

How to diagnose lupus enteritis early? Lessons learned from a multicenter case series

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ABSTRACT

Introduction: Lupus enteritis (LE) is a rare, potentially life-threatening manifestation of systemic lupus erythematosus (SLE). Early diagnosis is crucial for early treatment and prevention of serious complications such as ischemic enteritis, bowel infarction with bleeding and/or perforation and peritonitis. The objective of this case review is to identify strategies for early diagnosis of LE.

Methods: Retrospective analysis of patients with SLE (fulfilling ACR 1997 and/or SLICC classification criteria) and presenting LE from three tertiary SLE centers was conducted. The diagnosis was based on clinical and imaging features consistent with LE and exclusion of other causes of GI disorders.

Results: We report seven cases of LE (female: 100%; age range: 16-55 years). All presented with acute onset abdominal pain, nausea and vomiting at the emergency room. Two patients had lupus enteritis as inaugural manifestation of SLE. Of the remaining five, one presented at the previous visit to the lupus clinic with clinically active disease and two had serologically active/clinically inactive SLE. High anti-dsDNA antibodies and low serum complement were universally present at time of the LE event. Abdominal ultrasound was the first imaging exam to be performed in the emergency room. In all cases it showed bowel wall thickening, dilatation of intestinal segments, increased reflectivity of mesenteric fat and mild ascites, raising the suspicion of LE and immediate start of treatment. These features were later confirmed by CT scan in five patients.

Discussion: Despite being rare, LE must always be considered in any SLE patient presenting with GI symptoms. Abdominal ultrasound can be a reliable first line diagnostic tool for LE.

Keywords: Systemic lupus erythematosus; Ultrasound; Gastrointestinal involvement.

INTRODUCTION

Gastrointestinal (GI) complaints are common in Systemic lupus erythematosus (SLE) patients^{1,2}. Early clinical presentation of lupus enteritis (LE) is unremarkable and non-specific, comprising diffuse abdominal cramps or persistent pain, nausea, vomiting, fever and diarrhea, making early clinical suspicion of LE difficult to elicit^{3,4}. Also, glucocorticoids and immunosuppressants can mask classical signs of an acute abdomen in SLE patients. When diagnosed early, LE usually responds well to treatment with high-dose glucocorticoids, but if left unchecked it can lead to life-threatening complications such as ischemic enteritis, bowel infarction with bleeding and/or perforation and peritonitis.⁵ The aim of this case review is to identify possible strategies for early diagnosis of LE.

METHODS

Retrospective analysis of patients with SLE (fulfilling ACR 1997 and/or SLICC classification criteria and registered in the reuma.pt national database) from three tertiary SLE centers, with a clinical diagnosis of LE, between 1999 and 2018, was conducted. The diagnosis was based on clinical and imaging features consistent with LE and exclusion of other causes of GI disorders. Patients with associated antiphospholipid syndrome or with positive antiphospholipid antibodies were excluded. Ultrasound scan was always performed by an experienced radiologist.

RESULTS

Seven cases of LE were identified in the participating cen-

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ters. The main characteristics of these patients are summarized in Table I. Each case is presented below.

PATIENT 1

An 18-years-old female was admitted in the emergency room with acute diffuse abdominal pain, fever, nausea, vomiting and absence of stools and gas emissions over the previous 4 days. She had been diagnosed with SLE almost one year earlier based on cutaneous, articular, hematological and immunological features. At admission, her abdomen was mildly tender without audible bowel sounds. Laboratory tests showed low complement, new onset anemia, slight hypoalbuminemia and increased serum ferritin. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and lactate dehydrogenase (LDH) were within normal ranges. An abdominal ultrasound (US) revealed moderate ascites and diffused wall thickening of the colon with increased reflectivity of subjacent fat tissue. Abdominal computed tomography (CT) clearly showed increased wall thickening with abnormal enhancement (target sign) - mainly in the jejunum and ileum but also in the ascending colon - and engorgement of mesenteric vessels. Multiple enlarged mesenteric lymph nodes were also present (Figure 1). She was started on IV methylprednisolone (MPDN) 500mg pulses followed by oral prednisone (1mg/kg/day). Twenty-four hours later the symptoms quickly started to resolve and she was discharged 6 days later. After more than a year, the patient remains free of GI symptoms although soon after the present episode lupus nephritis developed. She was started on induction therapy with mycophenolate mofetil (MMF) 2.5g/d with good response.

