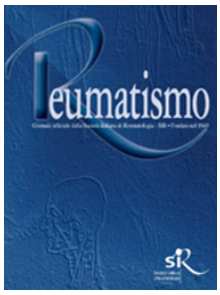

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Antisynthetase syndrome with anti-glycyl tRNA synthetase antibodies in a patient with axial spondyloarthritis treated with tumor necrosis factor-α inhibitors

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Summary
We present a case of interstitial lung disease arising in the course of antisynthetase syndrome (ASSD) in a patient with axial spondyloarthritis (ax-SpA) undergoing tumor necrosis factor-α (TNF-α) inhibitors therapy.
Only two cases of ASSD in ax-SpA patients have been described in the literature, although with a different autoantibody profile. Only in one case, ASSD manifested with lung involvement, without the possible implication of TNF-α inhibitors in the pathogenesis, as it occurred concurrently with spondyloarthritis.
Our case is the first to emphasize the coexistence of ASSD with anti-glycyl tRNA synthetase antibodies and ax-SpA, reminding us of the possible, although rare, adverse effects on the lungs with TNF-α inhibitors.

Introduction

Antisynthetase syndrome (ASSD) is a rare syndrome classified within the group of idiopathic inflammatory myopathies (IIM). It is characterized by the presence of antibodies against aminoacyl-transfer RNA synthetases, which are crucial for diagnosis. These antibodies include anti-Jo-1, anti-PL-7, anti-PL12, anti-glycyl tRNA synthetase (anti-EJ-1), anti-OJ, anti-KS, anti-Zo, anti-YRS/Ha, anti-SC, anti-JS, and anti-Wa. Clinically, ASSD typically presents with six main features: fever, myositis, interstitial lung disease (ILD), inflammatory polyarthritis, Raynaud's phenomenon, and mechanic's hands. However, the presentation may vary widely among patients, leading to a heterogeneous clinical picture. The development of ILD may occur independently, precede, coincide with, or follow myositis onset. This variability can make diagnosis challenging, often resulting in misdiagnosis and delayed initiation of appropriate therapies (1). Treatment for active myositis and long-term maintenance of disease remission includes the use of conventional synthetic disease-modifying anti-rheumatic drugs, such as methotrexate, azathioprine, tacrolimus, cyclosporine, and mycophenolate mofetil, or, in refractory cases, biologic disease-modifying anti-rheumatic drugs, such as rituximab, or intravenous (IV) immunoglobulin (2).

We report a case of ASSD with antibodies to anti-EJ-1 in a patient with axial spondyloarthritis (ax-SpA), who had been treated with adalimumab and golimumab over the previous 8 years.

To the best of our knowledge, this is the first reported case of anti-EJ-1 ASSD in a patient with ax-SpA previously treated with tumor necrosis factor-α (TNF-α) inhibitors.

Case Report

A 48-year-old man was admitted to the emergency department with epigastric pain, breathlessness, dyspnea, and fever that had been worsening over the past month. The patient had been diagnosed 25 years earlier with peripheral spondyloarthritis, fulfilling the 2009 Assessment of SpondyloArthritis international Society classification criteria (3).

At the onset, he exhibited recurrent episodes of dactylitis and arthritis of the small joints of the feet and hands. Due to isolated peripheral joint involvement, therapy with methotrexate was initiated but stopped several years later due to gastrointestinal disturbances. Subsequently, he was treated with sulphasalazine and steroids for an unspecified period. Owing to the onset of low back pain due to MRI-confirmed, bilateral sacroiliitis, the patient has been treated with the TNF-α inhibitor drug adalimumab for the past 7 years. This treatment was switched to golimumab 8 months ago, following two episodes of bilateral uveitis. A diagnosis of ax-SpA was made. HLA-B27 was positive. The patient was a former smoker with no other noteworthy medical history except for bronchial asthma and previous episodes of kidney stones, but had no family history of autoimmune diseases. He worked as a computer technician.

