Aorto-mitral inflammation in rheumatological disease: Transoesophageal echocardiographic presentation

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Abstract
Thickening of the aortic root and anterior mitral leaflet has been described in patients with aortic valve insufficiency associated with ankylosing spondylitis. We report identical findings made by transthoracic and transoesophageal echocardiography in three patients with inflammatory, non-infective aorto-mitral pathology as manifestation of various rheumatological disorders. All three patients had significant aortic valve incompetence. All three had thickened walls of the sinuses of Valsalvae and a thickened anterior mitral leaflet, in one case with chordal rupture. These findings were confirmed at open heart surgery, and further characterized by histological examination.

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Introduction

Thickening of the aortic root and anterior mitral leaflet has been described in patients with aortic valve insufficiency associated with ankylosing spondylitis.1–3 We report similar findings made by echocardiography, transthoracic (TTE) and transoesophageal (TEE) in three patients with various rheumatological disorders in whom underlying inflammatory, non-infective aorto-mitral pathology was confirmed by histological examination.

Patient 1

A 39-year old male positive for HLA-B27 had a 22-year history of Reiter’s disease with reactive polyarthritis following Shigella induced gastroenteritis. He was
referred to our hospital because of aortic valve insufficiency and exertional dyspnoea, developing over months to NYHA-class III. Prior to transferral from the department of rheumatology MRI of the thoracic aorta had shown wall thickening in the aortic root, but no dilation. His CRP was 363 nmol/L (normal <75 nmol/L) despite long-lasting treatment with Prednisolone (2.5 mg daily) and Methotrexate (17.5 mg once weekly). According to the rheumatologists there was no active joint affection.

TTE showed aortic valve insufficiency with severe volume overload of the left ventricle (LV). The diastolic dimension (LVDd) was 7.9 cm and the systolic dimension (LVDs) 6.2 cm. TTE suggested increased echointensity of the aortic root and the anterior mitral valve leaflet. On TEE the three aortic cusps appeared mildly thickened, with severe central valve regurgitation and a vena contracta of 8 mm. There were no vegetations. The walls of the sinuses of Valsalvae were thickened up to 5 mm, and the increased thickness with accentuated echogenicity extended downwards into the anterior mitral leaflet tapering towards the leaflet tip and forming a characteristic subaortic bump. Here the maximum thickness of the anterior mitral leaflet was 7 mm (Fig. 1). From the sinotubular junction and downstream the aortic wall appeared to be of normal thickness.

The echocardiographic findings were interpreted as potential active inflammatory manifestations of Reiter’s disease. Prednisolone (60 mg daily) and cyclophosphamide (100 mg daily) were administered for six weeks in addition to treatment for congestive heart failure. However, the severe aortic valve incompetence remained unchanged and aortic and mitral valve replacement was performed. According to the surgeon the aortic wall appeared and felt normal, and mechanical St. Jude valve prostheses were inserted in the aortic and mitral valve position, respectively.

Histopathological examination of the aortic valve revealed thickening caused by fibrosis, but there was no oedema nor inflammatory cells or fibrinoid necrosis. In contrast the anterior mitral leaflet

Figure 1 A: TEE, long-axis view through the aortic root (AO) and the thickened anterior mitral leaflet (arrows) in a 39-year old patient with Reiter’s disease (Patient 1). B: Corresponding view in a patient of the same age and sex with normal thickness and no inflammation of the aorto-mitral complex. The lower panels show the corresponding color-Doppler presentations of the two patients. Both had severe aortic insufficiency. LA, left atrium; LV, left ventricle; RV, right ventricle.
exhibited signs of active inflammation with marked infiltration of lymphocytes and plasma cells as well as severe thickening with fibroblast proliferation. Microorganisms were not demonstrated.

The patient had an uneventful postoperative recovery, and resumed his usual daily activities.

Patient 2

A 42-year old male had a history of pain and intermittent swelling of the joints of hands, knees and feet caused by seronegative rheumatoid arthritis according to a department of rheumatology where he had been treated as an outpatient for 15 years. He was transferred urgently to our centre from his local hospital where he was admitted with suddenly occurring pulmonary oedema because of severe mitral insufficiency. CRP was 195 nmol/L and the WBC count $15 \times 10^9$/L. TTE indicated thickening of the aortic root, aortic valve and anterior mitral leaflet (Fig. 2A) and showed a hyperkinetic left ventricle and severe mitral insufficiency. The calculated mitral valve regurgitant volume was more than 100 mL according to the PISA method. In addition, there was considerable insufficiency of the aortic valve and mild dilatation and pronounced wall thickening of the aortic root confined to the sinuses of Valsalvae (Fig. 2B,C). The wall thickening of the sinuses extended downwards into the proximal part of the anterior mitral leaflet with increased echogenicity and a maximum thickness of 7 mm of the leaflet. In short axis views the wall thickening of the aortic root was most pronounced in relation to the commissures of the tricuspid aortic valve where the thickening exceeded 1 cm (Fig. 2C). TEE clearly demonstrated a thickened anterior mitral leaflet with chordal rupture (Fig. 3).

