Intestinal pseudo-obstruction in patients with systemic lupus erythematosus: A real diagnostic challenge

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease caused by an aberrant immune response[1]. Its manifestations range from positive serology to one (or multiple) organ dysfunction and even death. Its course is unpredictable and involves periods of remissions and relapses[1-3]. Gastrointestinal (GI) manifestations may occur in up to 50% of patients with SLE[4,5] with the majority being mild, such as secondary effects to medication[6-8]. However, the clinical spectrum reported in the literature shows that presentations are usually associated with activity at another level[4,5,8-10] and can be aggressive, placing the life of the patient at risk[4,5,10]. Intestinal pseudo-obstruction is characterized by an ineffective propulsion of the intestine without obvious mechanical cause[6,10]. Its association with SLE is described infrequently.

Key words: Intestinal pseudo-obstruction; Systemic lupus erythematosus; Uretero-hydronephrosis; Urinary tract infection; Diagnostic challenge

Core tip: We present a summary of the most important clinical points in four clinical cases of intestinal pseudo-obstruction secondary to systemic lupus erythematosus using a suggested approach in order to reach a prompt diagnosis due to this pathology presenting a picture of acute abdomen. It is a case series of Mexican patients and, to the best of our knowledge in this particular presentation, is the first report in the international medical literature.

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lies in that a large percentage of these patients can initially present the condition together with activity at the renal, hematological and neurological levels. The most frequently described treatment is based on corticosteroids or immunosuppressants. We describe four cases of intestinal pseudo-obstruction in patients with SLE associated with severe infections, with an emphasis on the fact that diagnostic delay modifies the course of the disease and may cause the patient to be subjected to surgical procedures that are not definitive and complicate the evolution.

### Table 1  Characteristics of patients with intestinal pseudo-obstruction due to systemic lupus erythematosus at the time of diagnosis

| Case 1 | Case 2 | Case 3 | Case 4 |
|--------|--------|--------|--------|
| General information |
| Age (yr) | 27 | 23 | 25 | 37 |
| Time of diagnosis of SLE | 0 mo/yr | 0 mo/yr | 0 mo/yr | 12 yr |
| SLEDAI | 27 | 11 | 15 | 10 |
| Clinical signs and symptoms |
| Weight loss (kg) | 10 | 15 | 8 | NR |
| Seizures/amorea | + | - | - | - |
| Fever | + | + | + | + |
| Serositis (pleural effusion) | + | + | + | + |
| Ascites | - | - | - | - |
| Dysuria | + | + | + | + |
| Sepsis | + | + | + | + |
| Paraclinical tests |
| Uretero-hydronephrosis (CT) | + | + | + | + |
| Esopagitis (endoscopy) | + | + | NR | NR |
| Hypomotility (manometry) | + | + | NR | NR |
| Laboratory tests |
| ANA (IU/mL) | 2 | 1.1 | 3.4 | NR |
| Anti-ds-DNA (IU/mL) | 29 | 34 | 40 | NR |
| C3 (mg/dL) | 36 | 40 | 44 | 36 |
| C4 (mg/dL) | 6 | 3 | 7 | 8 |
| Anti-SM (IU/mL) | > 100 | NR | NR | NR |
| Anti-Ro | + | + | - | - |
| Hemolytic anemia | + | + | + | + |
| Leucopenia/lymphopenia | + | + | + | + |
| High CRP | + | + | + | + |
| Proteinuria (g/24 h) | 1.8 to 21 | 3 to 10.76 | 10 | ESCKD |
| Blood culture | E. coli | E. coli | E. coli | E. coli |
| Uric culture | E. coli/PA | E. coli | E. coli | E. coli |
| Treatment |
| Methylprednisolone pulse | + | + | + | NU |
| IV IgG | + | + | NU | NU |
| Cyclophosphamide | NU | NU | + | NU |
| Oral prednisolone | + | + | + | + |
| Prokinetics | + | + | + | + |
| Antibiotics | + | + | + | + |
| Others | | | | |
| Total parenteral nutrition | + | + | + | + |
| Surgery prior to diagnosis | + | + | + | + |