Blood tests upon admission revealed a white cell count of 6.04×10^3/uL, a neutrophil count of 4.01×10^3/uL, a C-reactive protein of 7.39 mg/dL and fibrinogen of 840 mg/dL. Renal and liver function were normal, as creatine kinase and lactic dehydrogenase. Clinical examination showed diffuse bilateral chest crackles and oxygen saturation levels of 98% on room air, with a respiratory rate of 14 breaths/min. His temperature was 37.5°C. No signs of active joint inflammation, rashes, or muscle weakness were observed. Thorax computed tomography (CT) scan revealed bilateral peribronchial and peri-ilar areas of parenchymal consolidation with some ground glass opacities, prevalent in the inferior lobes. Pleural and pericardial effusions were absent. The arterial blood gas analysis showed mild hypoxemia which required oxygen supplementation at 2 L/min, and treatment with antibiotic therapy (ceftriaxone 2 g/day plus clarithromycin 500 mg twice daily) and glucocorticoids (prednisone 25 mg/day) was initiated. Golimumab was withdrawn.

Within a week after hospital admission, the patient experienced a severe progressive deterioration in respiratory function, which required non-invasive ventilation. The contrast-enhanced CT scan confirmed the presence of the consolidative areas and showed worsening of ground-glass opacities, extending predominantly to the middle and lower lung fields without signs of pulmonary embolism (Figure 1). Antibiotic therapy was intensified, initially with azithromycin 750 mg/day plus levofloxacin 750 mg/day, then with meropenem 1 g/day. Glucocorticoid IV therapy was started with methylprednisolone

40 mg/day. For a better characterization of the possible infectious pneumonia, sputum testing and bronchial washing were performed, yielding negative results for bacteria, viruses, and fungi infection. Quantiferon tuberculosis gold test, blood cultures, and urine examination were negative for microbial species, too. Cytological analysis of the bronchoalveolar lavage did not reveal any malignant cells. Transbronchial lung biopsy was compatible with organizing pneumonia (OP).
Heart failure was ruled out by an echocardiogram performed in the following days, which showed normal left ventricular systolic function. Rheumatological workup revealed 1:160 fluorescent antinuclear antibodies with a nucleolar and cytoplasmic pattern, negative extractable nuclear antigen screen, anti-aminoacyl tRNA synthetase antibodies, and anti-EJ-1 elevated at 61 AU (immunoblotting) and anti-SSA/Ro52 at 22 AU (immunoblotting). A diagnosis of acute ILD in the course of ASSD was made according to Connors, Solomon, and Lega criteria (4). Subsequent management involved IV methylprednisolone 1 g for 3 days, followed by 1 mg/kg/day, IVIG (200 mg/kg × 5 days) and rituximab (1000 mg/2 infusions spaced 2 weeks apart). Trimethoprim/sulfamethoxazole therapy was initiated for *Pneumocystis jirovecii* pneumonia prophylaxis. In the initial days since the start of therapy, there was no clinical improvement, and the patient continued to require respiratory ventilation. After the second dose of rituximab, while still receiving methylprednisolone 1 mg/kg/day, the patient started to improve. Gradually, he was able to discontinue non-invasive ventilation, and the need for oxygen diminished. The patient was discharged in good clinical condition, requiring oxygen supplementation only during exertion and at night. Corticosteroid therapy was gradually reduced to 0.5 mg/kg/day.
A follow-up, chest high-resolution CT after 2 months of treatment showed substantial improvement in bilateral lower lobe peribronchial consolidation, along with scattered areas of ground glass attenuation and reticulation. Corticosteroid therapy was further tapered, and treatment with TNF-α inhibitor was not resumed.

