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CASE REPORT

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Guillain–Barré syndrome following herpes zoster in a patient with systemic sclerosis

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Abstract We report the case of a patient with systemic sclerosis (SSc) who developed Guillain–Barré syndrome (GBS) 6 weeks after herpes zoster. Muscle weakness developed first, and thereafter severely in the muscles in the same segment as the zoster. Serum anti-GM1 and -GD1b IgM autoantibodies were detected in the acute phase. The clinical course and the findings of nerve conduction studies and a sural nerve biopsy were compatible with GBS accompanied by underlying chronic polyneuropathy. SSc might have affected the neurological manifestation via the development of underlying neuropathy and a possible contribution to the autoimmune basis in GBS.

Key words Antiganglioside antibodies · Guillain–Barré syndrome · Herpes zoster · Myelodysplastic syndrome · Systemic sclerosis

Introduction

Guillain–Barré syndrome (GBS) (acute inflammatory demyelinating polyradiculoneuropathy) is clinically characterized by a monophasic course of muscle weakness and areflexia with or without sensory disturbance. Although infection is often recognized to precede the occurrence of GBS, herpes zoster is not a common preceding event.[1] Here, we describe the case of a patient with systemic sclerosis (SSc) and myelodysplastic syndrome (MDS) who developed GBS 6 weeks after herpes zoster. The potential roles of the preceding zoster, SSc, and MDS in the pathogenesis and clinical manifestation of GBS are discussed.

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Case report

A 71-year-old man was admitted to our hospital with a 4-day history of increasing muscle weakness in his right arm.

At the age of 66, the patient was diagnosed with SSc because of sclerodactylia and Raynaud's phenomenon, in addition to an elevated erythrocyte sedimentation rate (ESR) (60 mm/h), and the findings of a finger skin biopsy which showed dermal compact collagen bundles and perivascular cuffing. One year later, anemia (red blood count (RBC) $292 \times 10^4/\mu l$, Hb 10.4 g/dl, hematocrit 32.1%, reticulocytes 32000/μl), and leukocytopenia (WBC 2400/μl; 51% neutrophils, 34% lymphocytes, 11% monocytes, 3% eosinophils, 1% basophils) appeared, and bone marrow findings resulted in a diagnosis of refractory anemia. The patient was treated with oral prednisolone at a dose of 20–30 mg/day for 4 years. At the age of 68, Raynaud's phenomenon was severe, and skin ulcers occurred at the distal portions of bilateral fingers, some of which later developed necrosis. At the age of 70, when the patient required further treatment for worsening of his finger skin ulcers, no sensory or motor disturbance or abnormal deep tendon reflexes were observed in his extremities. Six weeks before admission, he suffered from herpes zoster involving his right shoulder and arm (C5 dermatome), but no antiviral agents were prescribed.

On the first day of hospitalization, his right shoulder and elbow did not function at all although he had good use of his right hand and fingers. He complained of mild gait difficulty due to right leg weakness, which was also proximal dominant. Systemic scleroderma was observed, and was especially severe at bilateral hands and feet. A pigmented scar due to herpes zoster was seen on his right shoulder. Laboratory examinations demonstrated a decrease in blood components of all three lineages (WBC 2400, RBC 192×10^4, reticulocytes 26000, Plt 78000 per μl, Hb 7.3 g/dl, hemat-

ocrit 21.6%), elevated ESR (25 mm/h), and positive antinuclear antibodies (speckled ×40), but anti-Scl-70, anticentromere, and anti-RNP antibodies were negative. The findings of a myelogram were consistent with refractory anemia,[2] showing a normocellular marrow with dyserythropoiesis (small erythroblasts containing a binucleus or Howell–Jolly bodies), dysgranulopoiesis (pseudo-Pelger change), and a decreased number of megakaryocytes, but without an increase in myeloblasts (4.2%).

After hospitalization, the muscle weakness in all extremities worsened each day, and he became unable to walk or even to sit upright by the 6th hospital day. Neurological examination revealed flaccid tetraparesis dominant on the right side, and no voluntary contraction of the right deltoid and biceps brachii muscles. The deep tendon reflexes of the extremities were absent or decreased. Babinski's sign was negative. Sensation was decreased in all modalities in the right C5 dermatome and distal portions of all extremities. Cerebrospinal fluid showed albuminocytological dissociation (protein 94 mg/dl, albumin 62.1 mg/dl, cells 0.3/μl).

