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Chronic intestinal pseudo-obstruction in the course of systemic sclerosis successfully treated with intravenous immunoglobulins and rituximab

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Abstract

Chronic intestinal pseudo-obstruction (CIPO) is an infrequent and menacing complication of systemic sclerosis (SSc). While researchers report positive impact of rituximab (RTX) on CIPO in paraneoplastic syndrome, no case reports exist for SSc-associated CIPO. The aim of this case-based review is to analyses current literature in context of particular CIPO case description.

This analysis was based on PubMed/MEDLINE database and was conducted using the selected key terms. Finally 40 studies/case reports and one case description from authors clinical experience were included into comparison and discussion.

As conclusion description of successfuly treatment with RTX and intravenous immunoglobulins can confirm the suggestions from other studies that B-cells participate in the pathogenesis of SSc, making RTX a potentially effective therapeutic option also in coexisting CIPO.

Key words: systemic sclerosis, intravenous immunoglobulins, rituximab, intestinal pseudo-obstruction.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease characterised by inflammation and vasculopathy leading to overproduction and deposition of collagen into the skin and visceral organs [1]. The gastrointestinal (GI) tract is the second most affected organ system, both in patients with diffuse systemic sclerosis (dSSc) and in those with localised SSc, concerning about 90% of SSc patients [2]. The oesophagus is the most commonly affected structure of the GI tract (80–90%) [3], followed by the stomach and intestines (40–88%) [4] (Table I). Chronic intestinal pseudo-obstruction (CIPO) is a rare, life-threatening phenomenon characterised by a recurrent intestinal obstruction without any mechanical causes [5]. Its pathophysiology is not fully understood [6], but 4 main stages of CIPO in SSc can be distinguished: vasculopathy, neural dysfunction, smooth muscle atrophy, and muscle fibrosis [7]. The main manifestations, such as abdominal pain, distension, vomiting and diarrhoea or constipation, are non-specific; hence, the troublesome diagnostic process, delayed diagnosis, and high mortality [8]. The fundamental diagnostic tools are X-ray or computed tomography (CT)/magnetic resonance imaging (MRI) enterography presenting air-fluid levels and dilated intestinal loops with exclusion of other obstruction and pseudo-obstruction causes [9].

Primary treatment of CIPO, including prokinetic drugs, oral antibiotics, and probiotics, are not effective when SSc is the underlying cause, especially late in the disease course [10–12]. Intravenous immunoglobulins (IVIG)

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have been used successfully in the treatment of severe SSc manifestations, such as skin sclerosis, lung fibrosis, myopathy, and CIPO, although the exact mechanism is not fully understood [10, 13, 14]. Intravenous immunoglobulins are thought to act in several mechanisms, such as neutralisation of pathogenic autoantibodies, modulation of lymphocyte activity, interference with antigen presentation, and interaction with Fc receptors, cytokines, and the complement system [15]. There is evidence of rituximab (RTX) alleviating CIPO symptoms in different conditions such as anti-Hu paraneoplastic syndrome, typically associated with neuroblastoma, either in paediatric or adult patients [16–19], but we have not found any case report of treating SSc-associated CIPO with RTX. Therefore, our objective is to report a relevant case regarding a patient with SSc and CIPO, successfully treated with IVIG and RTX as a salvage therapy, as well as to provide a clinical discussion on the management of the disease.

Material and methods

A comprehensive narrative review was conducted to address the following questions: "What is a CIPO?", "What is the course of CIPO in systemic sclerosis?", and "How can we treat patients with CIPO in the course of SSc?". To find related literature a systematic search of the PubMed/MEDLINE database was conducted using the terms "chronic intestinal pseudo-obstruction AND systemic sclerosis" OR "gastrointestinal AND systemic sclerosis" OR "gastrointestinal AND scleroderma", which yielded 54 results as of May 2024. To ensure comprehensive coverage of this rare condition, the only applied data restrictions were Polish or English language and relevance to the subject. Articles were allowed if they focused on CIPO in SSc (pathoaetiology, prevalence, epidemiology, clinical implications, and especially available treatment). Articles were case reports, case series, review articles, and original research papers.

