

# Anti-PL-7 (Anti-Threonyl-tRNA Synthetase) Antisynthetase Syndrome

## Clinical Manifestations in a Series of Patients From a European Multicenter Study (EUMYONET) and Review of the Literature

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**Abstract:** Autoantibodies against several aminoacyl-transfer-RNA synthetases have been described in patients with myositis; anti-threonyl-tRNA synthetase (anti-PL-7) is one of the rarest. We describe the clinical and laboratory characteristics of a cohort of European anti-PL-7 patients, and compare them with previously reported cases. This multicenter study of patients positive for anti-PL-7, identified between 1984 and 2011, derives from the EUMYONET cohort. Clinical and serologic data were obtained by retrospective laboratory and medical record review, and statistical analyses were performed with chi-squared and Fisher exact tests.

Eighteen patients, 15 women, were anti-PL-7 antibody positive. Median follow-up was 5.25 years (interquartile range, 2.8–10.7 yr), and 4 patients died. All patients had myositis (12 polymyositis, 5 dermatomyositis, and 1 amyopathic dermatomyositis), 10 (55.6%) had interstitial lung disease, and 9 (50%) had pericardial effusion. Occupational exposure to organic/inorganic particles was more frequent in patients with interstitial lung disease than in the remaining patients (5 of 10 vs. 1 of 7;  $p = 0.152$ ), although the difference was not significant. Concurrent autoantibodies against Ro60 and Ro52 were seen in 8 of 14 (57%) patients studied. In the literature review the most common manifestations of anti-PL-7 antisynthetase syndrome were interstitial lung disease (77%), myositis (75%), and arthritis (56%). As in other subsets of the antisynthetase syndrome, myositis and interstitial lung disease are common features of the anti-PL-7 antisynthetase syndrome. In addition, we can add pericarditis as a possible manifestation related to anti-PL-7 antibodies.

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**Abbreviations:** ANA = antinuclear antibodies, DLCO = diffusing capacity of the lung for carbon monoxide, DM = dermatomyositis, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ILD = interstitial lung disease, IQR = interquartile range, PM = polymyositis.

## INTRODUCTION

Idiopathic inflammatory myopathies—polymyositis (PM) and dermatomyositis (DM)—are systemic autoimmune diseases characterized by skeletal muscle inflammation, but other organs are frequently involved such as skin in dermatomyositis and lungs and heart in both polymyositis and dermatomyositis. Up to 56% of patients with myositis are positive for various autoantibodies, which can be classified as associated (present in other rheumatic disorders) or specific (positive predominantly in myositis).<sup>4</sup> Among the myositis-specific autoantibodies group, antisynthetase antibodies are the most commonly found, and are directed against aminoacyl-transfer-RNA synthetases, a group of cytoplasmic enzymes that catalyze binding of an amino acid to its cognate tRNA, a necessary step in the formation of polypeptides. To our knowledge, 8 autoantibodies against different synthetases have been described to date: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-YRS, and anti-Zo.<sup>1,5,11,14,21,24,28</sup>

The clinical profiles associated with these various anti-synthetase antibodies, in particular anti-Jo-1, have been investigated previously.<sup>7,22</sup> The main associated clinical features are myositis, interstitial lung disease (ILD), arthritis, fever, Raynaud phenomenon, and mechanic's hands, comprising the "antisynthetase syndrome." In addition, individual autoantibody specificities may be associated with distinctive clinical features. Non-Jo-1 antisynthetase antibodies seem to be markers of hypomyopathic forms with prominent lung involvement.<sup>10,13,15</sup> Few studies have focused on the clinical manifestations of patients with anti-PL-7, an antibody directed against threonyl-tRNA synthetase.<sup>12,25,33</sup> We conducted the current study to investigate the clinical and laboratory profiles of patients with anti-PL-7 antibody in a large cohort of European patients, and to compare them with previously reported cases.

