

## Case report

# Intravenous immunoglobulin therapy for severe gastrointestinal involvement in systemic sclerosis

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### ABSTRACT

**Objective.** *Gastrointestinal (GI) disease is one of the major causes of morbidity in patients with systemic sclerosis (SSc). The most common manifestation of GI disease is oesophageal involvement affecting 70–90% of patients. Severe GI disease is uncommon, but results in symptoms such as early satiety, pseudo-obstruction, weight loss and malnutrition. The pathogenesis is relatively poorly understood, and management focuses on symptomatic control rather than immunomodulation.*

**Methods.** *We describe two cases of patients with SSc myositis overlap syndrome with severe GI involvement who demonstrated improvements in swallowing, early satiety and diarrhoea following the administration of intravenous immunoglobulin (IVIg).*

**Results.** *Clinical data related to the two cases were collected by review of medical records.*

**Conclusion.** *GI complications range from mild symptoms to debilitating and life threatening. We propose that IVIg may have an immunomodulatory effect in a subset of patients with SSc myositis overlap syndrome.*

### Introduction

Systemic sclerosis (SSc) is a rare disease characterised by autoimmunity, vasculopathy and fibrosis. The disease is heterogeneous in nature involving the skin and internal organs. Approximately 80% of patients have gastrointestinal tract involvement, which accounts for a large burden of morbidity (1). 70–90% of patients with gastrointestinal manifestations develop oesophageal complications with reflux and dysphagia (2). Delayed gastric emptying and involvement of the small intestinal, colonic and anorectal can lead to significant

symptoms including abdominal pain, vomiting, distension, diarrhoea, constipation and incontinence. Pseudo-obstruction, bacterial overgrowth and malabsorption can result in severe malnutrition (3) and the need for parenteral nutrition.

The pathogenesis of GI involvement in SSc is poorly understood, but is characterised by vascular and neuronal damage, inflammation and fibrosis. There is some evidence supporting mucosal hypoxia as the initial event in GI pathology, supported by studies showing reduced mucosal blood flow to the stomach and duodenum (4) and vascular insufficiency preceding smooth muscle atrophy (5). In addition, neuronal dysfunction may also play a role; with vascular damage to the vasa nervorum resulting in ischaemia and nerve injury in addition to compression of the nerves by collagen tissue. Smooth muscle cells are often fragmented and atrophied, with no increase in collagen deposition (6). This is consistent with neural damage occurring before fibrosis, but whether the primary insult is vascular or neural remains uncertain.

SSc has co-existing clinical features of related autoimmune rheumatic conditions, termed overlap syndrome with features ranging from mild to severe. We recently reported a study from our centre confirming that 20% of SSc patients had features of an overlap disease, and 43.8% of those had features of SSc-myositis overlap (7).

Management of severe GI complications in SSc is challenging. There is currently no evidence that immunomodulation prevents or halts progression of GI disease and symptomatic control using pharmacological interventions and nutritional supportive therapy are the mainstay of treatment. Intravenous immunoglobulin

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(IVIg) is known to have a beneficial effect in inflammatory muscle conditions such as refractory dermatomyositis and polymyositis (8, 9).

Here we present two cases of systemic sclerosis with overlap myositis and severe GI disease unresponsive to conventional therapy to illustrate the potential effect of IVIg on the GI manifestations of their disease.

### Case 1

A 43-year-old woman was diagnosed with diffuse SSc with a positive anti-RNA polymerase III antibody following an episode of collapse. She was found to be in left ventricular failure with suspected cardio-myositis. Her disease was characterised initially by Raynaud's, rapidly progressive skin involvement (Modified Rodnan skin score increased from 19/51 to 29/51 in 5 months) and GI symptoms including nausea, intermittent vomiting, weight loss, abdominal bloating and alternating diarrhoea with constipation. These were initially managed conservatively with proton pump inhibitors, anti-emetics, laxatives and a trial of antibiotics for small bowel overgrowth each with varying degrees of response. In 2012 she was noted to have increasing muscle weakness and falling lung volumes (68.3% predicted FVC from 91% over 1 year). EMG confirmed a diffuse myopathic process, despite a normal CK. There was concurrent worsening of GI symptoms with increasing constipation, diarrhoea, bloating and severe reflux.

#### *Treatment and outcome*

Initial SSc specific treatment comprised low dose prednisolone and methotrexate for immunosuppression. Treatment was escalated to 6 infusions of IV cyclophosphamide at 4 weekly intervals for rapidly progressive skin disease. Post cyclophosphamide, she was established on maintenance mycophenolate mofetil (MMF). None of these treatments made a significant difference to her GI symptoms. IVIg at a dose of 2g/kg split over 5 days was commenced in March 2013.

Prior to IVIg, she experienced symptoms of reflux on most days a week

(based on the Reflux Disease Questionnaire - RDQ) and now only experiences symptoms occasionally often less than once a week. The UCLA SCTC GIT 2.0 (freely available at <http://uclascleroderma.researchcore.org/>) score was 2.75 pre-treatment. 11.5 months on, this is now 2.05 and continues to do well.

### Case 2

A 48-year-old man was diagnosed with U3-RNP antibody associated DeSSc following an abrupt onset of peripheral neurological symptoms, Raynaud's and skin changes.

