Particularly severe form of refractory gastrointestinal involvement in systemic sclerosis

Ana Bento da Silva [1,2], Maria Helena Lourenço [1,2,3], Jaime Cunha-Branco,[1,3] Maria João Gonçalves[1,2,4]

[1]Rheumatology, Centro Hospitalar de Lisboa Ocidental - Hospital de Egas Moniz, Lisbon, Portugal
[2]Rheumatology, Comprehensive Health Research Center, NOVA Medical School, Lisbon, Portugal
[3]Faculdade de Ciências Médicas, NOVA Medical School, Lisbon, Portugal
[4]Escola Superior de Tecnologia da Saúde de Lisboa, Lisbon, Portugal

Correspondence to
Dr Ana Bento da Silva; adbentosilva@gmail.com

Accepted 24 March 2023

Check for updates

© BMJ Publishing Group Limited 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Bento da Silva A, Lourenço MH, Cunha-Branco J, *et al*. *BMJ Case Rep* 2023;**16**:e254537. doi:10.1136/bcr-2022-254537

SUMMARY

A woman with systemic sclerosis presents with a severe and rapidly progressive form of gastrointestinal involvement, mainly marked by recurrent refractory episodes of pseudo-obstruction, culminating in severe malnutrition and dependence of parenteral nutrition. The impact on her quality of life was extremely significant. As a last resort, she started intravenous immunoglobulin with progressive improvement of her symptoms, allowing for the reinstitution of oral diet and removal of parenteral nutrition. After more than 1 year, she maintains clinical stability. Systemic sclerosis has a heterogeneous phenotype, but gastrointestinal involvement is one of the most frequent. Severe manifestations are rare, but can lead to severe malnutrition and are associated with high morbidity and mortality rates. Their management is challenging, as the available treatments are still very limited. A better understanding of its pathophysiology, which seems to be unique, is essential to provide more effective treatments and improving quality of life.

BACKGROUND

Systemic sclerosis (SSc) is a rare and highly heterogeneous immune-mediated rheumatic disorder, first described in 1753 by Carlo Curzio, but only later named as 'sclérodermie' in 1847 by Gintrac.[1–3] Two of the main features of SSc are Raynaud's phenomenon and skin sclerosis, but virtually any organ system can be affected.[2 4] In the systematic literature review by Bairkdar *et al*, the pooled overall prevalence was 17.6 per 100 000 individuals, with a female to male ratio of almost 5:1.[5]

SSc pathophysiology is not clearly understood, but three main factors are considered: vasculopathy, autoimmunity and fibrosis, resulting from predisposing genetic factors and environmental triggers.[4] The severity spectrum of SSc is highly variable, ranging from a mild disease to a rapidly progressive and life-threatening disorder. Mortality rates can be 2.82-fold higher than the general population, which does not seem to be significantly decreasing over time, despite the therapeutic breakthroughs and systematic monitoring of major organ involvement.[4 6]

Although not always the most perceptible, the involvement of the gastrointestinal (GI) tract is one of the most frequent (up to 90% of patients) and it is associated with high rates of morbidity and mortality.[2 7] The clinical features are highly heterogeneous and any region across the GI tract can be affected.[2] A high level of suspicion is necessary to promote early diagnosis and treatment, however, little is known regarding the pathophysiology behind GI complaints, making its management a major challenge.[8]

With the aim of contributing to the knowledge of these serious clinical manifestations, the authors present a case of a particularly severe and rapidly progressive form of intestinal involvement, highlighting the diagnostic and therapeutic challenges, as well as the great impact on the patient well-being.

