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Acute respiratory distress syndrome – an undercover antisynthetase syndrome: a case report and review of the literature

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ABSTRACT

We present the case of a 48-year-old male with an acute respiratory distress syndrome which later proved to be an unexpected and initial manifestation of antisynthetase syndrome.

Recognising this as a rare combination of an acute respiratory failure and a connective tissue disease in a previously asymptomatic subject is possible only by means of diagnostic exclusion. Based on similar case reports, the only way to reverse the disease and minimise the sequelae is to begin long-term immunosuppressive therapy as soon as possible once the diagnosis has been made. A review of similar cases with antibody anti-Jo-1 is presented with the aim of providing clinicians with useful indications for promptly recognising this poorly-defined and life-threatening emergency.

Introduction

Antisynthetase syndrome (ASyS) is a subset of the spectrum of the idiopathic inflammatory myopathies (IIMs), which include polymyositis (PM), dermatomyositis (DM) and inclusion-body myositis (IBM). ASyS lacks diagnostic criteria and is generally defined as a group of signs and symptoms and namely, myositis, interstitial lung disease (ILD), arthralgias, Raynaud's phenomenon, and hyperkeratosis, with fissured skin on the finger tips ("mechanic's hands"). Even when ASyS presents in different combinations, the presence of at least one antisynthetase autoantibody (ASyAb) is required. These are a constellation of autoantibodies, the most common of which is directed at histidyl-tRNA synthetase (anti-Jo-1), with a prevalence of 20–30% in patients with IIMs (1), and more specifically 60–80% in ASyS (2), 10-40% in PM and 2–10% in DM (2). Other specific synthetases with catalytic activity for other amino acids different from histidyl are the target of rarer autoantibodies whose presence is less than 5% primarily in ASyS, and equally as low both in PM and in DM (3).

Some ASyAb are related to peculiar clinical features or outcomes. After inflammatory myopathy with proximal muscle weakness, a nearly constant finding in IIMs, pulmonary involvement is the second most frequent complication, with a prevalence exceeding 50% in anti-Jo-1 autoantibody positive cases (4). Respiratory manifestations include opportunistic infections, malignancy, aspiration pneumonia, chronic respiratory failure due to thoracic muscles weakness, spontaneous pneumomediastinum, alveolar haemorrhages, and finally, acute or chronic ILD. The latter is the major prognostic factor in IIMs, with mortality exceeding 40%, mostly related to the acute form (5).

There is evidence that pulmonary involvement can follow one of 3 clinical patterns (6): patients with gradual onset, those with acute onset, or a third subset of patients who remain asymptomatic. Acute onset is associated with a rapid progression toward respiratory insufficiency and is characterised by 1) a higher titre of anti-Jo-1 antibody (7), 2) diffuse alveolar damage (DAD) at histology, alone or in combination with other symptomatic or subclinical forms of ILD (8), and 3) a bilateral diffuse ground glass opacities at high-resolution CT-scan (HRCT) (9).

Acute Respiratory Distress Syndrome (ARDS) is the most acute form of presentation, with rapid progressive respiratory failure; very few cases have been reported in association with IIM or ASyS (Table I).

It is conceivable that due to the variable clinical forms of IIMs, and to the difficulties related to diagnosis, the prevalence of this association is higher than the few reported cases suggest.

When ARDS is first manifestation of ASyS in a previously healthy subject, the diagnosis can be easily overlooked. Patients with ARDS at onset may be part of the subset of IIMs characterised by an acute onset and are different from those with gradual onset in terms of the outcome. Indeed, these cases may provide an interesting model on the role of ASyAb as silent predisposing factors for an hyper-acute lung injury.

Clinical case

A 48-year-old man was admitted to the Emergency Department (ED) at our hospital for fever, dyspnoea, cough, headache, and diffuse arthralgias.

Table I. Synopsis of published cases of idiopathic inflammatory myopathies (IMMs) that developed adult respiratory distress syndrome (ARDS). CK values are the first available before the diagnosis (w/o treatment) of ARDS.

