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Case Report

Methotrexate toxicity complicating a case of rheumatoid arthritis associated Interstitial Lung Disease: Lessons to learn ☆,☆☆

H. Ikrou[a,*], M. Salek[b], S. Boustani[c], W. Bouissar[c], S. Wakrim[b], S. Abdala[a], H. Serhane[a]

[a] Pulmonology Department, CHR HASSAN II, CHU Souss-Massa, Laboratory LARISS, FMPA, UIZ - Agadir, Morocco
[b] Radiology Department, CHR HASSAN 2, CHU SOUSS MASSA, FMPA, Agadir, Morocco
[c] Internal Medicine Department, CHR HASSAN 2, CHU SOUSS MASSA, FMPA, Agadir, Morocco

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ABSTRACT

Rheumatoid arthritis (RA) is one of the most common types of autoimmune arthritis. It can also involve other organs, including vascular structures, and lungs which are affected in 60% to 80% of cases. Other complications may present as airway infections and drug related pulmonary toxicity. We present the case of 75-year-old male patient of North African decent that was hospitalized initially for chronic dyspnea associated with other systemic manifestations, and in whom we confirmed the diagnosis of Rheumatoid arthritis associated interstitial lung disease. The patient was treated with methotrexate (MTX) and later on, he developed a fatal case of methotrexate related pulmonary toxicity.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that primarily causes symmetric polyarthritis. There might also be some extra-articular involvement in various organs, but interstitial lung disease (ILD) is the most important co-morbidity [1]. It can manifest as an acute/subacute or chronic form. The most commonly used drug in the initial therapeutic management of rheumatoid arthritis is methotrexate, but in many cases, it can induce pulmonary toxicity, worsening the lung damage, and prognosis of the patient [2].

We describe the case of a 75-year-old male patient, initially admitted for respiratory exploration for chronic dyspnea which revealed a case of rheumatoid arthritis associated ILD, treated initially with methotrexate, who developed a severe case of drug-induced ILD.

☆ HI and SB were involved in the diagnosis and surveillance of the patient, analysis of the data and the literature search and wrote the manuscript. SW, SA and HS helped with the patient management, supervision of diagnosis and treatment of the patient and also revision of the manuscript. MS AND SW contributed to the diagnosis by interpretation of the radiological findings and preparation of the images. All the authors have read and approve the final version of the manuscript.

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* Corresponding author.
E-mail address: hanane.ikrou95@gmail.com (H. Ikrou).

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Our objective is to bring more attention to this paradoxical adverse event and how to manage similar cases.

Case presentation

This is a 75-year-old patient, a former welder by profession (exposure to welding fumes for over 50 years), a chronic smoker of 75 pack-years, and a cannabis user, followed up in the pulmonology department for chronic obstructive pulmonary disease (COPD) since October 2022.

The patient has had inflammatory arthralgia of small, medium, and large joints with deformation and lower back pain for the past year, without any other associated symptoms, particularly no hemoptysis, xerostomia xerophthalmia, or cutaneous signs. The symptomatology has been complicated for the past 3 months by the gradual onset of dry cough sometimes becoming productive of whitish expectorations and Mmrc stage 3 dyspnea, associated with significant asthenia, and weight loss of 10 kg over 3 months.

The clinical examination revealed a conscious patient, afebrile at 37.2°C, positive Campbell's sign, barrel chest; pleuropulmonary examination revealed blood oxygen levels at 91% in ambient air, respiratory rate of 26 cpm, bilateral Basi thoracic crackles, and no digital clubbing. Cardiovascular examination revealed tachycardia at 126 bpm, no murmur, and no signs of heart failure. The osteoarticular examination showed joint deformation predominantly in the small joints and wrists of both hands and pain on palpation of the lumbar spine.

The rest of the examination was unremarkable (mainly there was no lymphadenopathy, no hepatomegaly or splenomegaly).

An EKG showed irregular sinus rhythm with extrasystoles, spirometry showed FVC of 3.81L, FEV1 of 2.55, and FEV1/FVC ratio of 67%. Transthoracic echocardiography (TTE) showed segmental hypokinetic cardiomyopathy with normal systolic function, LVEF of 53%, and no pulmonary arterial hypertension (PAH).

