

Rheumatoid arthritis overlapping systemic sclerosis with interstitial lung disease

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ABSTRACT

Lung disease is the second most frequent extra articular manifestation in rheumatoid arthritis (RA) patients.

It can be present in up to 80% RA cases and represents a major cause of morbidity and mortality.

One of the most common types of lung involvement in RA patients is the interstitial lung disease (ILD). Computed tomography studies show evidence of ILD in a large proportion of patients with RA (over 50% in some studies) and it can be clinically symptomatic in 5% of cases. The CT aspect classifies four forms of ILD, listed in order of frequency: usual interstitial pneumonia (UIP) - the most common form, non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP) and diffuse alveolar damage (DAD) which is the least common form. We present a long-standing case of rheumatoid arthritis overlapping systemic sclerosis with interstitial lung disease.

Keywords: rheumatoid arthritis, interstitial lung disease, usual interstitial pneumonia

INTRODUCTION

Considering the frequency of lung disease in rheumatoid arthritis (RA) and its related high morbidity and mortality, screening in selected patients is imperatively necessary. One common form of lung involvement is the interstitial lung disease, documented by high-resolution computed tomography studies. The most common form of interstitial lung disease associated with RA is usual interstitial pneumonia, which has the same radiological and histological pattern as the idiopathic pulmonary fibrosis, also in terms of the poorest outcome form. We present a long-standing case of rheumatoid arthritis overlapping systemic sclerosis with interstitial lung disease with a usual interstitial pneumonia pattern.

CASE PRESENTATION

We present the case of a 71-year-old female patient known with rheumatoid factor positive, ACPA positive, erosive rheumatoid arthritis who was ad-

mitted in the Clinical Center of Rheumatic Diseases “Dr. Ion Stoia” for generalized inflammatory polyarthralgia.

At the time of presentation, the patient was on conventional synthetic disease modifying drugs (csDMARDs) and low dose steroids (hydroxychloroquine 400 mg daily, methylprednisolone 4mg daily) and the DAS 28-CRP score at admission indicated a high disease activity (DAS 28-CRP = 5.4).

Previously, the patient underwent biological therapy with Tocilizumab 162 mg SC weekly with a good outcome, but despite of the improvement of the articular disease, she developed left calcaneal ulceration. This event was considered an adverse reaction to the biological treatment which was discontinued one month before presentation. The patient is also known with type II diabetes with secondary vascular and neuropathic damage.

At admission, the patient had productive mucosal cough and dyspnea with diffuse subcrepitan rales on both lung fields with a spontaneous oxygen saturation of approximately 92 - 95%. Her skin had multiple ulcers of the toes and she experienced in-

