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Case report

Mizoribine treatment in an elderly diabetic patient with antisynthetase-associated interstitial lung disease

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Abstract

Objective: Immunosuppressive therapy for interstitial lung disease (ILD) is often necessary, but the standard regimen for antisynthetase-associated ILD has not been established.

Patient: An 80-year-old man was hospitalized for severely progressive dyspnea. Bilateral interstitial shadows occurred 1 month before the event. Serological findings showed that he had antisynthetase-associated ILD, as identified by strong positivity for anti-aminoacyl-transfer RNA synthetase (ARS) antibody, despite no evidence of myositis. He was treated transiently with noninvasive positive pressure ventilation and steroid-pulse therapy followed by 60 mg/day of oral prednisolone. However, his diabetes mellitus was aggravated by corticosteroid therapy; thus, a combination of low-dose steroid and mizoribine (MZB), which has a low risk of aggravating glucose intolerance, was used.

Results: The patient's clinical symptoms and daily life activities have been well persevered as an outpatient and well maintained with 200 mg of MZB and 10 mg of prednisolone for several months without obvious clinical recurrence and without any remarkable steroid- and MZB-related side effects.

Conclusion: The use of MZB appeared to suppress the pathophysiology of anti-ARS antibody-associated ILD.

Key words: anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibody, interstitial lung disease, mizoribine, purine antimetabolite imidazole nucleoside

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Introduction

No definitive protocol has been determined for the use of immunosuppressants for interstitial lung disease (ILD). The "antisynthetase syndrome", which is observed in many patients with anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies, is characterized by myositis, fever, ILD, inflammatory arthritis, and Raynaud's phenomenon. ILD is a frequent manifestation of myositis, and its prevalence in patients with anti-ARS antibodies has been estimated to be 50%[1–3]. Corticosteroids are still the first-line therapy for myositis-associated ILD, but additional immunosuppressive agents are often required, including azathioprine, cyclophosphamide, cyclosporine, and tacrolimus[4, 5]. Moreover, immunosuppressive therapy should be aggressively considered for patients who are steroid-resistant and/or have adverse reactions to steroids[6].

However, such immunosuppressive agents also have side effects, such as infection in compromised hosts, including elderly patients and those with glucose intolerance. Mizoribine (MZR) is effective for suppressing the activation of T cells and B cells[7]. It is a purine antimetabolite imidazole nucleoside that is used as an immunosuppressant after renal transplantation and is also used to control rheumatoid arthritis along with other disease-modifying anti-rheumatic drugs.

A case of an elderly patient with acute onset ILD due to suspected anti-ARS antibody is presented in this paper. As he had diabetes mellitus that was incompatible with high-dose corticosteroid therapy, MZB was used in combination with a mild to moderate dose of prednisolone, and he was discharged 2 months after starting immunosuppressive therapy. His diabetes has been manageable, and he has been free of other complications, such as infection and blood cell count abnormalities.

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Patient and Clinical Course

An 80-year-old man had regularly visited the surgical department of our hospital for follow-up of gallbladder stones, but he developed progressive exertional dyspnea days before visiting our emergency room. His oxygen saturation was below 85% even with oxygen administration. Upon review of his serial chest radiographs were reviewed, it was found that bilateral interstitial shadows had occurred 1 month earlier. Though his echocardiogram and electrocardiogram were apparently not abnormal, computed tomography (CT) showed bilateral severe interstitial infiltration; thus, the patient was diagnosed with dyspnea due to acute ILD (Figure 1).

Arterial blood gas analysis showed hypoxia and hyperventilation, as the PaO_2 was 70.1 mmHg, and $PaCO_2$ was 33.1 mmHg even at O_2 of 10 L/min. He did not complain of any dyspnea at rest, but he could not speak a sentence, and he could not take any food at all. Therefore, on day 2, it was decided to manage him with noninvasive positive pressure ventilation (NPPV) during diagnosis and possible treatment.