Discussion

ASSD is classified as an IIM, even though inflammatory muscle involvement may be absent or appears years after lung disease, which occurs in approximately 90% of patients (5). The clinical presentation of ASSD varies considerably between patients, with many presenting only with isolated interstitial lung involvement. ILD, found in 70-90% of patients, is frequently predominant at disease onset and is the major determinant of morbidity and mortality. Common ILD patterns include non-specific interstitial pneumonia (NSIP), OP, mixed NSIP-OP, and rarely, usual interstitial pneumonia (6). The suspicion of ASSD should always be considered in cases of ILD and other characteristic features of the disease, such as Raynaud's phenomenon, mechanic's hands, arthritis/arthralgia, and myopathy. Joint involvement occurs in up to 90% of patients and can manifest in four patterns: arthralgia, non-erosive non-deforming arthritis of small joints, non-erosive deforming arthritis of small joints, and symmetric erosive polyarthritis (7). Most papers describe findings stratified by anti-Jo1 and non-anti-Jo1 ASSD patients, with decreased survival rates in the former (8). Among these cases, anti-EJ-1 are strongly associated with ILD, with pulmonary manifestations typically presenting acutely and myositis being less common (9). The coexistent positivity of anti-SSA/Ro52 is considered to be associated with an increased frequency of ILD, with a still debated role in the progression of lung disease (10). The mainstay of treatment is immunosuppression, although there is currently no standardized treatment due to the absence of randomized controlled trials. Therefore, the choice of immunosuppression typically follows treatment strategies adopted for ILD secondary to IIM in general. Steroid-sparing immunosuppressants include azathioprine, mycophenolate mofetil, and methotrexate as first line; cyclophosphamide and tacrolimus as second line; and rituximab in refractory cases (1).
The association between spondyloarthritis and ASSD is extremely rare and primarily documented through case reports: as far as we know, ax-SpA has not been previously reported in association with anti-EJ-1 ASSD. Only eight cases of the coexistence of IIM with ax-SpA have been described in the literature, with two patients treated with TNF-α inhibitors in the 2 years before. Among them, two patients carried anti-MDA5 antibodies, one SRP antibody, one PL-7 antibody, and one Jo-1 antibody. The other three patients did not show positivity to myositis-specific or associated antibodies. Seven out

of eight were diagnosed with myositis many years after the diagnosis of spondyloarthritis; one was diagnosed with ankylosing spondylitis together with myositis onset (Table 1). Notably, the diagnosis of ASSD was confirmed in only two cases (11, 12).
The co-occurrence of these two conditions is very intriguing, as it prompts a multitude of unresolved questions. The potential mechanism underlying the simultaneous onset of the two diseases remains unknown: Chen *et al.* excluded the incremental risk of developing myositis in patients with spondyloarthritis (13), and many studies suggest that environmental factors may play a role in genetically predisposed individuals. Based on these premises, our clinical case raises an important question about the potential role of TNF-α inhibitor therapy as trigger of ASSD. ILD and various autoimmune conditions have been reported to be induced by TNF-α inhibitor therapy during the past years, including IIM and ASSD in rheumatoid arthritis patients. The pathological mechanism appears to be based on the inhibition of cytotoxic T lymphocytes, which in turn suppress auto-reactive B cells, resulting in an increase in interferon-γ, which is implicated in the pathogenesis of myositis (14). However, the occurrence of ILD is quite rare when compared to the overall number of TNF-α inhibitor drug users, and this is particularly true for patients with SpA, where ILD affects patients to a lesser extent compared to those with rheumatoid arthritis.

Conclusions

To the best of our knowledge, this is the first reported case of the coexistence of ax-SpA and ASSD with EJ-1 positivity. Cases of ASSD have been previously described in patients with rheumatic diseases treated with tumor necrosis factor inhibitors, but none of these has been definitively attributed to the use of this class of drugs.
The case we presented highlights several aspects: firstly, it describes an unusual overlap between two rheumatologic conditions and, when considered alongside other clinical cases in the literature, it may alert the clinician in diagnosing this rare overlap. Additionally, it remains unclear whether our patient developed ASSD as a result of long-term immunosuppression with TNF-α inhibitors or whether it would have occurred regardless of the therapy. Some studies have identified a positive association between TNF-α inhibitor therapy and ILD development within the first 12 months of treatment and advise against using these drugs in patients with ILD (15). There is uncertainty regarding whether the specific type of TNF-α inhibitor might have impacted the onset of ASSD, as it became apparent 8 months into golimumab therapy with no ILD detected on chest radiographs performed before starting the drug.

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Table 1. Clinical symptoms, findings and treatment of axial spondyloarthritis and idiopathic inflammatory myopathy patients from the literature.