Acyclovir was administered intravenously from the 5th to the 9th hospital day because of the possibility of zoster myelitis,[3] but his symptoms did not improve. On the 9th hospital day, nerve conduction studies disclosed slow motor conduction velocity, prolonged distal latency, and temporal dispersion of compound muscle action potentials (Table 1 and Fig. 1). Sensory nerve action potentials of the sural nerves were not detected. Serum IgM antibodies against GM1 (×80), GD1b (×80), and asialo-GM1 (×160) were positive, although antiganglioside IgG antibodies were not found. A left sural nerve biopsy was performed on the 10th hospital day. The nerve was embedded in hard connective tissue and could not easily be detached. Histologically, the epineurial vessels had thickened walls. Myelinated fiber density was reduced (3410/mm^2) (Fig. 2A). Thin myelinated fibers and Büngner's bands (denervated Schwann cell subunit of the myelinated fiber type) were increased in number, but unmyelinated fibers were well preserved. Teased fiber preparations disclosed an increased incidence of segmental remyelination (40%), and occasional paranodal and segmental demyelination (Fig. 2B,C). These findings, in combination with the clinical course of the patient, indicated acute-on-chronic polyneuropathy; the acute component was considered to be the development of GBS. From the 10th to the 12th hospital day, steroid pulse therapy with daily 1-g methylprednisolone injection was given, followed by treatment with oral prednisolone at 60 mg/day. During the pulse therapy, however, his symptoms still progressed, and urinary retention appeared. After high dose administration of a total of 95 g γ-globulin over the period from the 13th to the 17th hospital day,[4] both muscle weakness and sensory disturbance ceased to progress and then gradually improved. The titers of serum anti-GM1, -GD1b, and -asialo-GM1 IgM decreased during these therapies. Four months later, the patient was able to walk by himself with almost complete neurological recovery.

During hospitalization, the patient suffered from bilateral bacterial pneumonia and was treated with antibiotics. Eight months later, he died of sepsis from methicillin-resistant *Staphylococcus aureus*.

Discussion

The patient discussed in this report demonstrated monophasic tetraparesis and sensory loss with acute onset, and

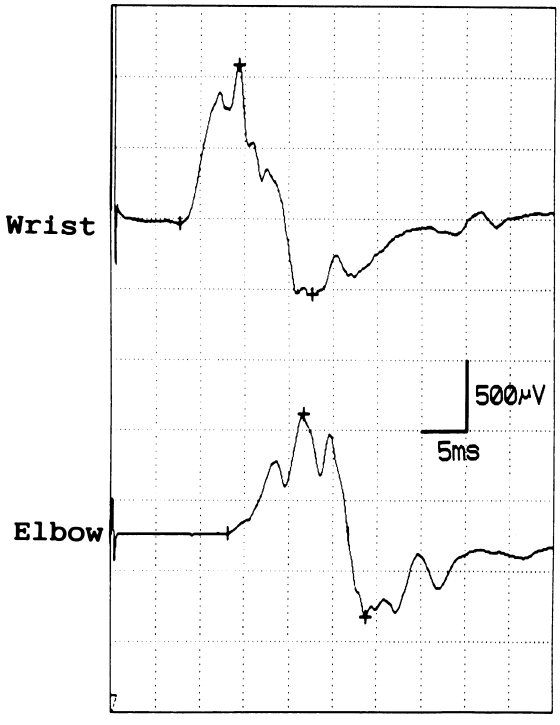

Fig. 1. Motor nerve conduction study of the right median nerve performed on the 9th hospital day. The wave forms obtained by supramaximal stimulation of the right median nerve at the wrist and elbow demonstrate dispersed, low-amplitude compound muscle action potentials

Table 1. Results of the motor-conduction studies on the 9th hospital day

Nerve	Conduction velocity (m/s)	Distal latency (ms)	Amplitude (mV)	Temporal dispersion
Right median	42.2	7.75	1.60	+
Right ulnar	42.7	3.05	3.62	+
Right tibial	22.3	8.80	0.65	+
Right peroneal	5.8	12.65	0.38	+