We omitted several articles that mainly focused on CIPO in non-rheumatologic patients or were lacking treatment details.

Following this initial screening, the reference lists of selected key articles were examined to identify additional relevant manuscripts not captured in the initial database search. This citation searching process allowed us to include important studies that might have been missed in the original PubMed search (Fig. 1). After careful assessment based on established selection parameters 40 articles were considered eligible and included in the final review. These included 15 reviews, 9 experimental studies, 7 case-control studies, 6 case reports, 2 case series, and 1 case-based review of literature.

Table I. Gastrointestinal manifestations in systemic sclerosis

Part of gastrointestinal tract	Clinical manifestations
Oral cavity	Microstomia, microcheilia
Xerostomia	
Dental diseases	
Oesophagus	Dysmotility with reflux
Oesophageal strictures with dilatation	
Barrett oesophagus	
Stomach	Gastroparesis
Gastric antral vascular ectasia	
Gastric strictures	
Small intestine	Small intestinal bacterial overgrowth
Chronic intestinal pseudo-obstruction	
Jejunal diverticulosis	
Malabsorption syndrome	
Intestinal structures	
Large intestine	Colonic hypomotility
Diverticulosis	
Anal canal	Rectum and sphincter dysfunction

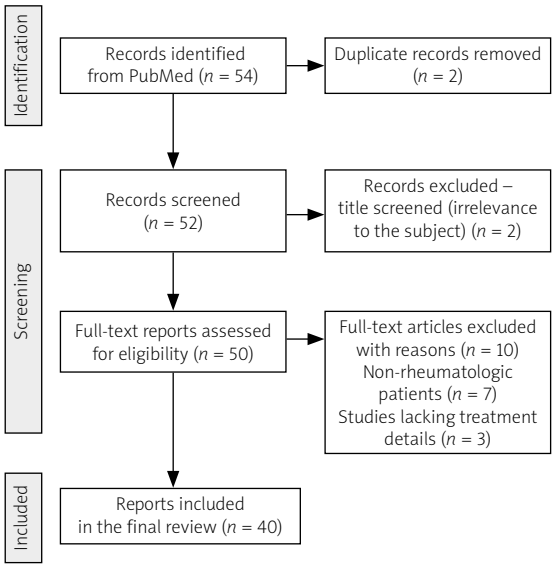

Fig. 1. PRISMA flow diagram of the article selection process.

Case description

A 42-year old male patient, admitted to Department of Internal Diseases and Metabolic Disorders, J. Strus Municipal Hospital in Poznan (Poland), was diagnosed