The patient underwent acute valve replacement with insertion of mechanical prostheses in aortic and mitral positions. The thickening of the aortic root and the anterior mitral leaflet were confirmed by the surgeon.

Histological examination revealed acute and chronic inflammation in the proximal aortic wall, the aortic valve and the anterior mitral leaflet. There were no bacteria.

Postoperatively renewed rheumatologic evaluation concluded connective tissue disorder of uncertain etiology, possibly Ehlers-Danlos syndrome of the hypermobility type (type III). This tentative diagnosis was based on joint hypermobility, soft velvety stretchy skin, and lack of molecular defects on collagen analysis (Villefranche classification) in combination with aortic root dilatation.

During the following year the patient was free of cardiac symptoms but developed only partial recovery of the rheumatological disease. He had persistent complaints of fatigue and joint pain in spite of ongoing treatment with Prednisolone.

Patient 3

A 60-year old man developed fatigue and pain and swelling of the right ankle joint a few weeks after prostatectomy. S-uric acid was normal, but C-reactive protein was increased 10-fold and the

Figure 2  A: TTE, parasternal long-axis view through the thickened aortic root and anterior mitral leaflet (arrows) in patient 2 (seronegative rheumatoid arthritis and possible Ehlers-Danlos syndrome). B: TEE, long axis view through the severely thickened wall of the aortic root (AO) and anterior mitral leaflet (arrows). C: TEE, short-axis view through the sinuses of Valsalvae showing the thickened aortic wall, in particular in relation to the commissures of the cusps (arrows). Abbreviations as in Fig. 1.
sedimentation rate was 120 mm/hour. Severe aortic valve insufficiency was diagnosed, and as the temperature was increased to 38.5 °C, the patient was transferred to our hospital suspected of infective endocarditis. However, multiple blood cultures remained negative. TTE showed dilatation and hyperkinesis of the left ventricle (LVDD/LVDS 6.8/4.0 cm), and a broad aortic regurgitant jet. There was mild mitral insufficiency. Thickening of the anterior leaflet and of the walls of the sinuses of Valsalvae was suggested.

TEE confirmed thickening with increased echogenicity and thickening of the anterior mitral leaflet (up to 8 mm), and this thickening appeared as an extension of the wall thickening of the sinuses of Valsalvae (Fig. 4A). The aortic valve

Figure 3  A: TEE, long-axis view through the mitral valve and left ventricular outflow tract in patient 2 (seronegative rheumatoid arthritis and possible Ehlers-Danlos syndrome). Arrows indicate chordal rupture to the anterior mitral leaflet. The thickening of the proximal part of the leaflet is also seen. B: Corresponding color-Doppler presentation in systole shows severe mitral insufficiency (arrow). C: Color-Doppler presentation in diastole showing significant aortic insufficiency (arrow). Abbreviations as in Fig. 1.

Figure 4  A: TEE, long-axis view through the thickened aortic root and anterior mitral leaflet in patient 3 with arthritis of undetermined etiology. Like patients 1 and 2 this patient also had significant aortic insufficiency. B: Same view showing an intramural haematoma for comparison. The intramural wall haematoma begins more distally in the aorta than the arthritis associated changes in patients 1–3. It also extends upwards, but not downwards into the anterior mitral leaflet, and in the short-axis view the haematoma is crescent shaped (C, arrows). Abbreviations as in Fig. 1.
was tricuspid with severe central insufficiency but no vegetations. 

A CT-scan of the thorax was unremarkable apart from thickening of the aortic wall confined to the sinuses of Valsalvae. The condition remained stable on anticongestive treatment over the next five weeks, while the patient fruitlessly underwent multiple examinations for continuous fever. He was also seen three times by a rheumatologist, who was unable to establish a specific diagnosis despite several laboratory tests and puncture of the ankle joint with microscopy and laboratory tests of the joint fluid. C-reactive protein remained significantly increased, and TTE and TEE were also unchanged. A coronary arteriogram was considered normal and eventually the patient underwent aortic valve replacement for the severe insufficiency. The surgeon found the aortic cusps and the walls of the sinuses stiff and fibrotic. Unfortunately, the patient succumbed to extensive myocardial infarction post-operatively.

Autopsy revealed a large anterior wall infarction and two stenoses in the left anterior descending branch of the left coronary artery, but no stenosis of the main stem or of the orifice of the left coronary artery. There were no valvular vegetations. Histological examination of the excised aortic cusps and of the anterior mitral leaflet showed valvular thickening with inflammatory foci, fibrosis and small spots of ulcerations and necroses. Bacteria were not identified by histological examination or PCR-technique. The aorta above the inserted prosthesis was considered macroscopically normal, but histological examination was not performed.