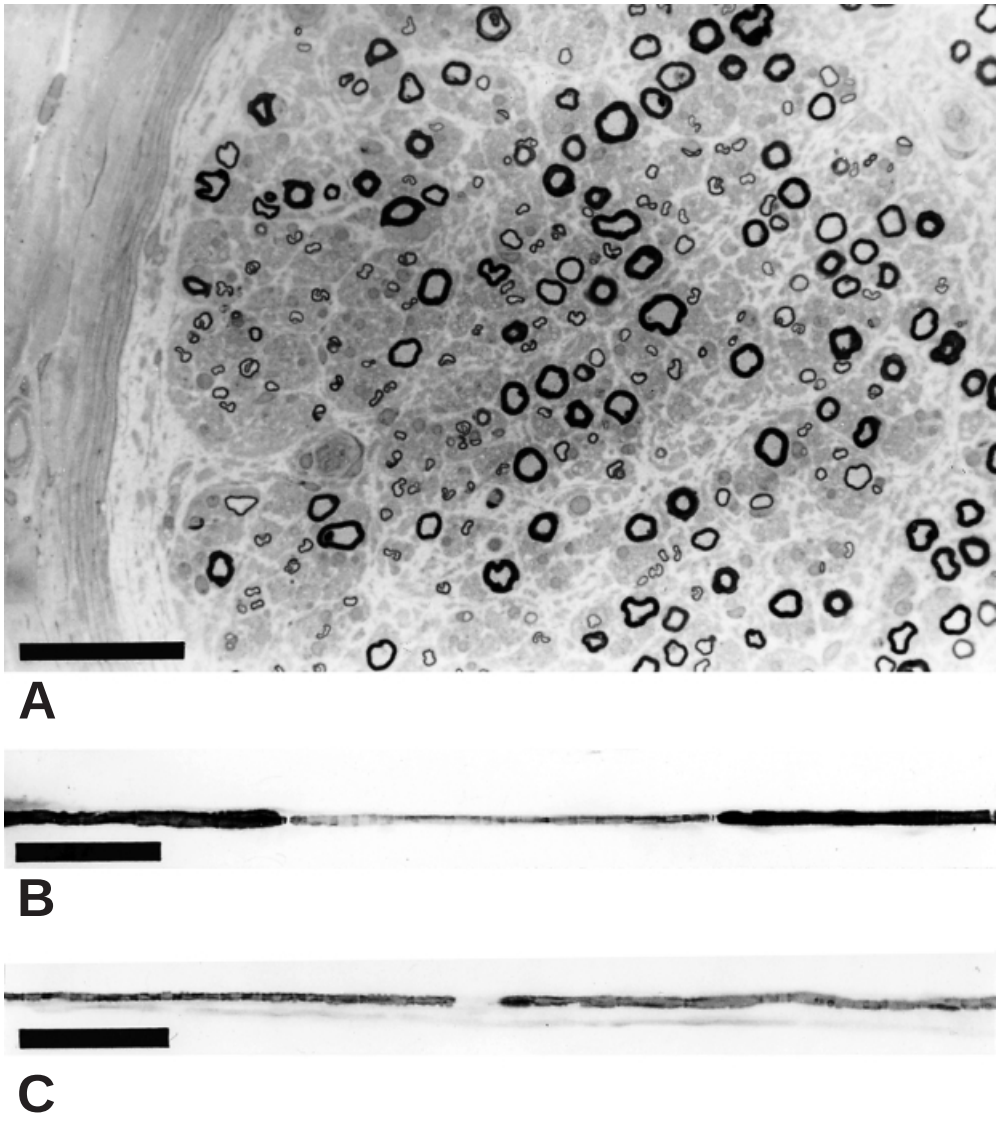

Fig. 2. Light microscopy of a left sural nerve biopsy specimen taken on the 10th hospital day. The density of myelinated fibers has decreased and the subperineurial space has widened in a toluidine blue-stained semithin section (**A**). Segmental remyelination (**B**) and paranodal demyelination (**C**) were present in teased fiber preparations. **A**, *bar* 40 μm; **B**, **C**, *bar* 100 μm

his deterioration reached a plateau in 3–4 weeks. Serum anti-GM1 and -GD1b IgM autoantibodies were detected in the acute phase. A sural nerve biopsy specimen showed occasional segmental demyelination. These features are consistent with GBS.

