Interstitial lung disease as first clinical manifestation within the antisynthetase syndrome – dermatomyositis

Pneumopatie interstițială difuză ca primă manifestare clinică în cadrul sindromului antisintetază - dermatomiozită

Abstract

Diffuse interstitial pneumopathies within the diseases of the connective tissue are often a diagnosis challenge, sometimes being the initial or dominant manifestation of the underlying autoimmune disease. The case of a young man shall be presented with relatively quick dyspnoea which has appeared under the conditions of an efficient physical status and without any notable pathological history. The cause of the dyspnoea is found to be a interstitial lung disease with radiological and histopathological pattern of non-specific interstitial pneumonia. The disease screening system discovers Ac anti Ro-52 which commits research in the direction of an autoimmune disease, confirmed by highlighting Ac anti PL-7 as being an antisynthetase syndrome. Subgroup of idiopathic inflammatory myopathies, the antisynthetase syndrome is a rare chronic autoimmune disease, which is characterised by the presence of antibodies directed against aminoacyl-t-RNA-synthetases (family of intracytoplasmic enzymes with a vital role in the protein synthesis). Shortly after specifying the relevant immunological status, the consistent clinical expression with dermatomyositis is also configured. The treatment is commenced with systemic corticoid and azathioprine; despite the treatment we are witnessing a slowly progressive clinical and functional deterioration.
Keywords: *interstitial lung disease, antisynthetase syndrome*

Rezumat

Pneumopatiile interstițiale difuze din cadrul bolilor de țesut conjunctiv reprezintă adesea o provocare diagnostică, putând fi manifestarea inițială sau dominantă a bolii autoimune subiacente. Se prezintă cazul unui tânăr cu dispnee cu instalare relativ rapidă aparută în condițiile unui status fizic performant și fără antecedente patologice notabile. Se depistează ca și cauză a dispneei o pneumopatie interstițială difuză cu pattern radiologic și histopatologic de pneumopatie interstițială nespecifică. Screeningul bolilor de sistem descoperă Ac anti Ro-52 care angajază cercetările în direcția unei boli autoimune, confirmate prin evidențierea Ac anti PL-7 a fi un sindrom antisintetază. Subgrup al miopatiilor inflamatorii idiopatice, sindromul antisintetază este o o boală autoimună cronică rară, caracterizată de prezența anticorpilor directionați împotriva aminoacil-t-ARN-sintetazelor (familie de enzime intracitoplasmatice cu rol vital în sinteza proteică). În scurt timp după precizarea statusului imunologic relevant se configurează și expresia clinică consistentă cu o dermatomiozită. Se escaladează tratamentul cu corticoid sistemic și azatioprină, în pofida căruia, asistăm la o deteriorare clinico-funcțională lent progresivă.
Cuvinte-cheie: *pneumopatie interstițială difuză, sindrom antisintetază*

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Introduction

The connective tissue diseases (CTD) represent a heterogeneous group of immune mediated inflammatory diseases which often involve the respiratory system in varied degrees of severity, from non-progressive forms, clinically insignificant, up to the devastating potential of the interstitial damage.

Interstitial lung disease (ILD) is to be found in the whole spectrum of CTD. The frequency, clinical presentation, prognosis and response to therapy vary according to the type of interstitial injury (usual interstitial pneumonia, non-specific interstitial pneumonia, organizing pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis interstitial lung disease, diffuse *alveolar lesions* or lymphocytic interstitial pneumonia) and underlying CTD. The damage of the pulmonary interstitium may be the first and only clinical manifestation, the detection of the occult collagenases being optimized through multidisciplinary assessment.

Case presentation

We shall present the case of a 37 years old man who arrived with progressive exercise dyspnoea developed in the last 6 months (from 10 swimming pool laps to MRC dyspnoea = 3). The patient is an ex-smoker for 7 years, with a smoking history of 10 packs per year. There is no history of drug consumption, occupational or environmental exposure to medicinal products.

