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CASE REPORT
Cardiac imaging

Mitral valvulitis as a severe extra-articular manifestation of rheumatoid arthritis: a case report

Anne Sofie Frederiksen [1]*, Steen Hylgaard Jørgensen [1,2,3], Henrik Wiggers [1,2], and Ellen-Margrethe Hauge [2,4]

[1]Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200, Aarhus N, Denmark; [2]Department of Clinical Medicine, Aarhus University, Palle Juul-Jensens Boulevard 82, 8200, Aarhus N, Denmark; [3]Department of Cardiology, North Denmark Regional Hospital, Bispensgade 37, 9800, Hjoerring, Denmark; and [4]Department of Rheumatology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 59, 8200, Aarhus N, Denmark

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Background Extra-articular manifestations (EAMs) are common in patients with rheumatoid arthritis (RA). Cardiac EAMs are rare but may cause complete heart block and damage to the heart valves.

Case summary We present the case of a middle-aged woman with long-standing RA and EAMs as the most prominent symptoms. The patient experienced complete atrioventricular heart block and developed nodular vegetations affecting the mitral valve, ultimately leading to severe mitral regurgitation and valve replacement.

Discussion The diagnosis of cardiac EAMs in RA may be challenging for the clinicians. Symptoms and findings may mimic more common conditions such as malignancy and infectious endocarditis. A multidisciplinary approach is of paramount importance in order to make an early diagnosis and to provide optimal treatment to patients with RA and cardiac complications.

Keywords Echocardiography • Autoimmune disease • Endocarditis • Valvulitis • Mitral regurgitation • Complication • Case report

Learning points

- Mitral valvulitis leading to severe mitral regurgitation is a rare extra-articular manifestation of rheumatoid arthritis.
- Early recognition of cardiac complications as signs of extra-articular manifestations in rheumatoid arthritis may lead to a more aggressive treatment strategy in patients who otherwise are in remission.
- The best management of cardiac complications in a patient with rheumatoid arthritis remains difficult and requires a multidisciplinary approach.

Introduction

Rheumatoid arthritis (RA) is a chronic debilitating inflammatory disease that primarily affects synovial joints and surrounding tissues.[1] Yet, up to 40% of the patients experience extra-articular manifestations (EAMs).[2] Extra-articular manifestations are more frequently seen in patients with positive rheumatoid factor (RF) and the presence of anti-cyclic citrullinated peptide antibodies (ACPA). Extra-articular manifestations are associated with a more progressive disease and increased mortality.[3] The most common cardiac EAMs are

* Corresponding author. Tel: +45 2327 0282, Email: anne.sofie.frederiksen@midt.rm.dk
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pericarditis, non-specific endocarditis, and myocarditis. These cardiac complications are, however, rarely clinically apparent.[1,4] In general, the subcutaneous rheumatoid nodule is the most common EAM, with a prevalence of 30% in RA.[5–7] Rheumatoid nodules may affect any organ and contribute to organ damage. Cardiac involvement by rheumatoid nodules is rare, but nodules may develop in the pericardium, myocardium, and valvular structures causing valve insufficiency, thrombo-embolic complications, and heart block due to damage to the conduction system.[4] In the present report, we describe a rare case of mitral valvulitis as a severe systemic manifestation of RA in an RF-positive female patient in the absence of joint symptoms.

