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SOLITARY RECTAL ULCER SYNDROME IN 102 PATIENTS: DO DIFFERENT PHENOTYPES MAKE SENSE?

Short running title: Solitary Rectal Ulcer Syndrome and Phenotypes

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ABSTRACT.

Background: Little is known about the pathophysiological mechanisms of solitary rectal ulcer syndrome (SRUS).

Aims: We aim to identify the different phenotypes, taking into account complaints, anatomy and anorectal physiology.

Methods: Complaints, endoscopy results, and physiology data of patients with histologically proven SRUS were collected and analysed. The associated anorectal diseases were faecal incontinence and obstructed defecation. The clinical aspects of SRUS were compared, and factors associated with anorectal diseases were identified.

Results: Overall, 102 consecutive patients were included. The predominant lesion was a rectal ulcer (66%), and inflammation of the rectal wall was present in 42% of patients. Abnormal rectal capacities and/or rectal perception was observed in more than half. Nearly half (52%) of the patients met the criteria for obstructed defecation and they tended to more frequently have psychiatric disease (66.7% vs 33.3%; $p=0.07$). Patients with faecal incontinence (17%) reported more self-perception of anal procidentia ($p=0.01$) and were more likely to have inflammation of the rectal wall ($p=0.02$), high-grade internal rectal procidentia ($p=0.06$) and anal hypotonia ($p=0.004$); their maximum tolerable volume was lower ($p=0.004$).

Conclusion: The characteristics of patients with SRUS suggest different phenotypes. This may be a way to develop a comprehensive treatment strategy.

Keywords: Solitary rectal ulcer syndrome; Faecal incontinence; Obstructed defecation; Anorectal manometry; Defecography

INTRODUCTION

Solitary rectal ulcer syndrome (SRUS) is very rare (1) but chronic disease. The diagnosis of SRUS is based on clinical, endoscopic and histological features (2). Therefore, as a chronic disease, the natural history of SRUS is characterized by periods of remission and relapse. Thus, the therapeutic management of SRUS remains challenging. A recent review of the literature showed that treatments have suspensive and non-perennial efficacy (3). Studies regularly mix the symptoms of SRUS with mucosal changes related to external rectal prolapse, while SRUS and rectal prolapse do not share the same physiology (4). There is a wide range of surgical and non-surgical treatments with uncertain pathophysiological support (3). Thus, it is very difficult to draw reliable conclusions.

Little is known about the mechanisms of SRUS, contributing in part to the major difficulties associated with care. Data on anorectal function based on anorectal manometry and defecography are scarce (5–7). Furthermore, although this syndrome includes the term “ulcer”, the appearance can be variable with solitary ulcers, inflammation of the rectal wall or polypoid changes (8). Thus, within the concept of SRUS, several phenotypes can be identified and might be related to different natural histories and therapeutic challenges.

The aim of this study was (i) to describe the clinical characteristics of patients with SRUS, (ii) to identify associations between symptoms and anatomy and (iii) to identify associations between these features and anorectal physiology. Together, these different phenotypes could

help with the decision-making of physicians in order to adequately adapt therapeutic strategies.

MATERIALS AND METHODS

Study population

Patients in this study had been referred to a tertiary unit (University Hospital, Rennes, France) between 1994 and 2020 for SRUS. Data were prospectively included in a dedicated database (*Fondamentum*, CNIL no. 1412467) and retrospectively reviewed. The diagnosis of SRUS was based on symptoms and typical proctoscopic findings and was confirmed by pathological features of rectal biopsies in all patients. Typical endoscopic findings may vary from preulcer hyperemic changes of rectal mucosa to ulcers (2). The ulceration is shallow and the adjacent mucous membrane may appear nodular, lumpy or granular. Only data from patients with histologically proven SRUS were retrieved and assessed, referring to the original criteria described by Madigan and Morson (2). Histological features include fibromuscular obliteration of the lamina propria, hypertrophied muscularis mucosa with extension of muscle fibers upwards between the crypts, and glandular crypt abnormalities (2). Histological analysis made possible to exclude differential diagnoses such as inflammatory bowel diseases or neoplasms.

The data were reviewed by 2 experts (LS and CB) to confirm the diagnosis of SRUS. Patients with external rectal prolapse were excluded.