Discussion

The findings by echocardiography in the three patients were indicative of non-infectious aorto-mitral inflammation. Wall thickening of the aortic root confined to the sinuses of Valsalvae with extension downwards into the anterior mitral leaflet and significant central regurgitation in a tricuspid aortic valve were the common findings. The wall thickening of the aortic root was most pronounced in relation to the commissures of the aortic valve.

In patient 2 chordal rupture to the anterior mitral leaflet necessitated acute valve replacement because of pulmonary oedema resistant to medical treatment. As chordal rupture is much more common to the posterior than to the anterior leaflet it may seem likely that the chordal rupture in patient 2 was a complication to the inflammation in the anterior mitral leaflet.

The pathoanatomic findings corresponded with the echocardiographic findings. Thickening of the anterior mitral leaflet was confirmed in all three patients by direct inspection of the surgeons or at autopsy. The wall of the aortic root was also considered stiff and thickened in patients 2 and 3. In addition, MRI and CT-scan at an early stage showed thickening of the sinuses of Valsalvae in patients 1 and 3. None of the three patients had visible vegetations, neither by TEE nor at direct inspection, and repetitive blood cultures remained negative. Microscopic examination of the anterior mitral leaflet revealed acute inflammation in all three patients. Inflammation was also demonstrated in the aortic cusps in patient 2 and 3 and in the proximal aortic wall in patient 2. No bacteria were demonstrated. Possibly, the preoperative immunosuppressive treatment in patient 1 had eliminated inflammation of the aortic wall and cusps. An immediate preoperative TEE was not performed in this patient.

The aorto-mitral inflammatory changes in these patients were likely to be related to rheumatological diseases. Apart from aortic insufficiency with new onset heart failure of various degrees, the common clinical features were a known history of rheumatological disease or new onset arthritis, increased phase reactants (all three patients), and fever in patient 2 and 3. Patient 1 received anti-inflammatory treatment that might eliminate fever. Patient 1 had age long Reiter’s disease with no active joint affection according to the rheumatologists. Patient 2 had a 15 year history of multiple joint affection, originally considered to reflect seronegative rheumatoid arthritis, although he was later classified as probably suffering from Ehlers-Danlos syndrome (Type III). Admittedly, it is unclear whether he suffered from rheumatoid arthritis or Ehlers-Danlos syndrome or both. However rheumatoid arthritis may sometimes give rise to aortitis and inflammatory vasculitis, and the association between Ehlers-Danlos syndrome and aortic root dilatation and valve incompetence is well known. Although speculative this condition may possibly in some cases be preceded by aorto-mitral inflammation as observed in patient 2. As such, the inflammation of the proximal aorta may possibly represent an early stage of the more chronic affection.

The third patient had ankle joint arthritis that lasted for months, but a firm etiology was not established even after multiple inspections by rheumatologists, numerous blood tests and joint fluid analysis.

Similar findings as in our patients have earlier been described in the HLA-B27 associated
ankylosing spondylitis. HLA-B27 may also predispose to Reiter’s disease as in our patient 1. Our three cases of inflammatory changes in the anterior mitral leaflet, aortic cusps and aortic root differs from other well known causes of aortitis and other aortic pathology. Aortitis caused by endocarditis is clearly identified by valve vegetations, root abscesses or pseudoaneurysms. Takayasu’s arteritis is a more generalised aortic disease, including wall aneurysms, adventitial thickening and fibrosis and in particular stenoses and occlusions of branches such as carotid, subclavian and renal arteries. In relation to imaging by means of TEE, incomplete aortic dissection with intramural haematoma is a more obvious differential diagnosis from these types of aortitis (Fig. 4B). However, the proximal limit of wall thickening caused by intramural haematoma is normally above the origin of the coronary arteries. In cross sections intramural haematoma presents semicircular and it extends further upwards through the ascending aorta, but not downwards into the anterior mitral leaflet (Fig. 4B). Furthermore, severe aortic insufficiency is rarely seen in patients with intramural haematoma of the ascending aorta, and the typical pain will also help to a correct interpretation of the TEE findings.

In conclusion we report three cases of significant aortic valve insufficiency in patients with rheumatological disorders. Echocardiography showed thickening of the aortic root with extension downwards into the anterior mitral leaflet with a characteristic subaortic bump as earlier reported in patients with ankylosing spondylitis. Histological examination revealed non-infective aorto-mitral inflammation in all three patients, two of whom had combined aortic and mitral valve replacement performed while the remaining patient was considered to need aortic valve replacement only. Although TTE in all three patients indicated thickening and increased echogenicity of the anterior mitral leaflet and the sinuses of Valsalvae, the pathology of the structures appeared much more obvious on TEE.

References