



Recurrent ACPA-positive pericarditis, would it be a pre-clinical manifestation of RA?

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with an autoimmune component that preferentially affects the small joints of the hands and feet. Extra-articular manifestations may be associated with it. These are rather long-term complications compared to the inaugural forms of the disease.

Observation: We report the observation of a 62-year-old female patient with a history of high blood pressure under monotherapy by a conversion enzyme inhibitor, followed for recurrent pericarditis for three years, who was initially treated with anti-bacillary drugs without improvement. She presented two years ago an episode of pericarditis of great abundance requiring a pericardial drainage. The pericardial biopsy was non-specific. The etiological work-up revealed the presence of anti-citrullinated peptide antibodies (ACPA) and a rheumatoid factor (RF) at very high levels. The patient did not present any other systemic signs, especially articular ones. Joint imaging was normal. The evolution was marked by the persistence of a pericardial effusion of a small to medium size. RA could not be retained according to the American College of Rheumatology/ European League Against Rheumatism's (ACR/EULAR) 2010 criteria. Glucocorticoids therapy at a dose of 0.5 mg/kg/day allowed the resolution of the pericarditis without recurrence, with a six-month follow-up period.

Conclusion: This is an extra-articular manifestation that would be inaugural of RA. It is an atypical presentation in the usual history of the disease. The inclusion of extra-articular involvement in the classification criteria and in the groups at risk of developing RA would be useful in these cases.

Keywords

pericarditis, ACPA, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease characterized by the presence of chronic destructive arthritis, typically of the hands and feet, in the presence of specific antibodies in most cases. It is an authentic systemic disease with multiple facets, and where extra-articular involvement is frequently encountered. Its etiopathogenesis, which is multifactorial, is becoming more clarified.

Observation

We report the observation of a 62-year-old female patient followed for high blood pressure under a conversion enzyme inhibitor, who was already treated three years ago for presumed tuberculous pericarditis and put under anti-bacillary treatment for six months. She presented to the internal medicine clinic for an etiological assessment of recurrent pericarditis. The second episode occurred two years ago, with the onset of constrictive chest pain, palpitations, and acute dyspnea NYHA stage III. The patient was admitted to the emergency department, her blood pressure was 160/100 mmHg, and she was afebrile and had no signs of heart failure or

other systemic signs (notably no skin signs, dry syndrome, muscle weakness, or neurological abnormalities). An electrocardiogram (ECG) was performed, which showed microvoltage and sinus tachycardia at 120 bpm. A chest X-ray was performed that showed a decanting heart, and a transthoracic echocardiogram was performed that demonstrated a large circumferential pericardial effusion, predominantly in posterior (at 34 mm) with the presence of a right atrial notch and without signs of compression of the right ventricle or paradoxical septum. The blood count was normal, the sedimentation rate was 60 s at the first hour, and the CRP was 40 mg/l (upper limit of normal for CRP is 6 mg/l). The diagnosis of a great abundance pericarditis was retained. The patient underwent pericardial drainage allowing for the evacuation of 650 cc of citrine yellow fluid. The pericardial fluid study showed a lymphocytic exudate, the bacteriology did not find any germs, and the GeneXpert test was negative. Anatomopathological study of the pericardial tissue was non-specific. During his follow-up in cardiology, ultrasound monitoring showed the persistence of a pericardial effusion of small to medium abundance (Figure 1) not responding to nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. An etiological workup was initiated and the cervico-thoraco-abdomino-pelvic CT scan was normal except for the moderate-abundance pericardial effusion (Figure 2), and anti-Nuclear as well as anti-Extractable Nuclear Antigens' (ENA) antibodies and the anti-Neutrophil Cytoplasmic Antigen (ANCA) came back negative. Anti-citrullinated peptide antibodies (ACPA) were positive at 891 IU/ml (upper limit of normal