Functional assessment and anorectal testing

During the evaluation, the results of self-administered questionnaires, physical examinations, and anorectal manometry and defecography were recorded in a database. All procedures were performed at the same time. Age, sex, height, weight, medical history (including cardiovascular disease, neoplasia, neurological disease, psychiatric disease and irritable bowel syndrome), and surgical and obstetrical histories were recorded. The category of psychiatric

disease was specified by the psychiatrist who followed the patient. Symptoms were recorded as previously described (9,10). The questionnaire focused on the following anorectal complaints: mucus discharge, rectal bleeding, dyschezia, pelvic pain, faecal incontinence, self-perception of anal procidentia and the use of digitation to defecate. It also included a stool diary using the Bristol stool chart. Irritable bowel syndrome (IBS) was defined according to the Rome criteria (11). Clinical dyssynergic defecation and the presence of pelvic floor disorders on clinical examination were recorded. Clinical dyssynergic defecation was defined as a contraction while straining during defecation. Endoscopy and/or rectoscopy defined the macroscopic appearance of SRUS. The following aspects were differentiated: rectal ulcers, inflammation of the rectal wall, and polypoid lesions (12). The association of two or more of the described aspects defined mixed lesions. Assessment of constipation was performed using the validated Knowles–Eccersley–Scott Symptom Constipation Score (KESS) (13). Faecal incontinence was assessed according to the validated Cleveland Clinic Incontinence Score (CCIS) (14), and severe faecal incontinence was defined as CCIS >8 (15). Quality of life was quantified using a validated scale for gastrointestinal complaints (Gastrointestinal Quality of Life Index (GIQLI)) (16), as previously published in studies of faecal incontinence cohorts (17).

Anorectal manometry was performed as previously described (18). To record the mean maximal resting pressures in the upper and lower anal canals and the anal canal length, anal canal pressures were monitored using a three-lumen water-perfused catheter assembly (R3B, Mui Scientific, Mississauga, Ontario, Canada) with radially distributed side holes. Each of the three lumens was perfused at a rate of 1 mL/min with distilled water from an electrically powered compressed pneumohydraulic perfusion system (PIP4-4, Mui Scientific, Mississauga, Ontario, Canada). The probe is gradually removed, allowing, the length of the high-pressure zone, the pressures in the upper and lower anal canal. The mean squeeze

pressure in the lower anal canal was obtained during a 30-second squeeze. Amplitude contraction was the variation between the resting pressures and maximal pressures during the contraction. Dyssynergic defecation was recorded during effort and was defined as increasing or stable pressure while straining during defecation. Rectal perception thresholds were recorded using isovolumic distension with balloon air inflation. The balloon used has a maximum volume of 500 ml and was inflated from 10 ml to 10 ml to evaluate the perception thresholds. A balloon expulsion test was performed at the end of the exam; and the inability to expel a 50-ml water-filled balloon) within one minute was recorded.

Defecography was performed as previously described using barium contrast medium (Microtrast) via oral, vaginal, and anal routes (19). The bladder was not catheterized. Rectal filling was sufficient to materialize the sigmoid loop. The ileum was filled via the oral intake of barium (Micropaque) 90 minutes before radiological examination. This radiological examination allowed the diagnosis of enterocele, rectocele, high-grade rectal procidentia, perineal descent, paradoxical puborectalis contraction and rectal emptying. Perineal descent was quantified as the maximal length that separated the upper anal canal site and pubococcygeal line during defecation (20). Paradoxical puborectalis contraction was diagnosed when a posterior impression was observed during evacuation of the contrast medium (19). The incompleteness of rectal emptying was defined by $\geq 80\%$ retention of barium during defecography. According to Rao et al (21), the criteria for dyssynergic defecation were as follows: (i) the patients must satisfy the diagnostic criteria for functional chronic constipation (Rome); (ii) the patients must demonstrate dyssynergia during repeated attempts to defecate on anal manometry, imaging or electromyographic recordings; and (iii) one or more of the following criteria must be present during repeated attempts to defecate: inability to expel an artificial stool (50-ml water-filled balloon) within one minute, inability to evacuate or $\geq 50\%$ retention of barium during defecography.

