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CASE STUDY

# ANCA-associated neuropathy in systemic sclerosis: A case report and review of literature

Kayo Takenaka MD[1] | Takuya Takeichi MD, PhD[1] | Ryoji Nishi MD, PhD[2] | Masashi Suzuki MD, PhD[2] | Haruki Koike MD, PhD[2] | Masahisa Katsuno MD, PhD[2] | Mariko Ogawa-Momohara MD, PhD[1] | Yoshinao Muro MD, PhD[1] | Masashi Akiyama MD, PhD[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

**Correspondence**
Takuya Takeichi, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
Email: takeichi@med.nagoya-u.ac.jp

## Abstract

Systemic sclerosis (SSc) is a multi-system autoimmune disease. Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against enzymes found within primary granules of neutrophils and lysosomes in monocytes. Although up to 12% of SSc patients have ANCA, only a minority of these patients develop an overlap syndrome with ANCA-associated vasculitis. We summarize previous reports on SSc patients with ANCA-associated neuropathy. In all the reported cases, the SSc diagnosis preceded the ANCA-associated neuropathy diagnosis. Seven of the eight patients with limited cutaneous SSc had interstitial lung disease (ILD). Thus, patients with ANCA-associated neuropathy in lSSc may be prone to complication with ILD.

**KEYWORDS**
ANCA-associated neuropathy, anti-neutrophil cytoplasmic antibody, interstitial lung disease, systemic sclerosis

## 1 | INTRODUCTION

Systemic sclerosis (SSc) is a multi-system autoimmune disease characterized by a triad of progressive skin and internal organ fibrosis, autoantibody production, and small-vessel vasculopathy.[1] Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against enzymes found within primary granules of neutrophils and lysosomes in monocytes, and they are implicated directly in the pathogenesis of small-vessel vasculitis.[1] Although up to 12% of SSc patients have ANCA, only a minority of these patients develop an overlap syndrome with ANCA-associated vasculitis (AAV).[1] In a large cohort study of SSc patients, the prevalence of ANCA was 8.9% (116 patients/1303 patients), although only three ANCA-positive SSc patients had AAV (0.23%, 3/1303).[1] A study of 2200 SSc patients found only eight patients (0.4%) with comorbid AAV and SSc.[2] The majority of published cases of AAV and SSc overlap were described to have microscopic polyangiitis or renal-limited vasculitis.[3] Here, we report a Japanese female patient suffering from SSc complicated with ANCA-associated neuropathy, and we summarize previous reports on SSc patients with ANCA-associated neuropathy.

## 2 | CASE REPORT

A 70-year-old woman who visited our hospital reported having had Raynaud's phenomenon for ten years. She also had digital ulcerations and skin sclerosis involving the forearms. Serological tests revealed positivity for the speckled pattern of anti-nuclear antibody and anti-Scl-70 antibodies. She was diagnosed with SSc.

**TABLE 1** Summary of SSc cases complicated with ANCA-associated neuropathy reported in the literature

| Patient No. | Age at diagnosis of ANCA-associated neuropathy | Histopathological features | Gender | Interval between the onset of SSc and ANCA-associated neuropathy | SSc type | Anti-Scl-70 antibody positivity | Extracutaneous symptoms of SSc | ANCA type | Ref. No. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 72 | Kidney: global sclerosis and cellular crescent formation | F | 20 years | diffuse | + | ILD | MPO-ANCA | [7] |
| 2 | 32 | N/A | F | 0 years | diffuse | − | N/A | PR3-ANCA | [2] |
| 3 | 65 | Nerve: necrotizing vasculitis | M | 6 years | diffuse | − | GI, ILD | PR3-ANCA | [8] |
| 4 | 54 | Nerve: necrotizing vasculitis | F | 9 years | N/A | + | N/A | MPO-ANCA | [6] |
| 5 | 68 | Skin: necrotizing vasculitis | F | 24 years | limited | − | GI, ILD | MPO-ANCA | [3] |
| 6 | 66 | Kidney: segmental glomerular necrosis and cellular crescent formation | F | 17 years | limited | − | GI, ILD | MPO-ANCA | [5] |
| 7 | 75 | Kidney: PIGN | F | 15 years | limited | − | GI, ILD, polyarthralgia | MPO-ANCA | [3] |
| 8 | 57 | N/A | F | 10 years | limited | − | GI, PAH | MPO-ANCA | [2] |
| 9 | 53 | Muscle: necrotizing vasculitis | F | 8 years | limited | − | GI, ILD | MPO-ANCA | [3] |
| 10 | 59 | Skin: necrotizing vasculitis | F | 1 year | limited | + | GI, ILD, polyarthralgia | MPO-ANCA | [3] |
| 11 | 77 | Nerve: necrotizing vasculitis | F | 2 months | limited | + | ILD | MPO-ANCA | [3] |
| 12 | 37 | Skin: leukocytoclastic vasculitis | F | 1 month | limited | + | GI, ILD | MPO-ANCA | [3] |
| 13 | 73 | Nerve: vasculitis | F | 3 years | limited | + | ILD | MPO-ANCA | The present case |

