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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

# Atypical clinical presentation of rheumatoid arthritis

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**SUMMARY**

**Introduction** Rheumatoid arthritis is a systemic autoimmune disease with inflammation of the joints as its hallmark. Extra-articular manifestations affect nearly half of the patients either at the onset of disease or later during the disease course.

**Case outline** A 43-year-old man complained of chest pain, dry cough, and fatigue. Diagnosis of pericarditis was made based on echocardiography findings. Due to worsening of respiratory symptoms, he was admitted to the hospital. Initial diagnostic workup revealed elevated concentrations of acute phase reactants, pericardial effusion, and bilateral pulmonary nodules. Pathohistological analysis of lung nodules ruled out malignancy and tuberculosis. He was treated with colchicine, which led to a regression of a pericardial effusion. Afterwards, due to arthritis of the right wrist, high erythrocyte sedimentation rate, and C-reactive protein, positive immunoserology and bone erosion at the distal ulna diagnosis of seropositive rheumatoid arthritis was established. He was treated with antimalarial, methotrexate, and glucocorticoids until he suffered from COVID-19 pneumonia, which triggered arthritis flare. Owing to the loss of efficiency of combination therapy with methotrexate and glucocorticoid, baricitinib was added to the treatment. Low disease activity was achieved after three months of administering baricitinib and methotrexate, and no adverse events occurred during 20-month-long therapy.

**Conclusion** Every patient with pericarditis of unknown etiology should be diagnostically evaluated in term of connective tissue disease including rheumatoid arthritis, because the initial clinical presentation in some group of patients could lack characteristic synovitis.

**Keywords:** pericarditis; lung nodules; rheumatoid arthritis; COVID-19 pneumonia; flare; baricitinib

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease with articular inflammation as the main feature. Inflammatory processes can also affect other tissues and these extra-articular manifestations are associated with a higher risk of morbidity and mortality in patients with RA [1].

The objective of this article was to present a case of atypical clinical manifestation of RA.

## CASE REPORT

In December 2014, a 43-year-old man complained of chest pain that worsened with deep inspiration and in supine position, dry cough, and fatigue. These symptoms were present for one month prior to the medical appointment. Electrocardiogram was normal, laboratory test results were within the reference range except low levels of red blood cells (RBC) indices. Echocardiography (ECHO) revealed circular separation of pericardium layers up to 3.1 mm with adhesions along the lateral wall and apex of the heart. The pericarditis was treated with nonsteroidal anti-inflammatory drug in combination with a proton pump inhibitor, which the patient stopped on his own initiative due to the onset of black stool after two days of taking these medications. In January 2015, owing to symptoms progression, the patient was admitted to the hospital with dyspnea, dry cough, and malaise. Physical examination was unremarkable. Laboratory findings showed a slight increase in acute phase reactants concentration (C-reactive protein (CRP) 13.9 mg/L, erythrocyte sedimentation rate (ESR) 24 mm/h) and iron deficiency (5 μmol/L). On the other hand, the results of the complete blood count and the biochemical panel were within the normal range. Remaining laboratory results are presented in Table 1. ECHO assessment demonstrated pericardial effusion up to 16.6 mm with the right atrium collapse (Figure 1). During the hospitalization, a computed tomography (CT) scan of the thorax detected bilateral soft tissue density nodules with 5 mm in diameter localized in the lower lobes and in the middle lobe of the lung along with mediastinal lymphadenomegaly. Pathohistological analysis of pulmonary nodules (PNs) ruled out malignancy, furthermore all performed tests indicative of *Mycobacterium tuberculosis* infection were negative. Characteristic pathohistological features regarding rheumatoid lung nodule were not present in taken samples. The patient was treated with colchicine and administration of this therapy led to a resolution of pericardial

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**Table 1.** Laboratory findings during hospitalization

| Parameter | Value | Reference range |
|---|---|---|
| CMV IgG<br>EBV IgG | 1/160<br>1/160 | Positive titer<br>Positive titer |
| C3 (g/L) | 1.717 | 0.9–1.7 |
| C4 (g/L) | 0.491 | 0.12–0.36 |
| ANA/AMA/ASMA/APA IgG<br>EMA IgA | negative | – |
| CA-125 (U/mL) | 42 | 0–21 |
| CA 19-9 (U/mL) | 2.9 | 0–34 |
| CA 72-4 (U/mL) | 3.4 | 0–6 |
| CEA (ng/mL) | 0.1 | 0–5.5 |
| NSE (ng/mL) | 2.7 | 0–17 |
| PSA (ng/mL) | 0.8 | 0–4.1 |
| AFP (ng/mL) | 1.5 | 0–7.08 |