*: Positive; -: Negative; SLE: Systemic lupus erythematosus; NU: Not used; NR: Not reported/not realized; ESCKD: End-stage chronic kidney disease; CRP: C-reactive protein; ACR: American College of Rheumatology; CT: Computed tomography; ANA: Antinuclear antibodies (normal, nondetectable); anti-dsDNA: Double-stranded DNA (positives > 25 IU/ml); C3: C3 Complement (90-189 mg/dL); C4: C4 Complement (10-40 mg/dL); LDH: Lactate dehydrogenase; E. coli: Escherichia coli; PA: Pseudomonas aeruginosa; anti-SM: Anti-smith antibodies; Ro: Anti-Ro antibodies; SLEDAI: Systemic lupus erythematosus disease activity index; IV IgG: Intravenous human immunoglobulin; IU: International units.

### CASE REPORT

#### Case 1

We present the case of a 27-year-old female. During the previous 8 mo the patient had intermittent episodes of abdominal pain and oral intolerance with a 10-kg weight loss. She was operated on during two occasions due to acute abdomen, without revealing any abnormalities. Prior to admission she had dysphagia to solid foods, dysuria and urinary incontinence, malar erythema, edema of the lower extremities and pleural effusion. Laboratory tests showed hypernatremia, proteinuria (up to 21 g/24 h), hemolytic anemia [Hb 8 g/dL, lactate dehydrogenase (LDH) 785 mg/dL], indirect bilirubin 0.83 mg/dL, schistocytes in blood peripheral smear, positive direct Coombs], low complement, positive antinuclear antibodies, anti-DNA, anti-SM and anti-Ro (Table 1). Therefore, a diagnosis of SLE was concluded. According to imaging studies, the patient was diagnosed with intestinal pseudo-obstruction with dilatation of the pyloecalyceal systems, ureterohydronephrosis and emphysematous pylonephritis (Figure 1). Panendoscopy was performed with report of esophagitis with esophageal hypomotility. Colovesical fistula was ruled out by colonoscopy and urethrocytography. The patient developed amauraosis fugax and seizures classified as central nervous system activity after resonance angiography, lumbar puncture and cerebral perfusion scan. E. coli was isolated from the urine culture with > 100000 colony-forming units (CFU). The patient developed sepsis (positive blood cultures for E. coli) and was given imipenem, amikacin and levofloxacin for a total of 35 d. Abdominal pain persisted along with radiographic manifestations of intestinal pseudo-obstruction. After ruling out other causes, it was decided that the clinical picture of pseudo-obstruction was secondary to SLE. Steroids were initiated for 5 d (methylprednisolone 1000 mg/d) and then oral prednisone with a reduction scheme, prokinetics (erythromycin) and total parenteral nutrition were administered. There was partial improvement in the clinical picture but without any resolution. After this regimen, the SLE disease activity index (SLEDAI) was calculated to be 24 points. There was persistence of growth in the cultures. It was decided to administer human immunoglobulin IV at a dose of 2 g/kg weight divided into 5 d (400 mg/kg per day), after which the complement levels increased, inflammatory markers and proteinuria decreased, hemoglobin increased, and microorganisms were eradicated. Intestinal motility was finally increased, with total resolution of the GI disorder. The patient was discharged from the hospital and continued with outpatient management with mycophenolate mofetil and oral prednisone without presenting new events of GI relapse to date.