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; F, female; GI, gastrointestinal symptom; ILD, interstitial lung disease; N/A, not available; PAH, pulmonary arterial hypertensionPIGN, pauci-immune glomerulonephritis; SSc, systemic sclerosis.

At age 73, she developed a persistent cough. Bibasilar lung interstitial changes were detected by computed tomography. She was admitted to our hospital for investigation of paresthesia in both lower limbs. Clinically, her temperature sensation, pain sensation, and sensory vibration of the lower limbs were decreased, and mild weakness was observed in the distal muscles of the lower limbs. In a nerve conduction study, the sensory nerve action potential of the bilateral sural nerves was not evoked. In addition, the amplitude of compound muscle action potential was decreased in the bilateral tibial nerves, and the motor nerve conduction velocity was decreased in the right peroneal nerve. Nerve biopsies from the right lower leg revealed reduction in myelinated nerve fiber density and findings suggestive of vasculitis (i.e., lymphocytic infiltration, obstruction, and recanalization). Additional serological tests showed her serum to be positive for MPO-ANCA (276 IU/ml; normal range < 3.5). She was diagnosed with ANCA-associated neuropathy and treated with three days of intravenous methylprednisolone (1000 mg/day), followed by high-dose oral prednisolone (1.0 mg/kg/day). Scleroderma kidney was not found during treatment. Her paresthesia improved gradually.

## 3 | DISCUSSION

Previously reported prospective studies indicated that between 20% and 25% of scleroderma patients have neuropathy.[4] When patients with SSc have paresthesia, the clinician should first consider whether the patient has vasculitis. In non-vasculitic cases, the neuropathy is due to increased perineurial connective tissue, myelinated nerve fiber loss, and axonal atrophy.[4] These changes might result from chronic noninflammatory vasculopathy.[4] ANCA-associated neuropathy is the most common vasculitic neuropathy in SSc patients. We diagnosed ANCA-associated neuropathy by nerve biopsy and measurement.[4]

We performed a literature search in MEDLINE to identify all relevant papers describing the clinical features of SSc patients complicated with ANCA-associated neuropathy (January 2000 to December 2019). We identified six papers describing the clinical features of 12 SSc patients with ANCA-associated neuropathy (Table 1).[2,3,5–8] In all the reported cases, the SSc diagnosis preceded the ANCA-associated neuropathy diagnosis. Positive results for anti-Scl-70 antibody were observed in five patients (5/12). According to one previous report,[3] anti-Scl-70 antibodies are frequently associated with the development of AAV; that is, up to 77% of SSc patients with AAV have anti-Scl-70 antibodies. Among the 12 patients, eight patients have limited cutaneous SSc (lSSc), three patients had diffuse cutaneous SSc (dSSc), and the type was not described in the remaining case. Seven of the eight patients with lSSc had interstitial lung disease (ILD). Thus, patients with ANCA-associated neuropathy in lSSc may be prone to complication with ILD. We need to investigate ANCA-associated neuropathy, especially when lSSc patients are complicated with ILD. In conclusion, if an SSc patient shows symmetric paresthesia of the extremities, it is important for the clinician to consider the possibility of ANCA-associated neuropathy, especially in an lSSc patient with ILD.

## CONFLICT OF INTEREST

The authors declares no conflict of interest.

## DECLARATION SECTION

Approval of the research protocol: N/A.
Informed Consent: The written informed consent was obtained from the patient.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

## ORCID

*Takuya Takeichi* https://orcid.org/0000-0001-5958-2875
*Yoshinao Muro* https://orcid.org/0000-0003-2329-8375

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