Timeline

Time	Event	Treatment
June, 2003	Diagnosed with seropositive, anti-cyclic citrullinated peptide antibodies-negative rheumatoid arthritis (In retrospective, meeting 9/10 of 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria)	Methotrexate
2003, 2007, 2015, and 2016	Scleritis	Oral and local glucocorticoid
March, 2016	Third-degree heart block Cardiac magnetic resonance imaging**:** Inflammatory activity in the region of the mitral valve. Echocardiography**:** Clinically insignificant nodules were noticed on the mitral valve.	Pacemaker-implantation
April, 2016	Scleritis	Infliximab added
April, 2017	Scheduled 1-year follow-up. Onset of exertional dyspnoea [New York Heart Association (NYHA) II]. Echocardiography**:** Severe thickening of the mitral leaflets. Large nodular vegetations involving the chordae tendinea. Trivial mitral regurgitation. FDG-PET/CT: Severe inflammatory activity at the mitral valve involving the chordae tendinea.	Warfarin
June, 2017	Cardiac findings were considered consistent with severe inflammatory activity and extra-articular manifestation, secondary to RA.	The immunosuppressive treatment was intensified by starting Rituximab and discontinuing infliximab.
September, 2017	Symptoms: Dyspnoea progression (NYHA III) Echocardiography**:** Regression in the valve lesions but severe mitral regurgitation due to fibrosis of the valves. Normal C-reactive protein, no tender or swollen joints.	Furosemide, 40 mg daily, was added to treat symptoms of heart failure.
March, 2018	Echocardiography: Increasing mitral regurgitation volume. Hyperdynamic left ventricle.	Surgery with insertion of a mechanical mitral valve.
September, 2020	Echocardiography: Normal function of the mechanical valve prosthesis, and normal left ventricular ejection fraction. Physical examination was unremarkable and the patient was asymptomatic.	

Case presentation

A 45-year-old Caucasian female with a medical history of seropositive non-erosive RA presented in the cardiac outpatient clinic for a routine echocardiographic evaluation, due to small nodules on the mitral valve, detected 1 year before. Fourteen years earlier, at the time of diagnosis, the patient met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Disease-modifying anti-rheumatic drug (DMARD) treatment with methotrexate achieved sustained remission throughout the years, with no swollen or tender joints. Repeated conventional radiographs were without signs of erosive joint disease. The main symptom was recurrent episodes of scleritis, treated with glucocorticoids and treatment was escalated with infliximab, a monoclonal antibody of tumour necrosis factor (anti-TNF).

One year prior to presentation, the patient was admitted to the emergency department with complete atrioventricular heart block and underwent pacemaker implantation. In the same setting, a cardiac magnetic resonance scan showed severe inflammatory activity in the region of the mitral valve. Additional echocardiography showed small

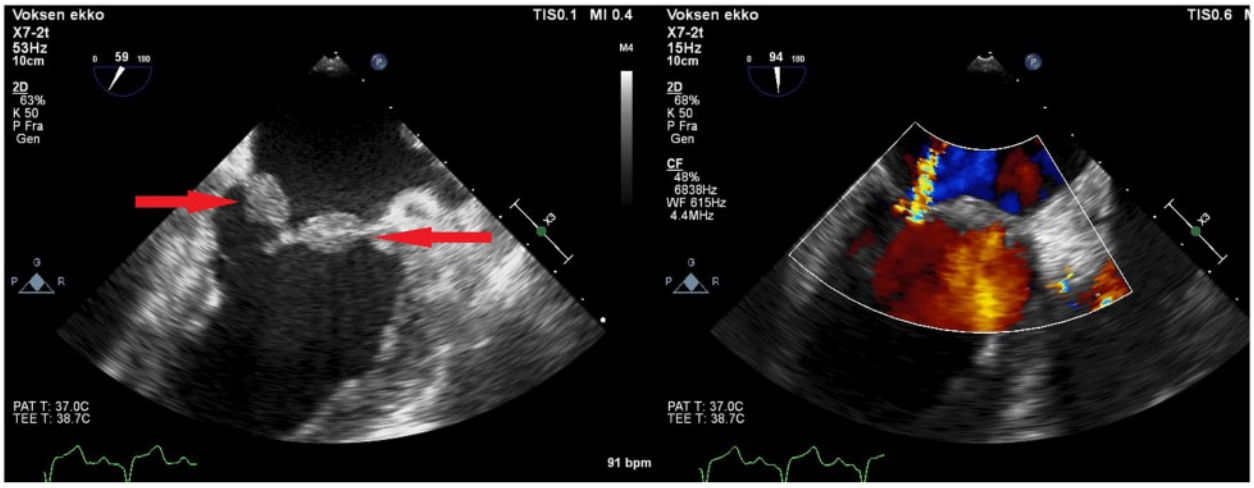

Figure 1 Transoesophageal echocardiogram of the mitral valve. Vegetations are nodular shaped, tightly attached to the surface of the valve, and without independent movement.

