

Successful treatment of a refractory dysbiotic intestinal pseudo-obstruction in a patient with systemic sclerosis-polymyositis overlap syndrome by intravenous immunoglobulin administration possibly related to gut flora normalisation

Sirs,

Systemic sclerosis (SSc) is a systemic disease that is characterised by excessive fibrosis in the skin and various internal organs including the lungs, kidneys, and gastrointestinal (GI) tract. The GI tract is the second most common site of SSc organ damage after the skin. It has been reported that about 80% of SSc patients have abnormalities noted during oesophageal motility testing. Involvement of the anorectum was the next most frequent, ranging from 50-70%, followed by small bowel hypomotility in 40%, and colonic involvement in 10-50% of patients (1). The hypomotility of the small bowel and colon can lead to intestinal pseudo-obstructions, which can result in death related to malabsorption caused by small intestinal bacterial overgrowth (2, 3). The management of pseudo-obstruction in SSc patients is critical to their prognosis and remains a challenge. We report on a patient with systemic sclerosis-polymyositis overlap syndrome with a refractory intestinal pseudo-obstruction who responded drastically to treatment with intravenous immunoglobulin (IVIG) possibly related to gut flora normalisation. The patient, a 45-year-old Japanese man, had suffered from progressive skin thickening and proximal muscle weakness of the lower extremities for a month. A primary care doctor diagnosed his condition as SSc and introduced him to our hospital. A physical examination revealed that cutaneous involvement had extended from the periphery to the center. A modified Rodnan total skin thickness score of 39 was assigned to grade the degree of skin sclerosis. Histopathological examination of skin biopsies from the forearm revealed a sclerotic change that had spread the full thickness of the dermis. Laboratory investigations revealed a white blood cell count of $21,750/\mu\text{L}$, a red blood cell count of $4.51 \times 10^6/\mu\text{L}$, a haemoglobin level of 12.3 g/dL, and a platelet count of $5.35 \times 10^5/\mu\text{L}$. In addition, increased levels of serum aspartate aminotransferase (101 U/L), alanine aminotransferase (68 U/L), lactate dehydrogenase (570 U/L), creatine kinase (2387 U/L), aldolase (32 U/L), myoglobin (540 ng/mL), C-reactive protein (2.33 mg/dL), and interleukin-6 (737 pg/mL) were identified. Autoantibodies were not detected by immunoprecipitation or specific enzyme-linked immunosorbent assays. Further evaluations, including gastrointestinal endoscopy, thoracoabdominal

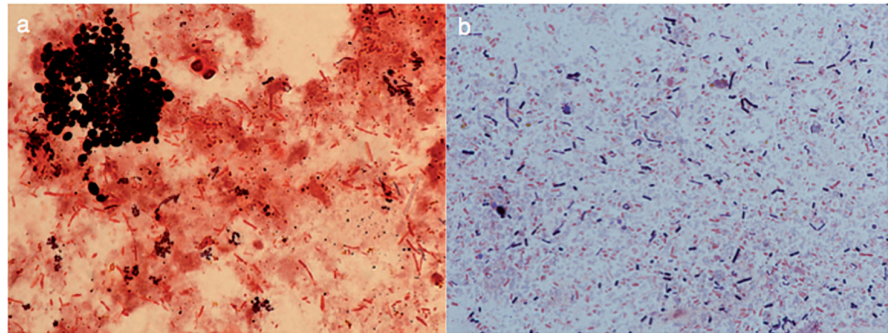
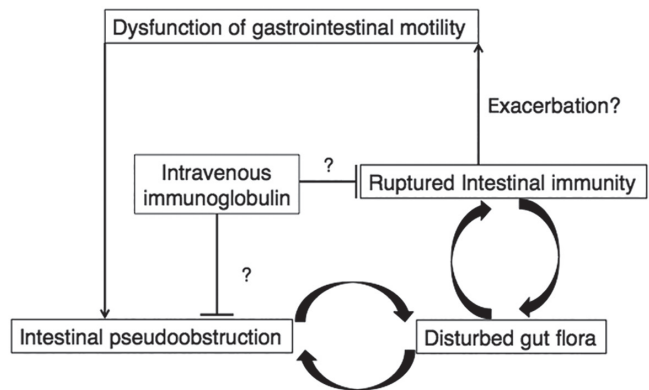