Chest CT scan shows no pulmonary embolism, but there is an early diffuse interstitial pneumopathy on an emphysematous lung (Fig. 1), while the abdominal-pelvic CT scan reveals a thrombosed aneurysm in the right common femoral artery (Fig. 2), heterogeneous prostate, and a biliary cyst. We completed the exploration by doing an ultrasound to better categorize the aneurysm, which confirmed the thrombosed nature of the aneurysm (Fig. 3).

An accessory salivary gland biopsy revealed grade 4 sialadenitis consistent with Sjögren's syndrome.

Complete blood count shows a white blood cell count of 11,020/mm3 with neutrophils at 7050/mm3, lymphocytes at

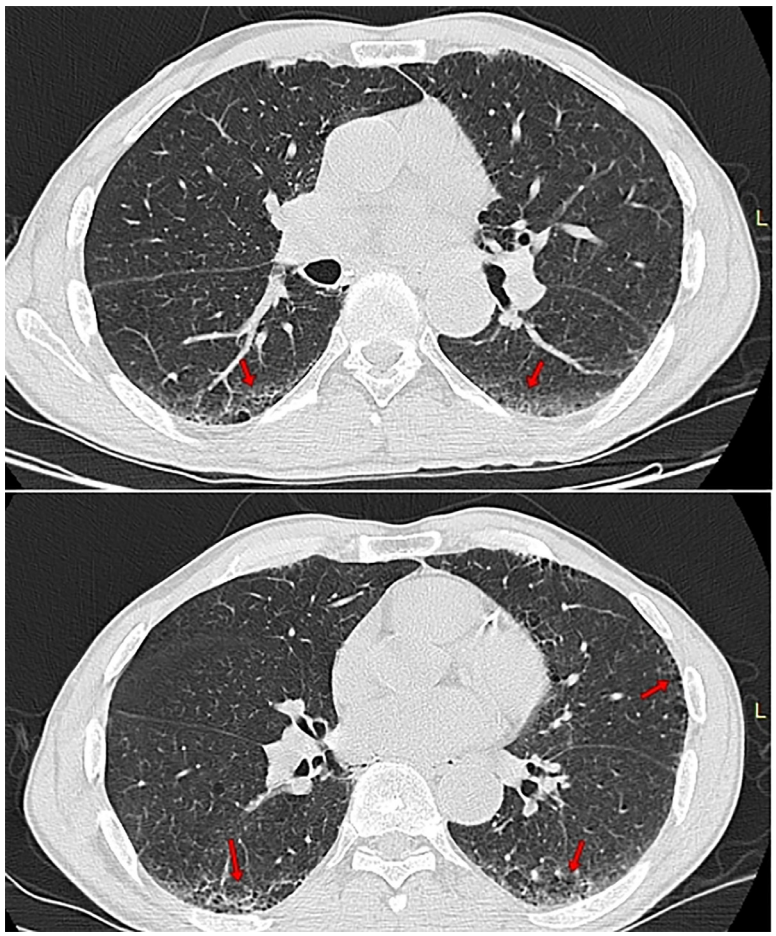

Fig. 1 – Initial RA-ILD lesions on the thoracic CT scan.