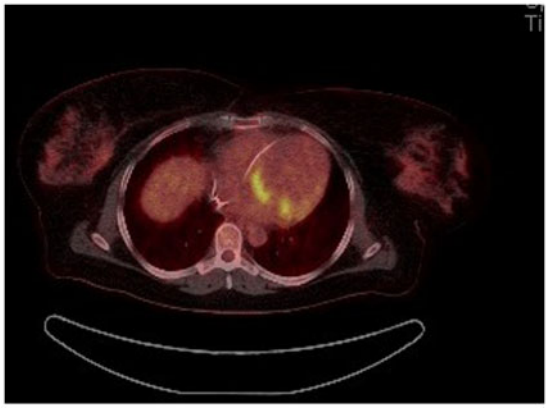

Figure 2 Positron emission tomography of the heart shows inflammatory activity the mitral valve.

nodular vegetations on the mitral valve without clinical significance. The patient did not have any other comorbidities. The patient was therefore scheduled for a routine follow-up visit 1 year later.

At examination 1 year later, the patient complained of exertional dyspnoea [New York Heart Association (NYHA) II]. Physical examination revealed no signs of heart failure. A new echocardiography revealed severe structural changes of the mitral valve with thickening of the leaflets and enlargement of the valvular vegetations, involving the chordae tendineae. Morphologically, the vegetations had a nodular shape, were tightly attached to the surface of the valve, and displayed no independent movement (*Figure 1*). A whole-body FDG-positron emission tomography (PET)-scan revealed severe inflammatory activity at the mitral valve, involving the chordae tendineae (*Figure 2*).

To prevent thrombus formation on the damaged valve, anticoagulant treatment with warfarin was started. This treatment did not alter the size of the vegetations at follow-up 2 months later. The diagnosis of RA was thoroughly evaluated, and a variety of differential diagnoses were considered (please refer to *Table 1*). Despite normal body temperature, endocarditis with a low-virulence pathogen was considered due to long-term immunosuppressive treatment. Serologic testing for multiple bacterial and viral infections was performed (please

Table 1 A list of differential diagnoses to consider, in a patient with valvulitis

Differential diagnosis: valvulitis:
Rare pathogens in infective endocarditis
• Human immunodeficiency virus (HIV)
• Syphilis
• Borrelia/Lyme disease
• Q-fever (*Coxiella burnetii*)
• Bartonella
Malignancies
• Lymphoma
• Secondary amyloidosis
• Intracardiac tumour (e.g. fibroelastoma)
Rheumatic disorder
• Systemic lupus erythematosus (SLE) with libman sacks endocarditis
• Anti-phospholipid syndrome
• Granulomatosis with polyangiitis (GPA)
• Rheumatic fever.
Other
• Sarcoidosis
• Thrombosis
• Side-effect to DMARD-treatment