The etiology of ILD was investigated by serological screening, as shown in Table 1, and it was concluded that this disease was associated with anti-ARS antibody, not including anti-Jo-1 antibody, because of the significant presence of anti-ARS antibody. Infectious disease was less likely based on negativity for inflammatory markers and the results of blood cell counts. Although fibrosis was predominant with elevated KL-6 at 1,960 U/mL (normal level: <500 U/mL), neither symptoms of myopathy and skin changes nor elevations of creatine kinase and aldolase were present.

Treatment with corticosteroid pulse infusion for three consecutive days, followed by oral prednisolone (PSL) 60 mg daily, was started just after blood samples were taken for examination, resulting in resolution of his respiratory symptoms and discontinuation of NPPV on day 11 of hospitalization. However, after PSL administration, his blood glucose level was extremely elevated, and intensive insulin injections had to be started, along with tapering of PSL in a biweekly manner.

He and his family could not manage multiple-injection of insulin each day; therefore, one injection of long-acting insulin was used instead of intensive injections. After deep consideration and careful discussion between our group and the patient's family, to achieve good control of glucose level and to minimize other side effects of immunosuppression, MZB was selected as an immunosuppressant with repeated explanation and the patient's consent. Blood tests showed that 150 mg MZB plus 30 mg PSL moderately suppressed immunoglobulin G (IgG) to approximately 500 mg/dL and successfully reduced the titer of anti-ARS antibody (Figure 2). As the anti-ARS titer gradually increased after tapering of the PSL dose, we up-titrated the dose of MZB into 200 mg daily with careful checking of IgG concentration and blood cell count. Finally, his clinical symptoms and daily life activities have been well persevered as an outpatient, and he has been well maintained with 200 mg MZB and 10 mg PSL for several months without obvious clinical recurrence and no marked side effects related to MZB.

Discussion

ILD is a common and serious complication in a subset of patients with anti-ARS autoantibody, and progressive ILD can be fatal[8–11]. Anti-ARS antibody has been identified in patients with polymyositis/dermatomyositis (PM/DM) and/or ILD[12]. Yoshifuji *et al.* summarized the clinical course of anti-ARS antibody-associated ILD and myositis by categorizing it into the ILD-preceding type (13 cases), simultaneous type (18 cases), and myopathy-preceding type (10 cases), and they found that ILD preceded myopathy by an average of 14 months in the anti-ARS-positive group[13]. In other words, the present case has the potential to shift from ILD alone to PM/DM-ILD, and it is reasonable that treat-

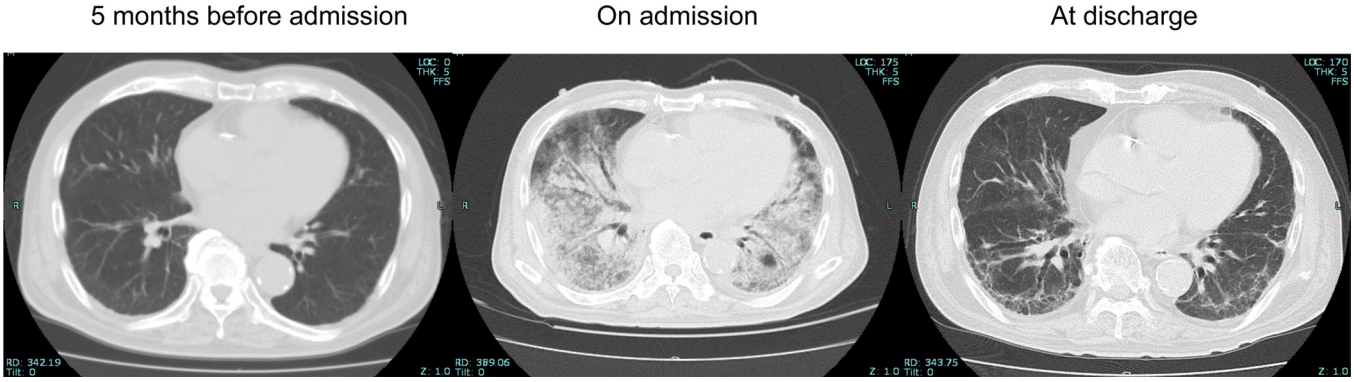

Figure 1 Serial computed tomography results showing interstitial lung disease.
Representative findings of computed tomography at 5 months before admission, on admission, and at discharge.

