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Title of the article:

A case of anti-synthetase syndrome in a rheumatoid arthritis patient with anti-PL-12
antibody following treatment with etanercept

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Abstract:

In our earlier study, we had reported the case of a patient with rheumatoid arthritis (RA), who had anti-Jo-1 antibodies. This patient had received etanercept (ETN) therapy for RA, after which she had developed overt polymyositis (PM). Although various autoimmune phenomena, including lupus-like diseases, vasculitides, or psoriatic skin lesions, are associated with anti-tumor necrosis factor (TNF) therapy, the development of PM/dermatomyositis (DM) or antisynthetase syndrome following anti-TNF therapy is extremely rare. Here, we report a case of an RA patient with anti-PL-12 antibodies, who received ETN therapy and subsequently developed the antisynthetase syndrome. She recovered when ETN therapy was withdrawn and high-dose corticosteroid was administered. To date, there have been only 5 reported cases of RA patients with anti-Jo-1 antibodies who developed overt PM/DM following anti-TNF therapy and only 1 case of antisynthetase syndrome in an RA patient with anti-PL-7 antibodies. Our patients and the abovementioned reports strongly suggest that onset of overt PM/DM or antisynthetase syndrome in RA patients with anti-aminoacyl t-RNA synthetase antibodies is associated with anti-TNF therapy.

Keywords:

anti-TNF therapy, polymyositis/dermatomyositis, anti-ARS antibodies, adverse drug effect

Introduction

We had previously reported the case of a patient with rheumatoid arthritis (RA), who had been positive for anti-Jo-1 antibodies and had developed polymyositis (PM) following etanercept (ETN) therapy for RA [1]. Although various autoimmune phenomena, including lupus-like diseases, vasculitides, or psoriatic skin lesions, associated with anti-tumor necrosis factor (TNF) therapy have been reported [2], the development of PM/dermatomyositis (DM) following anti-TNF therapy is extremely rare. Only 5 such cases have been reported, including our previous report [1, 3-7], and only 1 report has shown the association of antisynthetase syndrome with anti-TNF therapy against RA [7]. Here, we report a case of an RA patient with anti-PL-12 antibodies (an anti-aminoacyl tRNA synthetase [ARS] antibody) who was successfully treated with ETN therapy for active RA; however, the patient subsequently developed overt antisynthetase syndrome.

Case report

A 63-year-old woman, who had been treated for nonspecific interstitial pneumonia (NSIP) with prednisolone (PSL) and cyclosporine for 3 years, was diagnosed with RA because she had morning stiffness, systemic joint swelling and tenderness, elevated levels of inflammatory markers such as C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR). Moreover, her serum was positive for rheumatoid factor (RF) and anti-citrullinated-cyclic-peptide (CCP) antibody. At the time of RA diagnosis, NSIP was not active, and she did not have any respiratory symptoms while she was

receiving a maintenance dose of PSL without concomitant administration of cyclosporine. Although tacrolimus (TAC) was chosen as the disease-modifying antirheumatic drug (DMARD), it was only minimally effective for the treatment of arthritis, despite adequate duration of treatment. The maintenance dose of PSL was 10 mg daily. ETN (25 mg, twice daily) was administered along with TAC and PSL for the adequate control of active arthritis. Consequently, the joint swelling and tenderness subsided, and the levels of the inflammatory markers decreased rapidly. However, systemic arthralgia recurred 2 months after the initiation of ETN therapy; this was accompanied by low-grade fever and erythema on the trunk. In addition, the chest roentgenogram revealed exacerbation of ground-glass opacities. Since adverse drug reactions were suspected, ETN therapy was discontinued, but the symptoms persisted. The patient was admitted for further examination and treatment.