Over the first 2 years, he was troubled predominantly by GI symptoms including dysphagia, severe acid reflux, slow gastric emptying and early satiety, abdominal bloating and significant diarrhoea. He was referred to our unit with a 40 kg weight loss and on-going GI symptoms. There was evidence of oesophagitis on endoscopy, positive hydrogen breath testing suggestive of small bowel overgrowth and CT scanning illustrated dilated stomach and small bowel with no evidence of obstruction. His medical therapy was optimised with maximal PPI therapy, pro-kinetic, treatment of small bowel overgrowth and he was established on parenteral nutrition.

In 2012, he developed an inflammatory myopathy despite normal CK as well as cardiac involvement of SSc with arrhythmias, peripheral oedema and elevated troponin despite a normal echocardiogram and cardiac MRI.

#### *Treatment and outcome*

Initially the mainstay of treatment was with conservative measures and low-dose prednisolone and MMF as immunosuppressive agent. He was converted to 6 cycles of IV cyclophosphamide for cardiac involvement of SSc. However, in January 2014, IVIg (at a dose of 2g/kg over 5 days) was commenced on the basis of progressive myopathy and general deterioration. Although there are no significant differences in RDQ scores before or after IVIG initiation, within 5 months of IVIG, his UCLA SCTC GIT 2.0 scores improved from 1.69 to

1.25. Having previously had 5 emergency admissions related to worsening GI symptoms, which included multiple episodes of pseudo-obstruction requiring emergency deflation of his large bowel, vomiting, and constipation, he currently remains stable with no further admissions.

#### *IVIg in myositis*

IVIg is a form of immune-modulating treatment, the mechanism for which is not fully understood. Its beneficial effect in autoimmune conditions, particularly inflammatory muscle disease, is well-established. It is derived of pooled plasma from thousands of blood donors, and comprises mainly of IgG dimers as well as small amounts of IgA, IgM, soluble CD4, CD8 and cytokines (10).

There are likely to be multiple mechanisms of action for IVIg in inflammatory muscle and autoimmune disease, through modulation of the dendritic cell function, lymphocyte effects and anti-inflammatory properties. The IgG molecule has been shown to bind to the surface of dendritic cells upon administration, which can then be destroyed through antibody-dependent cellular cytotoxicity by natural killer cells. This ultimately reduces T-cell priming by the dendritic cells, which in turn reduces the number of antigen-presenting cells found in the inflamed tissues (11). The IgG dimers also inhibit the maturation of dendritic cells, by suppressing the upregulation of costimulatory molecules such as IL-12, preventing activation and proliferation of T cells (11). Anti-idiotypic antibodies present directly inhibit pathogenic autoantibodies as well as interacting with B cells, and arresting the growth of autoreactive B cell clones (12). Through this mechanism B cell differentiation is inhibited, and thus production of autoantibodies is downregulated. The anti-inflammatory activity of IVIg arises through the prevention of complement-mediated tissue damage. It inhibits the formation of the membrane attack complex (MAC), as well as accelerating the conversion of C3b into its inactive form, thus controlling immune complex formation.

IVIg has also been shown to decrease the production of pro-inflammatory cytokines, and accelerate production of inflammatory cytokine antagonists *in vitro* (12, 13). In addition, IVIg has an important role in promoting tissue repair in particular it has a regulatory effect on matrix metalloproteinases; enzymes shown to be involved in degradation and restoration of the extracellular matrix in SSc (14).

The above mechanisms are likely to underlie the beneficial effects of IVIg in dermatomyositis with improvement in muscle fibre diameter and reduced endomysial inflammatory infiltrate. Alteration in gene expression levels including CCL18 by immature dendritic cells has been reported and interestingly, it was recently reported that activated IgG of SSc patients expresses high levels of CCL18 and this may be relevant in disease pathogenesis (15).

The experimental and clinical challenges of IVIg therapy have received significant attention over the last decade (16). Its benefit has been studied in other autoimmune conditions with GI involvement. This includes steroid-resistant Crohn's disease, where case series has shown rapid benefit in patients who have not improved with anti-TNF (17). Similar approach has been reported for SSc myositis overlap syndrome although the effect on GI disease was not explored. There is evidence that it has beneficial effects on skin sclerosis (18) and arthritis leading to improved function (19). More recently, marked improvement in lung fibrosis following IVIg with azathioprine was noted in a patient with SSc and myositis (20).

The two cases here illustrate the specific potential therapeutic effect of IVIg for patients with SSc associated severe gastrointestinal involvement, supported by clinically significant improvement in a validated disease-specific GI outcome measure. There was also evident benefit for myositis. Gastrointestinal involvement in SSc leads to significant morbidity. The improvement in their GI symptoms coincided with the initiation of IVIg to their treatment. Since IVIg

has a beneficial role in patients with myositis, this flare in their muscle disease may also extend to increased severity in their GI disease. The exact mechanism of how IVIg works in the intestine is not known. It also remains to be seen whether this improvement in early satiety, abdominal distension and appetite is only transient, or with continued use a lasting improvement can be obtained.

### Conclusion

GI manifestations in SSc are common, and range from mild to debilitating and life-limiting manifestations. The emphasis of current approach in management of this aspect of the disease is primarily on symptomatic relief and supportive therapy. Evidence from experimental models suggests the potential for immunomodulatory approach and our cases provide support that IVIg may be useful in a subset of patients with SSc who have severe GI involvement as well as evidence of myositis. In this subset, we believe their severe and rapidly progressive GI disease may be driven by a myopathic process, and thus treating their muscle disease can result in significant improvement in their gastrointestinal symptoms.

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