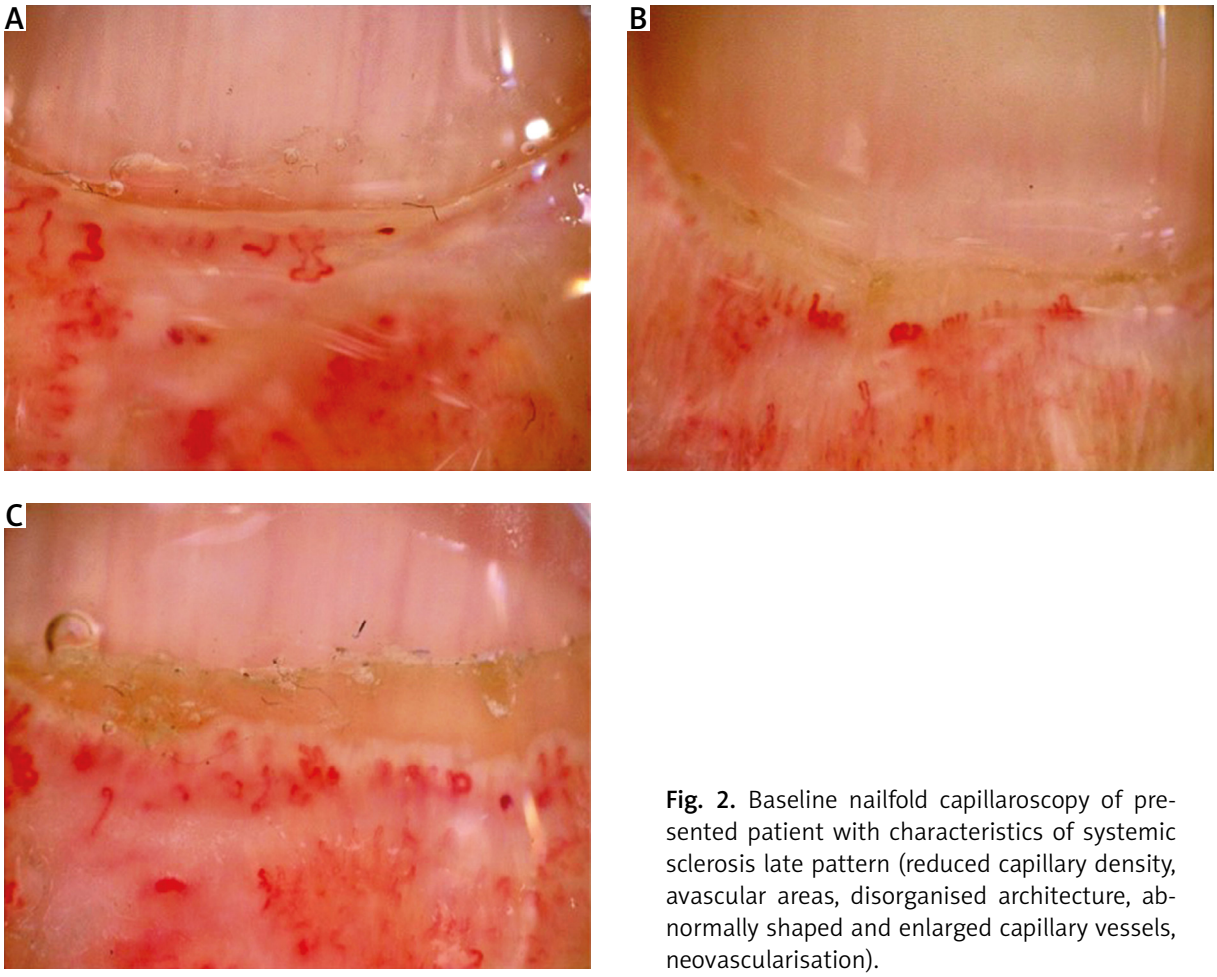

Fig. 2. Baseline nailfold capillaroscopy of presented patient with characteristics of systemic sclerosis late pattern (reduced capillary density, avascular areas, disorganised architecture, abnormally shaped and enlarged capillary vessels, neovascularisation).

with dSSc in June 2021, presenting skin thickening of the arms, legs, trunk, and face (modified Rodnan skin score, mRSS = 13), Raynaud's phenomenon, multiple telangiectasias, microstomia with microcheilia, digital tip ulcers, abnormal nailfold capillaries (Fig. 2), anti-smooth muscle antibodies (ASMA), and anti-Ku antibodies fulfilling 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) SSc classification criteria. Additionally, he suffered from hypertension and chronic pancreatitis. He was initially treated with methotrexate, but due to pancreatitis exacerbation and severe skin involvement, to intensify immunomodulation, cyclophosphamide was introduced. Low disease activity with skin improvement was achieved, and mycophenolate mofetil was initiated in remission consolidation. However, it was not tolerated due to abdominal pains and diarrhoea. Eventually the patient's condition exacerbated with skin progression and multiple ulcerations on the fingertips, eyelids, scrotum and elbows; IVIG were administered. To manage Raynaud's phenomenon firstly sildenafil was administered, but then due to poor improvement it was exchanged with tadalafil and subsequently titrated up to 20 mg per day. In September 2023 he was admitted to the A & E (Accident and Emergency) Department due to lower abdominal pain, vomiting, diarrhoea, and general malaise. Laboratory findings indicated slightly elevated C-reactive protein, white blood counts, and procalcitonin levels. On physical examination painful, tender, distended abdomen and decreased bowel sounds were noticed. The small and large intestinal passage was evaluated using contrast radiography. Ultrasound and CT scan were performed. Subileus features, such as dilated intestinal loops in the middle abdomen, were discovered. Moreover, imaging tests indicated existing *pneumatosis intestinalis* (Fig. 3). The patient was classified for RTX treatment due to the progression of the disease and GI manifestations with weight loss. In October 2023 the drug was first administered intravenously according to the scheme: 2 doses of 1,000 mg with 2 weeks between them. The results of a small intestine biopsy indicated lymphocytic infiltration but without features of fibrosis. The patient has remained under the care of the rheumatology department. The skin condition has