Table 2 Overview of biochemical and microbiological blood tests in the patient

Laboratory findings/parameters	Observed values	Reference range
Complete blood count (CBC)		
B-haemoglobin	7.4 mmol/L	7.3–9.5 mmol/L
B-thrombocytes	521 × 10^9/L	165–400 × 10^9/L
B-leukocytes	11.2 × 10^9/L	3.5–10.0 × 10^9/L
B-neutrophils	8.71 × 10^9/L	2.00–7.00 × 10^9/L
B-lymphocytes	2.01 × 10^9/L	1.30–3.50 × 10^9/L
B-monocytes	0.37 × 10^9/L	0.20–0.70 × 10^9/L
B-eosinophils	003 × 10^9/L	<0.05 × 10^9/L
B-basophils	0.06 × 10^9/L	<0.10 × 10^9/L
Kidney function		
P-creatinine	88 µmol/L	45–90 µmol/L
eGFR/1.73 m^2	69 mL/min	>60 mL/min
P-calcium	2.47 mmol/L	2.20–2.55 mmol/L
P-albumin	34 g/L	36–45 g/L
Liver function		
P-alanine aminotransferase	28 U/L	10–45 U/L
P-alkaline phosphatase	106 U/L	35–105 U/L
Inflammatory markers		
C-reactive protein	**26.7 mg/L**	<8.0 mg/L
P-procalcitonin	<0.1 µg/L	<0.5 µg/L
P-complement C3c	1.35 g/L	0.90–1.80 g/L
P-complement C4	0.19 g/L	0.10–0.40 g/L
P-immunglobulin A	4.33 g/L	0.80–3.90 g/L
P-immunglobulin G	9.9 g/L	6.9–15.7 g/L
P-immunglobulin M	1.03 g/L	0.55–2.3 g/L
Rheumatoid factor (IgM)	27 kiU/L	< 20 kiU/L
Autoantibodies		
Anti-cyclic citrullinated peptide antibodies (ACPA) IgG	1 × 10^3 arb. unit/L	<10 arb. unit/L
Anti-nuclear antibody (ANA)	Negative	
Anti-double stranded DNA (IgG)	1 × 10^3 IU/L	<10 IU/L
Anti-Smith antibody (IgG)	<10.0	<10.0
P-Sjøgrens syndrom (SSA)-antibodies (IgG)	<10.0 kiU/L	<10.0 kiU/L
P-proteinase 3-Ab(IgG)(PR3)	14.0 kiU/L	<2.0 kiU/L
C-ANCA (IgG)	Positive	
Serological tests for infection		
Human parvovirus B19-Ab	Negative	
P-bartonella-Ab	Negative	
Human immunodeficiency virus 1 + 2 (HIV)-Ab	Negative	
P-*Coxiella burnetii*-Ab	Negative	
P-syfillis screen (*Treponema pallidum*-Ab)	Negative	
P-streptolysin O-Ab	**1600 arb.enh./L**	<200 arb.enh/L
P-Streptococcus anti-DNAse	<50	
Other		
Blood cultures	Negative	
Monoclonal protein	Not detected	
Angiotensin-converting enzyme	50 U/L	12–60 U/L

refer to *Table 2*). Yet, repeated blood cultures were negative for bacterial and fungal growth. Also, the absence of an independent movement of the vegetations was inconsistent with the classic findings in infectious endocarditis. Since cardiac manifestations more commonly occur in other systemic rheumatic diseases, the investigation included an extensive autoimmune screen. Of particular interest was systemic lupus erythematosus (SLE) with Libman-Sacks endocarditis. However, the patient showed no skin manifestations. A skin biopsy

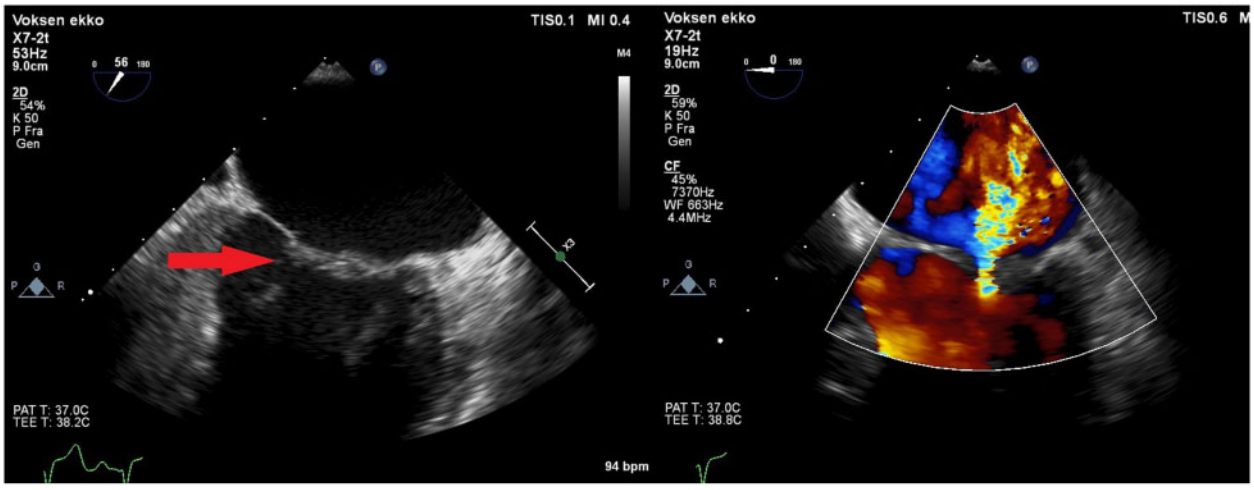

Figure 3 Transoesophageal echocardiogram of the mitral valve at follow-up visit 3 months later, after rituximab treatment. Images show regression in the valve lesions and development of severe mitral regurgitation due to fibrotic changes of the valve.

