Mortality, Recurrence, and Hospital Course of Patients with Systemic Sclerosis-related Acute Intestinal Pseudo-obstruction

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ABSTRACT. ***Objective.*** Acute intestinal pseudo-obstruction is a rare gastrointestinal manifestation of systemic sclerosis (SSc) with few data existing as to its demographics, clinical course, outcomes, and mortality.

Methods. We undertook a case-control study to describe 64 cases in 37 unique patients, of whom 70% had spontaneous resolution with conservative measures of intravenous hydration and bowel rest, 9% underwent surgical resection, and 25% required prolonged total parenteral nutrition (TPN).

Results. Hospital course was for a mean of 12 ± 12.5 days and there was a 16% patient mortality in our population. In a subgroup analysis, patients who had recurrent episodes of pseudo-obstruction were less likely to have esophageal involvement from SSc, and more likely to need prolonged TPN. Mortality tended to be higher in male patients and patients who did not have SSc-related esophageal involvement, and also in patients who had low hemoglobin and serum albumin at presentation. The need for a nasogastric tube for decompression and a surgical intervention correlated with a more prolonged hospital stay.

Conclusion. To the best of our knowledge, ours is the largest study looking at this rare manifestation of SSc. (First Release Aug 15 2014; J Rheumatol 2014;41:2049–54; doi:10.3899/jrheum.131547)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS GASTROINTESTINAL
CLINICAL INTESTINAL OBSTRUCTION

Intestinal pseudo-obstruction is a clinical syndrome caused by decreased intestinal propulsion, resulting in obstructive symptoms in the absence of a mechanical cause[1,2]. A variety of causes exist, but one of the most frequently associated conditions is systemic sclerosis (SSc). Pseudo-obstruction was first described in a patient with SSc in 1931, and for the next 40 years, only a handful of case reports have been published[3,4,5,6,7,8,9,10]. Since then, pseudo-obstruction has often been quoted as a gastrointestinal (GI) complication in the SSc literature, but few data exist on demographics, clinical course, and outcomes. The consensus to date is that the condition typically presents with abdominal pain and nausea, is usually self-limited, and its recurrence is highly variable. Our study details our efforts to gain further insight into this subpopulation of patients with SSc and possibly to advance prognosis and treatment methodology.

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MATERIALS AND METHODS

Our clinical question was to better define the phenotype of patients with acute intestinal pseudo-obstruction and describe predictors for different outcomes. To do this, we undertook a retrospective chart review of patients admitted at 2 university medical centers in the city of Philadelphia over an 11.5 year-period (January 2001–June 2012). Institutional Review Board approval was obtained from both institutions. Medical records included both electronic and paper charts. The records were searched using International Classification of Diseases (ICD), 9th ed., codes for SSc (710.1) in combination with ICD codes for "intestinal obstruction" and "fecal impaction" (560, 560.1, 560.3, and 560.9). The medical records were then reviewed by 2 independent abstractors involved in our study. Both abstractors and all 4 of the authors used a unified definition of pseudo-obstruction in SSc as a clinical and/or radiological appearance of intestinal obstruction without a clearly defined ischemic, mechanical, or postsurgical cause in a patient with SSc. If one of the abstractors was unable to clearly define a case, both abstractors had to review the data and come to a unified decision. For those patients who were identified as having true cases of pseudo-obstruction, we collected demographic data, laboratory and radiological studies, hospital presentation and course, medical and surgical treatment, outcomes, and mortality. Inpatient medical records were reviewed for each patient, including all physician and nursing notes, as well as all laboratory and radiological studies. SSc-related clinical characteristics were abstracted from the medical records using the Medsger disease severity scale[12] as a definition of end organ involvement, though based on the available data, we were only able to determine whether there was organ involvement, and we were unable to clearly define severity. To collect the data, a paper data abstraction tool was developed and used. Data were stored and analyzed using Microsoft Excel. Continuous variables were analyzed by a Student's unpaired 2-tailed t test while categorical variables were done by the Fisher's exact test. For missing data, the variable was not included in the final analysis.