Ref	11				12			
Gender	Male	Female	Male	Female	Female	Female	Male	Male
Onset age of Ax-SpA (years)	22	29	39	32	30	30	16	57
Onset age of IIM (years)	28	49	55	32	44	30	26	57
HLA-B27	Yes	Yes	Yes	Yes	No	No	No	Yes
Skin rash	Gottron sign	No	Gottron sign	No	No	Heliotrope sign	No	Hyperkeratosis
Muscle weakness	Grade 3	Grade 3	Grade 5	Grade 4	Grade 3	Grade 4	Grade 5	NA
Peripheral arthritis	Yes	No	Yes	No	No	Yes	No	Yes
Low back pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MSA/MAA	No	SRP	MDA5	No	No	MDA5	PL-7	Jo-1
Muscle MRI	NA	IE	NA	NA	Normal	IE	IE	NA
Muscle biopsy	PA	Necrosis	PA	Necrosis	Necrosis	Inflammatory infiltration	PA	NA
ILD	No	NSIP	OP	No	No	OP	No	Yes, undefined pattern
SpA treatment	THD	IFX	ETA, SSZ	NSAIDs	NSAIDs	NSAIDs	NSAIDs	GC, CYC
IIM treatment	GC, HCQ	GC, TAC, TCZ	GC, CsA	GC, MTX	GC, MTX	GC, CsA, IVIG	GC	GC, CYC
Outcome	54 months improved	36 months improved	18 months improved	36 months improved	36 months improved	16 months improved	12 months improved	NA

AX-SpA, axial spondyloarthritis; IIM, inflammatory myopathy; MSA/MAA, myositis specific antibodies/myositis associated antibodies; MRI, magnetic resonance imaging; NA, not available; IE, inflammatory exudation; PA, perifascicular atrophy; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia, THD, thalidomide, IFX, infliximab, ETA, etanercept; SSZ, sulphasalazine; NSAIDs, non-steroidal antiflammatory drugs; GC, glucocorticoids, CYC, cyclophosphamide; HCQ, hydroxychloroquine; TAC, tacrolimus, TCZ, tocilizumab; CsA, cyclosporine; MTX, methotrexate; IVIG, intravenous immunoglobulin therapy.

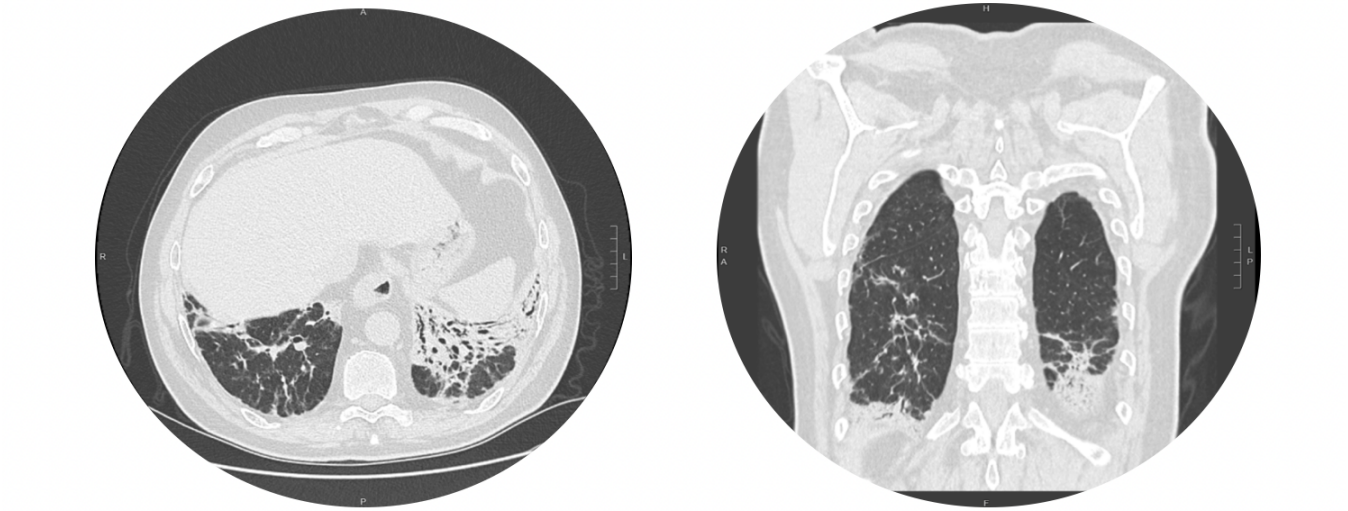

Figure 1. Chest high-resolution computed tomography showing consolidative areas in the basal lobes and bronchial distortion within the opacities: organizing pneumonia.