Regarding the cardiac status, she is currently on watchful follow-up. The TEE demonstrated QAV (Figure 1) with moderate to severe aortic regurgitation, with regurgitant orifice area of 0.25 cm^2, a regurgitant volume of 72 ml, vena contracta width of 0.6 cm. Left ventricular (LV) diastolic diameter was 58 mm, LV ejection fraction 60%, aortic bulb diameter 31 mm, and left atrium 41 mm. Since first detected, the aortic regurgitation has advanced from moderate to moderate-severe grade, whereas LV diastolic diameter from 55 to 58 mm. The patient also suffers from arterial hypertension and long standing RA. ECG showed sinus rhythm, heart rate of 90 beats per minute and electrocardiographic signs of left ventricular hypertrophy. Coronary angiography was without remarks, regarding lumen stenosis or coronary artery anomalies. Due to her cardiac status, she was treated by cardiologist with Angiotensin Receptor Blocker (Candesartan 16 mg *pd*), Diuretic (Furosemide 40 mg *pd*), Beta Blocker (Bisoprolol 5 mg *pd*), Aspirin (100 mg *pd*), and Statin (Rosuvastatin 5 mg *pd*).

Concerning RA, she was diagnosed more than 15 years earlier based on her clinical scenario, laboratory results (elevated rheumatoid factor, C-reactive protein, erythrocyte sedimatation rate and the presence of anticyclic citrullinated peptide antibody) and X-ray images. On physical examination there were deformations of hands (Figure 2), legs, feet and spine.

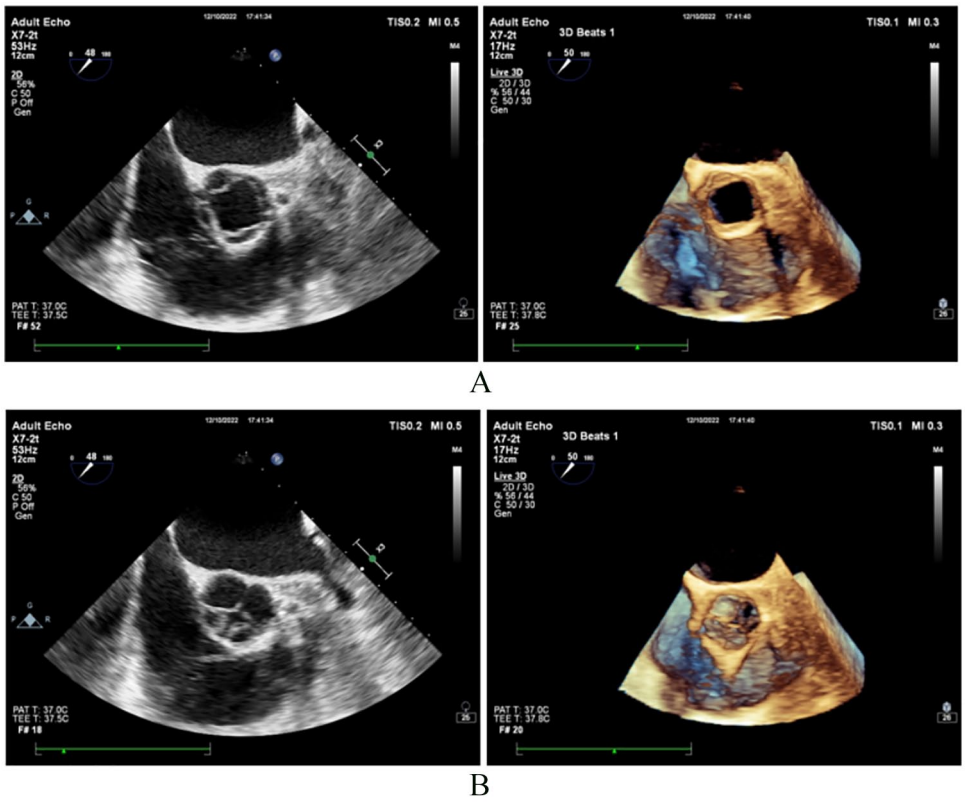

Figure 1. Figure 1 demonstrates quadricuspid aortic valve during systole (A) and diastole (B) depicted by TEE images 2D (left) and 3D (right).