Fig. 1. Findings on Gram staining before and after intravenous immunoglobulin (IVIG) administration. (a) Gram negative rod and fungus dominantly cover the field prior to the treatment. (b) Nearly normal gut flora pattern observed that is none of fungus, reduced gram negative rod, and appeared gram positive rod after the treatment.

Fig. 2. Hypothesis relating recovered dysfunction of gastrointestinal motility and intestinal pseudo-obstruction. Intestinal pseudo-obstruction, disturbed gut flora, and ruptured intestinal immunity creates negative linkage, respectively. Administration of IVIG is a potential therapeutic target in the treatment for intestinal pseudo-obstruction and ruptured intestinal immunity and is improved disturbed gut flora indirectly, resulting in a normalisation of gastrointestinal motility.



computed tomography, a respiratory function test, electromyography, and muscle biopsies revealed SSc complicated by polymyositis. The patient was initially administered steroid pulse therapy (1 g/day for 3 days), which was followed by 30 mg/day of prednisolone. The cutaneous involvement had gradually improved, but the myositis persisted. Oral cyclosporine (2 mg/kg/day) was administered under controlled conditions with prednisolone, but impaired swallowing continued. Two months later, the patient suffered from an intestinal pseudo-obstruction but recovered with fasting and the administration of metoclopramide (20 mg/day) and erythromycin (800 mg/day). After another nineteen months, the patient was hospitalised with exacerbations including vomiting, diarrhea, and bloating. Octreotide (50 $\mu\text{g/day}$), prostaglandin f2 alpha (2 mg/day), neostigmine (0.25 mg/day), and metronidazole (750 mg/day) were administered in conjunction with prednisolone (20 mg/day) under fasting conditions. Despite the administration of these therapies, the exacerbation of the GI symptoms and aspiration pneumonia related to dysphagia were diagnosed. Administration of IVIG (0.4 g/kg/day for 5 days) was started to treat the dysphagia in conjunction with ampicillin sodium/sulbactam sodium (9g/day). His GI symptoms and aspiration pneumonia drastically improved for 2 weeks. In parallel, the gut flora had been normalised for 5 weeks (Fig. 1). The patient had not experienced GI

symptoms or aspiration pneumonia during the previous 13 months.

Although there has been a report of improvements in swallowing, early satiety, and diarrhea following the administration of IVIG in patients with SSc (4), the mechanism of action and effectiveness against GI symptoms are still unknown. Meanwhile, there is clear evidence that IVIG affects the diverse effects on the immune system in inflammatory muscle disease patients (5). Recently, dysbiosis of the gut microbiome has been detected in rheumatoid arthritis patients; furthermore, it was partially improved after rheumatoid arthritis treatment (6). In fact, there are possible close associations between the gut bacterial flora and the pathogenesis of autoimmune diseases. Remarkably, the patient's refractory intestinal pseudo-obstruction drastically improved, which was potentially related to the gut flora normalisation after IVIG administration. Unfortunately, the detailed mechanisms of action of therapeutic IVIG are complex (7). However, normalisation of disturbed gut flora by the administration of IVIG is potentially an option for refractory intestinal pseudo-obstruction in patients with SSc complicated by polymyositis (Fig. 2). However, we have reported that the administration of IVIG rescued the refractory pseudo-obstruction possibly related to gut flora normalisation in only a single patient; thus, it is difficult to draw any definite conclusions. Nonetheless, additional case se-

ries might confirm the usefulness of IVIG administration against refractory intestinal pseudo-obstruction in patients with systemic sclerosis-polymyositis overlap syndrome.

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Competing interests: none declared.

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