Age Gender	Prodromal Symptoms due to ARDS onset	Clinical profile Pre-date ARDS	Dyspnea prior to ARDS onset	Creatine Kinase UI/l	High-resolution CT scan pattern	Bronchoalveolar lavage	Pathology	Auto-Ab	Therapy [Outcome]	Reference
64 F	F° Fatigue My Arth Dysphagia Weakness (1 month)	Previously healthy (ARDS as onset)	N	5.110	not done	not done	not done	Jo-1	Cs [D]	
47 F	F° Dyspnea Weakness (rapid onset)	PM ILD from 3 yrs	Y	2.229	not done	not done	DAD + OP + fibrosis	Jo-1	MTX CYC CsA Cs [D]	Clawson K, 1995 (16)
40 F	F° Cough Dyspnea Arth (1 month)	PM from 2 yrs	N	13.000	not done	not done	DAD + acute BP	Jo-1	Cs AZT MTX [D]	
66 F	F° Cough Dyspnea	PM	N	650	GG opacities	PMN alveolitis	NSIP	Jo-1	Cs CYC AZT [H]	Tomsic M, 2000 (17)
59 F	Cough Dyspnea Fatigue (<1 month)	My Arth Ry from yrs (ARDS as onset)	N	431	GG Areas of consolidation peripheral nodular infiltrates	CD8 alveolitis	NSIP	Jo-1	Cs CsA AZT [H]	Jordan Greco AS, 2007 (18)
57F	F° Cough Dyspnea Fatigue (<1 month)	My Arth from 6 months (ARDS as onset)	N	237	Pleural effusion Alveolar infiltrates air bronchogram	51% PMN alveolitis	OP	Jo-1	Cs CsA AZT [H]	
60 F	F° Dyspnea Weakness Arth MH (<1 month)	SSc from 14 yrs (ARDS as onset)	N	1038	GG Bilateral consolidation air bronchogram	mixed alveolitis (ly 18% PMN 9%)	not done	Jo-1 Scl-70	Cs CYS Ig RTX [H]	Fagedet D, 2008 (19)
52 M	F° Cough Dyspnea (48 hrs)	F° Cough chest pain from several weeks (ARDS as onset)	N	940	GG Diffuse bilateral infiltrates pleural effusion	PMN 47.5% Ly 18.5% CD4 /CD8 =0.1	cellular (>CD8) NSIP	Jo-1 SSA RF	CsA- Tac [H]	Guglielmi S, 2008 (20)
48 F	F° Cough Dyspnea Fatigue (7 days)	previously healthy (ARDS as onset)	N	Normal and 890	GG Areas of consolidation, air bronchogram	PMN alveolitis	not done	Jo-1	Cs AZT [H]	Polosa R, 2008 (21)
48 M	F° Dyspnea	previously healthy (ARDS as onset)	N	x5 > normal	multiple areas of alveolar infiltrates, lobular in medium and lower field	not done	not done	Jo-1	Cs CYC [W]	BenGhorbel I, 2009 (22)
48 M	F° Cough Dyspnea Arth Headache (10 days)	previously healthy (ARDS as onset)	N	645	Bilateral consolidation, air bronchogram, some parenchimal nodules		OP	Jo-1	Cs CyC CsA [H]	Present case

ARDS: Acute Respiratory Distress Syndrome; Arth: Arthralgias; AZT: Azathioprine; BP: Broncopneumonia; Cs: Corticosteroids; CsA: Cyclosporine; CyC: Cyclophosphamide; D: Deceased; DAD: Diffuse Alveolar Damage; F°: Fever; GG: Ground Glass; H: Healthy; ILD: Interstitial Lung Disease; MTX: Methotrexate; My: Myalgias; N: Not present; NSIP: Non-specific Interstitial Pneumonia; OP: Organising Pneumonia; PM: Polymyositis, PMN: Neutrophils, Ry: Raynaud's phenomenon; SSA: Autoantibody anti-SS-A; RF: Rheumatoid Factor; RTX: Rituximab; Scl-70: Autoantibody anti-Scl-70; SSc: Systemic sclerosis; Tac: Tacrolimus, Y: Present, W: Worsening.