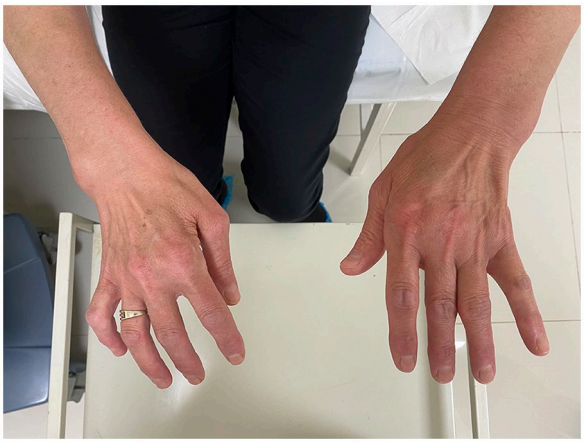

Figure 2. Hand deformations in our patient with rheumatoid arthritis.

Tenderness was noted during palpation, as well as during passive and active range of motion in bilateral metacarpal, interphalangeal, and ankle joints. This was accompanied by restricted finger movements. Recent X-ray images of the hands revealed characteristic signs of RA, including joint space narrowing, bone erosions, and some subluxations of metacarpophalangeal and interphalangeal joints (Figure 3). The DEXA osteodensitometry indicated signs of osteopenia. Based on the provided information, the patient's rheumatologic status was classified as stage 3 RA. She was treated with methotrexate (15 mg per week), prednisone (20 mg *pd*), folic acid (5 mg

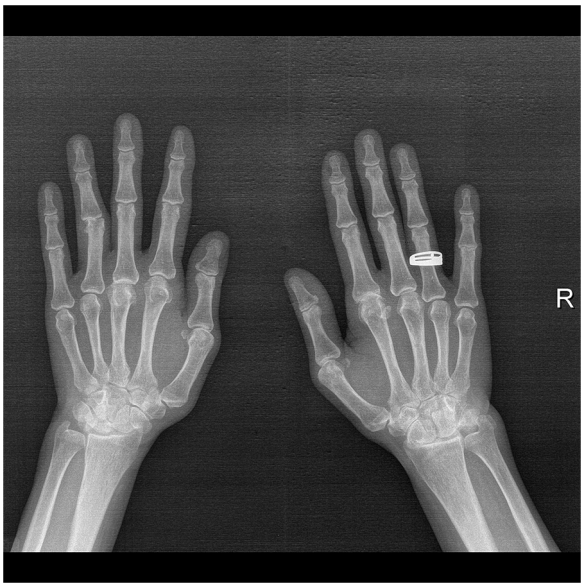

Figure 3. X-ray images of the hands showing signs typical of rheumatoid arthritis, such as joint space narrowing, bone erosions and some subluxations of metacarpophalangeal and interphalangeal joints.

following methotrexate), vitamin D (300000 IU per month), calcium supplements, proton pump inhibitors (Pantoprazole 40 mg *pd*), analgesics (Tramadol/Paracetamol 37.5/325 mg *as required*). With the aim of reducing joint inflammation and radiographic progression, the patient was put on biological

therapy several times according to our Rheumatology Clinic principles. Regarding biological treatment, patient was first treated with Infliximab (TNF-alpha inhibitor) 3 mg/kg of body weight in agreement with the EULAR protocol for RA, at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks thereafter, for a total of 7 doses. Subsequently, due to seriousness of the disease patient was put in Rituximab (a monoclonal antibody medication) 1 g in 2 doses, separated by 2 weeks. Maintenance infusions were administered after 6 months. Her most recent biologic therapy was completed 1 year ago. Subsequent to that treatment, she suffered a severe manifestation of meningitis.

Her current cardiologic and rheumatologic condition remains stable.