PATIENT 2

A 43-years-old female, with a 10-year history of SLE - based on the presence of oligoarthritis, pericarditis, lymphopenia, photosensitive malar rash and immunological markers - presented with a two-day history of diffuse acute abdominal pain, vomiting and dysuria. She also described pain and swelling of her left ankle for the last two months. Physical examination showed a tender abdomen and left ankle arthritis. ESR (58 mm/1st hour) and LDH (326 mg/dl) were high while CRP was slightly elevated (0.62 mg/dl). Urinary sediment analysis showed new onset proteinuria (527.5 mg/24h). Large ascites and jejunum-ileum wall thickening were seen on US. Abdominal CT scan confirmed the presence of thickened intestinal loops with

target sign at the left iliac fossa, dilatation of the small bowel lumen and multiple enlarged mesenteric lymph nodes. Additionally, the lateral wall of bladder was also thickened suggesting concomitant involvement of the urinary tract. She was started on IV MPDN 1g pulses followed by oral prednisone 1 mg/kg/day, with complete resolution of symptoms within 3 days. At 1-year follow-up, under no therapy apart from hydroxychloroquine (HCQ), the patient remained free of abdominal complaints or other signs of disease activity.

PATIENT 3

A 16-years-old female had been diagnosed with SLE 3 years earlier, with cutaneous, articular, neurological, hematological, renal and immunological involvement. She suffered from late stage chronic kidney disease and secondary hypertension as a result of a previous severe class IV lupus nephritis. She was admitted to the emergency room with acute onset diffuse abdominal pain, nausea and vomiting that started less than 24 hours before. She was hemodynamically unstable, had a tender abdomen and no bowel sounds. Laboratory tests showed worsening of renal function and hypoalbuminemia. Both ESR and CRP were normal. US revealed small bowel wall edema, increased vascularization on Doppler and moderate ascites. She wasn't submitted to abdominal CT since her renal function didn't allow the administration of iodate contrast. IV MPDN 1g pulses were immediately started with excellent clinical response, although she maintained changes in control US 3 days later. After hospital discharge, recurrent self-limited abdominal pain episodes persisted. Two years later, she presented again with abdominal pain, this time more focused on the right iliac fossa, and diarrhea. US confirmed the presence of thickened and hypoechogenic ascending colon wall with enhancement of the surrounding fat tissue and associated bilateral hydronephrosis with bladder wall thickening. CT scan showed thickening of small bowel wall, multiple small mesenteric adenopathies, increased number of observed mesenteric vessels and mild ascites. She was again treated with IV MPDN 1g pulses, with no relapse until today, after 5 years follow-up. Due to progressive renal function deterioration, she is currently being considered for kidney transplant.

PATIENT 4

A 40-years-old female, with a 21-year history of SLE with hematological, renal and immunological involvement, had been suffering from recurrent episodes