On admission, she was mildly febrile, and we observed a flare-up of systemic joint swelling and tenderness after ETN cessation. She experienced dyspnea on exertion, but the arterial oxygen saturation and the findings of the pulmonary function test were almost normal. Trunk erythema disappeared completely, and eruptions, including Gottron's papule, heliotrope rash, or mechanic's hand, were not detected. She had no muscular symptoms, and manual muscle tests yielded normal findings. Further, nerve conduction study and electromyography did not reveal any specific abnormal findings. Plain radiography of the joints of the hands and feet revealed periarticular osteoporosis, multiple bony erosions, and joint space narrowing, thereby indicating stage II RA of the Steinbrocker classification. Chest

roentgenography and computed tomography showed exacerbation of interstitial markings at the base of both the lungs (Figure 1). Laboratory examinations revealed that the CRP level was 6.9 mg/dL; ESR, 85 mm/h; and IgG level, 2,538 mg/dL. The creatine kinase level was normal. The autoantibody profiles showed IgM-RF level of 284 IU/mL, anti-CCP antibodies of >100 U/mL, 1:320 fluorescent antinuclear antibodies with speckled and nucleolar patterns, and anti-Sjogren's syndrome antigen A (anti-SS-A/Ro) antibodies of 84.8 U/mL. In addition, the analysis of her serum by the RNA-immunoprecipitation (IPP) method with HeLa cell extracts revealed that her serum was positive for anti-PL-12 antibody. On the basis of these findings, she was diagnosed with antisynthetase syndrome. Treatment with 1 mg/kg of PSL was highly successful: dyspnea subsided and radiography images showed rapid disappearance of interstitial markings (Figure. 3, 4). Presently, she is healthy and she is receiving a maintenance dose of PSL, and the disease has not recurred. Although TAC is only a DMARD used for the control of RA, arthritis has never recurred, and no additional treatment agents, including biologic agents, are required.

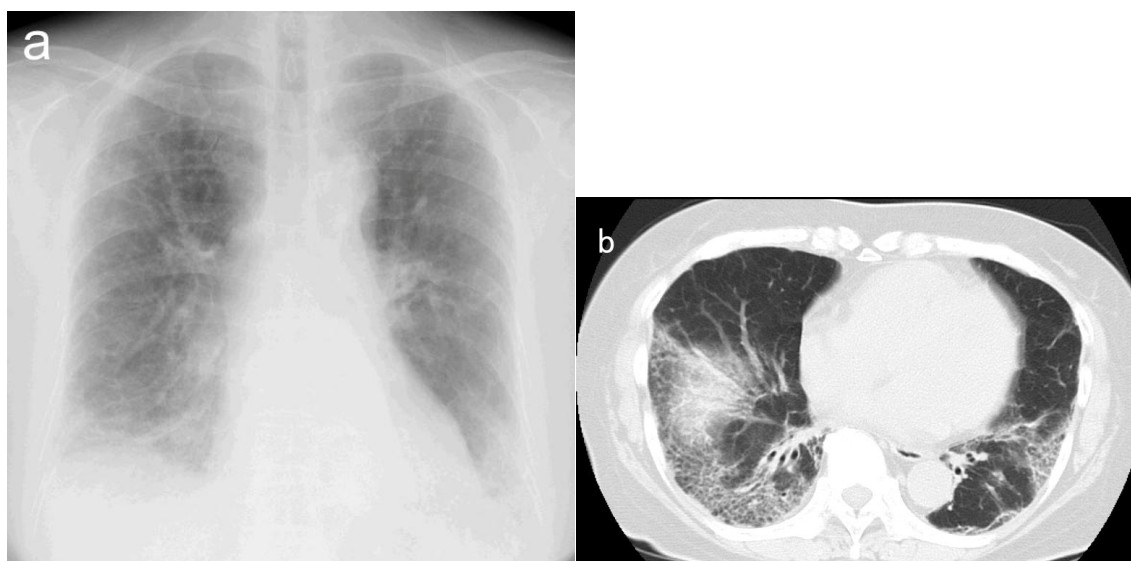


Fig. 1 Chest X-ray and computed tomography scan on admission, showing reticulonodular shadows at the base of both the lungs.