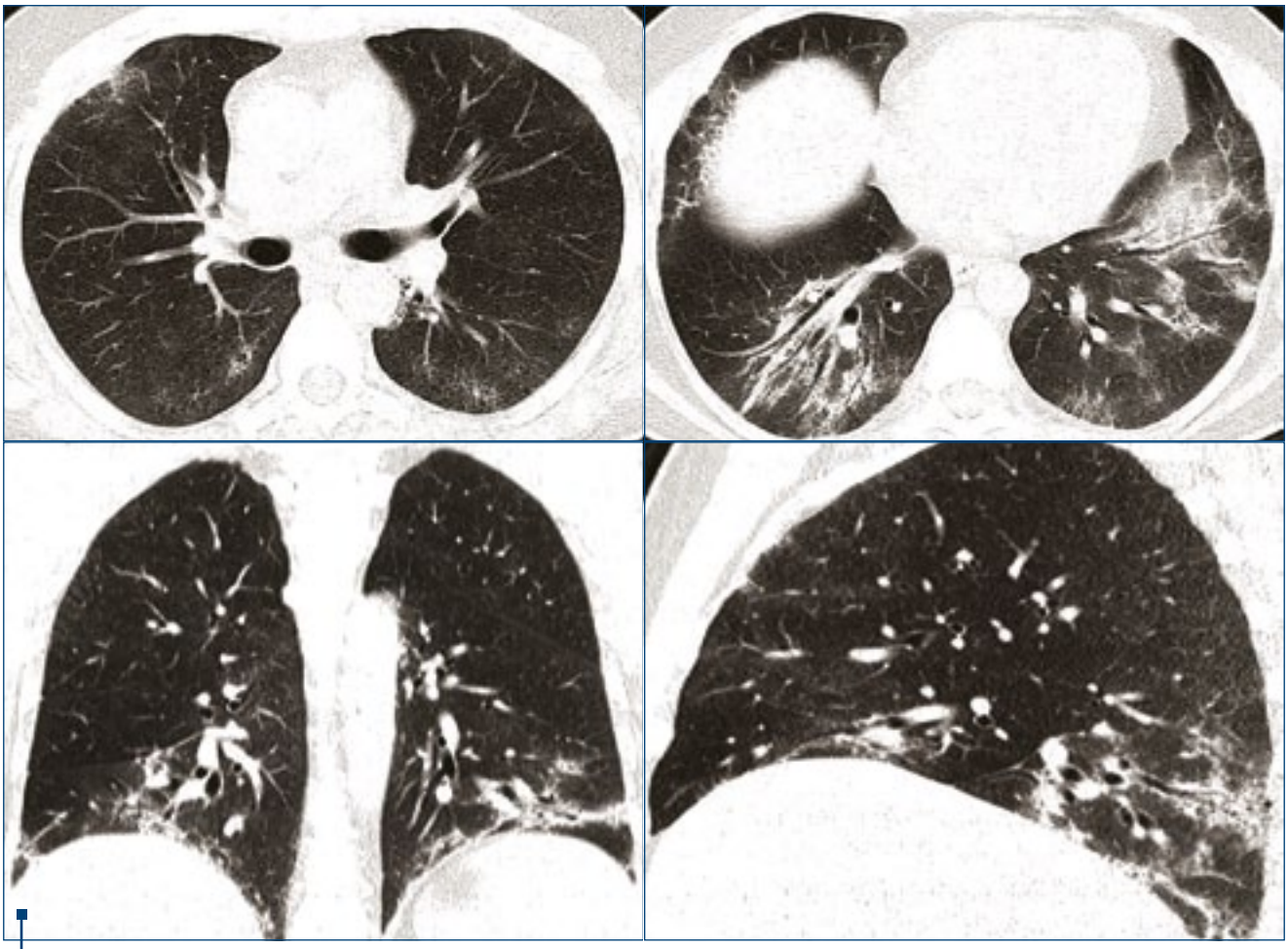

Figure 1. *High resolution CT scan of the lungs suggestive of NSIP pattern*

The physical examination of the lungs highlighted discrete basal bilateral crepitant rales in velcro, without digital clubbing or cyanosis.

