

# A case of antisynthetase syndrome with chilblains-like lesions and microangiopathy

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## Abstract

We present the case of a 50-year-old woman with febrile myalgia, chilblains-like lesions, and cough. Antinuclear antibodies and anti-PL-12 antisynthetase autoantibodies were found in complementary examinations. Interstitial lung disease was found on chest computed tomography. Nailfold capillaroscopy showed microangiopathic lesions.

Antisynthetase syndrome is a recently described entity in inflammatory myopathies, with specific clinical criteria. Interstitial lung disease is very common, especially in anti-PL-12 associated antisynthetase syndrome. Raynaud's phenomenon is another well-defined criterion. However, microangiopathic damage is probably underestimated and the role of nailfold capillaroscopy in the diagnosis has not been established yet.

## KEYWORDS

acrosyndrome, antisynthetase syndrome, microangiopathy, myalgia

## 1 | INTRODUCTION

Antisynthetase syndrome (ASS) is defined by the presence of anti-RNA-synthetase autoantibodies and several clinical signs (myositis, fever, interstitial lung disease, arthralgia, Raynaud's phenomenon, mechanic's hands).<sup>1,2</sup> Depending on the autoantibodies involved, the incidence of these signs is variable and isolated forms may occur.<sup>3,4</sup> The prognosis depends mainly on lung involvement.<sup>4</sup> Raynaud's phenomenon is a well-defined criterion, but microangiopathy and the role of capillaroscopy are probably underestimated.<sup>5</sup> The treatment is based on a multidisciplinary approach that includes radiologists, pneumologists, internists, and/or rheumatologists.<sup>2</sup>

## 2 | CASE REPORT

A 50-year-old woman was admitted to the emergency department for asthenia, myalgia, and shivering. The patient had been experiencing these symptoms for 10 days. Myalgia was predominant in the axial (cervical, paravertebral, and lumbar regions) and proximal (shoulders and thighs) muscles and was associated with morning stiffness. She also described dysphagia and discrete hands and feet edema, without any joint complaints. A dry cough appeared the day before she was admitted, occurring especially in the evening, without dyspnea. She had a history of lactose intolerance, and her usual treatment consisted of estroprogestative contraception only.

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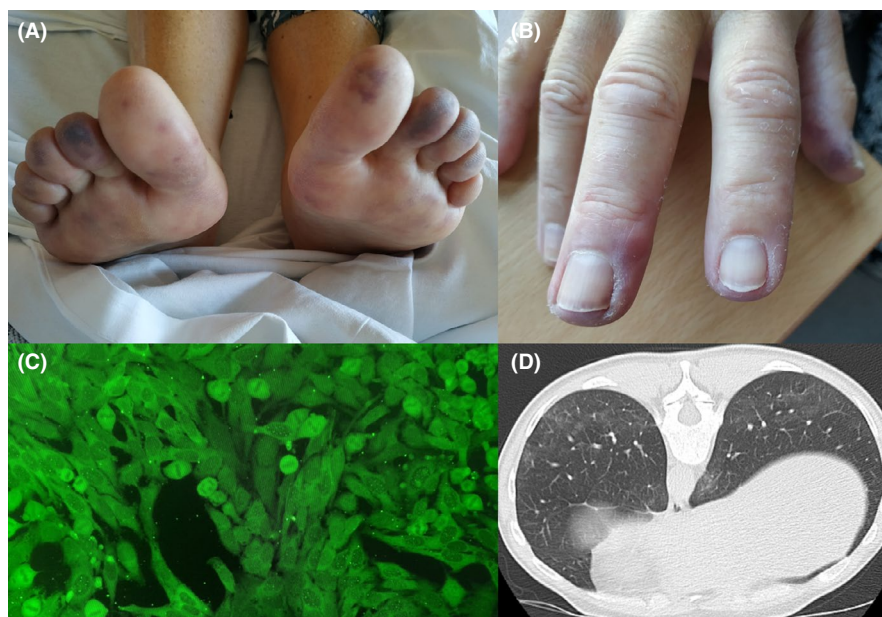
Physical examination showed a mild fever and sore muscles, without any redness, warmth, or edema. Distal, fixed, and initially nonpainful purpuric lesions suggestive of chilblains-like lesions were observed on both feet (Figure 1A). Fingers of the right hand recently presented a slightly desquamating periungual hyperkeratosis. Acrocyanosis was also objectified on several occasions, but the patient did not present with a Raynaud's phenomenon (Figure 1B). There was no synovitis, adenopathy, or splenomegaly.