## PATIENTS AND METHODS

### Patients

Patients positive for anti-PL-7 recorded during the period of 1984 to 2011 were identified from the laboratory databases or rheumatology clinics of the following university hospitals: Vall

d'Hebrón General Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; Medical and Health Science Center, University of Debrecen, Debrecen, Hungary; Karolinska University Hospital, Stockholm, Sweden; Institute of Rheumatology, Charles University, Prague, Czech Republic; and Imperial College Healthcare NHS Trust, London, United Kingdom. In total 964 myositis patients were identified.

Clinical data were obtained by a retrospective review of medical records. Clinical findings included the presence or absence of inflammatory myopathy, ILD, arthritis, Raynaud phenomenon, mechanic's hands, fever, skin rash, heart involvement, history of smoking and environmental exposures related to profession, and other relevant clinical features. The diagnosis of dermatomyositis and polymyositis was based on the criteria of Bohan and Peter,<sup>2,3</sup> and only patients with definite or probable disease were included. The Sontheimer criteria<sup>27</sup> were used to diagnose amyopathic dermatomyositis. The diagnosis of ILD was established when any of the following conditions were present: interstitial infiltrates on chest radiography or high-resolution computed tomography (ground-glass opacities, honeycombing, fibrosis, and/or interstitial thickening) and/or a restrictive pattern on pulmonary function testing (forced vital capacity [FVC] <80%, forced expiratory volume in 1 second [FEV1] <70%, diffusing capacity of the lung for carbon monoxide [DLCO] <75%), and/or positive histology. Pericardial effusion was assessed by transthoracic echocardiography.

### Autoantibody Analyses

Myositis-specific and -associated autoantibodies were identified by line immunoassay (Myositis Profile Euroline, Euroimmun, Lübeck, Germany) or RNA and protein immunoprecipitation assay. Anti-PL-7 antibodies were confirmed by at least 2 of the following techniques: ELISA, line immunoassay (Myositis Profile Euroline), or RNA and protein immunoprecipitation assay. To exclude false-positive cases, we included only patients who repeatedly tested positive for anti-PL-7. Antinuclear antibodies (ANA) and extractable nuclear antigens were assessed by ELISA. Serum samples were obtained after patients provided oral informed consent.

### Human Leukocyte Antigen Typing

Human leukocyte antigen (HLA) class II was detected with a sequence-specific primer and sequence-specific oligonucleotide polymerase chain reaction technique.

### Ethics

The institutional review boards of all the participating centers approved the study.

### Literature Review

We searched the English-language literature in the PubMed database (National Library of Medicine, Bethesda, MD) for related articles published up to March 2011, using the following key words: "PL-7 antibody," "anti-PL-7," "anti-threonyl-tRNA synthetase," and "antisynthetase syndrome."

### Statistical Analyses

Qualitative data are presented as numbers and percentage, and quantitative data as the median and interquartile range (IQR). Association between the presence of anti-PL-7 antibodies and qualitative variables was assessed using the chi-squared and Fisher exact tests. All statistical analyses were performed with SPSS 13.0 software (SPSS, Chicago, IL). Significance was set at a *p* value of less than 0.05.

## RESULTS

### Clinical Features

Eighteen anti-PL-7-positive patients were identified out of 964 patients tested from the contributing centers (1.87%). The median age at diagnosis was 52.5 years (IQR, 40–58.8 yr), and there was a predominance of women (15 patients, 83%). Eight (44.4%) patients were current or former smokers. PM was diagnosed in 12 (66.7%) patients, DM in 5 (27.8%), and amyopathic DM in 1 (5.6%) patient. Two patients had overlap syndromes: 1 patient with DM met the criteria for rheumatoid arthritis, with positive testing for rheumatoid factor and anticyclic citrullinated peptide, and the other had PM and Sjögren syndrome.