CMV – cytomegalovirus; EBV – Epstein–Barr virus; IgG – immunoglobulin G; C3 – complement component 3; C4 – complement component 4; ANA – antinuclear antibodies; AMA – anti-mitochondrial antibody; ASMA – anti-smooth muscle antibody; APA – antiphospholipid antibody; EMA – anti-endomysial antibody; IgA – immunoglobulin A; CA-125 – cancer antigen 125; CA 19-9 – cancer antigen 19-9; CA 72-4 – cancer antigen 72-4; CEA – carcinoembryonic antigen; NSE – neuron-specific enolase; PSA – prostate-specific antigen; AFP – alpha fetoprotein

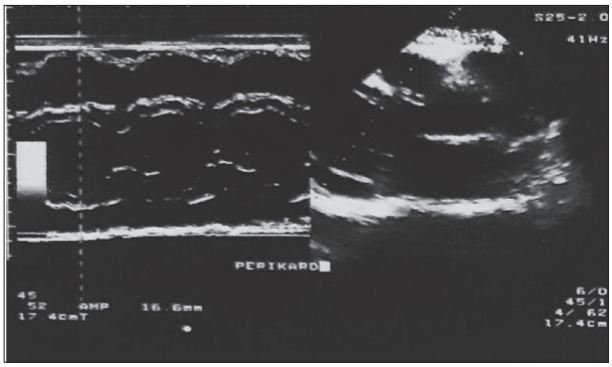


**Figure 1.** Echocardiogram showing pericardial effusion up to 16.6 mm, with right atrium collapse

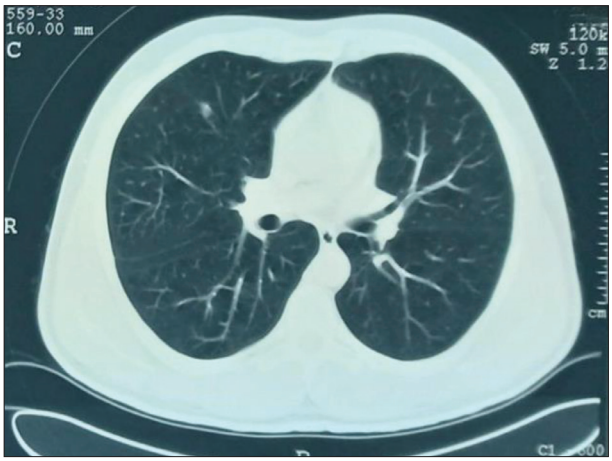


**Figure 2.** Computed tomography scan of the lung showing parenchymal nodule

effusion. A follow-up CT scan two months after discharge from the hospital revealed the regression of pulmonary changes. Several subpleural and parenchymal micronodules were present, of which the larger ones were up to 4 mm and 3 mm. No signs of enlarged lymph nodes in the mediastinum were observed. (Figure 2). Due to the reduction in the size of the lung nodules, bronchoscopy was not performed. Simultaneously, in March 2015, he was examined by a rheumatologist for the first time due to pain and swelling of the right wrist. These symptoms were not accompanied by morning stiffness. Upon medical examination, there was evidence of active arthritis of the right wrist. Results of a laboratory analysis indicated on the high ESR, CRP, slightly low levels of hemoglobin, and RBC indices as well as thrombocytosis. Immunoserological tests for systemic connective tissue diseases were positive for anti-cyclic citrullinated peptide (anti-CCP) antibody and anti-citrullinated protein antibody (ACPA) with a titer of 59.8 U/mL and 146.3 U/mL, respectively, while rheumatoid factor (RF), p antineutrophil cytoplasmic antibody (p ANCA) and c ANCA were within normal range. Plain radiography of both hands, wrists, and feet did not reveal any of the radiographic hallmarks of RA. Ultrasound of the soft tissues of the right wrist showed moderate synovial proliferation with a positive Doppler signal suggestive of acute arthritis accompanied with bone erosion at the distal ulna. Considering synovitis lasting more than six weeks, abnormal CRP and ESR, positive immunoserology, patient had a score of six points which met the American College of Rheumatology / European Alliance of Associations for Rheumatology 2010 diagnostic criteria for RA [2]. Treatment was initially started with hydroxychloroquine with a daily dose of 400 mg. Three months later, concomitant Methotrexate was added at a weekly dose of 15 mg and then increased to 20 mg (Disease Activity Score-28 (DAS28) – 3.86). Also, low doses of glucocorticoids were prescribed depending on disease activity. In a period from 2015 to 2020 disease activity estimated with DAS28 index was within the range of low disease activity. In July 2020, the patient had COVID-19 pneumonia presented with mild symptoms. Three months after this viral infection, he suffered from arthritis flare up (DAS28 – 5.74). Regarding the loss of efficiency of combination therapy with Methotrexate and glucocorticosteroid, an inhibitor of Janus kinase (JAK) – baricitinib was added in a daily dose of 4 mg in August 2021. Low disease activity was achieved after three months (DAS28 – 2.18). During the most recent visit, the patient did not have any signs of active synovitis and inflammatory markers were in the reference range (DAS28 – 2.52). Additionally, no adverse events were reported during a 20-month period of baricitinib administration.