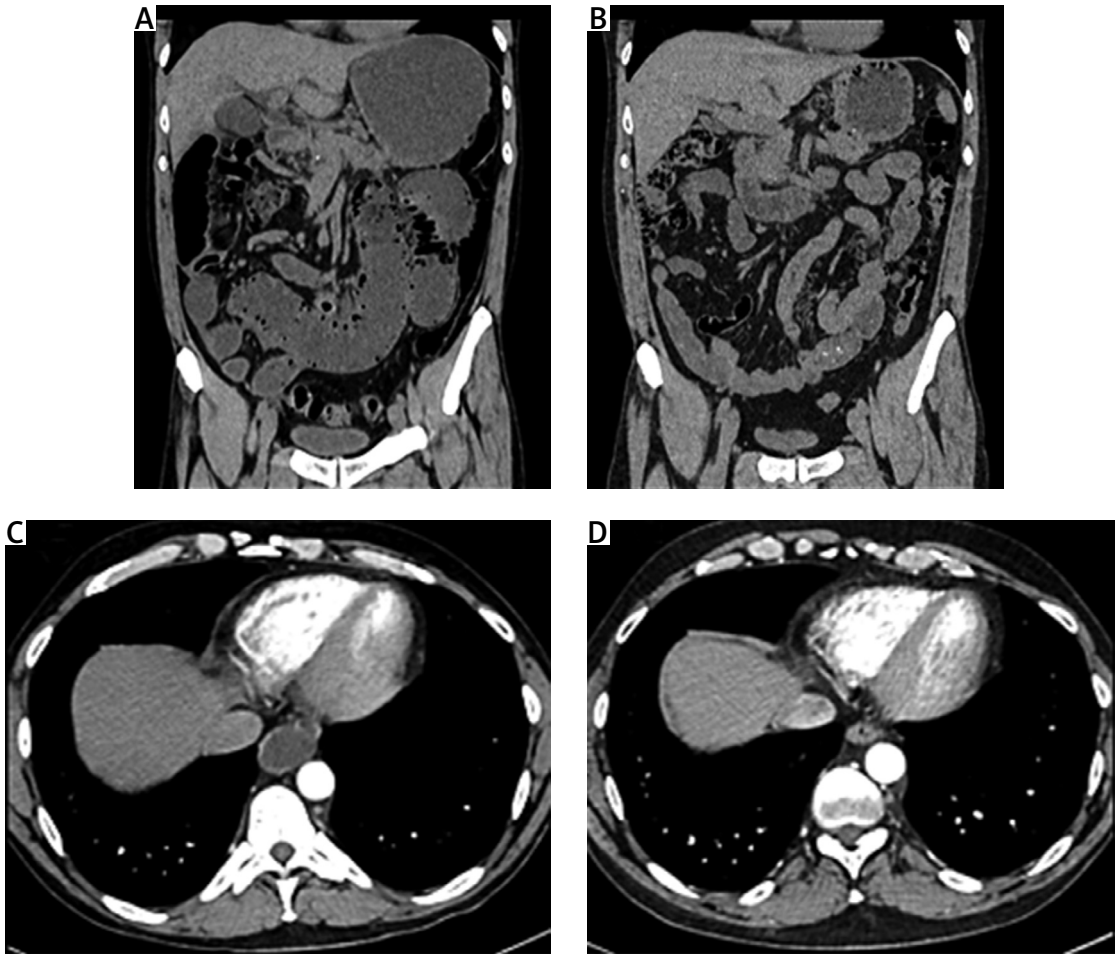

Fig. 3. A) Frontal abdominal CT scan during pseudo-obstruction episode in July 2023 showing dilated intestines, stomach, and pneumatosis intestinalis. B) Frontal abdominal CT scan after 12 months (July 2024) of treatment showing improvement in intestinal and stomach dilatation. C) Transverse chest CT scan in July 2023 showing oesophageal dilatation and D) transverse chest CT scan in July 2024 showing its regression.

