CASE REPORT

A large chronic pericardial effusion in an ultramarathon runner with anti-CCP positive rheumatoid arthritis

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SUMMARY

Pericardial effusions arise as an extra-articular manifestation of rheumatoid arthritis (RA). Pericardial effusions are often asymptomatic, particularly in the early phase, but patients are at risk of cardiac tamponade as the effusion progresses. We discuss the case of a 40-year-old male ultramarathon runner with RA who presented with mild pleuritic chest pain and exertional dyspnoea after a recent long-haul flight. Despite a relative tachycardia, his observations were otherwise unremarkable. His blood tests revealed a C-reactive protein (CRP) of 86 mg/L and an anti-cyclic citrullinated peptide (anti-CCP) titre of 360 units/mL. He was initially diagnosed with a pulmonary embolism; however, a large pericardial effusion was found incidentally on CT pulmonary angiogram with over 1500 mL subsequently drained. The patient's symptoms resolved and CRP normalised 2 weeks later. This unique case illustrates that physically fit patients may physiologically compensate for large pericardial effusions and that arthritic symptoms do not correlate with the severity of extra-articular features in RA.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic autoimmune disease that has characteristic extra-articular features including pericardial effusions that arise from inflammatory myocardial dysfunction. This case report documents an example of a large subclinical pericardial effusion in a 40-year-old male ultramarathon runner who was initially believed to have a pulmonary embolism following recent long-haul travel. The high baseline fitness of this patient masked the extent of his pericardial effusion on presentation to secondary care. With the knowledge that an elevated anti-cyclic citrullinated peptide (anti-CCP) titre increases the risk of pericardial effusion, regardless of symptom severity, clinicians must thoroughly investigate and exclude life-threatening complications in patients presenting with cardiopulmonary symptoms such as pulmonary nodules, effusions, fibrosis, pericarditis, coronary vasculitis, aortitis, myocardial infarction or effusions on a known background of RA.¹

CASE PRESENTATION

A 40-year-old male extreme endurance runner, diagnosed with anti-CCP positive RA three years previously, presented with a six-week history of pleuritic chest pain, exertional dyspnoea and

a non-productive cough. The patient had just returned to the UK from the far east after an ultramarathon (typically classified as races over 50 km), where he reported several near-syncopal episodes on exertion and episodes of right-sided pleuritic chest pain. These symptoms occurred acutely on a background of a four-month history of fatigue and weight loss (4 kg). His initial treatment for RA was an intramuscular depot of dexamethasone in addition to disease-modifying antirheumatic drugs (DMARDs) which had recently been changed from methotrexate to sulfasalazine. This relative step-down in treatment was in line with the patient's wishes, and stopping methotrexate was advisable on the premise he wished to have another child. This medication regime did lead to successful remittance in joint symptoms, and, although mild flares did occur in periods of high stress and physical inactivity, the appropriate biological agents were declined by the patient.

On observation, the patient was found to be unwell but clinically stable with vital signs within normal ranges. The patient was afebrile, normoxic and normotensive, with a heart rate of 72 bpm (a relative tachycardia considering the patient's resting heart rate of 42 bpm). On examination, dullness to percussion was noted at the right lung base. On auscultation, heart sounds were muffled but no pericardial rub was audible. Significant negative findings included a non-raised jugular venous pressure, no pulsus paradoxus and no signs of active inflammatory arthritis.

Work-up revealed a full blood count, urea and electrolytes, and liver function tests within normal range with the exception of raised inflammatory markers (C-reactive protein (CRP) level of 86 mg/L). Due to regular blood monitoring for DMARD therapy, we noted this was consistent with an upward trend of CRP levels over the previous three months. The serum rheumatoid factor (RF) was 26 units/mL and anti-CCP titre was 360 units/mL (>60.0 units/mL is considered a strongly positive result). Further investigations revealed a low amplitude, but otherwise normal ECG and radiographic evidence of an enlarged cardiac silhouette with mild blunting of both costophrenic angles.

Suspecting a pulmonary embolism due to the presenting clinical features alongside a recent long-haul flight, a CT pulmonary angiogram (CTPA) (figure 1) and chest radiograph (figure 2) were performed. Subsequently, there was an incidental

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Figure 1 CT pulmonary angiogram showing a large pericardial effusion with >40 mm separation of pericardium and myocardium with associated bilateral pleural effusions.

finding of a massive pericardial effusion with a >40 mm separation of pericardium and myocardium with associated bilateral pleural effusions.