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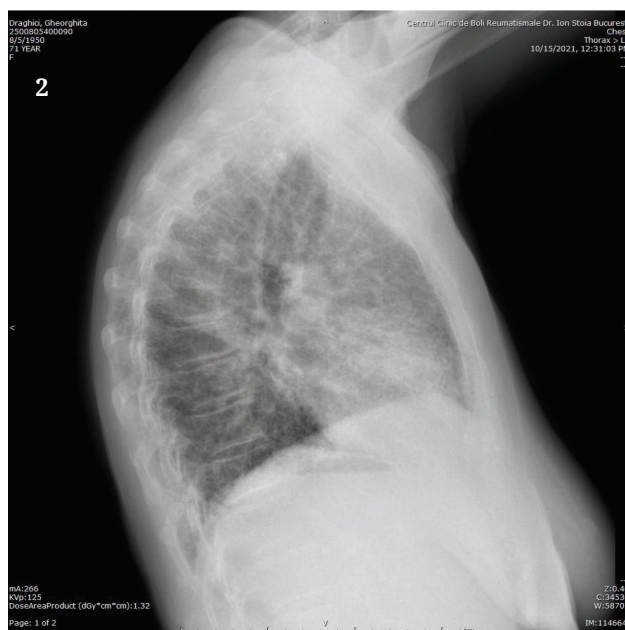
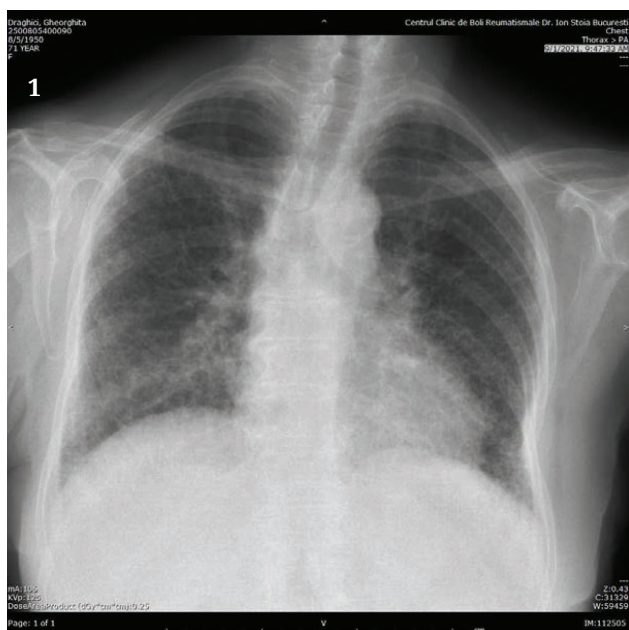


FIGURE 1 and FIGURE 2. Plain chest X-ray: diffuse interstitial lung fibrosis – “honeycomb” appearance

termittent Raynaud’s phenomenon of the extremities.

Her blood work showed normochromic, normocytic anemia, thrombocytosis, leukocytosis with neutrophilia and lymphopenia and an intense inflammatory syndrome with an ESR of 86 mm/h and a CRP of 127.12 mg/dl. Routine pulmonary radiological examination (Figures 1 and 2) revealed diffuse interstitial fibrosis with a reticulo-areolar appearance (“honeycomb”) on both lung areas.

During hospitalization, the patient’s expiratory dyspnea worsened and her oxygen saturation in the atmospheric air dropped down to 84%; several causes for an acute cause of respiratory failure were discussed. The patient’s ECG was stationary, the PCR SARS-CoV-2 test was negative, the D-dimers level was two times higher the upper limit of the normal value and there was a significant improvement in the inflammatory syndrome under glucocorticoid iv pulse therapy with 125 mg of Methylprednisolone for five days.

An emergency contrast HR-CT examination was performed and excluded a pulmonary blood clot embolism, instead it showed a predominantly peripheral, bilateral pulmonary interstitial changes, with the appearance of “honeycomb”; the radiologist’s interpretation indicated a moderate to severe form of pulmonary fibrosis with the appearance of “usual interstitial pneumonia” (UIP). (Figures 3, 4).

The clinical presence of Raynaud’s phenomenon and the presence of digital ulcerations with a capillaroscopic pattern of early scleroderma lead to the determination of systemic sclerosis specific antibody panel, which was positive for anti-fibrillar collagen antibodies, anti-NOR90 antibodies, and anti-Th/To antibodies and anti-Ku antibodies.

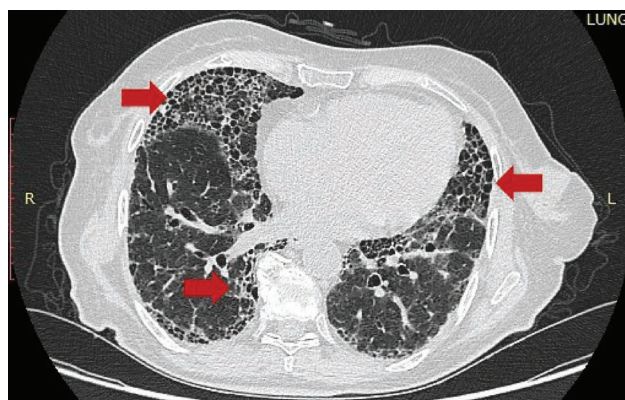


FIGURE 3. High-resolution pulmonary CT with fine cups - honeycomb pattern with bilateral basal subpleural disposition (indicated by red arrows), thickened septa, classified as a moderate to severe form of pulmonary fibrosis with the appearance of “usual interstitial pneumonia” (UIP)