Biologically: Hb = 13.7 g/dl; serum creatinine = 0.8 mg/dl; ESR = 2 mm at 1h; CRP = 2 mg/l; fibrinogen = 2.6 mg/l; CPK, LDH, STGO, STGP within normal limits.

The cardiac evaluation (echocardiography, right catheterism) has revealed patent foramen ovale without important functional implications, normal ejection fraction (EF = 60%) and the absence of pulmonary hypertension.

Initial pulmonary investigations revealed a severe restrictive ventilatory dysfunction (FVC = 2.0 l (42.6%), FEV1 = 1.7 l (43.7%), FEV1/FVC = 85.1%) and a severe decrease of the gaseous transfer through the alveolo-capillary membrane (DLCO = 31.3%).

The high resolution computed tomography examination (HRCT) revealed ground-glass opacities with apico-basal gradient and condensing processes associated with traction bronchiectasis with bilateral basal distribution, a suggestive aspect for a interstitial lung disease (ILD) of the non-specific interstitial pneumonia type (NSIP) (Figure 1).

The non-specific imaging appearance, without a clinical explanation, required the further diagnosis evaluation; the pulmonary biopsy obtained through video-assisted thoracoscopy confirming the radiologic appearance: high density inflammatory infiltrate, maintained pulmonary architecture, without any honeycomb modifications or fibroblastic foci: elements for NSIP histological pattern (Figure 2).

So, we are faced with a patient with clinical and functional data for a ILD, confirmed by the NSIP radiological and histopathological appearance. The main shaped form up to this moment, without other clinical manifestations, being the idiopathic NSIP. Other frequently manifested conditions with this form of ILD are the connective tissue diseases (CTD) and hypersensitivity pneumonitis (HP).

The serological evaluation for CTD and HP included a panel of respiratory allergens (Specific IgE Micropolyspora faeni, Thermoactinomyces vulgaris, Aspergillus fumigatus) - negative, the rheumatoid factor (RF) - negative, anti-cyclic citrullinated peptides (anti-CCP) antibodies - negative and anti-nuclear antibodies screening (Ac anti-nRNP/Sm, Sm, SS-A, Ro52, SS-B, Scl-70, PM/Scl, Jo-1, CENP B, PCNA, ds DNA, nucleosomes, histones, P-ribosomal protein, AMA-M2) which highlighted Positive ***Ac anti-Ro52.***

The presence of Ac anti-Ro52 has clinical relevance in a variety of autoimmune diseases. A significant asso-