#### Case 2

We present the case of a 23-year-old female with a history of left optical neuritis associated with generalized erythema for 3 years. It was treated as multiple sclerosis...
and urticarial vasculitis and managed with β-interferon and topical steroids. The patient was admitted to the hospital with generalized abdominal pain, vomiting and oral intake intolerance. She was diagnosed with acute abdomen and received two surgical interventions with findings of only ascites and splenomegaly. Three months afterwards she was readmitted with similar complaints, as well as findings of dysphagia, dysuria and a weight loss of 15 kg. ANA and anti-DNA titers were obtained with positive results, and she also had leucopenia, lymphopenia, proteinuria (up to 10.76 g/24 h), hemolytic anemia (8 g/dL, LDH 840 mg/dL, direct Coombs positive 1/6, schistocytes in FSP) and low complement (Table 1), and urinary tract infection with urine culture isolating 100000 CFU of *E. coli*. An abdominal X-ray scan reported images characteristic of intestinal obstruction, ruling out a mechanical cause (Figure 1). The patient subsequently underwent panendoscopy with manometry with reports of incompetence of the gastroesophageal junction and esophageal and duodenal hypomotility. Metabolic causes for ileus were ruled out. The patient continued with the same symptomatology with the suspected diagnosis of SLE with GI involvement. She was managed with methylprednisolone boluses at 1000 mg/d for 3 d and broad spectrum antibiotics, obtaining partial improvement of the GI symptoms. However, she developed severe sepsis (blood cultures positive for *E. coli*). Based on information of activity (SLEDAI 11) and sepsis it was decided to administer human immunoglobulin IV at a dose of 2 g/kg per total dose (400 mg/kg per day), after which the cell counts normalized, proteinuria, ANA and anti-DNAs decreased, cultures became negative and there was improvement in intestinal transit. The patient was discharged from the service, continuing on oral steroids and monthly cyclophosphamide without severe GI symptoms.

**Case 3**

We present the case of a 25-year-old female with a history of photosensitive malar erythema and intermittent symmetrical polyarthritis. Diarrhea, abdominal pain and vomiting had a 1-mo evolution and the patient was being managed conservatively. One week after discharge, the patient again presented with abdominal pain, vomiting, dysphagia to solids, diarrhea and fever. She arrived at the hospital where she was admitted and surgically intervened due to suspicion of acute appendicitis with insidious progression. During hospitalization she developed hypertension, edema of the lower extremities, acute renal failure and radiological picture of intestinal pseudo-obstruction (Figure 1). Hypokalemia was documented (2.9 mmol/L) and corrected. There were hemolytic anemia (direct Coombs positive 1/8, elevated LDH 479 mg/dL, schistocytes in FSP), leukopenia with lymphopenia, elevated anti-dsDNA, ANA antibodies, low complement, and proteinuria (10 g/24 h) as well as *E. coli* infection in the urine culture (> 100000 CFU). With the criteria mentioned, a diagnosis of active SLE was made (SLEDAI 18). Management with parenteral hydration was begun along with replacement of electrolytes and broad spectrum antibiotics, without improvement being noted. She
developed anuria and acute pulmonary edema and temporary hemodialysis was begun. There was no improvement in the GI symptoms, with persistent air fluid levels with thickening of the intestinal wall and ureterohydronephrosis seen on X-ray and tomographic images (Figure 1). With the infection resolved and with the possibility of severe renal damage, methylprednisolone was administered at a dose of 1000 mg for 3 d, with reduction scheme with oral prednisone and cyclophosphamide at a dose of 1 g/m² SC, after which renal and gastrointestinal function improved. The patient was discharged from the hospital and was managed with a monthly dose of cyclophosphamide. Abdominal symptoms recurred 2 mo later, and the patient was managed in a similar manner.

Case 4

We present the case of a 37-year-old female with a history of SLE diagnosed for 12 years. The patient was treated with prednisone, cyclophosphamide and azathioprine, progressing towards end-stage renal disease managed with peritoneal dialysis and subsequently with hemodialysis. During the 3 years prior to admission she presented recurrent pictures of diarrheal syndromes, requiring hospital management. A month prior to admission she presented the same gastrointestinal symptoms as well as fever, paresthesia, and Raynaud’s phenomenon. Tomography at the time of hospitalization showed intestinal visceromegaly and bilateral uretero-hydronephrosis (Figure 1). E. coli was isolated from the urine culture (>100000 CFU). Antimicrobial therapy was administered, and bacterial culture was negative after 7 d of treatment. Despite treatment, she persisted with fever, pain and abdominal distension without an obvious focus of sepsis. She developed bilateral pleural effusion, polyarthritis, leukopenia with lymphopenia, hypocomplementemia, and hemolytic anemia (positive Coombs 1:6, LDH 780 mg/dL, FSP with schistocytes). The remainder of the serological exams was not done because of the low suspicion of activity (SLEDAI 6). She was treated conservatively for 28 d with laboratory tests being within normal limits. The SLEDAI was once again calculated with a score of 9. The dose of oral steroids was increased, maintaining prednisone at 1 mg/kg weight. GI symptoms improved after 5 d. Levels of activity increased and feeding was reinitiated. Due to improvement, the patient was discharged to home. Unfortunately, she again experienced GI symptoms recurred 2 mo later, and the patient was discharged from the hospital and was managed with a monthly dose of cyclophosphamide. Abdominal symptoms recurred 2 mo later, and the patient was managed in a similar manner.