On admission, serum C-reactive protein (CRP) was high at 70 mg/L (standard: 0-5 mg/L), associated with lymphopenia at 900/mm<sup>3</sup> (standard: 1500-4000/mm<sup>3</sup>). Laboratory data reported the following results: alanine aminotransferase (ALT) of 264 U/L (standard: 7-40 U/L), aspartate aminotransferase (AST) of 95 U/L (standard: 7-37 U/L), and total bilirubin of 1.5 mg/dL (standard: 0.3-1.1 mg/dL). Kidney function was normal, as well as creatine kinase (CK) at lactate dehydrogenase (LDH) levels. C4 was low at 4 mg/dL (standard: 10-40 mg/dL), and C3 was in normal range. Urine examination showed no abnormality. There was no evidence of myopathy on electromyography. Antinuclear antibodies were positive showing a cytoplasmic pattern and titer of 1/640 (Figure 1C). The anti-PL-12 antisynthetase autoantibody was identified. Chest computed tomography showed subpleural ground-glass opacity, compatible with interstitial lung disease (Figure 1D). Spirometry was normal (no restrictive disorder or diffusion anomaly). No sign of pulmonary arterial hypertension was found on the echocardiography. The positron emission tomography scan (PET scan) showed hypermetabolic pulmonary infiltrates, without muscle capture or any argument in favor of an underlying neoplasia. Nailfold capillaroscopy showed pericapillary edema, dilated loops, microhemorrhages, and disorganization of capillary architecture with a nonspecific pattern. The diagnosis of

antisynthetase syndrome (ASS) associated with anti-PL-12 autoantibody was retained. Magnetic resonance and muscle biopsy were not performed, because a rapid treatment needed to be initiated, as the digital vasculopathy was progressing. Moreover, we already had clinical and serological arguments for the diagnosis. A corticoid-based treatment and intensive physiotherapy were started, with a rapid improvement of the symptomatology (disappearance of fever, reduction of myalgia, and cough). The patient was referred to a tertiary care hospital, where methotrexate was started concomitantly with the corticosteroid tapering.

### 3 | DISCUSSION

Myositis-specific autoantibodies (MSA) are clinically useful biomarkers to help the diagnosis of polymyositis/dermatomyositis. Several autoantibodies have been described such as aminoacyl tRNA synthetase, SRP, MI2, MDA5, TIF1 gamma/delta, NXP2, SAE, and TRIM33.<sup>6</sup> The antisynthetase syndrome (ASS) belongs to the group of idiopathic inflammatory myopathies and affects mostly women with an average age of 50 years.<sup>3</sup> It is defined by the presence of anti-RNA-synthetase autoantibodies and one or more of the following clinical signs: myositis, fever, interstitial lung disease, arthralgia, Raynaud's phenomenon, and mechanic's hands.<sup>1,2</sup> Several MSA are currently known. The anti-JO1 is the most frequently identified. More rarely, anti-PL-12, PL-7, EJ, OJ, KS, ZO, YRS, JS, and SC can be involved.<sup>1-3,7</sup> Specific MSA identification is important because of their association with clinical specificities, forming clinical subgroups.<sup>3,4</sup> Muscle biopsy (after magnetic resonance imaging) can be useful when the diagnosis is difficult and shows relatively homogeneous anomalies regardless of the ASS subgroup. However,



**FIGURE 1** (A) Chilblains-like lesions (B) Periungual hyperkeratosis (can correspond to early mechanic's hand)—Acrocyanosis (C) Antinuclear antibody—Cytoplasmic pattern on immunofluorescence (D) Subpleural ground-glass opacity, compatible with interstitial lung disease

muscle inflammation may be absent despite a compatible clinical and serological profile.<sup>1</sup>

In the early phases of the condition, diagnosis can be difficult, as ASS may be incomplete or vary over time. In the beginning, only half of the patients with ASS present myositis.<sup>3</sup> The absence of initial creatine kinase (CK) or myopathy pattern in electrophysiology should therefore not rule out the diagnosis. In the ASS, lung damage, characterized by interstitial lung disease (ILD), is very common compared with other inflammatory myopathies, with a generally more severe and more rapidly progressive clinical course.<sup>2,8</sup> It may be an initial or even isolated disease, preceding the muscular injury or appearing in an amyopathic form.<sup>1-3</sup> It is therefore an important prognostic factor, with the risk of developing pulmonary restrictive syndrome or pulmonary arterial hypertension, which is a major source of morbidity and mortality among these patients, who should benefit from regular multidisciplinary follow-up. Clinical presentations may differ depending upon the antibody involved. Cavagna et al showed that the forms with anti-PL-12 had a higher incidence of ILD, while myositis was less frequent than those with anti-Jo1.<sup>3</sup> Hervier et al showed identical results for ASS associated with anti-PL-12 but also with anti-PL-7. Survival was lower in these groups relative to lung disease.<sup>4</sup>