The associated functional anorectal diseases included faecal incontinence and obstructed defecation.

Some patients did not performed manometry or defecography in our centre. Patients who did not have a manometry or defecography did not fill in the scores (CCIS, KESS, GIQLI).

Data Analysis

Data were prospectively collected but retrospectively studied. Data are expressed as the mean \pm standard deviation (SD). Qualitative variables are expressed as numbers and percentages. Patients with rectal ulcer were compared with those without rectal ulcer and patients with inflammation of the rectal wall were compared to those without. Patients with self-reported faecal incontinence were compared those who did not. Patients suffered from objective obstructed defecation were compared with those who had not. Comparisons between groups were performed using t-tests for normally distributed variables, the Wilcoxon test for non-normally distributed variables and the chi-squared test or Fisher's exact test for categorical variables. For each analysis, *p* values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using JMP Pro Software, version 13.0.0 (SAS Institute Inc., Cary, NC, USA).

Ethical consideration

The study was approved by the Committee for the Protection of Persons (CPP) (N° ID-RCB: 2018-A01977-48).

RESULTS

Patient characteristics and anorectal physiology

Data from 138 patients referred to our tertiary referral centre for SRUS between 1994 and 2020 were extracted from the database. Among them, 36 patients were excluded: 24 for a differential diagnosis (external rectal prolapse (n=16), ulcerative colitis (n=2), traumatism (n=2), haemorrhoid disease (n=1), and other (n=3)) and 12 because a diagnosis of SRUS could not be concluded with the data available after review by 2 experts. Overall, 102 patients were included. The patient characteristics and scores are summarized in **Table 1**. The duration of symptoms was more than 5 years and 10 years for 47 (46%) and 26 (25%) patients, respectively. One patient was asymptomatic at diagnosis. Psychiatric disease was frequently reported for almost one-third of the patients, mostly anxiodepressive disease (26/32, 81%; 4/32 eating disorders, 13% and 2/32 psychotic disorders, 6%). A diagnosis of IBS was reported in 29/56 (52%) patients with IBS-constipation, in 9/56 (16%) with IBS-diarrhoea and in 17/56 (30%) with IBS-mixt. The anorectal complaints are described in **Table 1**. The 2 main complaints were dyschezia and mucus discharge in respectively 71 (70%) and 68 (67%) patients. Three patients (3%) had anaemia related to SRUS. Among the 55 (54%) patients using anal digitation to defecate, most used endoanal digitation (n=46/55, 84%). Thirty-six patients (35%) had both mucus discharge and used anal digitation to defecate. One out of five patients reported urinary symptoms, predominantly urinary incontinence (n=16/20, 80%). Hard stools were reported in 28/64 (44%), but the average transit was 12 stools per week. According to the symptomatic score quantifications (16,17), 41/52 (79%) patients were constipated, and 16/47 (34%) had significant faecal incontinence. The anorectal characteristics and defecography items of the patients are listed in **Table 2**. Abnormal rectal capacities and/or rectal perception was observed in more than half of the study population: 36

patients (43%) had a maximum tolerable volume <150 ml, and 9 (11%) patients had a maximum tolerable volume >300 ml. More than two-thirds of patients had high-grade internal rectal procidentia, and approximately one-quarter had enterocele. Differences between clinical examination and defecography were observed: procidentia, descending perineum and rectocele were found clinically in 50, 40 and 17 patients, respectively whereas they were found radiologically in 61, 54 and 8 patients, respectively. Rectal emptying was incomplete in 37 patients (43%). According to strong criteria (21), dyssynergic defecation was observed in 43 patients (52%).

Complaints & anatomy

A description of the lesion was available in all patients. A rectal ulcer was described in 67 patients (66%), inflammation of the rectal wall in 43 patients (43%) and a polypoid lesion in 22 patients (22%). Twenty-six patients (26%) had mixed lesions: 18 had both rectal ulcers and inflammation of the rectal wall, 2 had rectal ulcers and polypoid lesions, 2 had inflammation of the rectal wall and polypoid lesions, and 4 had all three. The topography was anterior in only 40 patients (39%).