INVESTIGATIONS

Cytological examination of the pericardial fluid revealed features of an acute inflammatory process comprising lymphocytes, polymorphs and reactive mesothelial cells. No malignant cells were found on microscopy. No organisms or acid fast bacilli were seen and aerobic and anaerobic bacterial cultures were negative. A negative TB ELISpot alongside negative long cultures for mycobacterium tuberculosis ruled out tuberculous pericarditis - an important negative given recent travel to Asia. Microscopic examination of pericardial tissue showed fibrinopurulent exudate and the tissue was culture negative. Although

Figure 2 Chest radiograph on admission: evidence of mild blurring of the costophrenic angles bilaterally, most marked on the right. The cardiac shadow appears enlarged.

this cannot rule out a viral cause of infection, it makes bacterial pericarditis highly unlikely. Two-dimensional echocardiography can be useful in investigation of the pericardial disease. In this instance, immediate management followed the diagnosis of the pericardial effusion by CTPA, and thus echocardiography was not performed.

DIFFERENTIAL DIAGNOSIS

We have discussed a less common presentation of a pericardial effusion due to a complication of RA. The important differentials to exclude in this case were an effusion secondary to infective pericarditis, namely viral or tuberculous, and a neoplastic infiltration of the pericardium secondary to metastatic malignancy.

Other differentials for pericardial effusions include congestive heart failure, postcardiac intervention, uraemia, aortic dissection and vasculitides, for example, systemic lupus erythematosus.

OUTCOME AND FOLLOW-UP

A diagnosis of pericardial effusion was confirmed and treated with thorascopic drainage of 1500 mL of viscous serous fluid via a pleuropericardial window. Resolution of symptoms followed with full inflammatory and homeostatic normalisation of the CRP levels within four days.

DISCUSSION

Pericardial effusions are a common extra-articular feature of RA and 13% of patients with RA will have evidence of asymptomatic pericardial involvement on transoesophageal echocardiogram.² However, pericardial effusions of the volume reported here are rare.³ A 2013 cross-sectional study of 80 patients divided into anti-CCP positive or negative revealed that 12.5% of anti-CCP positive patients had pericardial thickening, while no anti-CCP negative patients had similar findings.⁴ Moreover, the same study revealed that mild pericardial effusions were four times more prevalent in the anti-CCP positive group.⁴ Symptomatic patients are more likely to be RF positive⁵ and the degree of positivity in the relatively specific anti-CCP test is strongly correlated with disease activity.^{6,7}

The majority of known cardiovascular risk factors⁸ carry a similar risk for the development of cardiovascular disease in patients with and without RA. However, others such as male gender, smoking and personal cardiac history impart significantly less risk in patients with RA.⁹ Therefore, there are likely alternate or, at least, additive mechanisms that contribute to cardiac disease in patients with RA.⁹ The role of antibodies such as anti-CCP in the pathogenesis of RA, and its extra-articular manifestations, has been widely discussed given their presence in target tissues affected by the condition.^{10,11} Since these antibodies drive the destructive pathological processes in the synovium of affected joints,¹² it can be hypothesised they exert similar action within cardiac tissues. With regard to cardiac tissues, antibodies to CCP share similarities to antifibronectin and anti-mentin antibodies which have been implicated in inflammatory myocarditis in animal models.¹³ Furthermore, tissues affected in inflammatory arthritis such as skeletal muscle and synovium are known to contain citrullinated peptides.¹⁴ With reference to this, it has been postulated that increasing anti-CCP titres causes increased myocardial inflammation either directly, through citrullinated proteins, or indirectly, through cross reactivity between the anti-CCP antibodies and similar proteins. Subsequently, this inflammatory response would lead to an exudative process culminating in a pericardial effusion. However, the exact pathogenesis of this complication of rheumatological disease is

unknown and more data on citrullination within the RA myocardium and the mechanisms of disease progression are required.