CASE PRESENTATION

A woman in her mid-60s, smoker and with history of arterial hypertension, peripheral arterial disease and osteoporosis presented a picture of swollen and painful hands with an inflammatory pattern, together with prolonged morning stiffness and numbness of all fingertips, beginning in the late 2010s. This led to a rheumatology referral 2 years later. Her family and social history were unremarkable. She was diagnosed with diffuse cutaneous SSc with cutaneous (skin sclerosis with a Rodnan score of 30/51 points; puffy hands; salt and pepper skin in the forearms; microstomy), vascular (Raynaud's phenomenon and capillaroscopy with an active evolving to late pattern of M Cutolo) and pulmonary involvement. High-resolution chest CT scan revealed a non-specific interstitial pneumonia pattern with an extension of less than 20% and centrilobular emphysema (predominating the latter); respiratory function tests showed a restrictive pattern (forced expiratory volume in the first second (FEV1) of 77% and forced vital capacity (FVC) of 73% with normal FEV1/FVC) and severely reduced diffusing capacity for carbon monoxide (37 mmol/(min×kPa)); arterial blood gases values were normal; after multidisciplinary discussion, a wait-and-see approach with tight surveillance was adopted. The immunological profile was remarkable for positive antinuclear antibodies with a titre of 1/640 and anti-th/to. On diagnosis, she started treatment with prednisolone 7.5 mg/day, subcutaneous methotrexate 20 mg/week, folic acid 10 mg/week, amlodipine 5 mg/day and acetylsalicylic acid 150 mg/day.

Two months later, she began to experience a rapidly progressive dysphagia for liquids, abdominal distension and crampy abdominal pain, abundant diarrhoeal stools, faecal incontinence and a weight loss of 10 kg in 2 months (from 63 kg to 53 kg), with a body mass index (BMI) of 19.5 kg/m^2 (previous BMI 23.1 kg/m^2). She was then admitted to the rheumatology department for further investigation.

BMJ Case Rep: first published as 10.1136/bcr-2022-254537 on 4 April 2023. Downloaded from http://casereports.bmj.com/ on April 20, 2023 at Hywel Dda University Health Board. Protected by copyright.

INVESTIGATIONS

The patient underwent a battery of complementary exams. Her blood work revealed moderately raised muscle enzymes (creatine kinase 655 U/L and myoglobin 17.87 nmol/L), a slightly elevated C reactive protein (CRP 9.8 mg/L) and low albumin levels (29 g/L); there were no relevant changes in haemoglobin levels (Hb 142 g/L), iron (Fe 11.5 µmol/L), ferritin (350 ng/mL), folic acid (37.9 nmol/L), vitamin B_{12} (242 pmol/L), parathormone (PTHi 3.1 pmol/L) and electrolyte levels besides a marginally decreased magnesium concentration (sodium (Na) 135 mmol/L, potassium (K) 3.87 mmol/L, calcium (Ca) corrected for albumin 2.3 mmol/L, phosphorus (P) 1.1 mmol/L, magnesium (Mg) 0.58 mmol/L). The bacteriological and parasitological examination of stools and *Clostridium difficile* screening were negative. The abdominopelvic CT scan showed a small amount of ascites with predominance in the pelvic cavity and in subhepatic topography, without other findings and the oesophageal transit revealed a decreased oesophageal motility. It was admitted a GI tract involvement secondary to SSc and she started prokinetic therapy with domperidone 10 mg two times per day, esomeprazole 20 mg/day, rifaximin 400 mg three times per day for 7 days due to suspected small intestinal bacterial overgrowth (SIBO) and high protein and hypercaloric lactose-free supplements. Initially, there was a significant clinical benefit, allowing her hospital discharge after 9 days.

However, her abdominal symptoms precociously recurred, leading to rapidly progressive weight loss of more 4 kg (weight 49 kg; BMI 18 kg/m^2), generalised muscle weakness and severe malnutrition, which motivated her readmission after 2 months. She scored 1.81 points in the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) questionnaire, scoring higher for the faecal soilage, social functioning and diarrhoea components (3, 2.33 and 2 points, respectively), which corresponded to a severe/very severe GI involvement.[9] This time, her blood work also revealed raised muscle enzymes (creatine kinase 1093 U/L; myoglobin 15.1 nmol/L) and CRP (5.3 mg/L), further decrease in albumin levels (26 g/L) and multiple hydroelectrolytic disturbances (hyponatraemia of 133 mmol/L, hypokalaemia of 3.27 mmol/L, hypomagnesaemia of 0.33 mmol/L and hypocalcaemia of 1.7 mmol/L, not present in the first admission). She also presented anaemia (Hb 117 g/L), iron deficiency (Fe 26 ug/dL) with raised ferritin (442 ng/mL) and low transferrin saturation (17%), and low 25-OH-vitamin D (37 nmol/L); folic acid and vitamin B_{12} levels remained without changes. The upper endoscopic study revealed duodenal-gastric reflux, oesophageal candidiasis and chronic gastritis associated with *Helicobacter pylori* infection; colonoscopy showed mucosal hyperaemia of the rectus and sigmoid with some adherent exudate and rectal prolapse.