RESULTS

A total of 1733 hospital admissions of patients with SSc to the 2 hospitals were identified during the 11.5-year time period studied. The ICD codes matched our search criteria in 103 admissions, and from them 64 admissions were identified as true acute intestinal pseudo-obstruction cases. The 64 admissions were in 37 unique patients with SSc. An additional 39 admissions matched our ICD code; however, they did not have true pseudo-obstruction, but rather other diagnoses such as ischemic bowel, abdominal adhesions, fecal impaction, or an intestinal mass. Of the 37 patients who were evaluable, 27 had a single case of pseudo-obstruction, while 10 patients had more than 1 episode. Of these 37 patients, 81% were women, with the average age of 59.6 years at presentation, while about two-thirds of the patients were white. Disease characteristics at presentation varied widely: 12 patients had limited SSc, 7 had diffuse SSc, and 18 were not defined in the medical records. We only had disease duration data on 15 patients, and this ranged from 9 months to 290 months. Antinuclear antibody titers were available in 20 patients (7 speckled/7 nucleolar/4 centromere/4 homogeneous), 2 patients had a history of myositis, and 3 patients were defined as overlap with systemic lupus erythematosus or myositis. Two patients had a diagnosis of hypothyroidism and 1 patient had endstage renal disease while having hemodialysis, attributable to scleroderma renal crisis. Most commonly, our cases had esophageal involvement (72%) and Raynaud phenomenon (RP; 63%). Seventeen percent of patients were taking opioid medications upon admission, while 48% were taking promotility agents.

The 2 most common presenting symptoms were nausea (77%) and abdominal pain (50%). An abdominal radiograph was performed in 45/64 cases and an abdominal computed tomography (CT) in 47/64 cases to confirm the diagnosis of pseudo-obstruction and to rule out a possible mechanical obstruction. At presentation, our population's mean hemoglobin was 11.8 ± 2.1 gm/dl, liver enzymes were normal, the mean creatinine was 1.1 ± 0.7 mg/dl, and the mean serum albumin was 3.6 ± 1.2 g/dl. Out of the 64 cases, 10 presented with an albumin < 3.0 g/dl, suggestive of a poor nutritional status, and in 4 cases, patients had a lipase over 200 U/l, suggestive of a concomitant pancreatitis. Treatment modalities included intravenous fluids (64%), surgery (9%), decompression (36% with a nasogastric tube, and an additional 9% with a gastro/jejunal tube), promotility agents (48%; metoclopramide in 25 cases, erythromycin in 4, and octreotide in 2), the use of total parenteral nutrition (TPN; 41%), and antibiotics (31%). Outcomes included spontaneous resolution (70%), prolonged TPN (25%), and death (16%). The mean hospital course was 12 ± 12.5 days. Comprehensive demographics and disease characteristics are presented in Table 1.

Mortality tended to be higher in male patients (p = 0.014), patients with a low hemoglobin (p = 0.00008), and those with a low serum albumin (p = 0.001) at presentation. Of interest, none of the 6 patients who died had a previous history of esophageal involvement (p = 0.001), gastric involvement, or bacterial overgrowth as compared to 72%, 29%, and 16%, respectively, among patients who did not die during their hospitalization. The clinical picture at presentation was also different in patients who died versus patients who did not, with none of the 6 patients who died having abdominal pain on presentation as compared to 48% of patients who did not die (p = 0.03; Table 2).

Table 1. Admission demographics, presenting symptoms, therapeutics, and outcomes. SSc disease characteristics are based on the Medsger severity scale classification[12].

Demographics	Patients, n = 37 (%)
Sex	7 males (11)
Age	59.6 ± 11.7
Race	14 AA, 23 W
Disease characteristics	Cases, n = 64 (%)
Raynaud phenomenon	40 (63)
Digital ulcers	15 (23)
Interstitial lung disease	17 (27)
Pulmonary arterial hypertension	26 (41)
Esophageal involvement	46 (72)
Gastric involvement	20 (31)
Bacterial overgrowth	10 (16)
Cardiac involvement	10 (16)
MSK involvement	12 (19)
Renal involvement	1 (2)
Opioid use (on admission)	11 (17)
Promotility agent (on admission)	31 (48)
Symptoms	
Diarrhea	9 (14)
Abdominal pain	32 (50)
Nausea	49 (77)
Weight loss	11 (17)
Hematochezia	2 (3)
Melena	2 (3)
Fever	4 (6)
Other	Constipation (13 pts), abdominal distention (7 pts), decreased PO intake (5 pts)
Treatment modality	
NPO	46 (72)
Surgery	6 (9)
Nasogastric tube**	23/29 (36/45)
Prokinetic	31 (48)
Antibiotics	20 (31)
Intravenous fluids	41 (64)
Total parenteral nutrition	26 (41)
Outcome	
Spontaneous resolution	45 (70)
Prolonged TPN	16 (25)
Death	6 (16)
Days hospitalized	12 ± 12.5