DISCUSSION

GI symptoms are rarely reported as manifestations of SLE and are rarely used as data that translate to severity[9,30]. This may be because, on one hand, they are not assumed to be part of the diagnostic criteria of SLE[3,5,9]. On the other hand, a high level of suspicion is required for making the diagnosis[11]. Because this disease has an inflammatory basis, it could affect any organ[9], which includes the GI tract and other related organs (the pancreas, liver, gallbladder, and pancreatic and biliary ducts)[4,5,8,10]. Intestinal pseudo-obstruction may be the initial manifestation in association with other organs, presenting in this manner in up to 50% of the cases[10-18], and representing a diagnostic challenge for the clinician as well as for the surgeon[13]. It is a serious disease that may compromise the life of the patient when not detected in a timely manner[8]. Patients may present symptoms of recurrent abdominal pain associated with bloating, nausea, vomiting and intolerance to oral feeding, noting that symptoms may precede the diagnosis of lupus from 11 to 66 d and even up to 2 years[8,14]. There are approximately 32 cases published in the English literature[10-18] of patients who have presented intestinal pseudo-obstruction secondary to SLE, the majority being female and of Asian origin. Medina et al[10] published a series of cases of acute abdomen in Mexican patients with lupus; however, emphasis was principally placed on the surgical findings where the suspicion was intestinal vasculitis and acute abdomen. The majority of the cases reported in the literature are young females, half of whom had a prior diagnosis of SLE[14,17] and who presented with a subacute progression of the GI symptoms associated, for the most part, with renal, hematological and generalized symptoms. In agreement with this information, our small sample shows the same described pattern (Table 1); 75% of the patients did not have a prior diagnosis of SLE but had renal and hematological alterations, ureterohydronephrosis, and serositis associated with an intestinal picture. They were subjected to laparotomy during more than one occasion because of suspected surgical abdomen pathology, without revealing the cause of the symptoms. In our case 4, the patient had a prior diagnosis of SLE and had a poor evolution, developing end-stage chronic renal disease requiring hemodialysis. Her history was notable for recurrent bouts of diarrhea and abdominal pain for 3 years, which would suggest a chronic course of the disease. It was not previously suspected that the symptoms may have been related with her baseline disease; therefore, directed treatment was not tested. During her latest hospitalization, steroid doses were increased with the goal of decreasing other signs and partially improved intestinal transit and feeding tolerance. Despite this, the patient continued with similar symptoms during her subsequent hospital admissions. This progression agrees with cases described by other authors, opening the possibility that the recurrence - and not the detection or early treatment - could condition a chronic type characterized by poor response to treatment and generalized dysfunction of the intestinal motility. These cases are described as generalized megaviscera[25]. It is believed that chronic sustained inflammation may trigger smooth muscle fibrosis as shown in previous histopathological reports or even in autopsies[8]. On the other hand, 100% of our patients manifested involvement of another organ or system and
were associated with positive serological markers with hypocomplementemia. Only two cases had a panendoscopy with manometry performed, which showed esophagitis and esophageal and gastric hypomotility. Only in the first case presenting with emphysematous pyelonephritis, colonoscopy and intestinal transit with barium enema were performed to rule out colovesical fistula (suspected due to emphysematous pyelonephritis). In terms of the rates of disease activity, 75% showed indices of Systemic Lupus International Collaborating Clinics (SLICC) and SLEDAI suggestive of activity. A notable difference found in this case series is that dysuria correlated with urinary tract infections documented by urine cultures (>100000 CFU E. coli in the four patients and Pseudomonas aeruginosa in one patient) in addition to the isolation of the same microorganism in blood cultures (E. coli) in two cases.

