Severe finger necrosis in antisynthetase syndrome with positive anti-OJ antibodies

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INTRODUCTION

Aminoacyl tRNA synthetases (ARSs) are a group of cytoplasmic enzymes that bind to transcribed RNA during protein synthesis, esterify amino acids to transcribed RNA, and function as catalysts for aminoacyl-transcribed RNA.¹ Patients who test positive for anti-ARS antibodies present with various extramuscular symptoms, such as interstitial pneumonia, mechanic’s hands, Raynaud phenomenon, polyarthritis, fever, and myositis. These symptoms share common clinical features, which led Targoff in 1992 to term them "antisynthetase antibody syndrome."² Since Jo-1 (histidyl-tRNA synthetase: HisRS) antibody was discovered in 1980³, eight ARS antibodies have been identified: histidyl-tRNA synthetase-1 (Jo-1), anti-threonyl (PL-7), anti-alanyl (PL-12), anti-glycyl (EJ), anti-isoleucyl (OJ) anti-asparaginyl (KS), anti-phenylalanyl (Zo) and anti-tyrosyl (Ha) tRNA synthetase⁴.⁵ ⁶ Among these antibodies, anti-OJ is the least prevalent (3.1%).⁷ Anti-OJ- positive anti-ARS syndrome is extremely rare, and is usually accompanied by interstitial pneumonia.⁸ Anti-OJ and anti-Sjögren’s-syndrome-related antigen A (Ro-52) antibodies are occasionally detected in patients with dermatomyositis and are a poor prognostic factor when associated with interstitial pneumonia.⁹ However, we encountered a patient with OJ-and Ro-52 positive anti-ARS syndrome without interstitial pneumonia and with severe phalanx necrosis due to Raynaud phenomenon. The activity of disease could be suppressed with steroid pulse therapy. We believe that this is an atypical clinical presentation that deserves acknowledgement by means of this case report. We also report it here with a review of the literature.

CASE PRESENTATION

The patient was an 80-year-old Japanese man. During the month before admission, he experienced progressive dysphagia and muscle weakness in the lower extremities. Because of difficulty with walking, he sought medical attention at the hospital. He had a 60-year history of smoking 10 cigarettes per day and infrequent hospital visits and was not currently on any medication. The patient had no history of Raynaud phenomenon.

On admission, the patient’s temperature was 37.3°C, and no other abnormalities were detected in his vital signs. Indurated edema was observed in both lower legs, and a purple color change was observed in the second to fifth fingers of the left hand (Fig. 1–A). Although muscle atrophy was not evident because of edematous changes, the patient experienced generalized muscle pain in the bilateral thighs. The strength in the upper extremities was assessed as a Muscle Strength Testing (MMT) score of 4, while the iliopsoas and quadriceps muscles were graded as an MMT score of 2.

Blood test findings revealed elevated levels of muscle enzymes (creatine kinase [CK], 7,930 U/L and C-reactive protein [CRP], 2.0 mg/dL), an erythrocyte sedimentation rate (ESR) of 16 mm/h, and an elevated inflammatory response. Results were negative for antinuclear antibodies, rheumatoid factor (RF), myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA), proteinase-3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA), anti-Scl-70, U1RNP, centromere, Jo-1, PL-12, anti-melanoma differentiation-associated gene-

5 (MDA5), and anti-transcriptional intermediary factor 1-γ (TIF1-γ), and for MI-2, Ku, PM-SCL75, PM-SCL100, SRP, PL-7, EJ, and OJ. However, Ro-52 (EUROLINE Myositis Profile 3; EUROMMUN Medizinische Labordiagnostika AG, Lubeck, Germany) demonstrated a strong positive result (3+). During the patient’s hospitalization, further testing using immunoprecipitation was conducted at another institute’s laboratory, and the patient was strongly positive for anti-OJ antibodies.

Contrast-enhanced magnetic resonance imaging (MRI) revealed a contrast effect in muscle electromyography, and positron emission tomography-computed tomography also showed extensive soft tissue accumulation despite normal blood glucose levels (Fig. 2A and B). Muscle biopsy findings were consistent with myositis, which led to a diagnosis of anti-ARS antibody syndrome. Chest CT upon admission indicated chronic obstructive pulmonary disease and mild interstitial pneumonia; however, no malignancy was detected. MRI of the head showed no abnormality.

After admission, the color of the patient’s fingers changed from purple to black, indicating necrosis (Fig. 1B). Contrast-enhanced CT images showed no signs of vascular stenosis or obstruction. Intravenous heparin sodium (10,000 U/day), prostaglandins (limaprost alfadex 30 µg/day), tocopherol nicotinate 600 mg/day, and warming agents for a week, the progression of the finger necrosis did not stop.

