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Antisynthetase syndrome positive for anti-threonyl-tRNA synthetase (anti-PL7) antibodies

To the Editors:

Antisynthetase syndrome (ASS) is characterised by an inflammatory myositis associated with interstitial lung disease (ILD) and antisynthetase antibodies. Other symptoms, including arthritis, Raynaud's phenomenon and mechanic's hands, are also associated with ASS. Several antisynthetase antibodies [1] have been described, with anti-Jo1 being the most common. Little is known about the clinical manifestations of ASS associated with anti-threonyl-tRNA synthetase antibodies (anti-PL7) [2–4], most probably because anti-PL7 antibodies are particularly rare (5% of myositis [5]) and have not been routinely researched in the past.

We conducted this retrospective multicentric study to describe the clinical, radiographic and biological manifestations of ASS in 12 patients.

This retrospective study was conducted in five university hospitals. The patients were followed from 2000–2010 in the Depts of Pneumology (n=7) and Internal Medicine (n=5). 16 anti-PL7 positive patients were identified due to immunological laboratory databases. To exclude false-positive patients, we only included patients who successively tested positive for anti-PL7 twice (n=13): the three patients tested only once did not disclose any symptoms in accordance with ASS. We excluded one patient for whom clinical data were missing. The 12 included patients tested positive for anti-PL7 antibodies at least twice by immunodot (immuno-DOT D-tek; Diasorin, Antony, France) and/or Western blot using protein extracts from Hep2 cells (n=7 and n=5, respectively). They presented with one or more ASS symptoms, including ILD and/or myositis. A search for anti-DNA and anti-extractable nuclear antigen antibodies was systematically performed, whereas rheumatoid factor and anti-citrullinated peptide were available in four and two patients, respectively.

The characterisation of the ILD pattern was made by several radiologists who were all experienced in ILD and were based on the American Thoracic Society/European Respiratory Society 2002 consensus [6].

Pulmonary hypertension was suspected by echocardiography when systolic pulmonary arterial pressure was >40 mmHg.

For the follow-up, we defined pulmonary aggravation/improvement as an increase/decrease in dyspnoea, according to New York Heart Association (NYHA) stages and/or deteriorating/improving pulmonary function tests (>10% decrease/increase in carbon monoxide transfer factor and/or total lung capacity between the first and the last tests).

This study was approved by hospital local ethical committees. The patients of this study are anonymously reported and in accordance with the French law, a patient consent was required.

The mean age at the first sign of clinical symptoms was 56.3 yrs (range 31–71 yrs). Three patients had interrupted smoking habits; none had known toxic environmental exposure or any family history of ILD.

All patients presented with ILD at the onset of the disease. Muscular symptoms occurred in half of the patients. Fever and other symptoms are detailed in table 1.

11 patients complained of mild (NYHA II, n=5) to severe (NYHA III–IV, n=6) dyspnoea as an initial symptom of ILD. Dyspnoea was chronic (n=7) or acute (n=4), and could be associated with dry cough (n=7) and clubbing (n=2). Examination revealed fine crackles in all patients. ILD was confirmed by high-resolution computed tomography (CT) scans in all cases. Based on this CT scan, nine out of 12 patients exhibited nonspecific interstitial pneumonia (NSIP) pattern with bibasal mild fibrosis, including ground-glass and intralobular reticulation. Traction bronchiectasia were initially described in four of these patients. A pattern of organising pneumonia (OP) was present in a further two cases, with subpleural and peribronchovascular condensations. Ground-glass opacities were associated with bronchial wall thickening and mosaïc pattern in the remaining case, in accordance with obliterative bronchiolitis (OB).

Bronchoalveolar lavage (BAL) revealed alveolitis with an increased number of neutrophils (five out of eight patients) or lymphocytes (three out of eight patients). Lung biopsy was

TABLE 1 Characteristics of the patients

	Patient											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Sex/ethnicity	M/C	F/Af	F/C	F/C	F/C	F/C	M/C	F/C	F/C	F/Af	M/C	F/Af
Age at diagnosis yrs	71	56	31	71	38	71	41	74	73	52	41	57
Follow-up months	41	45	115	95	3	70	19	4	18	7	13	31
TLC– $D_{L,CO}$/AV	109/63	56/26[#]	70/74	79/ND	98/73	73/88	47/41	ND/ND	69/32	75/69	52/53	59/48
Lung involvement HRCT scanner	NSIP	NSIP	NSIP	OB	NSIP	NSIP	NSIP	OP	NSIP	OP	NSIP	NSIP
Alveolitis (BAL) %	N 36	N 39	ND	N 85	L 43	ND	N 40	ND	ND	L 42	L 46	N 36
Muscle involvement	No	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes
Raynaud's phenomenon	No	No	No	No	Yes	No	No	No	No	No	No	No
Fever	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Mechanic's hands	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No
Rheumatic symptoms	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No
Signs of SSc	No	No	Megacap. SSc-l oesophagus	PHT	Megacap. GOR	GOR anti-Scl70	No	PHT	SSc-l oesophagus	No	No	PHT
Signs of SS	No	Parotidomegally	Chisolm III anti-SSA-60	Dry eyes, dry mouth	Dry mouth, Chisholm III anti-SSA-60	No	No	No	No	Dry eyes, dry mouth	No	Dry mouth
First-line treatment	Steroids CYC	Steroids CYC+ *I.V.* Ig	Steroids MTX	Steroids	Steroids	None	Steroids CYC - AZA	Steroids *I.V.* Ig	Steroids	Steroids	Steroids	Steroids
Nth-line IS treatment (reason)	0	1 (Muscle)	4 (Muscle)	2 (lung)	ND	0	0	0	0	0	0	3 (lung)
Pulmonary evolution	Better	Stable	Stable	Worse	ND	Stable	Better	Worse, death	Better	Better	Better	Worse, death