The patient had been in good health until ten days before, when fever appeared; his general practitioner therefore prescribed antibiotics and NSAIDs. The patient's clinical history indicated alcohol abuse and gastric ulcer. He was obese, BMI 32 kg/m^2, and was not on any continuous therapy.

On arrival at the ED, the patient's body temperature was 38.0°C, blood pressure was 120/70 mmHg, pulse was 105 beats per minute, respiratory rate was 28 breaths per minute, and oxygen saturation was 84% while breathing ambient air. Bilateral crackles were present in the bases of the chest. Respiratory failure was confirmed by the arterial blood gas, pO2 46 mmHg, pCO2 38 mmHg, pH 7.43. Leucocytes, 10.890/mm^3, (nv 4.000–10.000/mm^3) and C-reactive protein 26.14 mg/dl (nv 0.05–0.30 mg/dl) were elevated. Chest radiograph showed bilateral patchy opacities, for the most part in the bases. The patient was admitted to the Respiratory Department, where he received antibiotics (IV meropenem and levofloxacine) and oxygen. Further blood tests were performed, which showed high values of alkaline phosphatase 51 U/L (nv 7–40 U/L), γ-glutamyl transferase (165 U/l nv 11–51 U/L), lactic dehydrogenase 763 U/l (nv 230–460 U/L), and creati-

nine kinase 645 U/l (nv 25–195 U/L); albumin was 2.9 g/dl (nv 4.02–4.76 g/dl). Respiratory failure worsened and the patient was thus transferred to the Intensive Care Unit, where orotracheal intubation and mechanical ventilation were performed.

HRCT showed extensive and bilateral pulmonary consolidations, with air bronchogram and some parenchymal nodules (Fig. 1A); The CT scan of the abdomen was unremarkable. Bronchoalveolar lavage and serologic exams for bacteria, virus and fungi were negative. Echocardiography was negative for pulmonary hypertension. On the 12th day, given the lack of any improvement, a transbronchial biopsy was performed. These specimens showed acute damage represented by buds of organising pneumonia, hyperplasia of pneumocytes, bands of fibrin and foamy macrophages with rare eosinophils. A histologic diagnosis of organising pneumonia was therefore made. Rheumatologic results were available at the same time as the histological report: anti-Jo-1 antibodies were positive 56.6 Units, (nv <2.0 by ELISA) with speckled ANA pattern 1/160 (nv negative); ANCAs and anti ds-DNA antibodies were negative. A diagnosis of ASyS was made and a high dose of corticosteroids was started (IV pulses of methylprednisolone 1 g/day for five days, then tapered to 80 mg/day), followed by an IV pulse of 1 g of cyclophosphamide eight days later. Therapy led to significant improvement of the PaO2/*F*IO2 ratio and it was possible to wean the patient from mechanical ventilation. The patient was discharged after fifty-two days of hospitalisation. Prior to discharge, a new HRCT was performed, which showed a resolution of the bilateral pulmonary consolidations with only some residual ground glass opacities left (Fig. 1B). The patient was referred to the Rheumatology outpatient clinic to taper prednisone. cyclosporine (300 mg/day) was started thirty-three days after the second pulse of cyclophosphamide.

At the six-month follow-up, the patient's condition continued to be good. Inflammatory markers, CPK and liver parameters had normalised and anti-Jo-1 antibodies had become undetectable. Pulmonary function tests showed a mild restrictive defect. The only complaint the patient reported was dysesthesia (ENG/EMG was negative) but there was no myalgia.