During hospitalisation, recurrent episodes of intestinal pseudo-obstruction occurred, marked by significant worsening of abdominal pain and distension, vomits and constipation. Serial abdominal radiographies were performed showing exuberant bowel loops distension with air-water levels (figure 1). The abdominal CT scan revealed a marked distension of the jejunum and proximal ilium loops, with filling of these loops by fluid and air content; mechanical occlusion was excluded (figure 2).

TREATMENT

After a multidisciplinary team discussion with the general surgery and gastroenterology departments, a conservative approach was adopted with institution of bowel rest and placing of a nasogastric tube. Additionally, besides correction of electrolyte disturbances and treatment of *H. pylori* infection and oesophageal candidiasis, the patient started prokinetic drugs (metoclopramide and domperidone) and laxatives and underwent rotative cycles of antibiotic therapy due to the hypothesis of SIBO, however, without any clinical benefit and even inducing diarrhoea and worsening of faecal incontinence. She later tried octreotide 100 µg/day, again without benefit and paradoxically increasing the episodes of intestinal pseudo-obstruction.

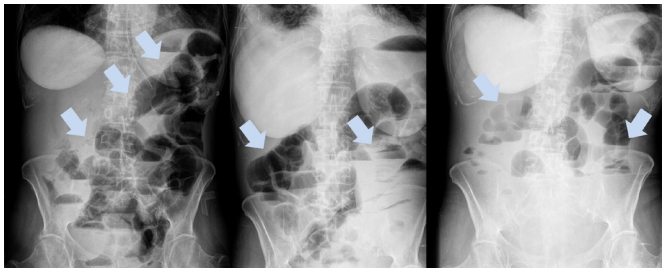

Figure 1 Serial abdominal radiographs of the patient during flares of abdominal pain and bloating, revealing exuberant distension of bowel loops with air-water levels (arrows).

She maintained recurrent episodes of intestinal pseudo-obstruction alternating with profuse diarrhoea, making it impossible to reinstitute diet and causing severe malnutrition (weight 43 kg and BMI 15.8 kg/m^2, with a Malnutrition Universal Screening Tool score of 4 points, indicating high risk of malnutrition), which culminated in the start of parenteral nutrition after 1 month (10 months after the diagnosis and 6 months after the onset of GI complaints). As no therapeutic strategy seemed to halt the progression of GI involvement, she started intravenous Ig in a dose of 2 g/kg monthly, in concordance to some previously published case reports demonstrating some efficacy in refractory cases of GI involvement, mainly improving abdominal distension, diarrhoea and faecal incontinence.[8 10 11] Regarding immunosuppression, she maintained subcutaneous methotrexate 20 mg/week, as there is no evidence of efficacy of immunosuppressive therapy in controlling the GI manifestations.[7] Psychological support was also provided.

OUTCOME AND FOLLOW-UP

After a couple of months, she started to slowly improve, allowing for gradual reintroduction of oral diet with tolerance and weight recovery (54 kg, 25% of weight gain; BMI 19.8 kg/m^2), always maintaining monthly perfusions of immunoglobulin.

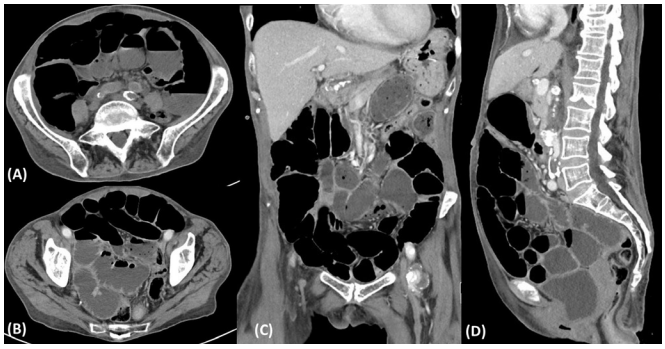

Figure 2 Abdominopelvic angio-CT scan of the patient during a flare of abdominal pain and bloating in axial (A, B), coronal (C) and sagittal (D) views. A marked distension of jejunum and proximal ilium loops, typically seen in cases of pseudo-obstruction, is easily identified.