Pathogenesis
Little is known about the pathogenesis of the disease. Etiologies such as the production of antibodies, smooth muscle myopathy, neurological involvement of the myenteric plexus and the autonomic nervous system, intestinal vasculitis with secondary ischemia, and immunocomplex deposits have been explored as probable mechanisms producing the disease. Intestinal sections most frequently affected are the jejunum or ileum and a high percentage of cases are associated with esophageal hypomotility and ureterohydronephrosis. Some authors previously demonstrated smooth muscle motility disorders in phase III of the migratory motor complex. This theory may be supported by the damage to the muscle layer caused by the immunocomplex deposit and secondary inflammation. Production of an antibody against the smooth muscle has been proposed that could cause tissue destruction, although until now it has not been demonstrated. Immunocomplexes that include anti-DNA antibodies and antibodies against the collagen-like region C1q facilitate their accumulation in the glomerulus. This affinity may be shared with any tissue that expresses the appropriate receptors, opening the possibility of the same mechanism of injury in the intestine. The hematological disorder manifested by cytopenia is associated with the presence of anticyclic antibodies TCD3/TCR and anti-Ro antibodies, the latter have the capacity of altering the function of the myocytes and of the cell conduction systems, presumed to be another mechanism of injury. For this reason, the association between leucopenia and intestinal pseudo-obstruction may not be coincidental, with it being a marker of suspicion. On the other hand, at the renal level, production of anti-α actinin antibodies. This is one of the proteins that comprise the contractile apparatus of the visceral smooth muscle, which may be a factor explaining the association between renal damage and intestinal pseudo-obstruction. Finally, some authors believe that the intestinal pseudo-obstruction may be a late manifestation of intestinal vasculitis due to the histopathological findings. These may evolve to atrophy and fibrosis which, in its chronic form, would correlate with the pictures described as generalized visceromegaly.

Diagnosis
The clinical picture, age and gender of the patient, together with imaging and laboratory studies, constitute the first tool for the suspected diagnosis. Plain X-ray of the abdomen may provide useful information when we are dealing with an obstructive process (air fluid levels, coffee ground loops, absence of air in the pelvic cavity, image of “stack of coins”); however, the noninvasive imaging study with the greatest diagnostic usefulness is abdominal computed tomography because it helps to rule out mechanical causes of the obstruction and identifies characteristic images such as target dilated loops of the jejunum and ileum, swelling of the intestinal walls, air fluid levels, pylolecaltasis and, above all, ureterohydronephrosis that may be present in up to 60% of cases. Panendoscopy and manometry have demonstrated esophagitis and disorders of esophageal motility as well as gastric and duodenal hypomotility. Invasive methods such as colonoscopy and double balloon enteroscopy provide information on portions of the small and large intestines that cannot be reached by other means, as well as the possible advantage of taking biopsies. However, it is not a method that is frequently used, given that there is currently no pattern or specific marker in the histopathological study in existence considered to be the gold standard. In addition, there are reports about the predisposition of causing greater ischemia by dilation of the loops and risk of intestinal perforation and secondary peritonitis. Disease activity indexes such as SLEDAI and SLICC do not always directly correlate with gastrointestinal pictures; therefore, it is difficult to consider them as useful markers. Differential diagnosis includes any disorder that causes dysmotility and is associated with extraintestinal symptoms. Among the most important of these are sporadic myopathies, systemic sclerosis, dermatomyositis, lymphoid and amyloid infiltration, to mention a few. We emphasize that early detection correlates with a better prognosis and avoids unnecessary surgical procedures that hinder evolution and lead to a poor prognosis. A last resort would be exploratory laparotomy, although this should be done when there are eminent signs of intestinal perforation (free air in the abdominal cavity or septic shock in the presence of acute abdomen).