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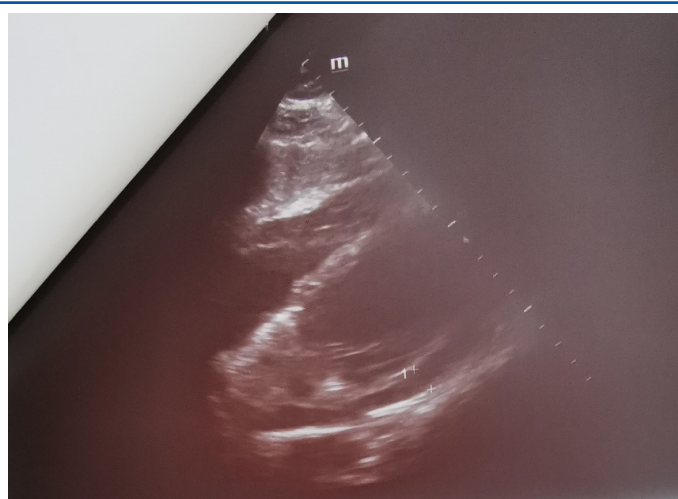


Figure 1 - Transthoracic ultrasound: persistence of a small pericardial effusion measured at 11 mm posteriorly.



Figure 2 - CT scan illustrating circumferential pericarditis.



Figure 3 - Standard X-ray of hands and wrists: absence of erosive lesions consistent with rheumatoid arthritis.

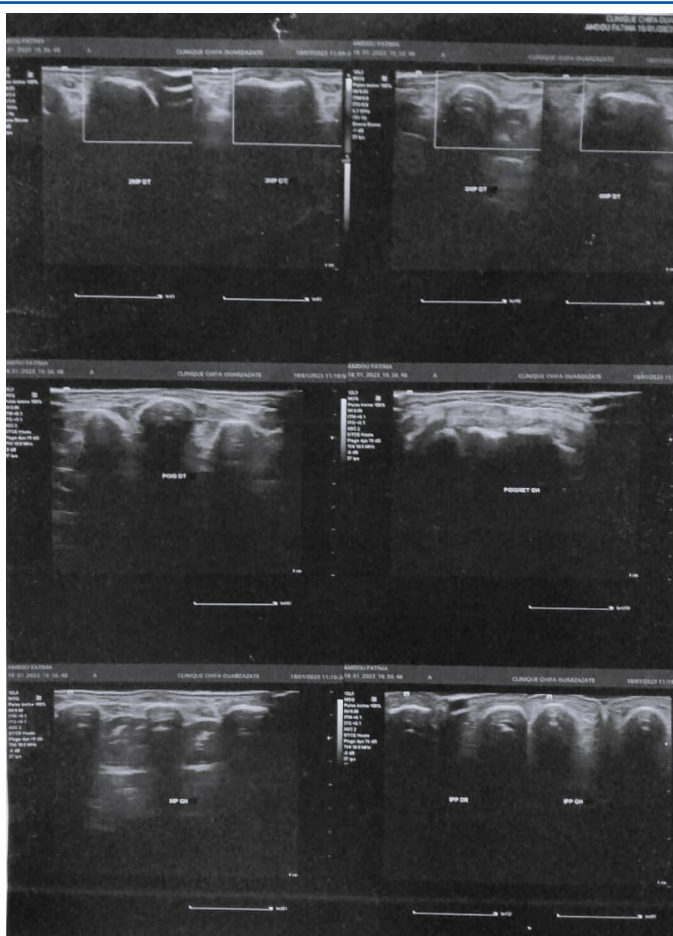


Figure 4 - Joint ultrasound of both wrists, hands, and the right elbow with no notable abnormalities.

for ACPA is 20 IU/ml) and had a rheumatoid factor (RF) at 66 IU/ml (upper limit of normal for RF is 18 IU/ml). Serologies for hepatitis B and C, HIV, and a tuberculin intradermal test came back negative. A standard X-ray of the hands and feet was performed that showed no abnormality (Figure 3), and a complementary ultrasound was then performed, which was without evidence of synovitis or erosive lesions (Figure 4). Diagnosis of established RA could not be retained according to classification criteria for typical RA cases, based upon clinical history, clinical examination, laboratory findings, and imaging findings. However, a pre-RA phase with an extra-articular manifestation inaugurating RA could be suggested in this context. The patient was put on glucocorticoids-therapy at a dose of 0.5 mg/KG/day, which allowed a drying of the pericardium without recurrence with a six-month follow-up period. The patient is still free of arthritis, as of three years since the first episode of pericarditis.

Discussion

The history of this patient's disease prompted several reflexions. Extra-articular manifestations usually occur in the course of known, long-standing RA.