TABLE 1. CLINICAL AND LABORATORY CHARACTERISTICS, TREATMENT AND FOLLOW-UP

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	18	43	16	40	36	34	18
Gender	F	F	F	F	F	F	F
Disease duration (years)	1	10	3	21	0	0	1
Previous SLE manifestations	Cutaneous Articular Hematologic Immunologic	Cutaneous Articular Hematologic Immunologic Serous	Cutaneous Articular Hematologic Immunologic Neurologic Renal	Hematologic Immunologic Renal	NA	NA	Cutaneous Articular Hematologic Immunologic
Therapy (mg/day)	HCQ 400 PDN 5	HCQ 400 PDN 7.5	HCQ 400 MPDN 4 MMF 2000	HCQ 400 PDN 5 MMF 2500	N/A	NA	None
Extra-GI manifestations	Lupus cystitis	Lupus cystitis Arthritis	Lupus nephritis relapse	Lupus cystitis Autoimmune hemolytic anemia	Arthritis	Arthritis	Nephritis Serositis
SLEDAI (previous/during flare)	0/13	4/17	0/13	4/16	-/18	-/16	12/33
Laboratory work-up	C3 0.6 C4 0.06 anti-dsDNA 140 CRP 0.2 ESR 2	C3 0.54 C4 0.07 anti-dsDNA > 50 CRP 0.6 ESR 54	C3 0.36 C4 0.02 anti-dsDNA > 50 CRP < 0.5 ESR < 15	C3 0.59 C4 0.03 anti-dsDNA 16 CRP 1.6 ESR 8	C3 0.49 C4 < 0.1 anti-dsDNA >50 CRP 5.1 ESR 100	C3 0.56 C4 0.13 anti-dsDNA 1284 CRP 0.2 ESR 23	C3 0.33 C4 0.08 anti-dsDNA >379 CRP 27 ESR 31
Abdominal US findings suggestive of LE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abdominal CT findings suggestive of LE	Yes	Yes	NA	Yes	Yes	Yes	NA
Flare treatment	IV MPDN 500mg 3 days	IV MPDN 1g 3 days	IV MPDN 1g 3 days followed by IV CYC 500 and PDN 1mg/kg/day	IV MPDN 1g 3 days followed by IVIG 400mg/kg/day 5 days	IV MPDN 1g 3 days	PDN 1mg/kg/day followed by IV MPDN 1g 3 days	IV MPDN 1g 3 days followed by Cpa 100 mg/day
Follow-up	No relapse	No relapse	Recurrent abdominal pain and relapse 2 years later	Relapse 3 and half months later	No relapse	Need of parental nutrition and slow clinical resolution	No relapse

C3: C3 complement (normal range: 0.80-1.85 g/L); C4: C4 complement (normal range: 0.15-0.53 g/L); CRP: C-reactive protein (normal range: 0-0.5 mg/dL); Cpa: Cyclosporine; CYC: cyclophosphamide; ESR: erythrocyte sedimentation rate (normal range: 0-20 mm/h); F: female; GI: gastrointestinal; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MPDN: methylprednisolone; N: within normal range; NA: not applicable; PDN: prednisolone; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; US - ultrasound. F: female.