of the abdomen was without lupus stigmata. There was no history of anaemia or lymphopenia. Also, no anti-nuclear antibodies, anti-double stranded DNA antibodies, anti-phospholipid antibodies, or systemic complement depletion were detected. Surprisingly, the blood tests showed the presence of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and PR3 antibodies. Thus, the patient was examined for granulomatosis with polyangiitis (GPA). There were no upper respiratory tract symptoms, pulmonary infiltrations, renal involvement, or neuropathy. A CT-scan of the sinonasal region showed no inflammatory activity. A biopsy from the maxillary sinus was without signs of inflammation, vasculitis, and granulomas. Secondary amyloidosis was considered, but a subcutaneous abdominal fat biopsy was without deposition of amyloid. The occurrence of valvulitis as a paraneoplastic phenomenon in association with cancer was suspected. But, clinically the patient did not have a fever, night sweats, or weight loss. Lymphoma was ruled out by normal haematology and a FDG-PET/CT-scan with no evidence of activity in the reticuloendothelial system or occult malignancy. After all, the cardiac findings were considered consistent with severe inflammatory activity and EAM, secondary to RA. The immunosuppressive treatment was intensified, and the patient started therapy with Rituximab (monoclonal anti-CD20 antibody). At follow-up 3 months later, the echocardiographic evaluation showed regression in the valve lesions, and normalization of C-reactive protein (*Figure 3*). Unfortunately, regression in the valve lesions, and fibrotic changes led to further dysfunction of the valve with the development of severe mitral regurgitation. The patient now experienced progressively worsening in dyspnoea (NYHA III) and was scheduled for mechanical mitral valve replacement. Histological examination of the excised valve revealed severe inflammation with infiltration of T-cells. Furthermore, many IgG4 positive plasma cells were detected, which raised suspicion of IgG4-related disease. No granulomas were detected. No bacterial or fungal growth was found. At the last follow-up visit in September 2020, echocardiography showed the normal function of the mechanical valve and normal left ventricular ejection fraction. Physical examination was unremarkable and the patient was asymptomatic.

Discussion

This case illustrates how EAMs in RA remain a diagnostic challenge. There is no agreed classification for EAMs symptoms may mimic other disorders such as infections, malignancies, and other rheumatic diseases. Extra-articular manifestations are associated with active RA, and reviewing the existing literature, we have only identified two cases of EAMs in patients with RA in the absence of joint symptoms.[8,9] Cardiovascular EAMs are often clinically silent and rarely need treatment. To our knowledge, we are the first to report a case of severe mitral valvulitis as an EAM in RA. The patient underwent a comprehensive examination before mitral valve surgery. Histological analysis of the excised tissue raised further questions concerning the diagnosis leading to yet another re-evaluation of the patient. Infections and malignancies were ruled out. PR3-ANCA-associated vasculitis could not entirely be ruled out as the cause for valvulitis. But histology was without granulomas or other signs of vasculitis. Thus, the patient did not meet the classification criteria for GPA and the diagnosis was considered highly unlikely. Suspicion of the rare IgG4 related disease was raised due to histological findings. However, co-existence of IgG4 related disease and RA is only scarcely described in the literature,[10] and there were no symptoms or organ involvement matching the traditional localizations of IgG4-related disease.[11,12] An isolated IgG4 attack on the mitral valve was considered unlikely. Before presentation with mitral valvulitis, the patient had already exhibited two EAMs of RA; scleritis and heart block, despite ongoing anti-rheumatic treatment. We therefore believe that this case represents a severe manifestation of seropositive RA, where the dominating problem is aggressive and uncontrolled EAMs.

Conclusion

This case demonstrates a rare manifestation of RA with mitral valvulitis and highlights the importance of extensive clinical examination in challenging patients, where re-evaluation of the disease always must be considered. There is no consensus regarding the treatment of valvulitis in the setting of RA. In patients, where the extra-articular disease is the dominating problem, we suggest a more aggressive treatment strategy.

Lead author biography

Anne Sofie Frederiksen is a junior doctor who worked in the Department of Cardiology, Aarhus University Hospital from 2017 to 2020. She has not yet specialized.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidelines.

Conflict of interest: none declared.

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