Table 1 Laboratory findings on admission

Blood count			Immunology etc.		
White blood cells	7,080	/μL	RF	41	U/mL
Hemoglobin	9.7	g/dL	ANA	80	×
Platelet	24.5 × 10^4/μL		(Speckled)	80	×
Arterial blood gas, artery, O2 10 L/M			(cytoplasm)	40	×
pH	7.47		Anti-DNA Ab	<2.0	U/mL
pCO2	33.1	mmHg	Anti-RNP Ab	<2.0	U/mL
pO2	70.0	mmHg	Anti-Jo-1 Ab	<1.0	U/mL
HCO3-	23.7	mmol/L	Anti-ARS Ab	108	(Normal: <25)
Urine test			MPO-ANCA	<1.0	U
Gravity	1.015		PR3-ANCA	<1.0	U
Proteinuria	2+		Anti-GBM Ab	<2.0	U
Glucose	4+		IgG	1,613	mg/dL
Ocult blood	-		IgA	427	mg/dL
RBC sediment	0–1	/HPF	IgM	240	/mL
Biochemistory			C3	131	mg/dL
Albumin	3.1	g/dL	C4	33	mg/dL
AST	25	U/L	CH50	54.8	/mL
ALT	11	U/L			
LDH	290	U/L	CK	69	U/L (range; 56–244)
Urea nitrogen	13.5	mg/dL	Aldrase	3.8	U/L (range; 2.1–6.1)
Creatinine	0.5	mg/dL	KL-6	1,960	U/mL (<500)
Uric acid	3.9	mg/dL	SP-D	29.6	ng/mL (<110)
Sodium	140	mEq/L	SP-A	31.6	ng/mL (<43.8)
Potassium	3.7	mEq/L	beta D glucan	19.5	pg/mL (<20.0)
Chloride	107	mEq/L	ACE	7.5	U/L (range; 8.3–21.4)

RBC: red blood cells; AST: aspartate amino transferase; ALT: amino alanine transferase; LDH: lactate dehydrogenase; RF: rheumatoid factor; ANA: anti-nuclear acid; DNA: deoxyribonucleic acid; RNP: ribonucleoprotein; MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody; GBM: glomerular basement membrane; Ig: immunoglobulin; C: complement; CK: creatine kinase; KL-6: Krebs von den Lungen-6; SP: surfactant protein; ACE: angiotensin-converting enzyme.

ment was chosen based on the conventional approach used for PM/DM-ILD.

Although various attempts using immunosuppressants have been reported[4, 5, 10], the standard regimen for ILD-associated myositis has not been established. Observational studies of patients with corticosteroid-resistant ILD have shown variable results with cyclophosphamide, azathioprine, and methotrexate treatment[14–16]. In one trial using intravenous cyclophosphamide to treat idiopathic pulmonary fibrosis, a certain proportion of patients died, implying major complications, including infectious pneumonia and other infectious processes[17]. Tacrolimus is a well-tolerated and effective therapy for managing refractory ILD in anti-ARS-positive patients, based on the results of a case series including 15 patients[4]. Conversely, calcineurin inhibitors, such as tacrolimus, lead to a high incidence of diabetes mellitus[18], and they were considered inappropriate for the present patient. The use of an agent with low side effects in elderly diabetic patients instead of cyclophosphamide and tacrolimus was collectively considered for the present case. Therefore, treatment was guided by referring to a previous case of a middle-aged woman who suffered from refractory polymyositis with corticosteroid-induced diabetes mellitus, who was treated with a combination of MZB and PSL[19], even though she did not have obvious ILD.