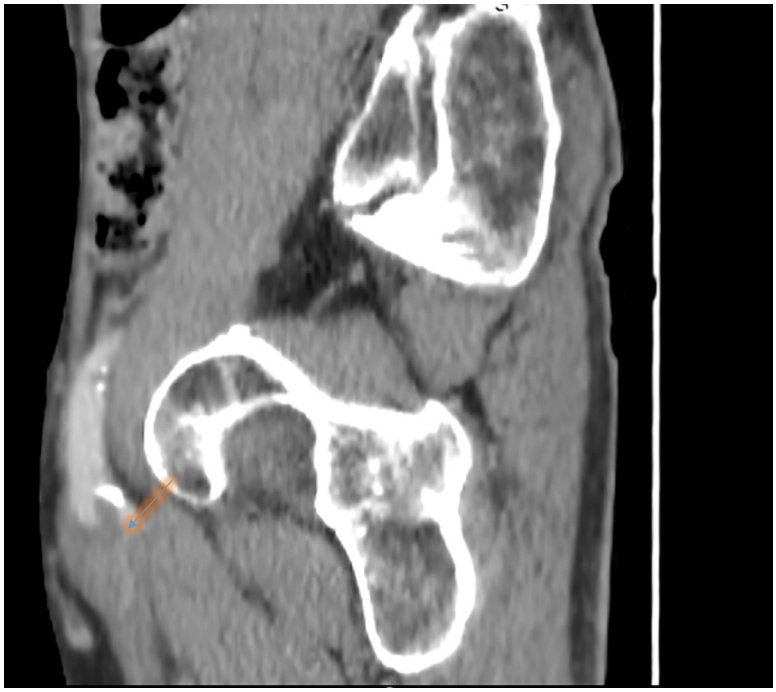

Fig. 2 – Thrombosed aneurysm of the femoral artery in the pelvic scan.

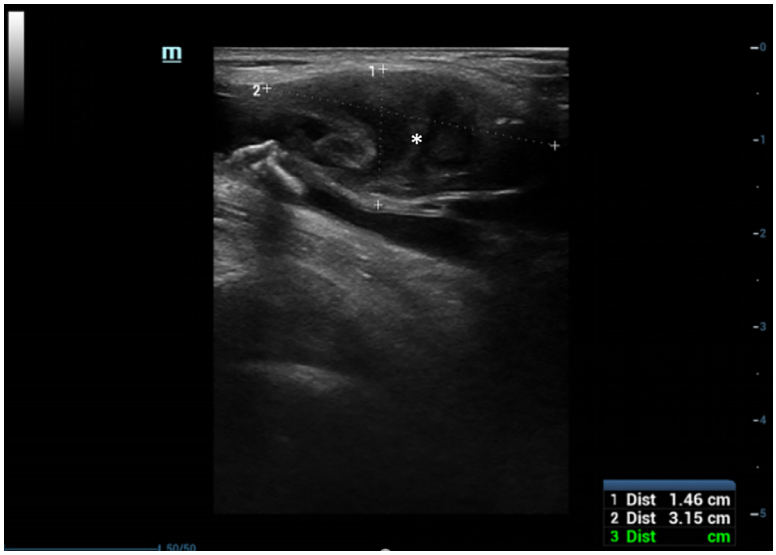

Fig. 3 – Thrombosed aneurysm image in the ultrasound.

3090/mm3, and eosinophils at 90/mm3. The hemoglobin level was 11.4 g/dL, and the platelet count was 273,000 per microliter. C-reactive protein (CRP) level was at 4.4 mg/L (normal range 6-12 mg/L), and erythrocyte sedimentation rate (ESR) was 50 mm/h in the first hour and 105 mm/h in the second hour. Hepatic and renal blood tests were normal. Anti-nuclear antibodies (ANA) test was negative, the Anti-cyclic citrullinated peptide antibodies level was elevated at 111.7 IU/mL (Negative if <17 IU/mL), so was the rheumatoid factor (RF) level at 104.94 IU/mL (Negative if <14 UI/mL). D-dimer level was 2103 ng/mL (positive if >500 ng/mL), Prostate-specific antigen (PSA) level was 0.98 ng/mL, Acid-fast bacilli (AFB) stain of sputum was negative, and HIV test was negative.

Finally, a treatment regimen of methotrexate 12.5 micrograms per week was initiated for 5 weeks before the patient was readmitted due to resting dyspnea accompanied by constrictive chest pain and progressive worsening confusion for the past month. All symptoms began one week after start-