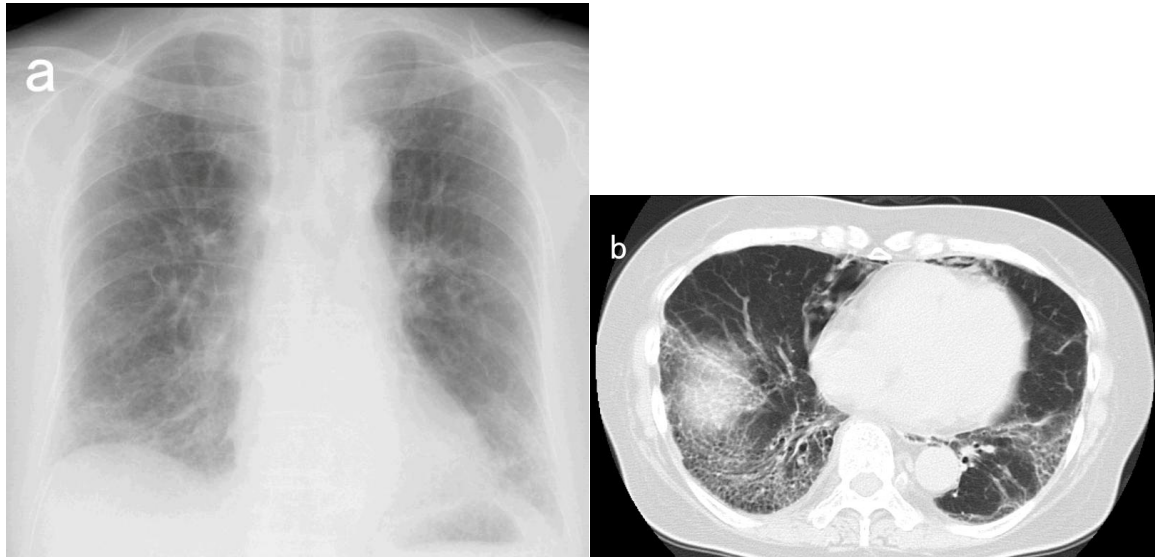


Fig. 2 Chest X-ray and computed tomography scan after treatment, showing improvement of interstitial markings.

Discussion

Antisynthetase syndrome is characterized by many clinical features, including mild to moderate grade fever; polyarthritis, usually without joint destruction; interstitial lung disease (ILD), especially NSIP; and characteristic skin eruptions called mechanic's hand, with or without inflammatory myositis in patients with anti-ARS antibodies [8]. Anti-ARS antibodies recognize ARSs in many cells, including myocytes; 6 major anti-ARS antibodies, of which the antigens are histidyl-(Jo-1) [9], alanyl-(PL-12) [10], threonyl-(PL-7) [11], isoleucyl-(OJ) [12], glycyl-(EJ) [12], and asparaginyl-tRNA synthetase (KS) [13], have been reported to date. However, the precise pathophysiological roles of these antigens have not yet

been clarified.

Only 5 cases of PM/DM associated with anti-TNF therapy for RA have been reported so far [1, 3-6]. Four of these 5 patients, including ours, had anti-Jo-1 antibody before the initiation of anti-TNF therapy, and PM/DM resolved after the cessation of anti-TNF therapy and the initiation of corticosteroid (CS) therapy. In addition, 3 of the 4 patients and our patient had ILD, which exacerbated after anti-TNF therapy and subsided after CS therapy (Table 1). Anti-TNF agents used in these reports included infliximab and ETN. New onsets or flare of ILDs following anti-TNF therapies have also been reported, most of which were RA cases [2]. Although the profiles of anti-ARS antibodies in these RA patients were unclear, it is possible that some of the patients had anti-ARS antibodies that may have been associated with exacerbation of ILD. In addition, a Japanese article recently showed a case of an RA patient with anti-PL-7 antibody: this patient had developed overt antisynthetase syndrome following treatment with ETN for RA, but his condition had improved after he discontinued ETN therapy and began treatment with 1 mg/kg of PSL [7]. This report is very similar to our case in its clinical course. Although present case did not show myositis, patients with anti-Jo-1 antibody show myositis more frequently than those with anti-PL-12 antibody [8]. On the other hand, anti-PL-12 antibody is more associated with ILD than with myositis [14]. Although several common clinical features characterize the antisynthetase syndrome, there are also some differences among patients with different anti-ARS antibodies, which will be clarified in a future study that shows the pathobiological roles of each antibody.

