

# Management of multiple neurological complications in mixed connective tissue disease

## A case report

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### Abstract

**Rationale:** Mixed connective tissue disease (MCTD) refers to an overlapping condition of different autoimmune disorders such as systemic lupus erythematosus, cutaneous systemic sclerosis, rheumatoid arthritis, polymyositis, and dermatomyositis. However, MCTD manifesting as transverse myelitis is extremely rare. Herein, we report a case of MCTD with both central and peripheral nervous system involvement.

**Patient concerns:** We describe and discuss the clinical findings and management of a 36-year-old man presented with a 2-week history of sudden bilateral lower-limb paralysis and dysuria. Further investigation of his medical history showed a 6-month history of autoimmune symptoms.

**Diagnoses:** The patient was diagnosed with MCTD, transverse myelitis, mononeuritis multiplex, and multiple lacunar infarctions.

**Interventions:** A combination of low-dose methylprednisolone (40 mg/d) and hydroxychloroquine sulfate (400 mg/d) was administered.

**Outcomes:** After treatment, the symptoms were significantly improved. The patient recovered well after 1 year follow-up and the sequela was urinary incontinence and grade 4/5 lower-extremity muscle strength.

**Lessons:** MCTD with multiple neurological complications is extremely rare and poses diagnostic and therapeutic challenges. Our experience suggests a combination of low-dose corticosteroids and hydroxychloroquine sulfate may be an effective therapeutic approach.

**Abbreviations:** ANA = antinuclear antibodies, AQP4 = Aquaporin-4, CSF = cerebrospinal fluid, EMG = electromyography, HLA = human leukocyte antigen, MCTD = mixed connective tissue disease, MRI = magnetic resonance imaging, NMO = neuromyelitis optica, SLE = systemic lupus erythematosus, U1-RNP = U1 small nuclear ribonucleoprotein.

**Keywords:** mixed connective tissue disease, mononeuritis multiplex, multiple lacunar infarctions, systemic lupus erythematosus, transverse myelitis

## 1. Introduction

Mixed connective tissue disease (MCTD), which was originally reported by Sharp in 1972,<sup>[1]</sup> refers to a systemic autoimmune rheumatic disease characterized by the combination of distinct autoimmune conditions such as systemic lupus erythematosus (SLE), cutaneous systemic sclerosis, rheumatoid arthritis, polymy-

sitis, and dermatomyositis.<sup>[2]</sup> This condition had been found to be associated with anti-U1 small nuclear ribonucleoprotein (U1-RNP) antibodies.<sup>[2,3]</sup> The clinical manifestation spectrum of MCTD is broad, including Raynaud's phenomenon, swollen fingers, erosive polyarthritis, sclerodactyly, myositis, and neurological symptoms.<sup>[4]</sup> According to previous studies, approximately 10% to 17% patients with MCTD have neuropsychiatric dysfunctions such as trigeminal neuritis, headache, aseptic meningitis, seizure, peripheral neuritis, cerebrovascular disease, and psychosis.<sup>[5,6]</sup> Transverse myelitis is an extremely rare complication of MCTD, with only 8 cases having been reported.<sup>[5,7-9]</sup>

Herein, we report a case of MCTD with both central and peripheral nervous system involvement. The authors declared that the patient have received and archived written informed consent for his information and images to be published.

## 2. Case report

This study was approved by the Ethics Committee and institutional Review Board of The First Hospital of Jilin University.

### 2.1. History

A 36-year-old man presented to us with a 2-week history of sudden bilateral lower-limb paralysis and dysuria. Six months

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before admission, he suffered from lobar pneumonia. After the pneumonia was cured, he developed weakness in the bilateral lower extremities, Raynaud's phenomenon in both hands, and whole-body scattered punctate rashes without pain or itch. Thereafter, the weakness progressed to involvement of all limbs, and the rashes increased and fused with ulceration. In addition, finger swelling and fingertip ulcers were noted. The patient also complained of fatigue, low fever (37°C–38°C), alopecia, inappetence, dysphagia, and weight loss (~10 kg). His previous medical history was unremarkable.

## 2.2. Physical examination

On admission, physical examination showed a low fever (37.9°C). The muscle strength was grade 4/5 in bilateral upper extremities, grade 3/5 in the left lower extremity, and 0/5 in the right lower extremity. Hyperreflexia was noted in both lower extremities with positive Babinski and Chaddock signs. Moreover, neurological examination revealed loss of pain and temperature sensations below the T10 dermatome and loss of proprioceptive sensations in the right lower extremity. All fingers were swollen like sausages, and multiple acral ulcers were noted in the fingertips. Patchy puce rashes with apparent pigmentation were observed in bilateral cheeks, back, and all limbs. He also had IV-stage pressure sores in the ischial tuberosus and sacrococcygeal regions. Pallor was observed on nail beds, oral mucosa, and eye conjunctiva.