The 67 patients who had rectal ulcers were compared with the 35 patients who did not have rectal ulcers. The two groups did not differ according to the medical, surgical and obstetrical histories. A disease duration less than 10 years was more often associated with the presence of rectal ulcers (53/67 (79.0%) vs 20/35 (57.1%); $p=0.006$). Patients with rectal ulcers tended to more often have IBS (41/67 (61.0%) vs 15/34 (44.1%); $p=0.10$). According to the symptoms and clinical data, patients with rectal ulcers were more likely to have rectal bleeding (29/67 (43.3%) vs 8/35 (22.9%); $p=0.04$), less likely to experience self-perception of anal procidentia (6/67 (9.0%) vs 9/35 (25.7%); $p=0.02$) and more likely to have clinical dyssynergic defecation (22/66 (33.3%) vs 4/32 (12.5%); $p=0.02$). The two groups did not differ according

to scores, anorectal functions or pelvic floor disorders.

The 43 patients who had inflammation of the rectal wall were then compared with the 59 patients who did not have inflammation. The two groups did not differ according to the medical, surgical and obstetrical histories. Patients with inflammation of the rectal wall were more likely to have mucus discharge (35/43 (81.4%) vs 33/59 (55.9%); $p=0.007$) and self-reported incontinence (12/43 (27.9%) vs 6/59 (10.1%); $p=0.02$). They tended to have more frequent pain than those who had no inflammation of the rectal wall (19/43 (27.9%) vs 16/59 (27.2%); $p=0.06$). Decreased rectal perception and/or rectal capacity were also reported: 20/36 (55.6%) patients with inflammation of the rectal wall had a maximum tolerable volume <150 ml (vs 16/47 (34.0%) patients without inflammation of the rectal wall; $p=0.05$). The two groups did not differ according to scores or pelvic floor disorders.

Complaints & function

Overall, 18 patients (17%) reported faecal incontinence, including 9 (50.0%) who had severe faecal incontinence according to scoring. Patients with self-reported faecal incontinence were compared with the remaining 84 patients who did not have faecal incontinence. The two groups did not differ according to the medical, surgical and obstetrical histories. Regarding the symptoms and clinical exam findings, patients with faecal incontinence reported more self-perception of anal procidentia (6/12 (33.3%) vs 9/75 (10.7%); $p=0.01$) and were more likely to have inflammation of the rectal wall, high-grade internal rectal procidentia (12/15 (80.0%) vs 38/70 (54.3%); $p=0.06$) and anal hypotonia (7/18 (38.9%) vs 9/80 (11.2%); $p=0.004$). The maximum tolerable volume was significantly lower in patients with faecal incontinence (130 (62.6) vs 181 (83.1); $p=0.004$): 12/37 (70.6%) patients with faecal incontinence had a maximum tolerable volume <150 ml (vs 24/66 (36.4%) patients without incontinence; $p=0.01$). While the duration of anal contraction was shorter in patients with

faecal incontinence (22.9 (8.2) vs 27.1 (12.1); $p=0.05$), the resting anal pressures were comparable between groups.

Overall, 43 patients (52%) suffered from objective obstructed defecation according to the Rao criteria and were compared with the remaining 40 patients who did not have obstructed defecation; the study population being reduced to the 83 patients who had defecography and manometry. The two groups did not differ according to the medical, surgical, and obstetrical histories; symptoms; clinical exam findings; or manometry and defecography items (except those associated with the Rao criteria). Among the patients with obstructed defecation, 26/43 (60.5%) had high-grade rectal procidentia, 10/43 (23.3%) had enterocele, and 11/43 (25.6%) had rectocele. Patients with obstructed defecation tended to more frequently have psychiatric disease (18/43 (66.7%) vs 9/39 (33.3%); $p=0.07$).

DISCUSSION

The present work described the clinical characteristics and pathophysiological features of patients with SRUS, with a special consideration for the link between complaints, anatomy and function.

The main strengths of this work are the sample size and the multimodal patient assessment, including clinical, manometry and defecography examinations. It is the largest cohort of adults with SRUS with all of these collected data. The data were prospectively recorded in a database of tertiary reference centres using recommended classifications and validated scales (13–16). All exams were performed following the same procedure. However, our study results should be interpreted with caution for several reasons. Even if it is the largest cohort, subgroups are small which underpower the statistical analyses. It is a retrospective analysis of data collected prospectively, some data were lacking. We did not perform endoscopic ultrasonography (EUS) of the rectum when this exam could be interesting to exclude malignancy (22). The absence of follow-up data makes it impossible to know the evolution of the aspect of the SRUS.