Clinical features of the 18 patients are summarized in Table 1. Twelve (66.7%) patients had arthritis. Ten (55.6%) patients had ILD. Fever attributed to the disease was present in 10 (55.6%) patients, and Raynaud phenomenon in 11 (61.1%). Nine (50%) patients had pericardial effusion with no apparent underlying cause (for example, heart failure). Two of them developed massive effusion with pericardial tamponade: 1 resolved with medical treatment (glucocorticoids), and the other required pericardiocentesis. Mechanic's hands were reported in 5 (27.8%) patients. Only 1 patient had a malignant disease, breast cancer, which was diagnosed 4 years after the PM diagnosis.

The onset of ILD was before the start of myositis in 2 cases, at the same time as myositis in 7, and after myositis in 1. In all 10 patients with ILD, pulmonary involvement was confirmed by high-resolution computed tomography, which showed various radiologic patterns. Signs of fibrosis were documented in 9 of the 10 patients, interstitial thickening in 5, honeycombing in 4, and ground-glass opacities in 4.

Pulmonary function tests were carried out in 5 cases and showed a restrictive pattern with a median FVC at diagnosis of 61% (IQR, 57%–75.5%) and FEV1 of 69.5% (IQR, 51.4%–74.3%). Transbronchial biopsy in 1 patient and autopsy findings in another disclosed alveolitis in both cases. One patient required orotracheal intubation due to respiratory failure caused by severe ILD, with later recovery.

Six patients in the cohort had been exposed to various organic/inorganic particles at work, including 2 factory workers, a plumber, a farmer, a cleaning worker, and a miner (uranium mines). All but 1 (a factory worker) had underlying ILD, which appeared before or at the same time as myositis. Nonetheless, there was no significant association between working exposure and ILD (5 of 10 with ILD vs. 1 of the 7 remaining patients, *p* = 0.152).

The median follow-up was 5.25 years (IQR, 2.8–10.7 yr), and 4 patients died. The cause of death was attributed to progression of ILD in 2 patients (1 complicated with *Pneumocystis jirovecii* infection), acute myocardial infarction in 1 patient, and sepsis secondary to *Salmonella* species in 1 patient.

The following treatment options were used either alone or in combination: glucocorticoids (100%), azathioprine (33%), cyclophosphamide (33%), methotrexate (22%), immunoglobulins (16%), and cyclosporine (5%). Four patients were treated with glucocorticoids alone, 5 patients with glucocorticoids plus 1 immunosuppressive drug, 7 patients with glucocorticoids and 2 immunosuppressive drugs, and 2 patients with 3 or more immunosuppressive drugs (see Table 1).

### Antibody Profile and HLA

Seven patients were ANA-positive, with titers ranging from 1/320 to 1/2560. Anti-Ro/SSA antibody was found in 4 patients, and anti-Ro52 antibody in 5 patients. Anti-La/SSB was found in 2 patients, and anti-PM-Scl, anti-RNP, and anticardiolipin