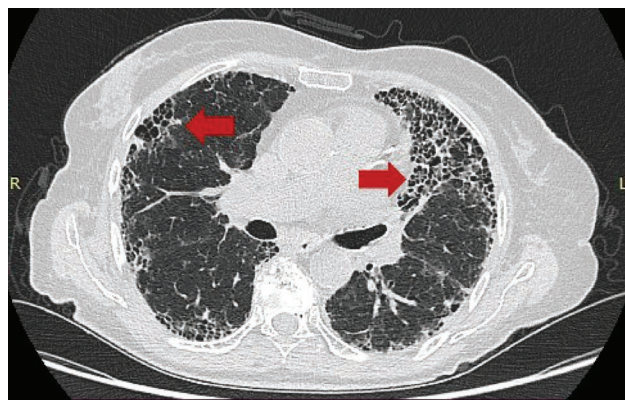


FIGURE 4. High-resolution pulmonary CT with fine cups - honeycomb pattern with bilateral basal subpleural disposition (indicated by red arrows), thickened septa, classified as a moderate to severe form of pulmonary fibrosis with the appearance of “usual interstitial pneumonia” (UIP)

The patient's disease was reclassified as RF positive, ACPA positive rheumatoid arthritis with interstitial lung disease (UIP pattern) overlapping systemic sclerosis (limited cutaneous form).

After healing of calcaneal ulceration, a switch of biological treatment to Abatacept 125 mg SC weekly was considered. Despite the indication for Nintedanib treatment for the lung disease, this drug was not available as a fully reimbursed drug by the national healthcare system, at the time of presentation. The patient was discharged with the recommendation of oxygen therapy at home with pulmonology and rheumatology follow up.

DISCUSSION

Lung disease is a frequent RA manifestation, the second most common. It can involve all of the lung compartments and needs to be carefully screened and monitored due to its high morbidity and mortality [1].

One form of lung damage in RA is the interstitial lung disease (ILD). Computed tomography studies show evidence of ILD in a large proportion of patients with RA (over 50% in some studies). Usually the lung damage is not widespread enough to cause respiratory symptoms and only 5% of cases are clinically symptomatic. The CT aspect classifies four forms of ILD, listed in order of frequency: usual interstitial pneumonia (UIP) - the most common form, non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP) and diffuse alveolar damage (DAD) which is the least common form.

Potential risk factors for the occurrence of ILD in patients with RA are smoking, rheumatoid nodules, old age occurrence, FR and ACPA seropositivity, and male sex.

ILD usually starts several years after the diagnosis of RA, but a quarter of patients may have interstitial lung disease at diagnosis or even before joint damage. Lung damage in RA is the second most common cause of premature death in these patients after cardiovascular events. Recent studies are relatively encouraging in terms of treatment, which potentially slows down or even stops the progression of ILD in RA, such as mycophenolate mofetil, rituximab, and abatacept [2].

Usual interstitial pneumonia (UIP) has no specific radiologic appearance; it may show decreased lung volume, reticulation, and more frequently, involvement of the lower lobes necessitating the use of lateral incidence X ray scans.

Regarding the CT aspect, UIP presents specific diagnostic criteria with a positive predictive value between 70-100%. Specific aspects include "honeycombs", reticular opacity, traction bronchiectasis, matte glass opacity, architecture distortion and loss

of lobar volume. Recent data even suggests specific issues that may help differentiate between UIP secondary to connective tissue disease and idiopathic pulmonary fibrosis. It is also important to note that there are two sets of CT diagnostic criteria for the 2018 UIP pattern [3].