Table.1 Clinical characteristics of RA patients who developed anti-synthetase syndrome after anti-TNF Therapy

Authors [referral number]	Harald AH et al [3]	Musial J et al [4]	Urata Y et al [5]	Ishikawa Y et al [1]	ishiguro et al [7]	Present case
Age & Sex	44 female	52 female	52 female	58 female	52 male	63 female
RF/CCP	-/-	+/ND ^{※1}	+/ND	+(724.7)/+(> 100)	+ (1376)/+ (523)	+(64.7)/+(> 100)
Disease duration of RA (years)	1	20	33	2	12	0.3
DMARDs ^{※2}	HCQ ^{※3} , MTX ^{※4}	MTX	MTX	BUC ^{※5} , TAC ^{※6}	BUC, MTX, TAC	BUC, TAC
Anti-TNF therapy	Etanercept	Infliximab	Infliximab	Etanercept	Etanercept	Etanercept
Onset from anti-TNF therapy initiation (months)	6	6	9	2	26	2
FANA ^{※7}	1:640, Spe. ^{※8}	1:320, pattern unknown	1:640, Ho. ^{※9} /Spe.	1:320, Ho./Nuc. ^{※10}	negative	1:160, Spe./Nuc.
Anti-synthetase antibody	Jo-1	Jo-1	Jo-1	Jo-1	PL-7	PL-12
Fever	ND	Yes	ND	No		Yes
Skin eruptions	erythematous rash over the extensor surfaces of the MCP, PIP, and DIP joints; periungual erythema	ND	ND	No	heliotrope rash, Gottron's macule	Erythematous rashes on trunk; disappeared without treatment
Exacerbation of ILD ^{※11}	Yes; NSIP ^{※12}	No; UIP ^{※13}	Yes; NSIP	Yes; NSIP	Yes; NSIP	Yes; NSIP
Muscle biopsy	Necrosis, perivascular interstitial infiltration	Diffuse necrosis, inflammatory infiltrates	Size variation, inflammatory infiltrates	Mild inflammatory infiltrates and necrosis	ND	ND
Diagnosis	Dermatomyositis	Polymyositis	Polymyositis	Polymyositis	Anti-synthetase syndrome	Anti-synthetase syndrome
Treatment ^{※14}	High-dose PSL ^{※15} plus AZP ^{※16} 150 mg & MTX 10 mg/wk	MP ^{※17} pulse 1.0 g plus PSL 1mg/kg	PSL 30 mg plus TAC 3 mg	PSL 1mg/kg plus MP pulse 0.5 g	PSL 1mg/kg plus MP pulse 1 g	PSL 1mg/kg
Treatment outcome	Improvement; NSIP also	Improvement; UIP unchanged	Improvement; NSIP also	Improvement; NSIP also	Improvement; NSIP also	Improvement; NSIP also

※1ND Not done or Not described ※2 DMARDs disease modifying anti-rheumatic drugs ※3 HCQ hydroxychloroquine ※4 MTX methotrexate ※5 BUC bucillamine ※6 TAC tacrolimus ※7 FANA fluorescent antinuclear antibody ※8 Spe. Speckled ※9 Ho. Homogenous ※10 Nuc. Nucleolar ※11 ILD interstitial lung disease ※12 NSIP non-specific interstitial pneumonia ※13 UIP usual interstitial pneumonia ※14 All treatment include withdrawal of anti-TNF therapy ※15 PSL prednisolone ※16 AZP azathiopurine ※17 MP methylprednisolone

RA patients with anti-ARS antibodies may have a risk for developing antisynthetase syndrome after undergoing anti-TNF therapies. Screening the profiles of anti-ARS antibodies in RA patients is not

recommended because RNA-IPP is currently not performed routinely, and the frequency of positivity of the anti-ARS antibodies among RA patients is unclear. However, if anti-TNF therapy is initiated for the treatment of RA, cautions should be taken for patients showing symptoms of the antisynthetase syndrome.

Disclosures: None

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