**TABLE 1.** Clinical and Serologic Features of 18 European Patients With Antisynthetase (PL-7) Syndrome

Patient	Age/Sex (yr)	Smoking Status	Job	Myositis	AR	Ray	MH	Fever	ILD	PD	Ab	Therapy	Death
1	65/F	No	Shop worker	DM	Yes	Yes	Yes	No	Yes	Yes	ANA, RF	GC + CP+ MTX+AZA	Yes; sepsis
2	52/F	Yes	Administration	DM	Yes	No	Yes	No	No	Yes	Ro, Ro52	GC+AZA+IG	
3	56/F	No	Housewife	ADM	Yes	No	Yes	No	Yes	Yes	ANA, Ro52	GC+CP+AZA	
4	37/F	No	-	DM	No	No	No	Yes	No	Yes	ANA, Ro	GC+CYS+IG	
5	45/F	No	Cleaning worker	PM	Yes	Yes	No	Yes	Yes	Yes	ANA	GC+AZA	Yes; MI
6	40/F	Yes	Administration	PM	No	Yes	No	No	No	No	PM-Scl	GC	
7	55/F	No	Administration	PM	Yes	Yes	No	No	No	No	-	GC	
8	32/F	No	Administration	PM	Yes	Yes	No	No	No	No	RNP	GC	
9	40/F	No	Waiter	PM	Yes	No	No	Yes	No	No	Ro, La	GC+MTX	
10	38/F	No	Toy factory	PM	Yes	Yes	Yes	No	No	Yes	Ro, La	GC+CP+AZA	
11	55/F	No	Farmer	PM	No	Yes	No	No	Yes	No	ANA, ACA	GC+CP	
12	53/F	Yes	Car factory	PM	Yes	Yes	No	Yes	Yes	Yes	-	GC+MTX	
13	62/M	Yes	Plumber	PM	No	Yes	Yes	Yes	Yes	Yes	ANA, Ro52, CL	GC+MTX	
14	61/M	Yes	Miner (uranium)	PM	No	No	No	Yes	Yes	No	Ro52	GC	
15	46/M	Yes	Song writer	PM	No	No	No	Yes	Yes	No	-	GC+AZA+MF	
16	58/F	Yes	Administration	DM	Yes	Yes	No	Yes	No	NA	RF, CCP	GC+AZA+ MTX	
17	69/F	No	Administration	PM	Yes	Yes	No	Yes	Yes	Yes	-	GC+CP+MTX	Yes; ILD
18	40/F	Yes	Administration	DM	Yes	No	No	Yes	Yes	No	ANA, Ro52	GC+CP+AZA+ MTX+IG	Yes; ILD

Abbreviations: Ab = antibodies, ADM = amyopathic dermatomyositis, AR = arthritis, AZA = azathioprine, CCP = cyclic citrullinated peptide, CL = cardiolipin, CP = cyclophosphamide, CYS = cyclosporin, GC = glucocorticoids, IG = intravenous immunoglobulin, MF = mycophenolate, MH = mechanic's hands, MI = myocardial infarction, MTX = methotrexate, NA = not available, PD = pericardial disease, RF = rheumatoid factor, Ray = Raynaud phenomenon.

antibodies were found in 1 patient each. Rheumatoid factor was positive in 2 cases, 1 of whom additionally had anticyclic citrullinated peptide. HLA typing was performed in 13 patients.

**TABLE 2.** Immunogenetic Profile (HLA Class II Alleles) of 18 Patients With Antisynthetase (PL-7) Syndrome

Patient	HLA-DRB1
1	-
2	HLA-DRB1*03,04
3	HLA-DRB1*04,15
4	HLA-DRB1*12
5	-
6	HLA-DRB1*03
7	HLA-DRB1*07,*07
8	HLA-DRB1*04,*11
9	HLA-DRB1*03,*04
10	HLA-DRB1*11
11	-
12	HLA-DRB1*04,*07
13	HLA-DRB1*03,*11
14	-
15	-
16	HLA-DRB1*01,*11
17	HLA-DRB1*03,*04
18	HLA-DRB1*08,*15

DRB1 haplotype is shown in Table 2. The most common haplotypes were DRB1\*04 in 6 patients and DRB1\*03 in 5 patients. Only 2 of the patients with ILD showed the DRB1\*03 allele.

**Literature Review**

We identified 54 additional cases of anti-PL-7 antisynthetase syndrome in the literature. The main clinical manifestations in the overall group of 72 patients (present cohort and reported cases) were ILD in 56 (77.8%) patients and myositis in 54 (75%). The prevalence of other signs and symptoms of anti-PL-7 antisynthetase syndrome is summarized in Table 3.

