Concise report

Clinical manifestations of anti-synthetase syndrome positive for anti-alanyl-tRNA synthetase (anti-PL12) antibodies: a retrospective study of 17 cases

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Abstract

Objective. To describe the clinical manifestations of the anti-synthetase syndrome (ASS) specifically associated with anti-alanyl-tRNA (anti-PL12) synthetase antibodies.

Methods. In a retrospective study, 17 patients (eight males, nine females, mean age = 60.3 years) with ASS symptoms confirmed by two consecutive tests (cyto-dot and/or immunoblot, or both), with positive results for anti-PL12 antibodies, were included.

Results. All patients presented with interstitial lung disease (ILD), which was associated with mild myositis in 41% of the cases. RP and general impairment were common, whereas rheumatic and dermatological symptoms were uncommon. Four patients suffered from SS, and four others had an atypical oesophageal involvement. The long-term course was assessable for 10 patients (follow-up of 41.1 months). Five patients required immunosuppressive drugs. Two patients are waiting for a lung transplant because of disproportionate and refractory pulmonary hypertension.

Conclusion. The severity of anti-PL12 ASS varied because of the constant pulmonary involvement. ILD was the predominant prognosis factor, which was notable in cases associated with pulmonary hypertension.

Key words: Myositis, Diffuse interstitial pneumonia, Anti-synthetase syndrome, Anti-synthetase antibodies, Anti-PL12 antibodies.

Introduction

Anti-synthetase syndrome (ASS) is characterized by inflammatory myositis associated with interstitial lung disease (ILD) and anti-synthetase auto-antibodies [1–4]. Anti-JO-1 is the most common anti-synthetase auto-antibody [5–7]. Anti-JO-1 antibodies are found in ~20% of adult patients with PM or DM [8]. Other anti-synthetase antibodies have been described in this context, including anti-alanyl-tRNA synthetase (anti-PL12) antibody [9]. Little is known about the clinical manifestations of this particular type of ASS, most likely because anti-PL12 antibodies are particularly rare (<2% of myositis [8]) 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 17 patients positive for both anti-PL12 antibody and clinical manifestations of ASS.

Methods

This retrospective study was conducted from January 2005 to May 2008 in three different university hospitals.
To exclude false positive patients, we included only patients who tested positive for anti-PL12 antibodies two times successively (by the same or by different tests). So we excluded six patients who had neither clinical ASS nor confirmed anti-PL12 antibody-positive test results.

Seventeen patients were included. They tested positive for anti-PL12 antibodies at least twice by immunodot (immuno-DOT D-tek provided by DiaSorin and/or western blot using protein extracts from Hep2 cells) and presented with one or more ASS symptoms.

For the follow-up, we defined pulmonary aggravation as an increase in dyspnoea, according to New York Heart Association (NYHA) stages, deteriorating pulmonary function tests (≥10% decrease in carbon monoxide transfer factor (TLCO), total lung capacity (TLC) per year) and/or clinical manifestations. The diagnoses of SS were made according to the 2002 American–European consensus [10].

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

Results

Among the 17 patients, 8 were males and 9 females (Table 1). Thirteen patients were French Caucasians, three were North Africans and one was African. The mean age was 60.3 years (range: 32–85 years) at the first sign of clinical symptoms. Two patients smoked significantly (≤40 packs/year), another had been exposed to asbestos and two others had a history of ischaemic cardiac failure.

All patients presented with ILD. In all but one patient, ILD was present at the beginning of the disease (in this case, pulmonary manifestations were evident after 1 year of myositis). Muscular symptoms occurred in seven (41%) cases, and RP or acrosyndrome was present in eight (45%) cases. General impairment, including fever, was present in eight cases, and RP or acrosyndrome was present in eight (41%) cases. General impairment, including fever, was present in eight cases, and RP or acrosyndrome was present in eight (41%) cases.

Examination revealed fine crackles in all 13 patients complaining of dyspnoea. No clubbing was noticed. A high-resolution CT scan was available for all patients, confirming the ILD in all cases: 15 out of 17 exhibited non-specific interstitial pneumonia (NSIP) pattern with bivalve mild fibrosis including ground glass, intralobular reticulation and traction bronchiectasis. In the two remaining cases, an organizing pneumonia (OP) pattern was present with subpleural condensations. Bronchoalveolar lavage (BAL) was performed in 11 patients, showing an increased number of immune and inflammatory cells: an increased percentage of neutrophils in five cases (from 19 to 70%), an increased percentage of lymphocytes in two cases (25 and 56%) and an increased percentage of eosinophils in three cases (8–12%). Asbestos bodies were present in one case.

Lung histology was available in seven cases (five transbronchial biopsies, two open-lung biopsies), confirming mild interstitial fibrosis in three cases and showing only alveolitis in four other cases.

The initial pulmonary function tests of 13 patients disclosed an isolated restrictive syndrome in 11 cases, and both restrictive and obstructive syndrome in the remaining two cases. The total lung capacity ranged between 41 and 90%, and TLCO ranged from 41 to 90%. Echocardiography, performed in 11 patients, did not reveal pulmonary hypertension at diagnosis.

The involvement of muscular disorders varied among the patients studied. One patient was asymptomatic, whereas four complained of myalgia. Two patients suffered from a mild pelvic muscular deficit. CPK levels increased up to twice the normal level only in two individuals. EMG revealed a myogenic syndrome in three patients. Muscular biopsies were performed six times and revealed DM in five cases, and PM in one case (according to the Bohan and Peter criteria [11]). No cardiac involvement occurred.

SS was diagnosed four times. A symptomatic inferior aperistaltic oesophagus was present in four patients, corresponding to a dramatic oesophageal enlargement on thoracic CT scans. A symptomatic seritis (either pleuritis or pericarditis) worsened the thoracic involvement in six cases.