**23 cases with nasogastric tube, 6 additional cases with gastro-jejunal tube. SSc: systemic sclerosis; AA: African American; W: white; MSK: musculoskeletal; PO: per os; NPO: nil per os; TPN: total parenteral nutrition.

Table 2. Subgroup analysis of admission mortality. SSc disease characteristics are based on the Medsger severity scale classification[12]. Data in bold face are statistically significant.

Demographics	Death (%) Patients, n = 6	No Death (%) Patients, n = 31	p
Sex	3 male	4 male	**0.014**
Age	62 ± 12	58.5 ± 13	0.52
Race	4 AA, 2 W	10 AA, 21 W	0.169
Disease characteristics	Cases, n = 6	Cases, n = 58 (%)	
Raynaud phenomenon	3	37 (64)	0.663
Digital ulcers	2	13 (22)	0.621
Interstitial lung disease	2	15 (26)	0.652
Pulmonary arterial hypertension	2	24 (41)	1
Esophageal involvement	0	42 (72)	**0.001**
Gastric involvement	0	17 (29)	0.181
Bacterial overgrowth	0	9 (16)	0.581
Opioids (on admission)	2	9 (16)	0.278
Promotility (on admission)	4	29 (50)	0.673
Symptoms			
Diarrhea	0	9 (16)	0.579
Abdominal pain	0	28 (48)	0.031
Nausea	3	45 (77)	0.159
Weight loss	1	9 (16)	1
Hematochezia	0	1 (2)	1
Melena	0	2 (3)	1
Fever	0	4 (7)	1
Laboratory values			
Hemoglobin	9.9 ± 0.6	12 ± 2.1	**0.00008**
White blood cell count	11.2 ± 4.4	10.7 ± 5.8	0.831
AST	42 ± 48	36 ± 26	0.799
ALT	18 ± 6.4	33 ± 35	**0.018**
Total bilirubin	0.6 ± 0.05	0.78 ± 1.1	0.454
ALP	68 ± 33	124 ± 75	**0.013**
Creatinine	1.8 ± 1.8	1 ± 0.5	0.405
Albumin	2.5 ± 0.5	3.7 ± 0.9	**0.001**
Lipase	17 ± 8.5	86 ± 199	0.058
Amylase	71 ± 21	110 ± 66	**0.03**
Treatment modality			
NPO	4	42 (72)	0.629
Surgery	2	3 (5)	0.065
Nasogastric tube	6	20 (34)	**0.003**
Prokinetic	4	27 (47)	0.419
Antibiotics	1	19 (33)	0.653
Intravenous fluids	3	38 (66)	0.658
Total parenteral nutrition	1	21 (36)	0.655
Outcome			
Spontaneous resolution	0	45 (76)	**0.0004**
Prolonged TPN	0	16 (27)	**0.0001**
Days hospitalized	27 ± 21	10.1 ± 9.9	0.098

SSc: systemic sclerosis; AA: African American; W: white; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; NPO: nil per os; TPN: total parenteral nutrition.

We divided hospital stay into 2 categories: stays longer than 7 days, and stays shorter than 7 days. Hospital stay did not correlate with sex, age, or race. Further, no disease characteristic, laboratory measure, or presenting symptom was associated with a more prolonged/shortened hospital stay.

Factors associated with a longer hospital stay included surgery (p = 0.008) and the use of a nasogastric tube (p = 0.009). It is also worth noting that patients who received a CT of the abdomen tended to have a more prolonged hospital stay even though it did not reach statistical significance (p = 0.078; Table 3)

In another subgroup analysis of patients who had recurrent versus single episodes of intestinal pseudo-obstruction, recurrence was more commonly seen in patients who did not have esophageal (p = 0.001) or musculoskeletal

Table 3. Subgroup analysis on hospital duration. Five cases missing admission or discharge dates. SSc disease characteristics are based on the Medsger severity scale classification[12]. Data in bold face are statistically significant.