How to suspect it?
Although GI symptoms are common to the majority of the presentations, there are key data that may represent the difference in recognition of the disorder. In young patients, especially females with recurrent clinical-radiological manifestations of intestinal occlusion, an exhaustive interview should be carried out in search of manifestations or information that may be related to SLE. The
When a young patient presents with a clinical-radiological picture of intestinal pseudo-obstruction, the need for urgent surgery must be ruled out at first instance. Extensive interrogation and thorough examination must be carried out along with information that could suggest the picture. Among the initial examinations are X-ray, contrast abdominal tomography if possible or renal ultrasound if not possible, along with blood and urine tests. If information is compatible with the disease, specific serology should be carried out to determine if disease criteria have been met. If the diagnosis is corroborated, the patient should be evaluated by a specialist in order to initiate timely treatment. AA: Acute abdomen; BC: Blood cytometry; BCH: Blood chemistry; UA: Urinalysis; C3-C4: Complement; US: Ultrasound; IPO: Intestinal pseudo-obstruction; SLE: Systemic lupus erythematosus; ACR: American College of Rheumatology; UHN: Ureterohydronephrosis.

**Treatment**

Treatment should be individualized and generally multidisciplinary[1]. Among the recommendations for management of SLE issued by the European League Against Rheumatism and established by the ACR, there is no scheme suggested for GI manifestations[9,33]. The most frequently described experience in disease management is based on corticosteroids administered in pulses (methylprednisolone 500-1000 mg daily for 2-5 d) associated with other immunosuppressants (cyclophosphamide being the most used)[10,13]. Cases have been reported where cyclosporine A, methotrexate, azathioprine[7,11,24], and tacrolimus were used[23]. The use of prokinetics should be considered, preferably erythromycin because of its antimicrobial properties, although the use of metoclopramide, octreotide and neostigmine should be considered. Finally, use of parenteral nutrition should be individualized in cases where oral feeding is not possible. Human immunoglobulin is extracted from the plasma of thousands of donors[27,28] and is mainly composed of a pool of antibodies, mainly IgG (97%). Its use has been described in reports of cases and small cohorts with good results[29-31]. The usual administered dose is 2 g/kg divided into 2-5 d in continuous IV infusion. The described mechanisms of action vary[27,29,32-35]. It is considered more than an immunosuppressive treatment and immune regulatory agent that obviates the toxic and teratogenic effects of other drugs, providing a favorable safety profile for infected patients[29,30]. Any prior condition should be taken into consideration, which may contraindicate its use along with the problem of its high cost, which hinders its accessibility for treatment[27]. Early directed treatment makes progression of the disorder highly reversible, avoiding the need for surgery and having an impact on survival, recovery of function and decrease in complication rates[29,30,22,25].

Intestinal pseudo-obstruction secondary to lupus is an infrequent disorder that may initially manifest together with other organ and system involvement. It should be suspected, especially in young women with clinical-radio-

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**Figure 2** Suggested approach of intestinal pseudo-obstruction in lupus. When a young patient presents with a clinical-radiological picture of intestinal pseudo-obstruction, the need for urgent surgery must be ruled out at first instance. Extensive interrogation and thorough examination must be carried out along with information that could suggest the picture. Among the initial examinations are X-ray, contrast abdominal tomography if possible or renal ultrasound if not possible, along with blood and urine tests. If information is compatible with the disease, specific serology should be carried out to determine if disease criteria have been met. If the diagnosis is corroborated, the patient should be evaluated by a specialist in order to initiate timely treatment. AA: Acute abdomen; BC: Blood cytometry; BCH: Blood chemistry; UA: Urinalysis; C3-C4: Complement; US: Ultrasound; IPO: Intestinal pseudo-obstruction; SLE: Systemic lupus erythematosus; ACR: American College of Rheumatology; UHN: Ureterohydronephrosis.
logical manifestations and information of disease activity at another level. Urinary tract infections may be associated with urinary manifestations and complicate symptom progression. Management of the disorder should include immunomodulators, principally corticosteroids and cyclophosphamide, prokinetics, and parenteral nutrition when required. In our short experience we believe that use of IV human immunoglobulin may be a good alternative where there are concomitant severe infection or sepsis and disease activity if there is no contraindication for its use.

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