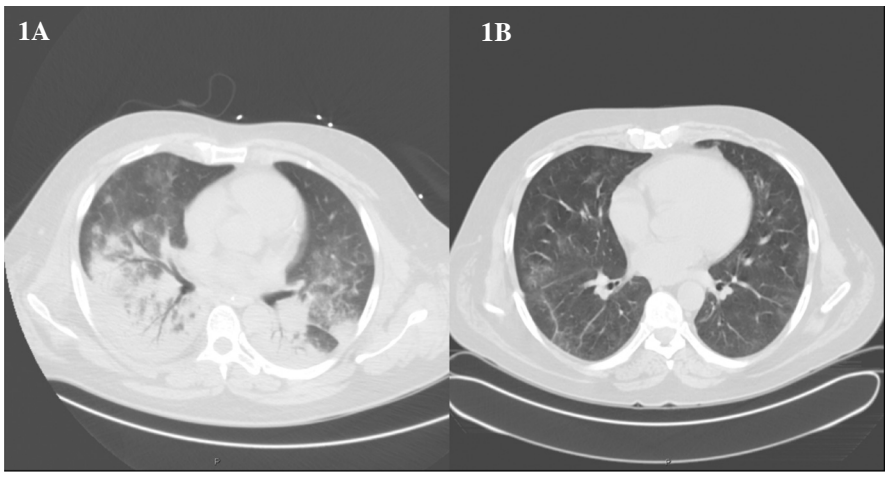

Fig. 1A. High-resolution computed tomography (HRCT) on the 7th day of hospitalisation. Extensive and bilateral pulmonary consolidation, with air bronchogram, and some parenchimal nodules.
B. HRCT repeated after 42 days from the previous one, showing a resolution of the bilateral pulmonary consolidations with only some residual ground glass opacities left.

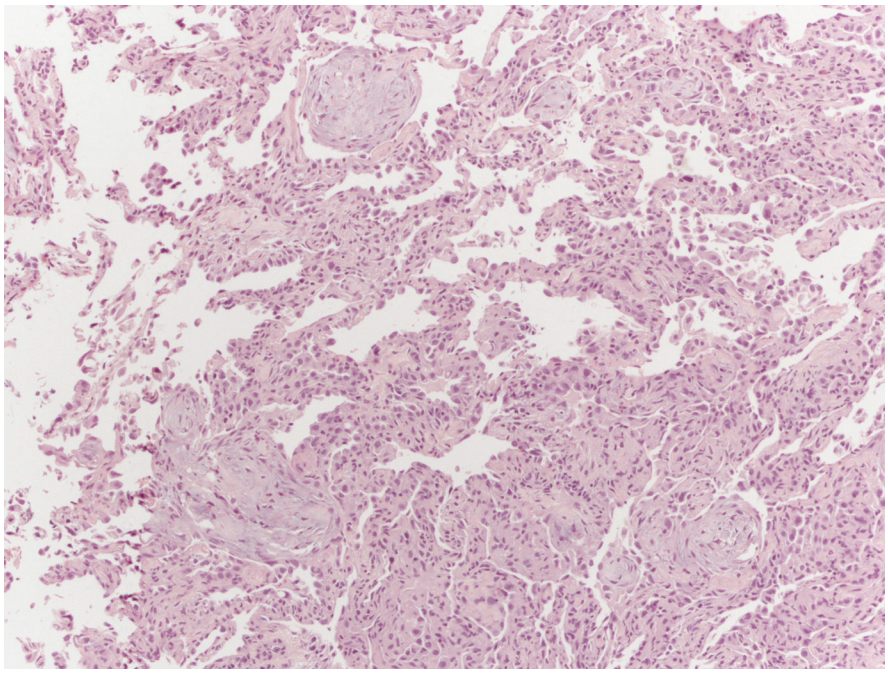

Fig. 2. Organising pneumonia. Original magnification x 100.

Discussion

We carefully searched the literature using the following free-text search words: "synthetase and anti-synthetase", "ARDS", "acute respiratory", "acute interstitial", "Jo-1", "polymyositis", "dermatomyositis", and "Hamman-Rich", in the English, French, German and Italian literature.

Seven case reports were retrieved (including 1 abstract), documenting a total of 10 patients (Table I) with PM/DM or ASyS with ARDS/acute respiratory failure as the presenting manifestation of the disease.