improved, and pre-existing ulcerations have healed completely. There have been no recurrent CIPO episodes since the RTX initiation, as of July 2024 (Fig. 4). Figure 5 presents the patient's disease activity.

Discussion

Successful treatment of SSc complications is challenging and requires close collaboration between many different medical specialists. The disease is associated with various comorbidities, but almost every patient will experience GI manifestations [20]. Eight percent of manifestations are severe, including malabsorption syndrome, repeated episodes of pseudo-obstruction, and hyperalimentation [21]. There are a few possible causes of the high number of fatal outcomes in patients with GI involvement due to SSc, including recurrent aspiration pneumonia, pneumatosis cystoides intestinalis, or sepsis [10]. The most relevant condition seems to be malabsorption, which increases the 10-year mortality rate by 50% and is usually caused by the bacteria overgrowth [22]. Chronic intestinal pseudo-obstruction prevalence in SSc patients varies from 3.7% [23] to 5.0% [24] and is more common in females [6]. Prospective causes include infiltrative or fibrotic myopathic and/or neuropathic process [25]. Normal motor intestinal function is disturbed, which causes difficulties in the digestion process and nutrient absorption [26]. Steen et al. [21] concluded that GI changes are the main cause of death in 5–10% of SSc patients. Domsic et al. [26] claim that the 5-year mortality rate due to severe GI manifestations in SSc exceeds 50%. Mayes et al. [27] reported that the mortality due to severe GI symptoms in SSc patients is between 5% and 12% of patients.

The most significant diagnostic tool is X-ray or CT/MRI enterography presenting intestinal dilatation and

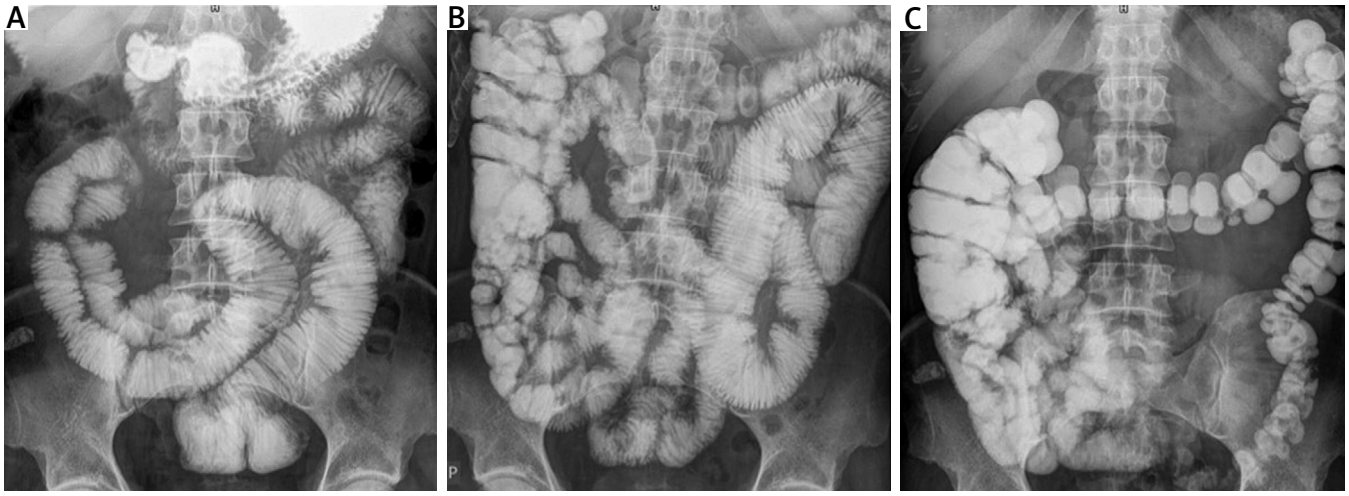

Fig. 4. Intestinal follow-through (radiography with barium based oral contrast) showing no signs of obstruction: A) stomach and jejunum, B) ileum and colon, C) colon.