Discussion

When the patient was first visited by cardiologist, aortic regurgitation was discovered. Knowing patient history of longstanding RA, a chronic inflammatory disease, it was considered as a possible cause for aortic regurgitation. Aside from inflammatory diseases, other potential causes of chronic aortic regurgitation include infectious diseases, structural leaflet abnormalities, degenerative disease, and genetic aortopathy. TEE demonstrated the presence of QAV type C, a very rare structural valve anomaly, as most likely explanation for aortic regurgitation in our patient. According to Hurwitz and Roberts the QAV anomaly, with 2 equal larger cusps and 2 equal small cusps belongs to type C.[12] Whereas, based on Nakamura et al. simplified classification, our patient belongs to type IV, which according to the authors is not frequent, with 9.5% of cases in 42 patients with QAV.[13] The functional status of QAV is mainly aortic regurgitation.[2] Unequal sheer stress is believed to cause cusp fibrosis and incomplete coaptation leading to aortic insufficiency.[14] In contrast, valvular heart lesions linked to RA manifest as nodules on the valves and fibrosis of the cusps, which can extend to the valve rings and subvalvular apparatus, ultimately leading to valve regurgitation.[15] This differs from the aortic morphology observed in our patient.

As mentioned earlier several cardiac disorders may be associated with QAV. Coronary artery and coronary ostium anomalies are the most common associated disorders, which include a single coronary ostium, displaced right coronary orifice, and so on.[16,17]

While our patient with QAV does not have documented evidence of other cardiac disorders, she suffers from an advanced stage of RA. There are 2 cases in the literature, to the best of our knowledge, which describe QAV in patients with RA. One case portrays an isolated QAV in a 58 year old male with longstanding RA who was treated surgically, with aortic valve replacement, due to severe aortic regurgitation.[7] At surgery they found 2 normal size leaflets and 2 smaller size leaflets, similar to our case. The other traced case presents a 44 year old female patient with long standing RA, diagnosed with QAV with 4 equal sized cusps and mild aortic regurgitation.[6] Our patient was also first diagnosed with QAV in the 5th decade of life, although with higher degree of aortic regurgitation. This may be due to different cusp morphology. We find it critical to remark that none of these cases highlight the possible interconnection between the 2 pathologies.

Rheumatic disorders may be associated with various cardiovascular diseases, including myocardial ischemia, arterial stiffness, systolic and diastolic heart failure, pericardial disease, valvular disease, conduction abnormalities, arrhythmias, and so on.[18,19] Cardiovascular disease significantly increases both mortality and morbidity in individuals with RA. Moreover, inflammation plays a crucial role in the pathogenesis of atherosclerosis, contributing to an elevated cardiovascular risk in RA.[20] Mitral and aortic regurgitation in patients with rheumatic disease may be present in as many as 65% of cases, although of mild degree.[21] Medications used in RA patients also play a role in cardiovascular disease. While steroids elevate the underlying cardiovascular risk,[10,11,20] methotrexate and IL-6 inhibitors have demonstrated improved cardiovascular outcomes.[20]

RA is a multigene disorder with a substantial genetic component and a heritability estimate of 60%. Large-scale Genome-Wide Association Studies (GWAS) and meta-analyses have revealed common disease-associated variants that may contribute cumulatively to RA pathogenesis. The most significant genetic variants associated with RA susceptibility to date are HLA class II genes.[22] On the other hand, QAV has also been described in some reports in association with genetic disorders.[23,24]

We acknowledge that a major limitation in this report is the inability to conduct cytogenetic analysis in our patient.

Conclusions

The co-occurrence of QAV and RA is an extremely uncommon phenomenon, with only 2 documented cases previously reported in the literature. While it is possible that this association is merely coincidental, considering the genetic background of both disorders, there is a potential for them to be interconnected comorbidities. Further investigation is required to shed light on this hypothesis. However, this should serve as a noteworthy signal to cardiologists that when encountering QAV, an assessment for RA should also be considered.

Author Contributions

AB: managed the patient in the cardiac aspect, main contributor in designing and preparing the manuscript; RA: managed the patient in the rheumatology aspect; MR: contributed in providing literature; KB: contributed in writing the discussion; XK: contributed in providing literature. All authors have read and approved the final version of the manuscript.

Informed Consent

Written informed consent was obtained from the patient for publication of the images and the case report.

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