TLC: total lung capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; AV: alveolar ventilation; HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; SSc: systemic sclerosis; SS: Sjögren syndrome; IS: immunosuppressive; M: male; F: female; C: Caucasian; Af: African; ND: not determined; NSIP: nonspecific interstitial pneumonia; OB: obliterative bronchiolitis; OP: organising pneumonia; N: neutrophil count; L: lymphocyte count; Megacap.: megacapillaries; SSc-l oesophagus: SSc-like mega-oesophagus; PHT: pulmonary hypertension; GOR: gastro-oesophageal reflux; anti-SSA-60: anti-Ro/SSA-60kDa antibodies; CYC: cyclophosphamide; Ig: immunoglobulins; MTX: methotrexate; AZA: azathioprine. [#]: $D_{L,CO}$

performed in only one patient and confirmed a diagnosis of OP. The initial pulmonary function tests in 11 patients (performed during the first 5 months after diagnosis, three patients being treated by immunosuppressive drugs) disclosed an isolated restrictive syndrome in six cases. The diffusing capacity of the lung for carbon monoxide/alveolar volume ratio was significantly decreased in eight patients. Only one nonreversible obstructive syndrome was encountered at diagnosis (the patient with an OB pattern at CT scan). This obstructive syndrome worsened during the follow-up: the ratio residual volume/total lung capacity became >140% [7].

Echocardiography revealed pulmonary hypertension at diagnosis in two patients and during the follow-up in a third patient (pulmonary arterial pressures of 55–70 mmHg). Asymptomatic pericarditis was fortuitously diagnosed in four patients.

Muscular involvement occurred mainly at diagnosis (five out of six patients). Two patients were asymptomatic and five complained of myalgia. Only two patients suffered from a mild pelvic muscular deficit, whereas another suffered from dysphagia. Two patients disclosed cutaneous lesions consistent with dermatomyositis. Creatine phosphokinase levels were elevated to five to 10 times normal levels in five of these patients. When performed (n=5), muscular biopsies showed signs of inflammatory myositis. There were no signs of cardiac or diaphragm involvement.

Cytoplasmic fluorescence of Hep2 cells was only reported five times.

Despite the absence of sclerodactyly and skin sclerosis, clinical signs consistent with systemic sclerosis (SSc) were encountered in seven patients: pulmonary hypertension (n=3), scleroderma like mega-oesophagus (n=2), gastro-oesophageal reflux (n=2), megacapillaries (n=2) and anti-Scl70 antibodies (n=1).

Five patients disclosed several clinical or biological symptoms in accordance with Sjögren syndrome (SS): xerostomy (n=4), xerophthalmy (n=2), salivary gland histology with Chisholm-Mason score grade III (n=2), parotidomegally (n=1) and anti-Ro/SSA-60-kDa (n=2).

The median follow-up period was 38.4 months (range 3–115 months). One weakly affected patient did not receive steroids and remained stable. Oral steroids alone were started in six patients: four of them improved or remained stable, whereas two others worsened, requiring additional immunosuppressive treatments. Various immunosuppressive treatments were initiated in combination with steroids as a first-line treatment in the five remaining patients. Thus, seven patients were treated with combined immunosuppressive therapy. At the end of the study, despite some muscle relapses, four patients improved or remained stable whereas three patients (25%) worsened in terms of lung involvement. Two deaths occurred due to acute respiratory failure: nondocumented bacterial pneumonia.

Despite the low number of patients, we further constituted several groups of patients according to the onset of their dyspnoea, the occurrence of myositis, the presence of SS or SSc symptoms, the ILD pattern and BAL results. We were not able to show any significant differences between these groups concerning the long-term evolution. However, two out of three patients suspected of pulmonary hypertension died.

Like anti-Jo1 or anti-PL12 ASS [1, 8, 9], this series of anti-PL7 ASS revealed that lung involvement was frequent (100%), whereas muscular involvement (50%) and other symptoms associated with ASS were less common, including Raynaud's phenomenon, which was particularly rare in this series (8%). Although these results should be interpreted carefully since our study is retrospective, the high prevalence of ILD and low prevalence of other symptoms is in agreement with observations from previous anti-PL7 series [2–4].