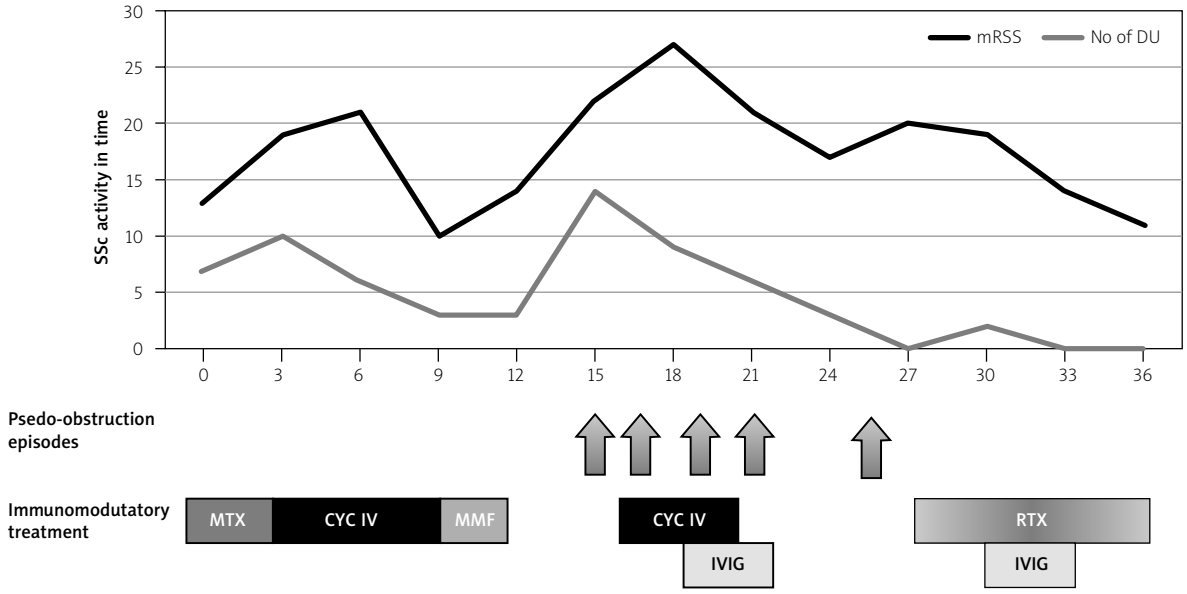

Fig. 5. Graph showing the patient's disease activity (measured with modified Rodnan skin score and number of digital ulcers), pseudo-obstruction episodes, and instituted treatment in 36-month follow-up.

CYC IV – intravenous cyclophosphamide, DU – number of digital ulcers, IVIG – Intravenous immunoglobulins, MMF – mycophenolate mofetil, mRSS – modified Rodnan skin score, MTX – methotrexate, RTX – rituximab, SSc – systemic sclerosis.

air-fluid level without any anatomic lesions [28]. To complete the diagnostic process, the evaluation of GI motility, using manometry, scintigraphy, and endoscopic studies, is highly recommended [29], but it is not always possible due to the severity of the patient's condition. Eventually, a full-thickness biopsy can be performed to rule out other possible underlying conditions, such as infections [28]. Chronic intestinal pseudo-obstruction can eventually be diagnosed when any other possible causes are excluded (Table II). *Pneumocystis intestinalis* (PI) is a rare condition defined as the presence of gas in the intestinal wall. Two types of PI could be distinguished: primary and secondary [30]. The underlying mechanism is not fully understood. The mechanical theory assumes that due to increased pressure in the intestinal lumen, which might be the result of intestinal pseudo-obstruction, the gas dissects into the intestinal wall [31]. In patients with SSc local peristaltic malfunctions can lead to CIPO, and

this condition could be the origin of secondary PI [32]. In the diagnostic process a CT scan is recommended because it has higher sensitivity than other imaging techniques. Due to a proper diagnosis, some patients do not have to undergo unnecessary surgeries [31].