ILD is commonly found in systemic sclerosis (SS), being included in the latest ACR/EULAR classification criteria in 2013, along with pulmonary hypertension. ILD-type pulmonary manifestation is usually determined during the course of the disease, but may be its first manifestation. Risk factors for ILD progression in patients with SS include diffuse skin involvement, African American ethnicity, older age at diagnosis, shorter duration of disease, presence of anti-SCL 70 antibodies, and/or absence of anti-centromere antibodies. Other incriminated autoantibodies are anti-fibrillarin, anti Th/To, anti PM Scl, anti U1RNP and anti U11/U12 antibodies. The presence of this risk factors is not a rule for ILD, as it can also occur in limited SS forms and active screening is very important because patients may be asymptomatic. The most common radiological form of interstitial lung disease in SS is non-specific interstitial pneumonia (NSIP). It is also the most common histopathological form, but the biopsy is performed only in exceptional cases such as atypical CT pattern, for differential diagnosis, or when looking for complications like neoplastic lesions [4].

The idiopathic interstitial pneumonia prognostic can be assessed using HRCT and histopathological analysis [5,6]. It has been shown that idiopathic pulmonary fibrosis has a usual interstitial pneumonia pattern described on radiological and histopathological findings, which is associated with a poor outcome (6-8), but at the moment it is unknown if the prognostic for RA-ILD patients is the same as for IPF patients. The specialty literature has also shown that RA-ILD has a higher incidence of UIP pattern, as compared to other forms of connective tissue disease-related ILD (SS, Sjogren's disease, UCTD, poly/dermatomyositis), in which the nonspecific interstitial pneumonia (NSIP) is more common [9,10].

The interstitial lung disease treatment decision should mainly take into account the severity of lung involvement. The disease progression can be assessed through clinical, functional and imaging studies. When choosing the most adequate therapy, we should also consider other individual factors such as the patient's age, associated disease and also the ILD pattern. At the moment there are no trials or treatment protocols to guide decision making.

Treatment options for RA-ILD include immunomodulating agents (corticosteroids, mycophenolate, cyclophosphamide), biologic agents (rituximab, abatacept) and antifibrotic medication (nintedanib).

Corticosteroid therapy alone or in combination with other immunosuppressive medication is the most common treatment option in RA-ILD because it can lead to clinical and/or imaging improvement. Different studies showed that the use of glucocorticoids improved or stabilized almost 50% of RA-ILD cases [11,12].

The use of cyclophosphamide and mycophenolate mofetil is based on retrospective and uncontrolled studies and on extrapolating experience from systemic sclerosis lung disease treatment [13].

The antifibrotic therapy is gaining interest in treating progressive fibrotic RA-ILD due to the similarities between IPF and RA-related UIP. Outcomes on a post-hoc analysis of the INBUILD trial showed that autoimmune-ILD patients treated with nintedanib presented improvement, although it is not known how many patients had RA-ILD [14]. Another study demonstrated that nintedanib ameliorated the FVC by about 50% in a heterogeneous group of PF-ILD patients with UIP pattern, which is why it is considered a treatment option for PF-ILD regardless of the underlying disease [15].

Nintedanib's summary of product characteristics states that this medication is recommended for idiopathic pulmonary fibrosis, other chronic fibrosing

interstitial lung diseases with a progressive phenotype and systemic sclerosis associated interstitial lung disease.

CONCLUSION

Usual interstitial pneumonia is the most frequent pattern of ILD found in RA, that unfortunately also has the worst prognostic. UIP does not respond to the usual DMARD treatment that is so effective for articular or other extraarticular manifestations of RA. It is challenging to manage the interstitial lung disease in RA, because currently there are no randomized controlled trials and we do not dispose of a clinical management guide. The effectiveness of recently identified therapeutic agents is based on observational or uncontrolled open studies, or extrapolated from other connective tissue diseases, like systemic sclerosis, and therefore inadequate to establish definite recommendations for management.

Conflict of interest statement

We undersign, certificate that we do not have any financial or personal relationships that might bias the content of this work.

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