**DISCUSSION**

Antisynthetase syndrome, to our knowledge first described in 1990, is recognized by its characteristic clinical manifestations associated with the presence of an anti-tRNA synthetase antibody.<sup>20</sup> Anti-Jo-1 is the most frequent, followed by anti-PL-12 and anti-PL-7. It has been suggested that in addition to a common core syndrome, different clinical features may be associated with different antisynthetase antibodies, but the scarcity of published studies, most of which are case reports, precludes any definitive conclusions in this regard.<sup>16</sup>

In the present study, we analyzed the clinical and laboratory features of a series of anti-PL-7-positive patients from 5 European countries. In common with other reported antisynthetase syndromes, myositis and ILD were the most frequent manifestations of anti-PL-7-associated syndrome, and these common features were confirmed in a review of all cases published

**TABLE 3.** Main Characteristics of Patients With Antisynthetase (PL-7) Syndrome, Previous and Present Reports

<b>Anti-PL-7 Report (First Author, Ref.)</b>	<b>No. of Patients</b>	<b>Myositis (No.)</b>	<b>ILD (No.)</b>	<b>Arth (No.)</b>	<b>Ray (No.)</b>	<b>MH (No.)</b>	<b>Fever (No.)</b>	<b>PE (No.)</b>
Hervier <sup>12</sup>	12	6	12	4	1	4	8	4
Sato <sup>25</sup>	7	6	7	6	4	2	4	-
Fischer <sup>9</sup>	7	3	7	-	-	-	-	-
Yamasaki <sup>33</sup>	6	4	6	3	2	-	-	1
Mathews <sup>21</sup>	5	4	1	3	2	-	-	1
Dugar <sup>7</sup>	4	3	2	1	2	1	1	-
Marguerie <sup>20</sup>	4	3	3	4	4	-	-	-
Targoff <sup>29</sup>	4	4	3	4	1	-	-	-
Lega <sup>17</sup>	3	1	3	2	1	1	-	1
Troyanov <sup>31</sup>	2	2	2	1	1	-	-	-
Labirua-Iturburu (PR)	18	18	10	12	11	5	10	9
Total, no. (%)	72	54 (75)	56 (77.8)	40 (55.6)	29 (40.3)	13 (18)	22 (30.5)	16 (22.2)

Abbreviations: Arth = arthritis/arthralgia, MH = mechanic's hands, PE = pericardial effusion, PR = present report, Ray = Raynaud phenomenon.

to date in the literature. An unexpected finding in the current cohort was pericardial effusion in half of our cases.

Due to the low patient numbers, few studies have focused on the clinical and laboratory characteristics of patients with anti-PL-7 antibodies. The most complete are 2 studies performed in Japan, comprising 7 and 6 patients, respectively,<sup>25,33</sup> and a 2011 report by Hervier et al<sup>12</sup> in France with 12 patients. In these studies, ILD was present in 100% of cases, while myositis appeared in 50%–86%. In the present series, 6 of 18 patients did not have diagnosed ILD, and there was a much higher prevalence of myositis (all patients had idiopathic inflammatory myopathies except 1, who had amyopathic dermatomyositis). These results differ to some degree from those of previous studies, in which the prevalence of myositis in patients with non-Jo-1 antisynthetase autoantibodies was lower than in patients with anti-Jo-1.<sup>10,15</sup> However, a pooled analysis of our findings together with those from all published case reports and series in the literature<sup>7,9,12,17,20,21,25,29,31,33</sup> (72 anti-PL-7-positive patients) showed that the frequency of ILD and myositis (77.8% and 75%, respectively; see Table 3) does not differ greatly from the clinical findings in patients with anti-Jo-1. One explanation for the discrepancies between individual studies could be the potential selection bias involved in the study of all rare diseases. In small series, some clinical manifestations might be overrepresented; hence to try to overcome these problems, we included a review of all cases published in the literature, in addition to our own cohort, and analyzed the pooled data set. Other possible reasons for the dissimilar results might be the racial/ethnic or genetic background of the patients, a different referral pattern (pulmonary, rheumatology, or internal medicine specialists), and the fact that in many cases, only patients with clinically evident myositis were tested for antisynthetase antibodies.