The clinical presentation of SRUS is mostly based on the triad of dyschezia, mucus discharge and anal digitation. In the literature, rectal bleeding is traditionally the most frequent symptom in patients with SRUS (91%) (2). The frequency of bleeding in our cohort (36%) was lower than that previously described in retrospective cohorts (80-82%) (23,24). However, the modality of referral in our unit was mainly for functional disorders. Furthermore, urinary disorders were described in one out of five patients. All these associated symptoms might participate in management issues and must be tracked to offer global care to patients with SRUS.

In this work, patients suffering from SRUS were frequently women with psychiatric disease and/or IBS. One-third of the patients had a psychiatric disease, and this prevalence was nearly three times higher than the only data available in the literature (12%) (2). Moreover, half of the patients with SRUS had IBS. This association has never been described. The interpretation is difficult. Indeed, in clinical practice, patients with SRUS frequently have constipation or alternating diarrhoea-constipation, and the emission of stools relieves these symptoms. We can assume that patients with SRUS have abdominal and visceral pain, not just rectal pain, and possibly have intestinal hypersensitivity via inflammation of the rectal wall. The association of psychiatric disease and/or IBS should be considered in the management of SRUS for several reasons. Physicians who take care of patients with IBS and/or depression need to think about SRUS in the case of anal symptoms. However, we can also presume that the management of patients with IBS and/or psychiatric disease is more difficult, for example, difficulties with rehabilitation, with accepting treatment, with the persistence of pain, etc. These assumptions have yet to be tested.

Rectal ulcers were frequently described, and they seem to be a “recent” form. These lesions were associated with rectal bleeding and clinical dyssynergic defecation. It would seem that this form could be accessible for stool regulation using softeners. The inflammatory form was associated with mucus discharge, self-reported incontinence, pain and abnormalities of rectal perception and/or rectal capacity. Overall, 40% of patients with SRUS were categorized as having a low threshold volume in our study. This is consistent with data from Keighley *et al* (25). Moreover, Rao *et al* showed that the thresholds for first sensation, desire and urge to defecate were significantly lower in SRUS patients than in healthy controls (26). Similar to IBS (27,28), abnormalities of the rectal wall might be associated with pain. Furthermore, we might think that sacral nerve modulation could improve changes in rectal sensitivity and be a therapeutic option in SRUS, especially since neuromodulation has an anti-inflammatory effect

(29).

Importantly, 17% of patients with SRUS reported faecal incontinence. One might argue that it is more associated with mucus discharge than loss of faeces, but that does not prevent patients from declaring a feeling of incontinence that invalidates their daily life. Patients with faecal incontinence have both anal and rectal abnormalities, each of which can be a therapeutic target. Anal weakness can be ameliorated by appropriate anal biofeedback. Recent data have shown the efficacy of botulinum toxin injections into the rectum for the treatment of faecal incontinence (30). Furthermore, there is evidence to suggest that botulinum toxin has an anti-inflammatory effect (31). Thus, performing botulinum toxin injections into the rectum could improve continence disorders by reducing rectal abnormalities and decreasing rectal inflammation. Finally, patients with faecal incontinence frequently had high-grade internal rectal procidentia, which re-evaluates the role of pelvic static disorders in faecal incontinence and also in SRUS.

Half of the patients suffered from objective obstructed defecation according to the Rao criteria, while three-quarters had symptoms suggestive of an evacuation disorder. This is consistent with data from the literature (4,25,26). From another point of view, patients with SRUS should be explored to objectively quantify the evacuation disorder, and strategies such as local or systemic laxatives should be offered to those who do not need them. Likewise, biofeedback retraining should only be offered to patients with an objective sign of obstructed defecation. Furthermore, these patients tended to more frequently have psychiatric disease, and we can presume that biofeedback will be more difficult to implement. In this particular population, other modalities (such as injection of botulinum toxin into the anus) to treat the obstruction could be evaluated. Finally, 61% of patients with objective obstructed defecation had high-grade rectal procidentia. The overall rate of high-grade internal procidentia (71%) reported in our study is consistent with the literature (5,6). The role of high-grade internal