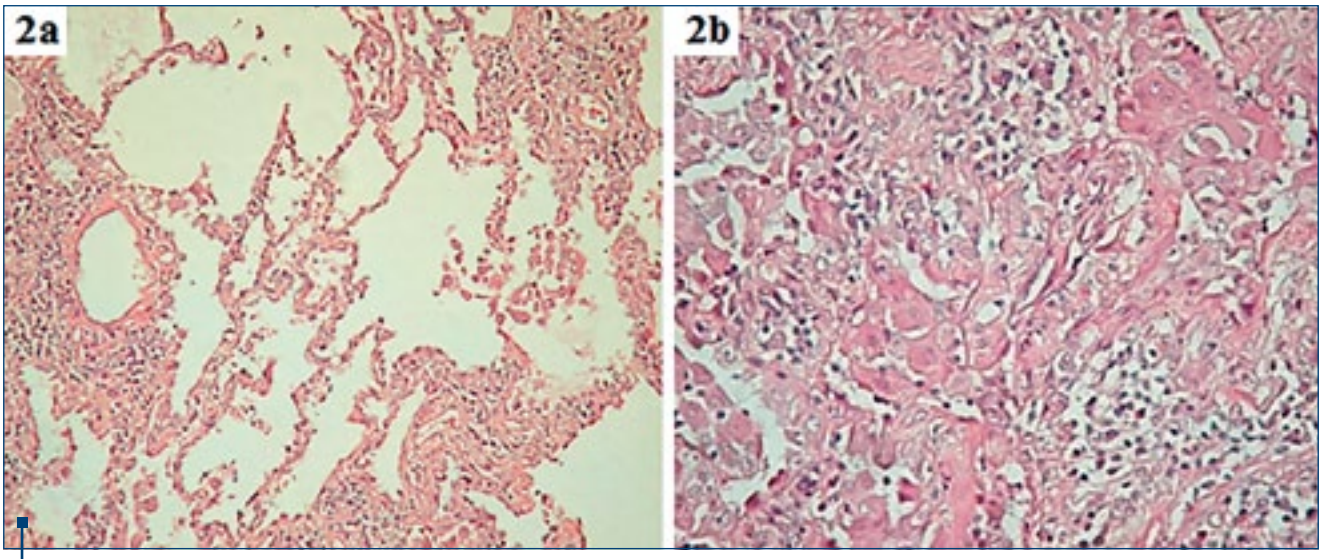

Figure 2. *Alveoli of different forms and sizes, with modified architecture; build-up of collagen at the level of the interalveolar septum (figure 2a, haematoxylin-eosin magnification, x100). The presence of collagen fibres organised in heterogeneous beams; focal inflammatory infiltrate, with high density, predominantly composed of lymphocytes and plasmocytes (figure 2b, haematoxylin-eosin, magnification x400).*

Table 1 Pulmonary functional scans

Date	FVC	FEV1	FEV1/FVC	DLCO
23/03/2012	2.00 l (42.6%)	1.70 l (43.7%)	85.1%	31.3%
13/06/2012	1.86 l (39.9%)	1.58 l (40.9%)	84.8%	35.4%
26/03/2013	1.77l (37.9%)	1.51 l (39.1%)	86.6%	39.3%

ciation has been described between the isolated reactivity of Ac anti-Ro52 and myositis, this being the most common antibody detected in polymyositis and antisynthetase syndrome.[1] The serologic evaluation and the exploration of the antibodies specific to myositis (Ac anti-Mi-2, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52) has expanded on this consideration, highlighting ***positive Ac anti-PL-7.***

A treatment with prednisone (1 mg/kg/day) and azathioprine (100 mg/day) has been chosen, the combination of corticosteroid and immunosuppressive agent being reported as more efficient than corticosteroid monotherapy[2] for idiopathic NSIP as well as for the antisynthetase syndrome.

12 months after initial admission to hospital, the patient develops ***muscle weakness, myalgia and muscle sensitivity to touch, polyarthralgia and erythema at the level of extension surfaces of the metacarpophalangeal and interphalangeal joints (Gotron tubers***), suggestive manifestations for dermatomyositis. The pulmonary evaluation highlighted a functional decline, but with a degree of improvement of the gaseous transfer through the alveolar-capillary membrane (table 1). Lung transplant has been discussed with the patient as a potential therapeutic option.

Discussions

The patient under discussion presented with clinical and functional elements for interstitial pulmonary damage, confirmed by the radiologic and histopathological appearance of non-specific interstitial pneumonia (NSIP). The results of the serological tests for the screening of the system diseases suggested the diagnosis of NSIP secondary to the antisynthetase syndrome due to the presence of specific antibodies (AC antisynthetase PL-7 positive).