In some instances, and as previously described for anti-Jo1 ASS [1], anti-PL7 ASS could appear as an overlapping syndrome. Besides myositis, an overlap between SSc [3] and ASS has been proposed by others. No signs of skin sclerosis were noted in any of the anti-PL7 ASS cases in this study. Nevertheless, potential signs of SSc were common (58%). However, no patient could be classified as SSc according to the 1980 American College of Rheumatology classification and only one patient was classified as limited SSc [10].

As also suggested for anti-Jo1 ASS, a potential overlap between anti-PL7 ASS and SS based on clinical and immunological arguments was indicated in 42% of cases: sicca symptoms being the most common. Indeed, one patient suffered from OB, a rare disease associated with SS, but which had not been previously reported in ASS. However, only one patient could be classified as primary/secondary SS according the 2002 American-European consensus.

Thus, more than an overlapping syndrome, anti-PL7 ASS could also be considered as an idiopathic ILD (n=1) or ILD associated with undifferentiated connective tissue disease (n=4) [11]. Clinicians must therefore be aware of these conditions and should screen for anti-PL7 antibodies in these clinical contexts. A lack of screening for anti-PL7 antibodies is a probable reason for underestimations of anti-PL7 positivity.

Interestingly, this series also showed high heterogeneities between patients in regard to clinical phenotype, disease severity and response to immunosuppressive drugs. Above all, ILD could appear heterogeneous, since three different subtypes of lung involvement were identified in this series. Nevertheless, as in anti-Jo1 and anti-PL12 in our experience [9], NSIP represented the main pattern of ILD. Unlike what had been reported for anti-Jo1 ASS, we were not able to show any difference in anti-PL7 ASS patients according to their onset of dyspnoea [8] or the ILD pattern. This was probably due to the low number of patients included in this series.

Larger studies with a prolonged follow-up period are needed to identify the best diagnostic parameters (clinical manifestations, pulmonary function tests or thoracic CT scans and repeated echocardiography) to allow the prognosis for these patients to be determined.

Our patient series revealed a high prevalence of ILD and a relatively lower prevalence of myositic involvement and Raynaud's phenomenon in anti-PL7 ASS. In common with other ASS, the phenotype of anti-PL7 ASS is broad and varies from isolated ILD to the involvement of several organ systems, including myositis and can lead to a syndrome with symptoms overlapping with SSc and/or SS. Both the severity at diagnosis

and the prognosis of anti-PL7 ASS under treatment were heterogeneous.

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Obstructive sleep apnoea and metabolic syndrome in Mediterranean countries

To the Editors:

Obstructive sleep apnoea (OSA) is often associated with metabolic disturbances, including altered glucose metabolism and dyslipidaemia, which probably contribute to the increased cardiovascular risk in these patients [1]. The concept of the metabolic syndrome (MetS) as a cluster of cardiometabolic risk factors has gained popularity in recent years, and a much higher prevalence of the MetS has been found in OSA patients compared with the general population in several studies [1]. While the MetS largely reflects the effects of visceral obesity, environmental factors, *i.e.* the type of diet, could also play some role. The Mediterranean diet, rich in olive oil and fish, is protective against the MetS [2–4], but no study has examined the association of MetS and OSA in Mediterranean countries. We hypothesised that prevalence of the MetS might be lower in OSA patients living in the Mediterranean area compared with the prevalence values found in non-Mediterranean countries. Therefore, we retrospectively assessed the prevalence of the MetS according to the modified National Health and Nutrition Examination Survey Adult Treatment Panel (ATP) III criteria [5] in consecutive patients referred to sleep laboratories in Italy (n=107), Spain (n=138) and Greece (n=218).

Patients diagnosed with OSA in the period July 2007–September 2008 in Palermo, Italy (Respiratory Section, DIBIMIS, University of Palermo, and CNR Institute of Biomedicine and Molecular Immunology), Palma de Mallorca, Spain (Hospital Son Dureta) and Alexandroupolis, Greece (Sleep Unit, Medical School, Democritus University of Thrace), were evaluated in this study. All underwent clinical examination for clinical suspicion of OSA, and full polysomnography or nocturnal cardiorespiratory monitoring (eight channel) according to the American Academy of Sleep Medicine guidelines [6]. OSA was diagnosed when the apnoea/hypopnoea index (AHI) was >5 events·h^{-1}; mean lowest arterial oxygen saturation (S_{a,O_2}) was recorded. Daytime sleepiness was subjectively assessed by the Epworth Sleepiness Score questionnaire. Body mass index (BMI) was defined as kg·m^{-2}. Neck, waist and hip circumferences (cm) were measured. The MetS was diagnosed based on the presence of three or more of the following factors: waist circumference ⩾80 cm in females and ⩾94 cm in males; serum triglycerides ⩾150 mg·dL^{-1} or lipid-lowering treatment; high-density lipoprotein HDL cholesterol <40 mg·dL^{-1} in males and <50 mg·dL^{-1} in females or statin treatment; systemic hypertension (systolic blood pressure >135 mmHg and/or diastolic blood pressure >85 mmHg) or anti-hypertensive treatment; and fasting blood