Three days after admission, the muscle strength further decreased to grade 0/5, and the proprioceptive sensations completely disappeared in the left lower extremity. The patient also developed fecal incontinence, suggesting the condition was progressively exacerbated.

## 2.3. Radiological and laboratory examinations

Thoracic magnetic resonance imaging (MRI) with gadolinium enhancement and visual evoked potentials were both normal. The results of serological examinations are presented in Table 1. The serum levels of folic acid, vitamin B<sub>12</sub>, and tumor markers were all normal. Cerebrospinal fluid (CSF) examination showed the following results: protein 1.33 g/L, glucose 1.83 mmol/L, leukocyte count  $2 \times 10^6$ /L, IgG 745.00 mg/L; anti-AQP4 antibody, neuromyelitis optica (NMO)-IgG, paraneoplastic antibodies, and oligoclonal bands were all normal. There was no

infection with hepatitis virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, tuberculosis, or syphilis.

## 2.4. Diagnosis

According to the aforementioned evidence, the diagnoses of spinal neoplasm, infection, subacute combined degeneration of spinal cord, paraneoplastic syndrome, multiple sclerosis, NMO, or trauma-induced spinal cord injury were excluded. Considering the clinical symptoms (e.g., Raynaud's phenomenon, swollen fingers, and rashes) and elevated IgG level in CSF, an autoimmune disease was suspected. Electromyography (EMG) showed fibrillation potentials and positive sharp waves in the right tibialis anterior muscle and gastrocnemius muscle, and the amplitudes of motor unit action potentials were reduced with shortened latency, suggesting a localized myogenic impairment. A biopsy of the skin rashes was performed, yielding a diagnosis of connective tissue disease (Fig. 1). In addition, genetic examination showed mutations of HLA-DRB1\*15:01 and \*09:01, which is a risk factor for MCTD. Further examination showed a high serum titer of anti-U1-RNP antibody and speckled antinuclear antibodies (ANA). These clinical profiles fulfilled the Kasukawa's diagnostic criteria for MCTD.<sup>[10]</sup>

## 2.5. Comprehensive evaluation

EMG showed peripheral neurogenic impairment mainly involving the motor nerves. The motor-nerve conduction velocity was reduced and the F-wave latency was prolonged in the right ulnar nerve and proximal median nerve. The amplitude and motor-nerve conduction velocity were both reduced in the right nervus peroneus communis. No electrical activity or H reflex was monitored in the left extremities. These results indicated a mononeuritis multiplex. Brain MRI showed multiple lacunar infarctions. The patient was further diagnosed with transverse myelitis, mononeuritis multiplex, and multiple lacunar infarctions.