Demographics	Hospital > 7 Days (%), n = 28	Hospital < 7 Days (%), n = 31	p
Sex	5 male (19)	2 male (7)	0.238
Age, yrs, ± SD	58.9 ± 13	58.3 ± 9	0.855
Race	9 AA, 19 W	11 AA, 20 W	1
Treatment modality			
NPO	20 (71)	24 (77)	0.765
Surgery	6 (21)	0 (0)	**0.008**
Nasogastric tube	17 (61)	8 (26)	**0.009**
Prokinetic	17 (61)	13 (42)	0.195
Antibiotics	14 (50)	13 (42)	0.606
Intravenous fluids	18 (64)	22 (73)	0.780
Total parenteral nutrition	11 (34)	11 (37)	0.79
Outcome			
Spontaneous resolution	14 (50)	29 (97)	**0.0003**
Prolonged TPN	8 (29)	8 (27)	1
Death	4 (14)	1 (3)	0.174
Days hospitalized	20.7	3.9	

SSc: systemic sclerosis; AA: African American; W: white; NPO: nil per os; TPN: total parenteral nutrition.

involvement (p = 0.002). It was more often associated with the clinical symptom of nausea at presentation (p = 0.00008) but not diarrhea (p = 0.02) or weight loss (p = 0.04), and it resulted in the prolonged use of TPN (p < 0.0008; Table 4).

DISCUSSION

This is the largest study to our knowledge attempting to characterize intestinal pseudo-obstruction in patients with SSc. On review of the literature, the incidence of pseudo-obstruction is unknown, but thought to be a rare entity. One database of over 900 patients with SSc was reviewed, to investigate prevalence of severe organ involvement[11]. Eight percent of these patients (n = 74) were found to have severe GI involvement over the 23-year study period, including pseudo-obstruction. However, this 8% included not only cases of pseudo-obstruction, but also malabsorption and the requirement for hyperalimentation.

Poirier and Rankin evaluated 364 cases of SSc who had GI manifestations, and even though most of the focus was on the esophagus, they presented very few cases of pseudo-obstruction[9]. Schuffler, *et al* reviewed 14 patients with pseudo-obstruction and reported RP and telangiectasia were most common in their patient group[13].

Based on our data, acute intestinal pseudo-obstruction is a rare cause of hospitalization of patients with SSc (64/1733 admissions, or 3.7%). At the time of admission, half of the patients were already taking promotility agents. It is unclear whether the need for promotility agents increases the risk of having an episode of pseudo-obstruction, or whether these patients already had GI issues that required promotility agents and thus had an increased risk for intestinal pseudo-obstruction. Alternatively, it is possible that promotility agents do not have a significant effect of preventing pseudo-obstruction at all. Similarly, 17% of patients were taking longterm opioid medications upon admission, which could have had an additive effect leading to a delayed intestinal transit time through the interaction with the opioid receptors in the intestine. The majority of patients presented with nausea, abdominal pain, and constipation. This is consistent with past studies evaluating this condition[9].

Treatment modalities most commonly used were bowel rest and intravenous hydration. Other management strategies, such as enteric tubes for decompression, antibiotics, prokinetic agents, and TPN, were used on a case-by-case basis. The majority of patients had spontaneous resolution with an average hospital stay of 12 days.

Mortality. Our subgroup analysis revealed that there was a protective trend for mortality for patients who had more clinical symptoms on presentation, and in whom abdominal pain reached statistical significance (p = 0.03), suggesting that the lack of significant clinical symptoms at presentation relates to a worse prognosis (Table 2). A possible explanation for this is that significant clinical signs at presentation may suggest a more treatable infectious process such as bacterial overgrowth or viral gastroenteritis.

From a laboratory standpoint, both anemia and hypoalbuminemia at presentation correlated with increased mortality. Both of these laboratory values can be markers of chronic disease, and may suggest a patient with less reserve,

Table 4. Subgroup analysis on recurrence of pseudo-obstruction. SSc disease characteristics are based on the Medsger severity scale classification[12]. Data in bold face are statistically significant.