Of paramount importance to this presentation was the athleticism of the patient. The cardiovascular and general physical status of this patient altered the disease presentation in two key ways. First, the cardiovascular adaptation of the endurance-trained heart allows compensation during a pathophysiological event such as pericardial effusion. Intensive endurance training increases both left ventricle diameter and left ventricular wall thickness.¹⁵ The evolution of these cardiac parameters altered aspects of the typical clinical manifestations of a pericardial effusion, namely tachycardia and hypotension. Following the three phases of haemodynamic changes in tamponade proposed by Reddy *et al*,¹⁶ tachycardia is the initial cardiovascular response to maintain cardiac output in the face of a marked reduction in diastolic filling. Diastolic filling becomes reduced due to imbalance between transmural distending pressures and the increased intrapericardial pressure. In this case, it is thought the large stroke volume due to physiological ventricular remodelling and, hence, an increased reserve capacity of the heart was permissive of a large pericardial effusion. Here, the increase in ventricular size allowed the heart the ability to withstand higher intrapericardial pressures such that a heart rate constituting a tachycardia by accepted ranges was not reached. Hence, observations in this patient fell within the normal population-level parameters, and thus were falsely reassuring. Large pericardial effusions have been documented in athletic patients before¹⁷ and thus, regardless of rheumatoid status, it is clinically important to consider the cardiovascular reserve of an athletic patient when interpreting objective clinical signs.

Second, the fitness of this patient may have contributed to the apparent disequilibrium between the manifestation of the articular and extra-articular features of RA in this instance. The Disease Activity Score 28 provides a validated and evidenced approach to grading of the severity of RA. It is heavily influenced by the number of swollen and tender joints in addition to the CRP and a global assessment of the patient's health,¹⁸ it is used to classify RA into active disease, low disease activity and remission. By this measure, the RA in this instance was in remission (<2.6); however, the patient suffered a severe complication of RA (as evidenced by the high anti-CCP titre in the effusion). Herein lies an example where there is an apparent disconnect between the articular presentation of RA (and hence clinical classification of severity) and extra-articular features. Pain and stiffness associated with rheumatoid articular pathology often incapacitate patients, a state further compounded by the reduction in joint range of motion and increase in joint instability and muscle atrophy. It follows that regular aerobic exercise would improve the body's musculature, improving joint function without worsening disease activity.¹⁹ Furthermore, it is known that cardiorespiratory conditioning programmes can be effective in pain control, improving functional ability²⁰ while having favourable effects on disease activity.²¹ In a patient of the kind described in this report, it is clear how undertaking an exercise regime as intense as this ultramarathon runner could mask the articular features of disease. Furthermore, given anti-CCP titres correlate with disease activity,^{6 7 22} it is possible the very high anti-CCP titres in this patient lead to a more insidious extra-articular complication while the normal indicators of disease severity in the form of swollen and painful joints were absent.

Furthermore, reference should be made to a further contributing factor in the development of the pericardial effusion in this patient—the switch in DMARDs from methotrexate therapy to sulfasalazine therapy. Although evidence regarding the safe use of methotrexate in men trying to conceive was emerging at this

time, it was deemed inappropriate DMARD therapy given its teratogenic potential.²³ Sulfasalazine is not optimal in these circumstances either, causing depression of sperm quality and reversible infertility in 60% of men.²⁴ However, there is no influence on plasma concentrations of prolactin, testosterone and gonadotrophins during this drug therapy, suggesting it has no adverse effects on the hypothalamic-pituitary-adrenal axis.²⁵ Current guidelines advise it is not necessary for men to stop sulfasalazine before trying for conception unless there is a failure of conception over the period of 1 year. There have been several case reports in the literature of drug-induced pericarditis arising from sulfasalazine or mesalazine therapy.^{26–32} Both drugs contain 5-aminosalicylic acid (5-ASA) and it is thought that antibodies to 5-ASA will cross-react with the pericardium causing inflammation.²⁶ While the majority of reports arise in patients being treated with 5-ASA for inflammatory bowel disease, we cannot exclude the contribution of sulfasalazine therapy in pericarditis preceding the pericardial effusion. Therefore, a high index of suspicion should be maintained when patients present with cardiovascular symptoms after recent changes to DMARD therapy.

Learning points

- ▶ Development of cardiac tamponade depends on effusion volume, rate of accumulation and physiological ability to compensate.
- ▶ The physical fitness and baseline observations in health of a patient should be considered when interpreting observations in illness, as they may fall within normal population-level parameters, and thus be falsely reassuring.
- ▶ It is important to monitor for extra-articular manifestations of rheumatoid arthritis in seropositive patients (rheumatoid factor positive and anti-cyclic citrullinated peptide positive), even in the absence of articular features.

Contributors RP and SK were involved in the patient's care. TJM, RP, SK and NSN prepared and wrote the manuscript.

Competing interests None declared.

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