The paper was approved by the Ethics Board of the Special hospital for rheumatic diseases Novi Sad and the patient gave written consent to publish all shown materials.

## DISCUSSION

RA is a systemic autoimmune disease that usually presents in the form of a symmetric polyarthritis. However, about half of patients with RA also have extra-articular manifestations that may occur at the very beginning or later in the course of the disease, but are rarely the presenting symptom of the disease [3]. In the group of cardiac involvement, pericarditis was observed to be the most common. Depending

on the method used for diagnostic assessment (ECHO or autopsy), pericarditis was found in about 30–50% of patients [4]. On the other hand, less than 10% of patients experience any symptoms during a lifetime. Symptomatic pericarditis is more frequent in male patients, in patients with high concentrations of RF, and rheumatoid nodules [5]. Bearing in mind the results of the previously mentioned study, it can be concluded that this manifestation of RA is not rare. On the other hand, after reviewing the literature, there were not many reports of pericarditis as the initial sign of RA as in the case of our patient.

The prevalence of PNs varies between 1% to 30% in patients with RA depending on the sophistication of the diagnostic method used. Therefore, the prevalence of PN detected by radiogram is less than 1%, CT scan between 10% and 22% and pathohistological analysis about 30% [6]. Risk factors for nodule development as well as its progression are older age, male sex, seropositivity, smoking, longer duration of the disease, certain drugs for the treatment of RA, and comorbidities [7]. PNs can be radiographically presented as single or multiple, with solid or cavitary structure, they are most often localized in the periphery in the subpleural region and they vary in diameter, which can range from a few millimeters to several centimeters [6]. Patients with PN are generally without symptoms and do not require treatment, however, due to the localization of these changes there is a risk of sustaining a pneumothorax, hydropneumothorax and bronchopleural fistula which are conditions seeking medical intervention [7]. In our patient presence of PN which preceded the articular symptoms was revealed incidentally on CT scan performed because of persistent pericarditis and it is a rare presenting feature of RA.

RA is characterized by a symmetrical polyarthritis, but in a small percentage of patients it is initially presented as monoarthritis, usually affecting the large joints such as hip and knee. Although monoarticular RA is uncommon, it usually progresses to a polyarticular form in a period of time, which was shown to be between three and five years [8]. In a cross-sectional study with a total of 400 patients included, only one patient had a monoarticular manifestation of disease [9]. Anti-CCP are a type of autoantibody with high diagnostic specificity for RA. Anti-CCP antibodies can be present in the blood years before the manifestation of disease [3]. The main difference between anti-CCP and ACPA is that anti-CCP is more specific to RA, while ACPA is a bit more sensitive and can be used to detect RA earlier. Anti-CCP is typically associated with more active cases of the disease, while ACPA could sometimes be found in milder cases. Our patient was tested positive for this type of antibodies which subsequently directed the diagnostic evaluation towards RA.