Demographics	Single Episode (%), n = 27 Patients	Recurrent Episode (%), n = 10 Patients	p
Sex	7 male	0 male	**0.011**
Age	61.1 ± 13.9	58.6 ± 9.9	0.467
Race	12 AA, 15 W	2 AA, 8 W	0.26
Disease characteristics	Cases, n = 27	Cases, n = 37	
Raynaud phenomenon	20 (74)	20 (54)	0.123
Digital ulcers	8 (30)	7 (19)	0.37
Interstitial lung disease	7 (26)	10 (27)	1
Pulmonary arterial hypertension	8 (30)	18 (49)	0.197
Esophageal involvement	25 (93)	21 (57)	**0.001**
Gastric involvement	6 (22)	14 (38)	0.28
Bacterial overgrowth	3 (11)	7 (19)	0.49
Cardiac involvement	3 (11)	7 (19)	0.49
MSK involvement	10 (37)	2 (5)	**0.002**
Renal involvement	1 (4)	0 (0)	0.42
Opioids (at admission)	8 (30)	3 (8)	**0.04**
Promotility (at admission)	9 (33)	22 (59)	**0.04**
Symptoms			
Diarrhea	7 (26)	2 (5)	**0.02**
Abdominal pain	17 (63)	15 (41)	0.12
Nausea	14 (52)	35 (95)	**0.00008**
Weight loss	8 (30)	3 (8)	**0.04**
Hematochezia	2 (7)	0 (0)	0.174
Melena	0 (0)	2 (5)	0.5
Fever	2 (7)	2 (5)	1
Treatment modality			
NPO	21 (78)	25 (71)	0.77
Surgery	4 (15)	2 (6)	0.38
Nasogastric tube	10 (37)	19 (54)	0.2
Prokinetic	10 (37)	21 (60)	0.12
Antibiotics	11 (41)	9 (26)	0.27
Intravenous fluids	18 (67)	23 (66)	0.22
Total parenteral nutrition	7 (26)	19 (54)	**0.03**
Outcome			
Spontaneous resolution	17 (63)	28 (80)	0.16
Prolonged TPN	1 (4)	15 (43)	**0.0008**
Death	5 (19)	1 (3)	0.077
Days hospitalized	15 ± 15	9 ± 9	0.06

SSc: systemic sclerosis; AA: African American; W: white; NPO: nil per os; TPN: total parenteral nutrition; MSK: musculoskeletal.

more prone to the effects of an acute insult such as pseudo-obstruction and thus the association with a poor prognosis. Esophageal involvement related to SSc also showed a protective effect, suggesting that the pathophysiology of pseudo-obstruction in patients who die during their hospitalization may be beyond the motility issues seen in SSc.

Recurrence. Examining our subgroup analyses between patients with recurrent versus a single episode of pseudo-obstruction, it was observed that neither race nor age were associated with recurrence. No men had recurrence, but the number was small (7 patients). As it was seen in mortality, esophageal involvement was again protective in developing recurrent episodes of pseudo-obstruction. Regarding outcome, the patients with recurrent pseudo-obstruction were more likely to require prolonged TPN.

Hospital stay. Examining duration of hospital stay, we noted that no demographic variable, disease characteristic, or presenting symptom predicted a longer hospitalization. The only factors that significantly prolonged the hospital course were surgery and the use of decompression (nasogastric or gastro/jejunal tube). While surgery is a rather intuitive factor for prolonging a patient's stay, the use of bowel decompression is not. It possibly suggests that the more severe cases warranted decompression, and thus typically stayed in the hospital longer as symptoms were controlled and enteric feeding was advanced.

Our study has a number of limitations. Given the

methods used, we were only able to see the medical records of the 1 admission in question. Despite being included in our data abstraction tool, the majority of the records reviewed did not include important data such as disease subtype (limited vs diffuse) and serological characteristics. This information could quite possibly be useful in identifying patients at increased risk for or increased severity of this condition. Further, we did not explore which specific agents were used in treatment, i.e., the kind of promotility agent. A subgroup analysis would be interesting with each agent; however, the number of patients in each group would likely limit the conclusions one could draw.

To the best of our knowledge, our study has the benefit of being the largest case series to date to investigate pseudo-obstruction in patients with SSc. It allows the following general statements to be made: limited clinical symptoms and markers of chronic disease at presentation relate to poor prognosis; the majority of cases are resolved with conservative therapy; esophageal involvement from SSc has a protective effect on recurrence and mortality; and surgery prolongs hospital stay.

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