procidentia in the pathogenesis of SRUS is misunderstood, and it is difficult to know whether this is a cause or a consequence. Furthermore, pelvic floor disorders should be screened, as they can be potential targets for surgical treatment. Defecography can be useful in the evaluation of pelvic static disorders because there are discrepancies between the data of the clinical examination and those of defecography. Nevertheless, functional and anatomic abnormalities should be considered with caution, as they are not necessarily related to symptoms. This might explain the poor outcomes after surgery, strengthening the necessity to perform a complete preoperative exploration (32) and warning patients before the operation.

In order to support our hypothesis that identifying phenotypes will allow us to better adapt therapeutic strategies, prospective studies assessing the efficiency of targeted treatment on SRUS are needed.

CONCLUSION: Lesion characteristics and associated anorectal disorders should be considered in the phenotype of SRUS in order to offer targeted treatment. Prospective cohort studies are needed to confirm these assumptions.

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Table 1: Characteristics of the study population

	<i>All (N=102)</i>	
<i>Variable</i>		<i>n(%) or mean (SD)</i>
Age (years)	102	53 (15)
Female/male sex (ratio F/M)	102	80 (78)/22 (22)
BMI (Kgs/m ²)	101	24 (5)
Vascular disease	102	19 (19)
Neoplasia	102	11 (11)
Neurological disease	102	11 (11)
Psychiatric disease	102	32 (31)
Irritable bowel syndrome	102	56 (55)
Past surgeries		
Haemorrhoidectomy	102	11 (11)
Surgery for anal fistula	102	4 (4)
Surgery for anal fissure	102	5 (5)
Surgery for pelvic floor disorders	102	11 (11)
Obstetrical history		
Vaginal delivery	80	32 (40)
Perineal tear	80	8 (10)
Symptoms		
Dyschezia	102	71 (70)
Mucus discharge	102	68 (67)
Rectal bleeding	102	37 (36)
Pain	102	35 (34)
Self-reported faecal incontinence	102	18 (17)
Self-perception of anal procidentia	102	15 (15)
Anal digitation	102	55 (54)
Urinary symptoms	102	20 (20)
Clinical characteristics		
Anal tonicity (hypertonia/normal/hypotonia)	102	19 (19)/63 (62)/16 (16)
Clinical dyssynergic defecation	102	26 (26)
Haemorrhoids (high grade)	101	8 (8)
Internal procidentia (high grade)	101	50 (50)
Descending perineum	101	40 (40)
Rectocele	101	17 (17)
Scores		
CCIS	60	6 (5)
KESS	52	17 (8)
GIQLI	59	87 (25)

Abbreviations: SD=Standard Deviation; BMI=Body Mass Index; CCIS=Cleveland Clinic Incontinence Score; KESS=Knowles-Eccersley-Scott Symptom Constipation Score; GIQLI=Gastrointestinal Quality of Life Index;

Table 2: Anorectal physiology

	<i>n=102</i>
<i>Variable</i>	<i>N (%) or mean (SD)</i>
Anorectal manometry	n=82
Anal canal length (mm)	3 (0.8)
Upper part resting pressure (mmHg)	37 (17)
Lower part resting pressure (mmHg)	57 (24)
Mean squeeze duration (s)	27 (12)
Threshold perception volume (ml)	26 (25)
Constant perception volume (ml)	82 (44)
Maximum tolerable volume (ml)	170 (81)
Increasing or stable pressure during strain	44 (54)
Inability to expel a 50-ml water-filled balloon within one minute	76 (93)
Defecography	n=84
Rectocele	8 (10)
Cystocele	11 (13)
Enterocoele	25 (30)
High-grade internal rectal procidentia	61 (71)
Resting perineal descent	31 (37)
Perineal descent during defecation with effort	54 (65)
Incomplete rectal emptying	31 (37)
Inability to evacuate or $\geq 50\%$ retention of barium during defecography	9 (11)
Rectal emptying (s)	43 (37)
Paradoxical puborectalis contraction	21 (25)
Dyssynergic defecation	43 (52)