Infections are a risk factor for disease exacerbation in patients with inflammatory arthritis [10]. The panel of proinflammatory cytokines that lead to severe forms of lung damage is comparable to cytokine profile responsible for the pathogenesis of the inflammation of the synovium in RA. Therefore, it could be presumed that COVID-19 infection could provoke a disease flare in RA patients [11]. In our patient, the disease presented mainly in the form of oligoarthritis until the patient had pneumonia caused by severe acute respiratory syndrome coronavirus 2. After the infection recovery, he suffered from exacerbation of joint ailments which manifested as polyarthritis. Baricitinib modulates signaling pathway of various cytokines involved in inflammatory processes throughout inhibition of JAK type 1 and type 2. Yang et al. [12] showed that in a group of patients treated with baricitinib, at week 12, a statistically significant improvement in American College of Rheumatology 20% (ACR20) response was achieved compared to patients randomized to a placebo group. Furthermore, they reported that treatment benefit was noticed even after one week of treatment and was kept during the 52 weeks. Study assessing a short-term effectiveness and safety of baricitinib in patients with RA, demonstrated that the effectiveness of baricitinib was significantly superior in targeted disease-modifying antirheumatic drug (DMARD) naïve patients compared to patients who were previously treated with targeted DMARD. Although the period of 24 weeks is short for evaluation of long-term adverse events, in this study six patients out of 113 involved in the trial discontinued baricitinib because of adverse events [13]. Treatment of RA patients usually considers prolonged use of DMARDs, thus it is very important to have an insight on the long-term safety profile of the prescribed drug. Group of authors conducted the largest integrated safety analysis of baricitinib with mean duration of the treatment lasting 4.6 years and up to 9.3 years. Results showed that the safety profile of baricitinib was comparable with other JAK inhibitors and biological DMARDs [14]. Furthermore, this JAK inhibitor can be used for a long period of time without concern of an increased risk of side effects in patients with RA. Our patient achieved low disease activity after three months of administering baricitinib. During 20 months of using combination therapy no side effects occurred.

In conclusion, every patient with pericarditis of unknown etiology should be diagnostically evaluated in term of connective tissue disease including RA, because initial clinical presentation in some group of patients could lack characteristic joint inflammation.

**Conflict of interest:** None declared.

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## Атипична клиничка слика реуматоидног артритиса


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**САЖЕТАК**

**Увод** Реуматоидни артритис је системска аутоимуна болест са запаљењем зглобова као главним обележјем. Екстраартикуларне манифестације се јављају код скоро половине болесника и то или на почетку или у каснијем току болести. **Приказ болесника** Мушкарац стар 43 године жалио се на бол у грудима, сув кашаљ и умор. На основу ехокардиографског налаза постављена је дијагноза перикардитиса. Због погоршања респираторних симптома примљен је у болницу. Иницијалном дијагностичком обрадом верификоване су повишене концентрације реактаната акутне фазе, перикардни излив и билатерални нодуси плућа. Патохистолошком анализом пулмонарних нодуса искључени су малигнитет и туберкулоза. Болесник је лечен колхицином, чиме је постигнута регресија перикардног излива. Потом му је због артритиса десног ручног зглоба, високе седиментације еритроцита и Ц-реактивног протеина, позитивне имуносерологије и коштане ерозије на дисталном окрајку улне постављена дијагноза серопозитивног реуматоидног артритиса. Лечен је антималаријком, метотрексатом и глукокортикоидима све док није оболео од пнеумоније ковида 19, након чега долази до погоршања артритиса. Због секундарног губитка ефикасности комбиноване терапије метотрексатом и глукокортикоидом, додат је барицитиниб. Ниска активност болести је постигнута после три месеца, а током 20-месечне примене овог лека нису се јавила нежељена дејства.

**Закључак** Сваки болесник са перикардитисом непознате етиологије треба да буде дијагностички евалуиран у правцу болести везивног ткива укључујући реуматоидни артритис, зато што иницијална клиничка слика код одређене групе болесника може да буде без карактеристичног синовитиса.



**Кључне речи**: перикардитис; плућни нодус; реуматоидни артритис; пнеумонија ковида 19; акутизација; барицитиниб