Some idiopathic inflammatory myopathies are associated with neoplasia, such as dermatomyositis with anti-TIF gamma antibody.<sup>9</sup> Regarding ASS, no association with neoplasia has been described. These patients should therefore benefit from age-appropriate cancer screening, but current data do not suggest a more extensive assessment.<sup>2</sup>

Raynaud's phenomenon is currently a diagnostic criterion for ASS. In our case, we described an acrocyanosis and chilblains-like lesions, without the characteristics pallor or hyperemic stages of Raynaud's phenomenon. Tree cases in the literature have described the existence of acrosyndromes (described as acrocyanosis, livedoid acrocyanosis, blue fingers, etc) in the absence of Raynaud's phenomenon among anti-PL-12-ASS patients.<sup>10-12</sup> We believe that there are probably other cases described, but our experience show that the characterization of skin lesions may differ depending on the physician. After consultation with dermatologists, we decided to describe foot lesions (Figure 1B) as chilblains-like lesions. However, in the absence of a skin biopsy, it is difficult to exclude an ischemic origin secondary to microangiopathy or the association of cutaneous vasculitis, with which these lesions can be confused.<sup>13</sup> Acrocyanosis should in this case be considered secondary to the underlying microangiopathy and should be distinguished from primary/idiopathic acrocyanosis, with a benign course.<sup>14</sup>

Nailfold capillaroscopy is a safe and noninvasive diagnostic tool for the study of periungual microcirculation. Its

use has been widely studied in systemic sclerosis. However, there are few capillaroscopy studies among ASS patients, and often with a limited number of patients. Data can be retrieved from studies of dermatomyositis and polymyositis patients. Recently, Sebastiani et al conducted a multicenter international study involving 190 ASS patients in comparison with controls.<sup>5</sup> Among ASS patients, 62% had microangiopathy at nailfold capillaroscopy (defined as at least one among giant capillaries, microhemorrhages, ramifications or reduction of the number of capillaries) compared with the control group (29%,  $P$ -value < .001). Among them, 35% had a systemic sclerosis-like pattern. Interestingly, they show that Raynaud's phenomenon in ASS was associated with the presence of avascular areas, but not with systemic sclerosis-like pattern. Nailfold capillaroscopy alterations were also more frequent in patient with ILD. They concluded that the presence of microangiopathy should be included in the ASS diagnostic criteria and that future studies are needed to verify the correlation between microangiopathy and ILD.

The first-line treatment used is based on corticosteroids. However, there is a risk of lung disease recurrence during the corticoid tapering. Immunosuppressive agents are then used in combination for lung disease, or for corticosteroid-resistant muscle/joint forms. They are also used as corticosteroid-sparing agents. Currently, there is no consensus on the immunosuppressive drugs used for the treatment of ASS. Pulmonary pathology determines the prognosis, so the patient should also benefit from pulmonary monitoring. Physical activity is important to avoid muscular atrophy secondary to the pathology and corticosteroid therapy. The treatment principle is therefore based on a multidisciplinary approach between radiologists, pulmonologists, and internists/rheumatologists, and on close monitoring of adverse effects and disease activity.<sup>2</sup> *Pneumocystis jirovecii* prophylaxis is recommended in case of high doses of corticosteroids or if combined with an immunosuppressive agent.<sup>2,15</sup> There are no specific recommendations for the treatment of acrosyndromes for antisynthetase syndrome. However, Herrick et al recently published recommendations on the management of connective tissue disease-related digital vasculopathy.<sup>16</sup> They are based on a nonpharmacological approach (avoiding cold, protecting extremities, stopping smoking) and a pharmacological approach, the latter depending on the existence of complications (digital ulceration and/or critical ischemia).

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTION

AT: initiated the manuscript preparation. All the authors: participated in the clinical management of this patient and contributed to the manuscript preparation.

## ETHICAL APPROVAL

Local approbation, patient consent.

## DATA AVAILABILITY

Available upon submission.

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