## 2.6. Treatment and outcome

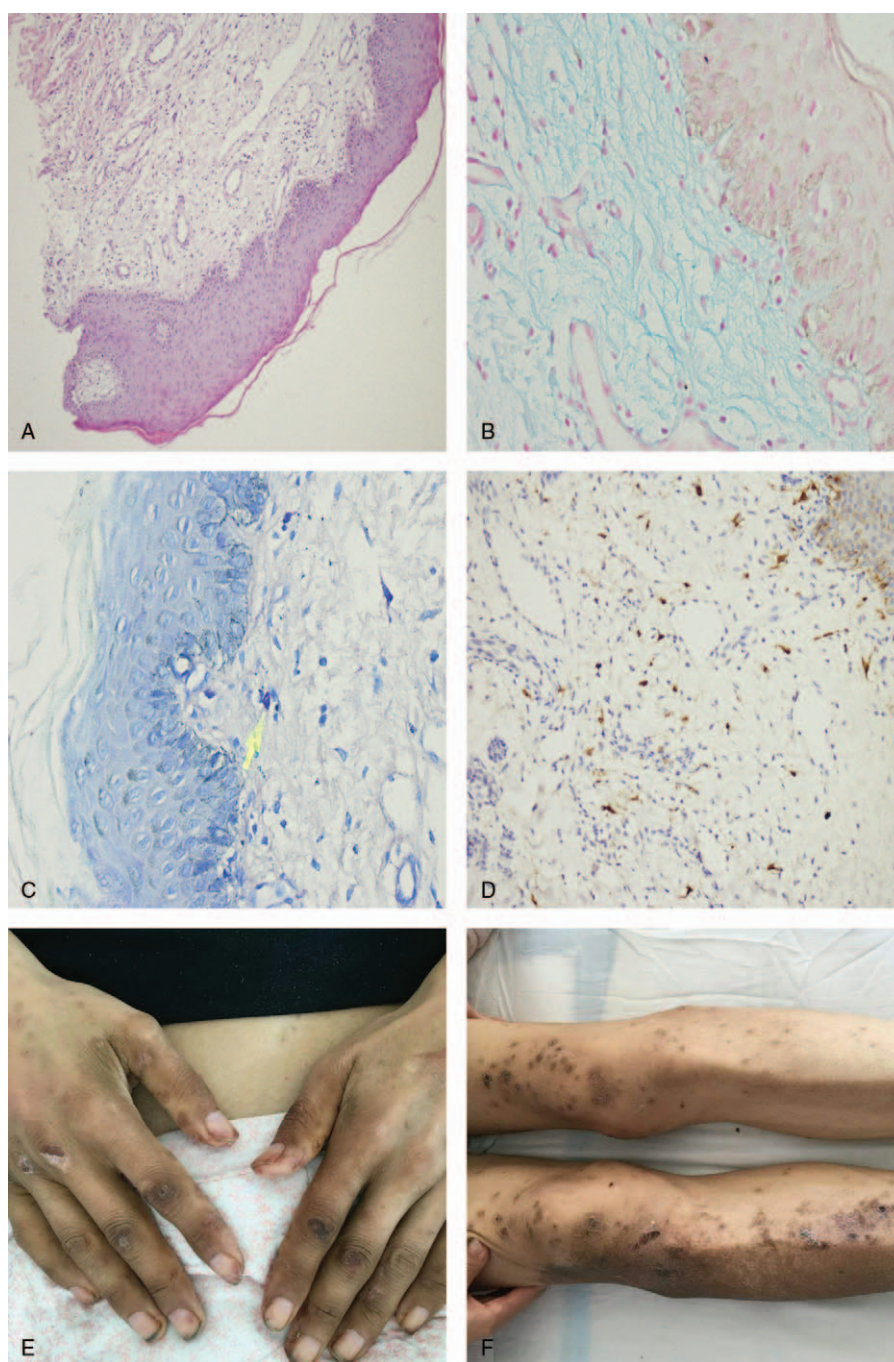
Considering the poor condition of the patient, we abandoned a steroid pulse scheme and used a combined regimen of intravenous low-dose methylprednisolone (40 mg/d) and hydroxychloroquine sulfate (400 mg/d). After 1 month of treatment, the symptoms

**Table 1**

### Results of serological examination.

Parameter	On admission	After treatment	Parameter	On admission	After treatment
White blood cell count, 10 <sup>9</sup> /L	3.56	5.23	Anti streptolysin, IU/mL	211.00	166.0
Neutrophil count, 10 <sup>9</sup> /L	3.04	3.84	High-sensitivity C-reactive protein, mg/L	22.99	6.16
Lymphocyte count, 10 <sup>9</sup> /L	0.29	1.07	Erythrocyte sedimentation rate, mm/1 h	59	21
Red blood cell count, 10 <sup>12</sup> /L	2.75	3.58	Immunoglobulin G, g/L	23.70	13.0
Hemoglobin, g/L	84	120	C3, g/L	0.32	1.24
Platelet, 10 <sup>9</sup> /L	111	216	C4, g/L	0.02	0.12
Alanine aminotransferase, U/L	155.9	16.5	Anti-U1-RNP	+++	+
Aspartate transaminase, U/L	217.4	31.4	Anti-Sm	+++	++
Albumin, g/L	23.5	32.5	Anti-SSA/Ro	+++	+++
Globulin, g/L	50.2	31.2	Speckled pattern ANA	1:3200	1:3200
Albumin/globulin	0.47	1.04	pANCA	1:10	1:10
Creatine kinase, U/L	387	73	Anti-PR3, AU/mL	32.01	0.53

C3 = Complement3, C4 = Complement4, Anti-U1-RNP = anti-U1 small nuclear ribonucleoprotein (U1-RNP) antibodies, Anti-Sm = anti-Sm antibodies, Anti-SSA/Ro = anti-SSA/Ro antibodies, Speckled pattern ANA = speckled pattern antinuclear antibodies, pANCA = perinuclear anti-neutrophil cytoplasmic antibody.