Standard CIPO treatment includes prokinetic drugs, oral antibiotics, and probiotics. The most well-known prokinetic drug in CIPO management is erythromycin, a motilin agonist that alleviates the symptoms by inducing strong phase III-like activity in the small intestine [33]. The same mechanism is indicated by another drug – octreotide, which was used successfully in SSc-associated CIPO treatment. Moreover, it reduced the bacterial overgrowth, alleviating GI symptoms [34]. Oral antibiotics are used empirically to reduce the bacterial overgrowth [35]. As mentioned before, standard CIPO treatment is usually not effective when SSc is the underlying cause, especially late in the disease course [10–12]. Recent studies indicate that B-cells play an important role in SSc pathogenesis by producing autoantibodies, activating other immune system elements, and secreting proinflammatory cytokines [36]. Hence, RTX, a chimeric monoclonal antibody targeting the B-cell specific antigen CD20, has been administered successfully to achieve B-cell depletion and improve various SSc manifestations, including skin involvement or lung fibrosis [37]. Due to progression of the disease and GI manifestations causing severe weight loss, our patient was classified for RTX treatment as a salvage therapy. Simultaneously, IVIG in a dose of 2 mg/kg/cycle were administered, because Kazuki et al. [10] proved this strategy successful.

Systemic sclerosis is often associated with disease-specific autoantibodies, such as anti-centromere, anti-Th/To, anti-topoisomerase I, anti-RNA polymerase III, and anti-fibrillarin antibodies, which are powerful tools to stratify patients including disease severity and further prognosis. Nevertheless, < 10% of SSc patients do not present any disease-specific antibodies. Anti-Ku antibodies could be found in 2–7% of SSc patients and were strongly related to the polymyositis-systemic sclerosis (PM-SSc) overlap syndrome; however, they are not specific and can be found in many different autoimmune diseases [38]. Anti-Ku antibodies are antibodiesagainst the Ku (Ku-70/Ku-80) DNA-binding protein involved in DNA repair, regulation of the transcription process, and telomere activity, which can be found in the nucleus, in the cytoplasm, and on the cellular surface [39]. The presence of anti-Ku antibodies has been proven to be highly associated with synovitis, joint contractures, and myositis. Moreover, they were negatively associated with vascular manifestations [38].

Table II. Prospective causes of chronic intestinal pseudo-obstruction relevant in differential diagnosis

Affected organ system	Potential cause of CIPO
Nervous system	Stroke
	Encephalitis
	Neurofibromatosis type 1
	Hirschsprung's disease
Immune system	Paraneoplastic syndrome (small cell lung cancer, ganglioneuroblastoma)
	Scleroderma
	Dermatomyositis/polymyositis
	Amyloidosis
	Ehlers-Danlos syndrome
Endocrine system	Diabetes
	Pheochromocytoma
	Hypothyroidism
	Hypoparathyroidism
Iatrogenic causes	Clonidine
	Antidepressant drugs
	Phenothiazine
	Bronchodilators (inhaled tiotropium bromide)

CIPO – chronic intestinal pseudo-obstruction.

Conclusions

Although in the general population CIPO is a rare condition, SSc promotes GI involvement in the course of this disease. The underlying causes of GI manifestations are difficult to differentiate; hence, a careful diagnostic process should be always conducted. In patients with SSc, who are unable to take standard CIPO treatment (including prokinetic drugs, oral antibiotics, and probiotics), IVIG as well as RTX should be considered, not only to increase the patient's quality of life, but also to decrease risk of malabsorption, weight loss, and subsequent high mortality rate. Against the background of the current knowledge and collected articles, the presented case description is extraordinary not only because of its rare prevalence, but also due to carefully and distinctly selected treatment for a life-threatening condition.

Disclosures

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Data availability: Not applicable.

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