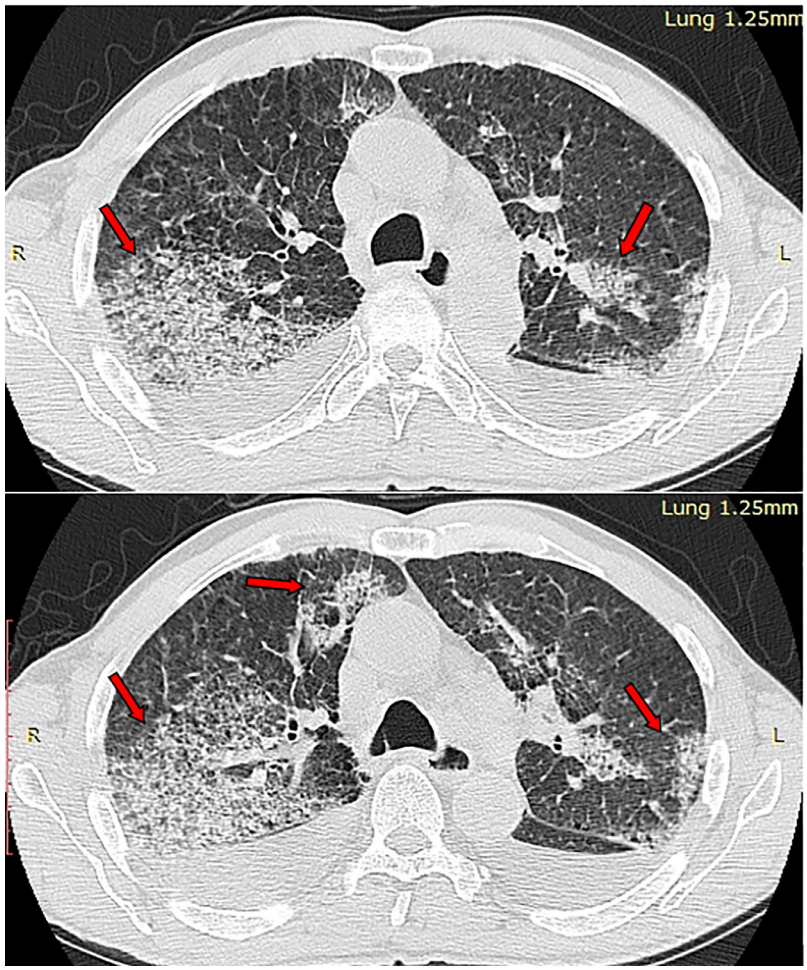

Fig. 4 – Thoracic CT scan showing a worsening of the pulmonary lesions.

Criteria
(1) Dyspnoea of acute onset
(2) Fever >38.0°C
(3) Tachypnoea >28/min and dry cough
(4) White blood cell count ⩽15.0 × 10^9/l with or without eosinophilia
(5) Negative blood and sputum cultures (mandatory)
(6) Radiological evidence of pulmonary infiltrates (interstitial or alveolar)
(7) Restrictive defect and decreased diffusion capacity on pulmonary function tests
(8) PO_2 at room air <7.5 kPa (55 mmHg)
(9) Histopathology: consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection

Fig. 5 – Diagnostic criteria proposed by Searles and al.

ing methotrexate treatment. On the clinical exam, the patient had polypnea at 33 cycles per minute; blood oxygen levels were low at 77% in ambient air, with bilateral diffuse crackles.

An emergency EKG was done without showing a significant difference from the first one. A thoracic CT scan showed the presence of multiple lesions including multiple dense nodular and patchy ground-glass opacities, predominantly in the central region, with more pronounced septal and nonseptal thickening in the upper, middle, culmen, and lingula lobes, Diffuse micro-nodular reticulation, Cystic lesions in the posterior basal and bilateral fissural regions, Diffuse peri-bronchial thickening. There was also bilateral pleural effusion (Fig. 4).

White blood cells were at 14,000/mm3, CRP was at 11 mg/L, and sputum cultures were negative. We put the patient off methotrexate and we started him on prednisolone 1 mg/kg/day with a slight improvement in blood oxygen levels but persistent dyspnea.

On the third day of admission, a control EKG showed a recent appearance of a bundle branch block. This led to us performing a TTE that showed acute heart failure with LVFE at 26% and pulmonary hypertension with a pulmonary artery pressure (PAP) of 74 mmHg. The patient passed away a few hours later due to acute cardiac and respiratory failure.