Pericarditis is a classic complication of RA, occurring in 30–50% of patients [1]. This incidence could be even higher, as pericarditis is often asymptomatic in RA patients and the search for cardiac involvement is not systematic. In most cases it follows polyarthritis, but in rare cases, it may be the first manifestation of the disease [1].

After a review of the literature by searching the MEDLINE and SCOPUS databases, ACPA and/or RF seropositivity in recurrent pericarditis has been reported in a few cases or small case series. To our knowledge, there are no large-scale studies that have assessed the prevalence of these immunological markers in pericarditis. This is probably due to the fact that they are not routinely tested for. Chirila et al. reported three cases of extra-articular manifestations of RA in the presence of ACPA, initially without arthritis. These were a case of scleritis, a case of pleuropericarditis associated with diffuse interstitial lung disease (DIL), and a third case of histologically confirmed subcutaneous rheumatoid nodule [2]. The first and second cases presented with joint signs after four and two years, respectively. While the third patient had no joint manifestations after two years of evolution. Another series of 74 patients with ACPA-positive lung diseases was published by Fisher et al [3]. In this series, 33 patients had high ACPA levels (≥ 60 IU), of whom only three developed joint involvement, after a median follow-up of 449 days. Rheumatoid meningitis is another extra-articular ACPA-positive event reported by Lee Ching et al. in the absence of polyarthritis, after a one-year follow-up period [4].

These observations are in line with our own concerning the fact that an extra-articular manifestation could precede RA. ACPAs are major immunological markers of RA and are highly specific (their specificity is about 96%) [5]. However, their sensitivity varies according to the stage of the disease, from 34% in pre-RP to 88% after twelve months in the state phase. Their presence can precede the clinical phase of RA by several years, up to a decade [7]. Their positivity is significantly correlated with the presence of extra-articular manifestations and the severity of RA [8, 9]. These antibodies also play a major role in the etiopathogenesis of RA, in patients combining genetic and environmental factors via the deposition of immune complexes and complement activation, as well as the stimulation of cytokine and chemokine production, such as TNF-alpha (tumor necrosis factor) and interleukin-6 [10, 11], resulting in synovitis and structural damage. The systemic passage of ACPAs results in a phase of autoimmunity, followed by the development of clinical signs, and although the synovium is the preferred site of adaptive inflammatory reactions, other tissues may be the site of this reaction [12].

The pre-RA phase is currently well-recognized; EULAR established in 2012 a definition of the development phases of RA [12] that goes through genetic factors, environmental factors, a systemic

autoimmune phase, the presence of symptoms without clinical arthritis, the phase of undifferentiated arthritis, and then established RA fulfilling the American College of Rheumatology/ European League Against Rheumatism's (ACR/EULAR) 2010 classification criteria [13]. Through this description, extra-articular manifestations are not clearly identified in the initial phase of the disease. This could be explained by the fact that they are rarely encountered before the status phase and are limited to reported cases.

Based on this observation and others reported in the literature, it would be legitimate to complete the etiological work-up by looking for ACPA/RF in cases where the first-line work-up (infectious, immunological, and neoplastic) is negative. Follow-up of patients with positive immunological markers of RA warrants vigilance for the first signs of articular disease.

Treatment of pericarditis in its idiopathic form being considered an autoinflammatory disease [14] is based on nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine in the first-line setting and the addition of glucocorticoids therapy in the second-line setting. If these therapies fail, anti-IL1 inhibitor treatment may be proposed, as well as IGIV therapy [15, 16]. In our patient, an autoimmune component to her pericarditis is strongly suspected, so the use of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and other biotherapies such as anti-CD20 or anti-TNF α could be considered in the case of refractory disease.

Conclusion

Our case suggests that pericarditis may precede RA, which is unusual in its classic course. While the history of RA is becoming better known, a global view of it as an authentic systemic disease from the earliest stages would allow earlier diagnosis and avoid disease-related complications.

Conflict of interest

The authors declare no conflict of interest.

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Author Contribution

1- Hamri Laila: diagnosis, treatment, design of the clinical case, bibliographic prospecting, and writing.

2- Rabhi Samira: supervision, proofreading, and validation of the manuscript.

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