Little is known about the etiopathogenesis of the antisynthetase syndrome, or for that matter, of myopathies in general. According to some authors, an unknown trigger (for example, viral infection) might enter the respiratory tract and lead to a conformational modification of aminoacyl-tRNA synthetase in the pulmonary alveoli. This could result in production of autoantibodies against the synthetase enzyme; this immune response (antibodies and specific T cells) would spread to other internal organs such as muscle and joints.<sup>18,19</sup> An interesting factor that should be investigated in well-designed studies is the contribution of organic/inorganic dust inhalation at work, which could be

another etiologic trigger of autoimmunity. There has been some evidence supporting the idea of environmental exposure to antigens as an initial step in the pathogenesis of antisynthetase syndrome.<sup>30</sup> In the current series, 6 patients had been occupationally exposed to different organic/inorganic particles and all but 1 had ILD. Nonetheless, statistical significance was not achieved for this factor, probably because of the small number of patients studied.

It is noteworthy that 9 of 18 patients in the current series had pericardial effusion. In the study by Hervier et al,<sup>12</sup> 4 of 12 (33%) patients with anti-PL-7 had pericardial effusion, and 3 other single cases have been reported in different studies.<sup>17,21,33</sup> Pericarditis is, compared to systemic lupus erythematosus, infrequent in patients with myositis. The reason patients with anti-PL-7 develop pericardial disease is unknown. It can be speculated that anti-PL-7 antibodies act against certain antigens in pericardial tissue, and thereby lead to pericardial inflammation. Nevertheless, some cases of pericarditis have also been reported in patients with anti-Jo-1.<sup>6,23</sup> In a study and a review of literature by Schmidt et al,<sup>26</sup> they found a prevalence of 18% of pericarditis in a total of 231 anti-Jo-1 patients, and we cannot exclude that pericarditis is underestimated in myositis patients because of low physical function due to muscle and lung involvement.

Other relevant observations can be drawn from this study. First, it seems that clinical heterogeneity is a feature of the antisynthetase syndrome, irrespective of the autoantibody implicated. The results from the pooled analysis indicate that although antisynthetase syndrome can present with a single clinical manifestation (for example, myositis, ILD, Raynaud phenomenon, arthritis, mechanic's hands), the most common features are myositis, ILD, and arthritis. The frequency of these symptoms is similar to that seen in patients with anti-Jo-1 antibodies. As for the prognosis of antisynthetase syndrome, which is currently poorly defined, ILD seems to be the major cause of death. It has been suggested that ILD associated with antisynthetase syndrome may have a better prognosis than antibody-negative ILD,<sup>8</sup> but this has yet to be confirmed. As was seen in the current study and 1 previously reported study,<sup>12</sup> ILD in patients with antisynthetase syndrome can be aggressive and refractory to treatment. It has been reported that coexisting Jo-Ro antibodies may predict more severe ILD,<sup>32</sup> but only 1 of our patients who died of ILD was anti-Ro52-positive. Further study of lung disease in larger antisynthetase syndrome cohorts is needed to elucidate these findings.

One limitation of the present study is its retrospective nature and the fact that complete data sets were not available for all patients. Not all patients underwent pulmonary function tests or high-resolution computed tomography; hence, asymptomatic ILD could be more prevalent in our cohort than our results suggest. In addition, a heterogeneous referral pattern could have led to both over- and underdiagnosis of some clinical features. Lastly, the small sample size due to the relative rarity of the syndrome probably contributed to a lack of statistical power in some of the comparisons.

In conclusion, our study of a European cohort of anti-PL-7 patients identified myositis as the most frequent clinical manifestation, with ILD being less prevalent than has been previously reported. Nevertheless, when these manifestations were evaluated in all the cases reported to date, including those from the present study, their prevalence did not vary greatly from the rates reported for other antisynthetase antibody syndromes. Occupational exposure should be taken into account in these patients, because environmental antigens could contribute to triggering the immune response and the development of the disease. The unexpected high percentage of patients with pericardial effusion in our cohort is a novel finding and needs to be confirmed in future series. It may be a characteristic of anti-PL-7 antisynthetase syndrome, which could warrant a recommendation of routine transthoracic echocardiography in patients presenting with this serotype.

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