The direct contribution of immunosuppressive agents has been difficult to assess because most of the patients also received steroids[20]. Nevertheless, the safety and steroid-sparing effect of MZR have been reported for various connective tissue diseases[21]. Moreover, in three patients in two reports, mycophenolate mofetil, which has the same mechanism as MZB, was used[22, 23]. T cells are thought to play a critical role in myositis-associated ILD[24], and rituximab, which acts by depleting immunoglobulin-producing $CD20^+$ B cells, has shown benefit for both lung function and radiologic parameters in antisynthetase syndrome[25, 26]. Though tacrolimus specifically suppresses the activity of T lymphocytes, MZR suppresses T and B lymphocytes, suggesting that is effective in autoantibody-associated diseases, such as anti-ARS syndrome.

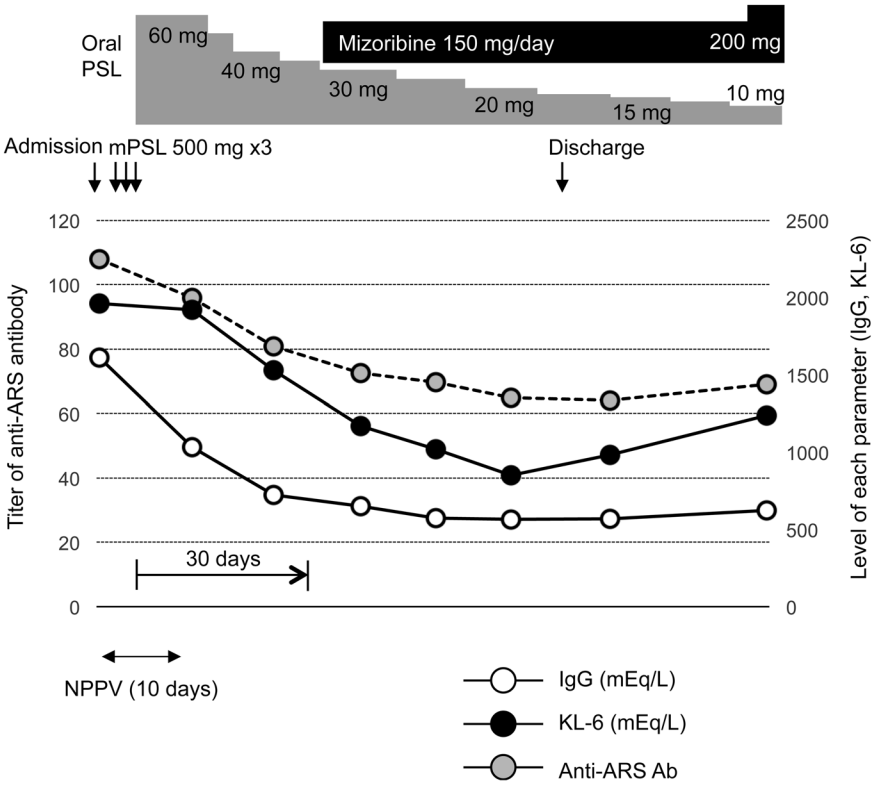

Figure 2 Patient's clinical course.
Steroid and immunosuppressive therapy as well as levels of serum IgG (immunosuppressive state), KL-6 (lung fibrosis marker), and anti-ARS antibody are shown.

Conclusion

The present case suggested that use of MZB might suppress the pathophysiology of anti-ARS antibody-associated interstitial pneumonia, which is partially dependent on the suppression of T cell activity and a decrease in the antibody titer, in association with corticosteroids. Moreover, in elderly patients with concomitant conditions including diabetes, steroid-resistant and steroid-incompetent ILD might be a good indication for MZB.

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