Do to the limitations of the clinical data we could not include the 4 cases of ARDS in a list of 20 anti-Jo-1 positive patients from Yousem's work (8); the case cited by Douglas (9) in a cohort of 70 PM/DM patients, the two

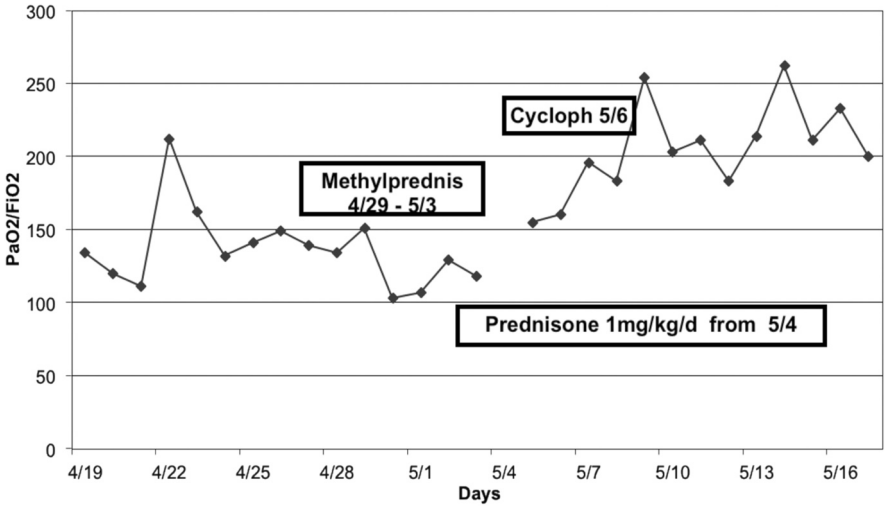

Fig. 3. The time course of (pO2)/(FiO2) arterial oxygen tension / inspiration oxygen fraction. Methyprednisolone IV 1g for 5 consecutive days was administered starting from 29th of april, followed by oral prednisone 1 mg/kg/day. On day 6th of may cyclophosphamide IV 1 g for one day was added.

amyopathic Friedman's patients (10) presented with an acute respiratory failure with anti-Jo1 and anti-alanyl (PL-12) antibodies, respectively. Finally, 4 patients who developed ARDS in the postoperative period (3 after open lung biopsy (11), and 1 after stem cell transplantation (12)).

As shown in the Table, in the 11 patients for whom data are available the prodromic symptoms of ARDS were cough (7 out of 11), dyspnoea (10 out of 11) and fever (10 out of 11). These signs appeared from 2 days to a few weeks before the overt onset. On the other hand before the presenting signs of ARDS, none of the patients had ever had respiratory symptoms. The only exception was the case with known ILD (case 2 in Table I).

Hence, a new onset or a worsening of respiratory symptoms together with fever were the features that led the patients to acute respiratory failure and ARDS.

Our observation is in keeping with that of other authors. Tillie-Leblond (6) found that fever >38.5 °C was twice as frequent in patients with acute onset as in those with a chronic disease, whereas dry cough and dyspnoea were equally distributed in acute and progressive onset. Furthermore, fever is a common symptom in anti-Jo-1 antibody-positive individuals, found in 35% of the cases in a cohort of 125 Dutch patients with myositis and statistically more frequent compared to patients without myositis-specific antibodies (13). Again, among the patients in Arsura's cohort (14) the most frequent clinical manifestation other than dry cough and/or dyspnoea was fever 58.5% (17/29).

Other prodromal signs of ARDS in the 11 patients in the Table were weakness and/or fatigue in 6/11 patients, arthralgias in 4/11, and mechanic's hands in 1.

A second notable point that emerged from our review is that in the majority of these patients (7 out of 11), ARDS began in previously healthy subjects. In the other four although they were patients with PM or SSc, ARDS emerged after a significant amount of time had passed from the diagnosis of PM (2-3 years) or SSc (14 year), hence as if it were an independent event. Accordingly, in our patient, we found neither histologic nor HRCT-scan imaging suggesting pre-existing underlying fibrosis, further supporting the concept of an acute onset of ASyS in an otherwise healthy subject.