The occurrence of GBS following zoster has occasionally been reported in the literature;[5–8] in most cases, the interval between skin eruption and the onset of muscle weakness is 1–2 weeks. Although this patient manifested motor weakness after a longer, 6-week, interval following zoster, such a long latency (up to 2 months) can happen.[5] An important feature of GBS in this case was that muscle weakness developed first at, and affected most severely, the muscles of the same segment (C5) as the preceding zoster eruptions, further supporting a link between zoster and GBS. Such an initial involvement of muscles of the same segment as the zoster has rarely been described.[5] Although the pathogenesis for this phenomenon is difficult to clarify, one possible mechanism is the injury of peripheral motor nerve roots or anterior horns by herpes zoster, which could be subclinical by itself, but locally demonstrates a severe clinical manifestation when systemic demyelinating radiculoneuropathy develops. This speculation is supported by a report that segmental motor system involvement by zoster is commonly detected by electrophysiological studies,[9] even when segmental muscle weakness[10] is clinically absent. We cannot formally exclude another possibility, which is difficult to prove in this case, that nerves affected by zoster tend to be profoundly damaged by the demyelinating process of GBS.

Patients with GBS often show positive serum autoantibodies to gangliosides in the acute phase, as did this patient, who showed anti-GM1 and -GD1b IgM antibodies. Although antiganglioside antibodies are not specific to GBS, immunohistochemical studies suggest that they may have an important role in the development of peripheral nerve lesions.[11] Recent studies have revealed that antigen specificity could be correlated with the pathogenic organism of the preceding infection. Patients with GBS following cytomegalovirus infection frequently demonstrate anti-GM2 IgM antibodies,[12] whereas *Campylobacter jejuni* is associated

with anti-GM1 antibodies.[13] On the other hand, anti-galactocerebroside antibodies are reported in GBS after *Mycoplasma pneumoniae* infection.[14] Details of antiganglioside antibodies in GBS following herpes zoster have not been described to date, but specific ganglioside(s) might also be involved.

It may be important to assess the role of SSc and MDS in the pathogenesis of neuropathy in this patient. One aspect we need to consider is that immunosuppression caused by leukopenia and corticosteroid therapy for MDS[15] may be responsible for the development of zoster, which preceded GBS in this case. On the other hand, the direct link between GBS and SSc seems less obvious to us than that between GBS and zoster. However, although the co-occurrence of GBS with SSc has not previously been reported, some reports have suggested that collagen disease-related immune disorders may predispose the patient to develop GBS.[16] In this context, a further analysis of the clinical significance of the high prevalence of serum antiganglioside antibodies in patients with SSc or other collagen diseases[17] will be useful to help us judge whether the association of GBS and SSc presented herein was more than a mere coincidence. Another prominent neurologic feature in this case was an underlying neuropathy, proved histologically by a sural nerve biopsy; increased incidence of segmental remyelination indicates the presence of subclinical neuropathy, presumably associated with SSc.[18,19] It is difficult to determine whether the primary damage was demyelinating or axonal because the myelinated fiber density was decreased, but the temporal dispersion and the very slow conduction velocity of the peroneal nerve observed in the early phase suggested underlying damage with a demyelinating component. The preexisting neuropathy probably enhanced the severity of the systemic symptoms of GBS. Although an autopsy was not performed, the patient's clinical course, in addition to the findings of electrophysiological and histological studies, clearly showed that the coexistence of acute and chronic polyneuropathy accounted for the clinical neurological manifestations in this patient.

In conclusion, the pathogenesis of the GBS in the present case clearly relates to the herpes zoster. It is important to recognize herpes zoster as an infection which can precede and affect the clinical manifestations of GBS. Chronic polyneuropathy due to SSc may intensify the clinical symptoms of overlapping neurologic diseases, including GBS.

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