BMJ Case Rep: first published as 10.1136/bcr-2022-254537 on 4 April 2023. Downloaded from http://casereports.bmj.com/ on April 20, 2023 at Hywel Dda University Health Board. Protected by copyright.

She stayed in the hospital for several months, despite clinical stabilisation under parenteral nutrition, due to the lack of social support available for a patient under long-term parenteral nutrition in an outpatient setting. Nevertheless, due to progressive clinical improvement, removal of parenteral nutrition was tried 8 months after its onset, without any reported clinical worsening of the GI manifestations, allowing her hospital discharge.

More than a year later, she maintains an oral soft diet with tolerance and without nutritional deficiencies. No recurrence of the episodes of intestinal pseudo-obstruction were reported and no hospital readmissions were necessary; she also currently denies abdominal pain or distension and reports a significant improvement of diarrhoea and faecal incontinence. She keeps a relatively ordinary life, only needing some support from her family and social security for transportation and demanding daily activities. A monthly scheme for treatment with intravenous Ig is ongoing.

DISCUSSION

The involvement of the GI tract is present in more than 90% of patients with SSc, however, the complaints are often non-specific and highly heterogeneous, making their diagnosis and management a challenge.[7 12] This is worrisome as GI involvement is the leading cause of morbidity and third most common cause of mortality in SSc, being responsible for 3.5% of deaths, especially secondary to severe intestinal involvement, where mortality rates can reach 85% at 9 years.[7 13–16] It is also associated with a significantly reduced quality of life, especially in the social functioning domain.[17]

Little is known regarding GI involvement pathophysiology, as it seems to move away from the mechanisms involved in other organ systems. Vasculopathy, autoimmunity, fibrosis and neuropathy have all been proposed to be involved in this, but contribution of diet, microbiota, comorbidities and drug iatrogenic reactions also play an important role.[7 16]

The small bowel is the second most frequently involved region of the GI tract (after oesophageal disease), affecting up to 88% of patients and manifesting as abdominal pain and distension, bloating and diarrhoea, as a consequence of dysmotility.[16] Two of the most feared complications are the development of SIBO (43% of patients) and chronic intestinal pseudo-obstruction (3.9% of patients), especially in diffuse cutaneous SSc of more than 3 years duration.[18 19] Colonic and internal anal sphincter affection are also significant, leading to diarrhoea, rectal prolapse and faecal incontinence in 70% of patients.[18]

Treatment of GI features is based on symptomatic relief and requires a multidisciplinary approach. Lifestyle changes, proton-pump inhibitors, prokinetics and laxatives have all been used with varying degrees of efficacy. For SIBO, cyclic antibiotics, such as rifaximin, amoxicillin–clavulanic acid, ciprofloxacin, metronidazole, trimethoprim–sulfamethoxazole and neomycin, are indicated for at least 14 days.[8 12] Rifaximin has been the preferred option, with an eradication rate of 70.8%,[20] but high recurrence (up to 40%) makes necessary the adoption of other treatments.[18] For pseudo-obstruction, a conservative approach in a hospital setting is the preferred strategy. Bowel rest, nasogastric decompression and intravenous hydration are the recommended approaches.[21] Octreotide 50–200 μg/day and pyridostigmine can have some benefit in decreasing pseudo-obstruction symptoms, but recent data are lacking.[8 18] Surgery is often avoided due to perioperative complications (mainly prolonged postsurgery ileus) and lack of efficacy, being reserved for severe chronic refractory cases.[8]

Although being one of the most often involved in SSc, severe GI disease is significantly less frequent, being reported in 8% of patients and characterised by malnutrition, pseudo-obstruction and dependence of supplemental nutrition.[13 15] Malnutrition is a major concern in SSc, with over 28% of patients being at medium to high risk of such complication.[22] In the most severe cases, total parenteral nutrition may eventually be necessary.[16] Few data are available regarding the use of parenteral nutrition in SSc, but two small sample size studies demonstrated the efficacy and safety of long-term parenteral nutrition in improving nutritional status.[23 24] However, the major issue is the necessity for the long-term use; in each study, only one patient had stopped parenteral nutrition (after 12 and 32 months) and one of them was still dependent on enteral feeding.[23 24]