Histopathology performed in 7/11 cases found non-specific interstitial pneumonia (NSIP) and organising pneumonia (OP) 3 times. Diffuse alveolar damage (DAD) was found twice. DAD together with UIP are known, to have the worst prognosis compared to the OP and NSIP, which have better outcomes. However, even with a better prognosis, our patient with OP, like that of Greco's (case 6 of the Table), required an aggressive treatment with cyclophosphamide followed by a second immunosuppressive chronic regimen (still ongoing) to achieve remission.

On the other hand a sampling error is still a possibility in our patient (*i.e.* the bronchial biopsy sampled an area of OP omitting a nearby area of DAD).

In terms of prognosis, Yousem (8), studying the clinicopathologic pattern of 20 ASyS patients, found that the subgroup of patients (6/20) presenting with an acute rapidly progressive hypoxemia had the worst prognostic histologic pattern due to the presence of DAD in 5 cases (and of OP in only 1). Hence, DAD once present truly represents a negative prognostic factor in patients with acute respiratory onset and in those with a flare up of a chronic disease.

As for chest CT findings, the main abnormality in our table of 11 patients was lung infiltrates. These are referred to indifferently as alveolar infiltrates (5 times, including the Clawson's 3 cases studied only on x-ray) or ground glass attenuation/opacities (5 times). Hence, 10 out of 11 patients had a description of ground glass or alveolar infiltrates. Multiple areas of consolidation and bronchogram (infiltrate/consolidation that surrounds the bronchi and bronchioles) were reported 4 times. Other features were pleural effusion (twice) and parenchymal nodules. Interestingly, none of the patients had honeycombing on HRCT, further supporting the hypothesis that ARDS represented an acute event in previously healthy patients.

Regarding treatments, all the cases showed in the table required immunosuppressive therapy used in sequence. Although corticosteroids were the mainstay of therapy, in none of the cases were they sufficient to control respiratory symptoms.

In summary, as other authors have already highlighted, there is a specific subset of IIMs with anti-Jo-1 antibodies that stands apart from the others because an acute respiratory decompensation presents at onset or as an exacerbation of a chronic respiratory insufficiency. Its rarity, together with the difficulty in its diagnosis (amyopathic subset, absence of anti-Jo 1) (15) and

a previously healthy condition, explain why it is easy to overlook the diagnosis of ASyS when ARDS is the presenting finding. In such cases, the clinical algorithm leading to suspecting an underlying ASyS is summarised by the following 5 points:

1) In the majority of the case reports the patients presented a recent history of what retrospectively seemed a persistent community-acquired antibiotic-resistant pneumonia. Symptoms were fever, cough, and dyspnoea, generally starting less than one month before the diagnosis of ARDS. Fever seems more frequent in this group of patients (10/11 see table) than in other Jo-1 positive IMMs (35–60%), probably because of the greater acuteness of the clinical presentation.

2) The patients' past history does not seem to have relevant, evident predisposing factors, with the exception of IIMs and ASyS or other connective tissue diseases when these are present.

3) Once the most likely causes of lung injury have been ruled out (*e.g.* pneumonia, sepsis, inhalational injury, aspiration of gastric contents), laboratory data of CK and antinuclear antibodies and ENA should be actively searched. Of note, all the patients we described except one, who had anti PL12 antibody, were anti-Jo1 positive. However, it is important to remember that an ASyS with "idiopathic interstitial pneumonia" has been described in ANA and anti-Jo-negative patients, and only 3 out 9 of them had elevated CK (15).

4) All the cases we retrieved had an increased CK (median 2.634 range 237-13.000 UI/L). Only one patient had initially normal CK, but 7 days later, with the worsening of symptoms, CK were 890 UI/L. This observation suggests repeating the CK more than once before excluding a myositis and it is possible that the wide variability of the CK detected in these patients is in relation to the course and the peak of the disease.

5) CT-findings are not specific. However, widespread alveolar infiltrates, ground-glass with or without multiple areas of consolidation and bronchogram are the most common features.

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