Biologically, CRP was elevated to eight times the normal limit (range: 30–108 mg/l). Polyclonal hypergammaglobulinaemia was present in eight patients (range: 16.8–24.2 g/l). ANA were positive only three times on Hep2 cells. Cytoplasmic fluorescence, with a titre of ≤1/80, was reported six times. Different specificities were positive on ELISA or LUMINEX technology testing: anti-Ro/SSA-52kDA, five times; anti-Ro/SSA-60 kDA, twice; anti-La/SSB, once; and anti-RNP, once.

The median follow-up was 26.8 months (range: 2–76 months). Ten patients were followed up for >12 months (41.1 months, range: 19–76 months after diagnosis). For two of these patients no treatment was started. Improvement occurred in one case whereas progressive pulmonary aggravation occurred in the other case. Three patients received only steroids. After a median follow-up of 23 months (range: 19–31 months), two patients improved and one worsened. The five remaining patients (medium follow-up: 51 months, range: 35–76 months) received steroids plus one or two immunosuppressive drugs at the same time (i.e. intravenous immunoglobulins, MTX, AZA or cyclophosphamide). Second-line treatment was required four times because of inefficiency or relapse.

Finally, based on pulmonary evolution, three stabilized their status and two worsened. These two patients developed severe pulmonary hypertension and are currently waiting for lung transplantation. No patient died during the follow-up.

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²Severe acoyndrome; ¹6 months after the first muscular symptoms; TLCO: diffusing capacity of carbon monoxide; AV: alveolar ventilation; nd: not determinable; Macroph: macrophage count (%); L: lymphocyte count (%); Eosino: eosinophil count (%); Neutro: neutrophil count (%); IVIg: intra-venous immunoglobulins; CYC: cyclophosphamide; ins.f-up: insufficient follow-up; 11thM: 11th month; TCL: total lung capacity.
Discussion

Positive test results for anti-PL12 antibodies are particularly rare, and the number of patients included in previous studies is usually small. Therefore, the specific characteristics of anti-PL12 ASS as opposed to the more common anti-JO1 ASS characteristics are not well described.

Interestingly, this series, which is the first European large series, is also the first to show a high prevalence of oesophageal involvement (23.5%), which to date has never been reported for ASS. This atypical manifestation, leading to severe gastro-oesophageal reflux, mimics achalasia of the one-third inferior oesophagus and may easily be screened as a gap on chest CT.

Unlike anti-JO1 ASS [2, 12], this series of anti-PL12 ASS revealed constant lung involvement, whereas muscular involvement concerned only 41% of the patients. The low prevalence and weak severity of the muscle involvement (often on a subclinical level) supports the previous anti-PL12 series [9, 12]. Notably, DM seems to occur more frequently than PM, based on muscular histology.

Similar to the North American series reported in Targoff and Arnett [9] and Kalluri et al. [12], our series also clearly showed a low prevalence of rheumatic symptoms; other symptoms, including mechanic’s hands and RP, are also rare.

Hence, ASS could appear as an isolated diffuse interstitial pneumonia (29.4% herein) [13]. As a result, clinicians must be aware of an isolated ILD form of anti-PL12 syndrome and wide screen for anti-PL12 positivity in such a clinical context: the lack of screening for anti-PL12 is one of the reasons why anti-PL12 positivity is probably underestimated. In this series and as already observed, anti-PL12 antibody was always the only anti-synthetase antibody detected, confirming their mutual exclusivity [14]. In some instances and as previously described for anti-JO1 ASS [2], anti-PL12 ASS could appear as an overlap syndrome.

In fact, oesophageal involvement and pulmonary hypertension could suggest overlapping SSc. However, an overlap between SSc and ASS has been proposed by others (in association with anti-PL7-antibodies, for example). Herein, any skin sclerosis has been noticed in case of anti-PL12 ASS. In none of the cases, anti-PL12 antibodies were associated with anticientromere antibodies or anti-ScI70 antibodies in this series. Also, there might be an overlap between anti-PL12 syndrome and SS based on clinical and immunological arguments (anti-Ro/SSA-60 kDa and anti-La/SSB). This situation was seen in 23.5% of the cases, and since we excluded patients with only a single anti-PL12 antibody-positive test, we can argue that this association is not fortuitous.

Similar to anti-JO1 ASS, the prognosis of anti-PL12 ASS seems to be determined by the pulmonary involvement, especially in the case of disproportionate pulmonary hypertension [12, 15]. Indeed, pulmonary hypertension, a particularly rare complication of anti-synthetase antibodies [12, 15].

Furthermore, the response to immunosuppressive treatments seems to be heterogeneous [16] and we were not able to show any predictable evolution factor. Larger studies with a prolonged follow-up are needed to find the best parameters at diagnosis (such as clinical manifestations, pulmonary function tests or thoracic CT scans) to determine the prognosis for these patients.

Conclusion

Even though further prospective investigations are needed to precisely determine the prognosis of anti-PL12 syndrome, especially a case–control study comparing anti-PL12 ASS with anti-JO1 ASS or idiopathic pulmonary fibrosis, our series clearly showed systematic ILD and mild myositis involvement in this particular ASS subtype. Clinicians must be aware of the occurrence of isolated lung involvement to systematically search for anti-PL12 antibodies in this context. Moreover, in cases with positive test results for anti-PL12, screening for pulmonary hypertension, which could be an important determinant for prognosis, must be regularly performed.

Rheumatology key messages

- Anti-alanyl-tRNA synthetase (anti-PL12) antibodies are particularly rare anti-synthetase antibodies.
- In anti-PL12 ASS, pulmonary involvement is systematic whereas muscular involvement occurs less frequently.

Disclosure statement: The authors have declared no conflicts of interest.

References

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