Discussion

Interstitial lung disease is a common extra-articular manifestation of rheumatoid arthritis. In addition to bronchiectasis, it

Major criteria

(1) Hypersensitivity pneumonitis by histopathology, without evidence of pathogenic organisms
(2) Radiologic evidence of pulmonary interstitial or alveolar infiltrates
(3) Blood (if febrile) and initial sputum (if produced) cultures negative for pathogenic organisms

Minor criteria

(1) Shortness of breath for <8 weeks
(2) Non-productive cough
(3) O_2 saturation ⩽90% on room air at the time of initial evaluation
(4) DLCO ⩽70% of that predicted for age
(5) White blood cells ⩽15 000 cells/mm^3

Fig. 6 – The modified diagnostic criteria proposed by Kremer and al.

can occur in up to 30% of cases [1]. Usually, it's diagnosed after clinical signs of respiratory involvement, but it can precede the articular lesions in 20% of the cases [3]. The male gender is more frequently associated with RA-ILD, as well as a history of smoking exceeding 25 years [1,3]. Similarly, our patient was a 75-year-old male, with a history of active smoking for more than 50 years.

Some studies have established that RF titers >90 IU/mL were significantly associated with incident ILD, unlike other markers that remained unassociated with incident ILD [4]. Moreover, serum positivity for anti-citrullinated protein/peptide antibodies (ACPA) is also noted as one of the predictors of ILDs and their severity in RA [1,3]. Our patient had an ACPA antibody level at 111.7 IU/mL, and the RF level was at 104.94 IU/mL.

Usual interstitial pneumonia (UIP) on HRCT is the most typical radiological pattern of RA-ILD, especially in older male patients with a history of smoking. It is also related to a worse prognosis and lower survival rates [1,2].

Other complications of RA include rheumatoid vasculitis, which can involve small and medium-sized vessels, resulting in aneurysms and other vascular manifestations. Its development is associated with the male gender, extra-articular features, and the presence of severe RA requiring intensive therapy [5]. Our patient had a chronic thrombosed aneurysm in the right common femoral artery.

Methotrexate (MTX) is one of the most effective medications available to treat RA, even if it has been associated with pulmonary toxicity and ILD, Thus, some authors suggest that RA patients with subclinical ILD and no risk factors for drug-related pneumonitis or acute exacerbation of ILD (e.g., undernutrition, chronic renal failure, reduced pulmonary function, or radiological honeycombing) should be treated with methotrexate as a first option [2]. Additionally, some studies suggest that MTX use is not associated with an increased risk of RA-ILD in patients with RA and that ILD was detected later in MTX-treated patients [6].

Methotrexate-associated pulmonary toxicity incidence is quite variable, occurring in between 2% and 33%. The pathogenesis is still unclear, but pulmonary toxicity occurs in patients treated with both high- and low-dose methotrexate [7].

Radiological aspects of MTX pneumonitis are similar to hypersensitivity pneumonitis, such as ground glass patchy opacities, with or without areas of consolidation [7].

Many diagnostic criteria have been suggested before, but MTX pulmonary toxicity remains a diagnosis of exclusion [7]. One of the most popular criteria was proposed by Searles and al [8,9] (Fig. 5), the diagnosis is definite if there are 6 out of 9 criteria; probable diagnosis: 5 out of 9 criteria; possible diagnosis: 4 out of 9 criteria.

Later on, the criteria were modified by Kremer et al [9,10] (Fig. 6). The diagnosis is definite when major criterion number 1 OR major criteria numbers 2 and 3 are present, along with at least three out of five minor criteria. Diagnosis is probable when major criteria numbers 2 and 3 are present in combination with at least 2 minor criteria.

In our case, the patient had significant multiple dense nodular and patchy ground-glass opacities, predominantly in the central region, with more pronounced septal and nonseptal thickening in the multiple lobes, and diffuse micro-nodular reticulation. He also had negative sputum cultures, dyspnea, dry cough, low oxygen levels at 77% on ambient air, and a white blood cell count at 14000/mm3. According to the previously mentioned criteria, our patient had definite MTX pulmonary toxicity.

Although many scholars have suggested that patients with pre-existing pulmonary involvement are susceptible to developing MTX pneumonitis [9,11,12], it is not recommended to monitor the respiratory function of these patients. Instead, they should be educated on the risks related to MTX toxicity and should be investigated if there is an appearance or exacerbation of respiratory symptoms [13].

Conclusion

The development of methotrexate-related ILD is a paradoxical adverse event. It is uncommon but patients should be warned about this rare but serious complication.

Patient consent

I confirm in my own words that there is no legal conflict, the consent was obtained and declare that the family was informed of all the written information related to the patient's medical case, and accept it to be published.

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