This highlights the need for the discovery of new treatment strategies for severe GI manifestations. Intravenous Ig has been a promising new option, with some case reports showing significant clinical benefit, especially in decreasing reflux, abdominal distension, diarrhoea and faecal incontinence and improving electrolyte disturbances.[8 10 11] The case here reported is another example of the potential efficacy of intravenous Ig. Autoantibodies against muscarinic acetylcholine receptor M3 (M3R) inhibit the contraction of smooth muscle cells in the GI tract through a cholinergic blockage of M3R at neural and muscular levels, leading to GI dysmotility.[25 26] This has been proposed to be involved in the pathophysiology of GI involvement in SSc and, in fact, the work by Kawaguchi *et al* revealed a higher frequency of these autoantibodies in patients with early severe GI manifestations.[25] Therefore, one explanation for the reported benefits of intravenous Ig could be its role in reverting the inhibitory effects of anti-M3R autoantibodies both at the neuropathic and myopathic stages,[26] but more studies are needed to derive conclusions. Unfortunately, as the search for these autoantibodies was not routinely performed in this medical centre, it was not possible to initially request this analysis for this patient. Severe refractory GI manifestations are rare in SSc, but can lead to severe malnutrition and dependence of parenteral nutrition. This case alerts to a particularly severe and rapidly progressive form of intestinal involvement, highlighting the therapeutic challenges, as well as the impact on the patient well-being and quality of life. One must be aware of these severe features, as a high level of suspicion is necessary to promote early diagnosis and treatment. Moreover, a better understanding of the pathophysiology of SSc

Learning points

- The involvement of the gastrointestinal tract is frequently reported in systemic sclerosis and severe forms can culminate in severe malnutrition and dependence of parenteral nutrition.
- The clinical manifestations are highly heterogeneous and the pathophysiology behind them seems to differ from that observed for other organs.
- Gastrointestinal involvement severely affects patients' quality of life and constitutes the third-leading cause of mortality in systemic sclerosis.
- Treatment is directed to symptomatic relief, and thus progression of the disease is not halted.
- New therapeutic strategies are necessary to better manage these manifestations; intravenous Ig seems to be a promising new therapy, but more robust studies are needed.

BMJ Case Rep: first published as 10.1136/bcr-2022-254537 on 4 April 2023. Downloaded from http://casereports.bmj.com/ on April 20, 2023 at Hywel Dda University Health Board. Protected by copyright.

and its GI involvement is essential, enhancing the need for the search of novel therapeutic strategies.

Contributors ABdS contributed actively for the diagnosis and treatment management of the patient presented in this case report and was also responsible for writing the first draft of the manuscript. MJG conceived the presented idea, was the principal physician of the patient and was the main reviewer of the first draft of the manuscript. MHL and JB contributed for the management of the patient and commented on previous versions of the manuscript. All authors read and approved the final manuscript and agreed with its submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Ana Bento da Silva http://orcid.org/0000-0002-8590-8119
Maria Helena Lourenço http://orcid.org/0000-0001-6796-0207