On day 10 of hospitalization, the patient’s respiratory status deteriorated, necessitating ventilator management. Worsening interstitial pneumonia was treated with a methylprednisolone pulse of 1,000 mg for 3 days and post-therapy prednisolone (PSL; 60 mg [1 g/kg]). Following initiation of treatment, his respiratory condition rapidly improved, and he was weaned off the ventilator within approximately 10 days. Close examination revealed no exacerbation of interstitial pneumonia or changes in Krebs von den Lungen 6 (KL-6; 216 U/mL) or surfactant protein-D (SP-D; 65 ng/mL). This was attributed to improved carbon dioxide (CO₂) narcosis. After the first day of PSL pulse administration, a purple transition zone appeared in the necrotic area of the fingers, which subsequently ceased expanding (Fig. 1C).

The patient experienced repeated episodes of aspiration pneumonia owing to dysphagia; however, over time, both swallowing ability and lower limb muscle strength gradually improved. On day 40 of hospitalization, the MMT score of the lower limbs recovered to 3–4, and CK levels were normal. Additionally, the CRP level and ESR had substantially decreased. Furthermore, the progression of finger necrosis had ceased. By day 70 of hospitalization, all MMT scores had improved to 5, indicating complete recovery of muscle strength. Swallowing function had also improved to the state before the disease onset, leading to the patient’s discharge from the hospital. Although the necrotic areas of the fingers became narrower and drier after pulse therapy, necrosis did not progress (Fig. 1D).

OUTCOME AND FOLLOWUP

Following discharge, the patient was transferred to a rehabilitation hospital for further care. After 2 months of rehabilitation, the patient was discharged from the rehabilitation hospital and did not experience any recurrence of symptoms. Furthermore, there was no progression of necrosis in the fingers following discharge from our hospital. A team conference was conducted involving nurses, collagen disease physicians, a plastic surgeon, an orthopedic surgeon, and a family member to discuss the possibility of amputating the necrotic fingers. Considering that the patient was receiving PSL and that future use of immunosuppressive drugs was contemplated, it was decided to not proceed with amputation because of the associated risk of infection. Instead, the patient’s progress would continue to be monitored.

DISCUSSION

We diagnosed an older patient with rapidly progressive finger necrosis and late-onset ARS syndrome who tested positive for anti-OJ and Ro-52 antibodies. The occurrence of ARS syndrome with positive anti-OJ antibodies is extremely rare, and reports of clinical manifestations of severe necrosis of the hands without significant interstitial pneumonia are limited. Additionally, the commonly used line immunoassay (LIA) method for measuring anti-OJ antibodies yielded false negative results in this case, highlighting the effectiveness of immunoprecipitation.
Ge et al.⁷ reported that only 10 (3.1%) of 320 patients with anti-ARS antibodies had anti-OJ antibodies. Among them, 90% had interstitial pneumonia, and 40% presented with myositis, mechanic’s hands, and arthritis. Most publications describing patients with anti-OJ antibodies have primarily focused on interstitial pneumonia⁸, with only one report mentioning myositis⁹ and none describing skin changes with necrosis. Our patient experienced mild interstitial pneumonia, while muscle weakness and necrosis of the fingers were prominent. Although the patient remained independent for activities of daily living, he faced difficulties in swallowing and lost the ability to walk after just 1 month. Finger necrosis was notably absent upon admission but progressed rapidly and intensely within 3 days.

On admission, anti-Ro-52 was strongly positive. Anti-ARS antibody syndrome typically involves anti-Ro-52 antibodies, and these are associated with a poor prognosis when anti-ARS antibody syndrome occurs along with concomitant interstitial pneumonia.¹⁰ Anti-Ro-52 antibodies are found in up to 37% of patients with myositis, and this often correlates with anti-Jo-1 reactivity.¹ This, together with the clinical presentation, indicated myositis involvement. However, anti-Jo-1 and anti-ARS antibodies were all negative. Few reports have described finger necrosis due to myositis, and we considered the possibility of a paraneoplastic acral vascular syndrome.¹² Consequently, we requested a test for anti-U5snRNP antibody, which was negative. Nevertheless, we retested anti-OJ antibody by immunoprecipitation, which was positive.