It should be noted that there are three ways of discovering the pulmonary fibrosis in the context of connective tissue diseases: a) ILD as a first clinical manifestation of a connective disease; b) the already known connective disease which is also accompanied by a ILD; c) ILD and connective disease pathogenically independent, with parallel evolution. For this reason the evaluation shall be performed in dynamics, for both the connective disease and the ILD, because the clinical development may occur after months or years of the acknowledgement of serological or radiological alterations (in the given case, 12 months after the fibrosis diagnosis).

Idiopathic inflammatory myopathies (IIM) include a group of autoimmune muscle inflammatory

conditions, mainly represented by polymyositis (PM), dermatomyositis (DM) and antisynthetase syndrome (S-AS).

Interstitial lung disease (ILD) is frequently encountered within IIM, 35%-40% of patients diagnosed with PM/DM developing ILD during the evolution of the disease[3]. More than 75% of patients with antisynthetase antibodies develop ILD and within S-AS, ILD is frequently the dominant manifestation.[4] Within the IIM there have been reports of multiple histological patterns of pulmonary interstitial damage, including non-specific interstitial pneumonia (NSIP) (most frequently), usual interstitial pneumonia (UIP), organising pneumonia (OP), lymphocytic interstitial pneumonia (LIP) and diffuse alveolar damage (DAD).[5]

The patients with classical manifestations for antisynthetase syndrome clinically reveal two or more associations of myositis with ILD, articulatory damage, fever or Raynaud phenomena; there is a subset of patients (55%)[2] to whom the début of the disease is represented by pulmonary interstitial damage in the absence of other extra-pulmonary manifestations. Our patient did not show clinical enzymatic manifestations of myositic type but in the absence of a biopsy, a myositis with subclinical evolution may not be excluded.

On the other hand, if we take a look at the clinical aspects of patients with idiopathic NSIP, we shall observe numerous elements of system diseases (40% show positive antinuclear antibodies, almost a quarter show a positive rheumatoid factor, 14% articulatory manifestations, 8% Raynaud phenomena, 7% myalgia)[6], epiphenomena which hinder the diagnosis of idiopathic disease.

For this reason, at the time of the initial evaluation, we have considered the idiopathic NSIP diagnosis as well as the possibility of facing an ILD as first manifestation of a connective tissue disease (antisynthetase syndrome respectively).

The association of ILD-IIM is characterised by a reserved prognosis, the presence of the pulmonary interstitial damage contributing to a mortality excess of 40%. The optimal treatment of ILD has not been established yet for patients with antisynthetase syndrome. Corticosteroids (CS) in large doses represent the first therapeutic indication. The association of immunosuppressive medication (azathioprine, cyclophosphamide, cyclosporine) is required in non-responsive cases.[8] Recent studies have reported the efficiency of Rituximab for patients with refractory interstitial damage.[9]

It is stated that the diagnosis of idiopathic pulmonary fibrosis and especially ILD-CTD shall be established following a consensus as a result of multidisciplinary discussions. Along with the presence of the pneumologist-radiologist-histopathologist triad, depending on the actual situation, the collaboration with the rheumatologist, cardiologist (current case), thoracic surgeon, immunologist etc. for diagnosis and during monitoring shall be required.

Conclusions

The presented case illustrates the multidisciplinary diagnosis process generated by the identification of an ILD of NSIP type to a young patient, without risk factors of toxic or drug exposure or family disease. The screening of the system diseases suggested an interstitial damage secondary to the antisynthetase syndrome, due to the presence of specific antibodies. The pulmonary interstitial damage may precede systemic symptom associated with underlying CTD, this chronology being frequent within idiopathic inflammatory myopathies. In the case of the above mentioned patient, the diagnosis confirmation occurred 12 months from the début of the pulmonary condition by development of consistent clinical signs for dermatomyositis. The pulmonary disease represents a dominant and responsible clinical manifestation for a reserved prognosis, being non-responsive to the corticosteroid and immunosuppressive treatment. The pulmonary transplant represents the recommended therapeutic option given the progressive pulmonary functional damage. ■

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