REFERENCES

1 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–99.
2 Luquez-Mindiola A, Atuesta AJ, Gómez-Aldana AJ. Gastrointestinal manifestations of systemic sclerosis: an updated review. *World J Clin Cases* 2021;9:6201–17.
3 Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma). *Ann Intern Med* 1962;57:305–19.
4 Lazzaroni M-G, Piantoni S, Angeli F, *et al*. A narrative review of pathogenetic and histopathologic aspects, epidemiology, classification systems, and disease outcome measures in systemic sclerosis. *Clin Rev Allergy Immunol* 2022;1–20.
5 Bairkdar M, Rossides M, Westerlind H, *et al*. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. *Rheumatology (Oxford)* 2021;60:3121–33.
6 Lee YH. Overall and sex- and disease subtype-specific mortality in patients with systemic sclerosis: an updated meta-analysis. *Z Rheumatol* 2019;78:195–201.
7 Hoffmann-Vold A-M, Volkmann ER. Gastrointestinal involvement in systemic sclerosis: effects on morbidity and mortality and new therapeutic approaches. *J Scleroderma Relat Disord* 2021;6:37–43.
8 Sakkas LI, Simopoulou T, Daoussis D, *et al*. Intestinal involvement in systemic sclerosis: a clinical review. *Dig Dis Sci* 2018;63:834–44.
9 Khanna D, Hays RD, Maranian P, *et al*. Reliability and validity of the University of California, Los Angeles scleroderma clinical trial Consortium gastrointestinal tract instrument. *Arthritis Rheum* 2009;61:1257–63.
10 Clark KEN, Etomi O, Denton CP, *et al*. Intravenous immunogobulin therapy for severe gastrointestinal involvement in systemic sclerosis. *Clin Exp Rheumatol* 2015;33:S168–70.
11 Raja J, Nihtyanova SI, Murray CD, *et al*. Sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement in systemic sclerosis. *Rheumatology (Oxford)* 2016;55:115–9.
12 McMahan ZH, Hummers LK. Gastrointestinal involvement in systemic sclerosis: diagnosis and management. *Curr Opin Rheumatol* 2018;30:533–40.
13 Miller JB, Gandhi N, Clarke J, *et al*. Gastrointestinal involvement in systemic sclerosis: an update. *J Clin Rheumatol* 2018;24:328–37.
14 Elhai M, Meune C, Boubaya M, *et al*. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017;76:1897–905.
15 Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis & Rheumatism* 2000;43:2437–44.
16 Kaniecki T, Abdi T, McMahan ZH. Clinical assessment of gastrointestinal involvement in patients with systemic sclerosis. *Med Res Arch* 2020;8:10.
17 Yang H, Xu D, Li MT, *et al*. Gastrointestinal manifestations on impaired quality of life in systemic sclerosis. *J Dig Dis* 2019;20:256–61.
18 Kröner PT, Tolaymat OA, Bowman AW, *et al*. Gastrointestinal manifestations of rheumatological diseases. *Am J Gastroenterol* 2019;114:1441–54.
19 Muangchan C, Canadian Scleroderma Research Group, Baron M, *et al*. The 15 % rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. A systematic review. *J Rheumatol* 2013;40:1545–56.
20 Gatta L, Scarpignato C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. *Aliment Pharmacol Ther* 2017;45:604–16.
21 Shah J, Shahidullah A. Chronic intestinal pseudo-obstruction in systemic sclerosis: an uncommon presentation. *Case Rep Gastroenterol* 2018;12:373–8.
22 Baron M, Hudson M, Steele R, *et al*. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma Research Group database. *J Rheumatol* 2009;36:2737–43.
23 Jawa H, Fernandes G, Saqui O, *et al*. Home parenteral nutrition in patients with systemic sclerosis: a retrospective review of 12 cases. *J Rheumatol* 2012;39:1004–7.
24 Brown M, Teubner A, Shaffer J, *et al*. Home parenteral nutrition -- an effective and safe long-term therapy for systemic sclerosis-related intestinal failure. *Rheumatology (Oxford)* 2008;47:176–9.
25 Kawaguchi Y, Nakamura Y, Matsumoto I, *et al*. Muscarinic-3 acetylcholine receptor autoantibody in patients with systemic sclerosis: contribution to severe gastrointestinal tract dysmotility. *Ann Rheum Dis* 2009;68:710–4.
26 Kumar S, Singh J, Kedika R, *et al*. Role of muscarinic-3 receptor antibody in systemic sclerosis: correlation with disease duration and effects of IVIg. *Am J Physiol Gastrointest Liver Physiol* 2016;310:G1052–60.

Copyright 2023 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit
https://www.bmj.com/company/products-services/rights-and-licensing/permissions/
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

Customer Service
If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow

BMJ Case Rep: first published as 10.1136/bcr-2022-254537 on 4 April 2023. Downloaded from http://casereports.bmj.com/ on April 20, 2023 at Hywel Dda University Health Board. Protected by copyright.