We considered initiating PSL at a dose of 1 mg/kg for the patient while awaiting the examination results. However, because of the sudden deterioration of the patient’s respiratory status, (necessitating the administration of 10 min of masked oxygen), and the possibility of exacerbation of the interstitial pneumonia, we opted for methylprednisolone pulse treatment. Imaging revealed a mildly exacerbated interstitial shadow, without elevated KL-6 or SP-D. He also had a history of chronic obstructive pulmonary disease as a cause of worsening respiratory status, which was thought to be due to CO₂ narcosis. After administering the methylprednisolone pulse, the expanding necrotic lesion, which had shown no signs of prior improvement, exhibited a purple transition zone at the border between the normal skin and black necrotic area (Fig. 1C). Subsequently, the expansion of necrosis halted. The pathogenesis of finger necrosis in anti-ARS syndrome has been documented. For example, Chan et al.¹³ reported a PL-7(+) case where conventional angiography revealed occlusion of the second to fourth fingers. Suma et al.¹⁴ reported Jo-1(+) anti-ARS antibody (+) mechanistic hand, with peripheral angiography revealing occlusion of both the ulnar and radial arteries. Linear hemorrhage of fingernails accompanied by digital ischemia or digital ulcer in anti-ARS syndrome has also been reported.¹³–¹⁵ In our case, no obvious stenosis or occlusion was observed on contrast-enhanced CT angiography, and there was no linear hemorrhage of the nails. However, we observed extreme necrosis, which was unprecedented in our experience. Nonetheless, the presence of necrosis would typically suggest ischemia caused by blood flow obstruction in the vessel, which may be a limitation of CT angiography. Furthermore, because of the patient’s intubation and poor general condition, angiography was not performed. Although the patient had no history of Raynaud phenomenon, spasms of the peripheral arteries in the fingers might have contributed to the significant necrosis. However, there are few reports of digital necrosis in patients who are positive for anti-OJ antibodies. Lastly, muscle strength showed significant improvement after PSL administration, showing the efficacy of PSL pulses in these patients.

The limited number of reports may be attributed to the rarity of this condition and challenges in testing. Anti-OJ antibodies are difficult to detect among all myositis-specific antibodies. Unlike other tRNA synthetase targets of autoantibodies, including Jo-1, PL-7, PL-12, KS, EJ, and Zo, OJ antibodies are complex high-molecular-weight proteins with several subunits, posing challenges for antigen selection.¹⁶ The LIA method has lower sensitivity in detecting anti-OJ antibodies.¹⁷–¹⁹ However, it is still widely applied in clinical practice owing to the lack of alternative methods and its ease of use, despite the superior diagnostic performance of advanced immunoprecipitation methods.²⁰, ²¹ In this case, although the patient initially tested negative for anti-OJ antibodies using the LIA method, he tested positive based on the immunoprecipitation method. The single enzyme-linked immnosorbert assay kit commonly used for the anti-ARS antibody assay no longer detects anti-Zo and anti-Ha antibodies, as they have only been reported in isolated cases.

If clinicians suspect the presence of anti-OJ antibodies and myositis and finger necrosis are more prominent
than symptoms of interstitial pneumonia, a diagnosis should be confirmed through immunoprecipitation.

CONCLUSION

We described the case of an older patient with late-onset ARS syndrome who tested positive for anti-OJ and anti-Ro-52 antibodies. Interstitial pneumonia is an established complication of anti-ARS antibody syndrome, particularly when accompanied by positive anti-OJ antibodies. However, it can also result in rapid necrosis of the fingers without interstitial pneumonia. Prednisolone pulse therapy was remarkably effective, leading to the rapid cessation of disease progression. Detecting anti-OJ antibodies by immunoprecipitation is potentially more reliable than the LIA method. Information on the clinical course of this atypical ARS syndrome and treatment could contribute to the daily practice of rheumatology for clinicians.

AUTHOR CONTRIBUTIONS

Yugo Horiuchi: Conceptualization; data curation; project administration; writing-original draft.

Kenichi Hashimoto: Conceptualization; data curation; project administration; supervision; writing-review and editing.

Ryochi Yoshida: Supervision; writing-review and editing.

Yuji Tanaka: Supervision; writing-review and editing.

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PATIENT CONSENT

Written informed consent was obtained from the patient.

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REFERENCES


FIGURE LEGENDS

**Figure 1**. Imaging findings of affected fingers

Hospitalization days 1 (A), 3 (B), 10 (C) after first prednisolone pulse and 70 (D) at discharge. Red arrow (D) shows purple transition zone between black necrotic area and normal skin.

**Figure 2**. PET-CT imaging findings on day 1 of hospitalization

Widespread accumulation centered on (A) soft shoulder tissues and on (B) quadriceps muscle.

Blood glucose levels are normal.

PET-CT, positron emission tomography-computed tomography