**Figure 1.** Dermatologic biopsy of rashes and clinical manifestations. (A) Hematoxylin and eosin staining (100 $\times$ ) showed epidermal thickening and dermal microvascular dilatation with loosely arranged collagen fibers and monocyte infiltration. (B) Alcian blue staining (400 $\times$ ) showed mucin deposition in collagen bundles of dermis. (C) Toluidine blue staining (400 $\times$ ) and (D) staining for CD117 (200 $\times$ ) showed mast-cell infiltration (arrow). (E) Sausages like swollen fingers and multiple acral ulcers in the fingertips. (F) Patchy puce rashes with apparent pigmentation in both legs.

were significantly improved. Considering the patient responded well to low-dose corticosteroids, the therapeutic regimen was changed to oral methylprednisolone (40 mg/d) and hydroxychloroquine sulfate (400 mg/d). After 2 months of treatment, the lower-extremity muscle strength was improved to grade 4/5 bilaterally. During the following months, the dosage of methylprednisolone was reduced with a gradient of 5 mg/mo, and azathioprine was continued for maintenance treatment. The patient recovered well after 1 year follow-up and the sequela was urinary incontinence and grade 4/5 lower-extremity muscle strength.

### 3. Discussion

Recent studies indicated that the expression spectrum of HLA varies considerably between MCTD and other connective tissue diseases, and relevant studies showed that MCTD is significantly associated with HLA-DRB alleles,<sup>[11]</sup> suggesting MCTD may be a distinct HLA-related autoimmune disease. In the current case, we identified mutations of HLA-DRB1\*15:01 and \*09:01. The diagnostic value of genetic examination in patients with MCTD still requires further research.

The pathogenetic mechanism of polyneuropathy in MCTD remains unclear. Adelaide et al observed myelinoclasts, axon disintegration, and perivascular lymphocyte infiltration by nerve biopsy in patients of MCTD with peripheral neuritis, suggesting this neuritis was correlated with regional vasculitis.<sup>[12]</sup> Weiss et al performed a postmortem examination in a case diagnosed with MCTD and transverse myelitis and found the thoracic spinal cord was atrophied and there were focal necrosis and gliosis in spinal parenchyma. Moreover, in the cerebral parenchyma, there were also multiple regions of necrosis and white-matter demyelination, and thickening of vessel walls with abundant inflammatory cell infiltrations was noted in both the spinal and brain parenchyma.<sup>[15]</sup> These findings also indicated that vasculitis and arterial thrombosis may be the potential pathogenic factors of central neuropathy in MCTD.

Transverse myelitis is a severe complication of MCTD, which dominantly involves the thoracic spinal cord.<sup>[9]</sup> MRI is the best choice for radiological examination, with the condition manifesting as hyperintensity on T2-weighted imaging with remarkable enhancement. However, MRI findings are normal for approximately 30% of patients with concurrent SLE and transverse myelitis.<sup>[13]</sup> Mok et al reported a case of MCTD with accompanying transverse myelitis for which MRI showed no abnormality.<sup>[8]</sup> CSF examinations can provide diagnostic clues for patients with MCTD-associated central nervous system involvement, and such clues include pleocytosis with a prevalence of granulocytes, increased protein levels, low glucose, and positive protein reactions.

The treatment for this complicated case was challenging. Along the disease spectrum, transverse myelitis is the foremost condition necessitating emergency control. As there has been no standard regimen for MCTD complicating transverse myelitis, we referred to the therapeutic schedule for SLE with concomitant transverse myelitis: intravenous methylprednisolone (1 g/d) combined with cyclophosphamide (1 g/m<sup>2</sup>) for 3 days, followed with oral glucocorticoids for sequential therapy. In addition, previous studies showed that hydroxychloroquine sulfate could significantly reduce the risk of recurrence in patients with SLE and transverse myelitis.<sup>[14]</sup> Considering the poor condition of the current patient, we eventually selected a combination of low-dose corticosteroids and hydroxychloroquine sulfate.

The prognosis of MCTD with transverse myelitis remains unclear due to the scarcity of clinical evidence. In the 8 patients previously reported, 5 responded well to the combination of corticosteroids and azathioprine, and 1 recurrent case achieved an improved outcome after treatment with corticosteroids, azathioprine, and intravenous immunoglobulin.<sup>[7]</sup> In the current case, the prognosis was favorable, but a much longer follow-up is still needed.

#### 4. Conclusions

MCTD with multiple neurological complications is extremely rare, and its diagnosis and treatment are challenging. This case report suggests the treatment for this condition should be

individualized, and a combination of low-dose corticosteroids and hydroxychloroquine sulfate may be an effective therapeutic regimen.

#### Author contributions

**Conceptualization:** Yulei Hao, Jiachun Feng.

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