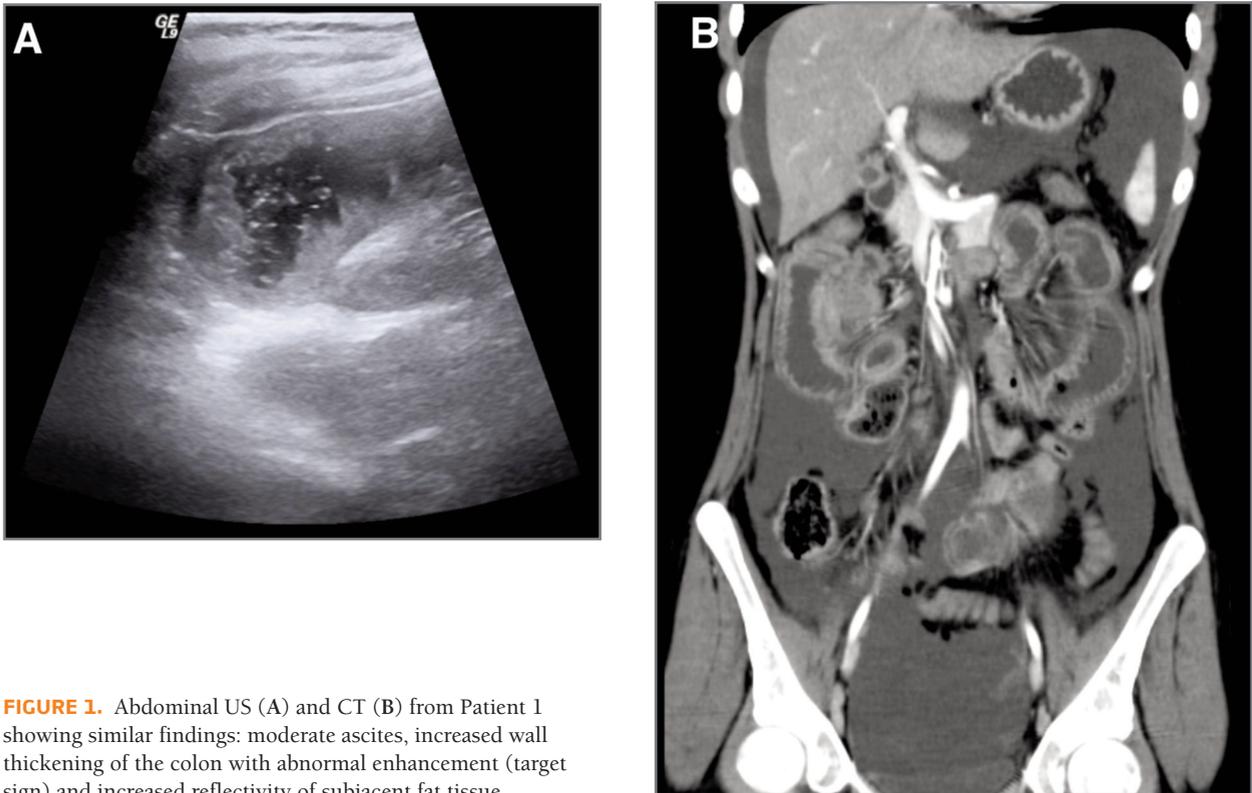


FIGURE 1. Abdominal US (A) and CT (B) from Patient 1 showing similar findings: moderate ascites, increased wall thickening of the colon with abnormal enhancement (target sign) and increased reflectivity of subjacent fat tissue.

of severe hemolytic anemia. She developed acute abdominal pain, nausea, vomiting, increased abdominal volume and anorexia. At hospital admission, the patient was pale and her abdomen tender and painful. Laboratory tests showed anemia, lymphopenia, increased CRP and decreased haptoglobin levels. US revealed ascites, increased echogenicity of renal parenchyma, slight right side hydronephrosis, and thickening of the bladder wall, pyloric region and several segments of the bowel wall. She was then submitted to an abdominal CT scan that revealed moderate to severe ascites, submucosal edema of the antral and pyloric regions, ileum and colon and severe, irregular, bladder wall thickening with reduced distensibility resulting in bilateral hydronephrosis. The treatment strategy was similar to the previous cases. Although the GI symptoms resolved after 48 hours, she kept showing signs of hemolytic anemia and was started on IVIg (400 mg/kg/day for 5 days), with benefit. Three and half months later, she suffered a relapse of the LE and repeated IV MPDN 1g pulses followed by rituximab 1g which had to be switched to MMF 2.5g/day after an infusion reaction. At 2-year follow-up the patient is asymptomatic and with no sign of relapse.

PATIENT 5

A 36 years-old female with a history of intermittent self-limited polyarthritis since the age of 15 and one episode of thrombocytopenia during pregnancy one year ago, was admitted with acute diffuse abdominal pain and persistent vomiting lasting for 24 hours. Physical examination showed signs of dehydration and a tender abdomen. Laboratory tests revealed thrombocytopenia, increased ESR and CRP, low complement fractions and positive antinuclear, anti-dsDNA and anti- α 2-glycoprotein I IgG antibodies. She was then diagnosed with SLE. In order to clarify the acute abdominal condition, she performed US which demonstrated moderate ascites and severe irregular thickening of bowel wall, suggestive of edema. CT scan suggested the diagnosis once more: it described diffuse thickening of the small bowel wall with intraluminal dilatation and fluid collection, increased attenuation of mesenteric fat tissue and slight left pleural effusion. A biopsy of the jejunum was performed: the mucosa did not present remarkable changes; the submucosa showed edema, vascular congestion and focal hemorrhage; in the serosal layer, there was diffuse fibrosis, congestive vessels and predominantly eosinophilic inflammatory in-

filtrate. She was successfully treated with IV MPDN 1g pulses with good response and remains without any signs of abdominal disease activity after more than 20 years. She is currently treated with HCQ and leflunomide for her arthritis.

PATIENT 6

A previously healthy 36-years-old black female had been complaining of inflammatory polyarthralgia for the last 4 months, when she started suffering from nausea, vomiting, diarrhea and diffuse abdominal pain. At hospital admission, the patient was dehydrated, pale, had a tender abdomen and peripheral polyarthritis. Infectious etiology was ruled out after an extensive workup. She tested positive for antinuclear and anti-Smith antibodies. Her anti-dsDNA was high and C3 complement fraction reduced. ESR and CRP were normal. US showed moderate ascites and diffuse small bowel wall thickening. Enteric MRI found diffuse wall thickening of the jejunum and distal ileum, intraluminal dilatation, congestive mucosal folds, target sign, engorgement of mesenteric vessels and increased suppression of mesenteric fat. A subsequent abdominal CT scan revealed similar findings: diffuse small bowel wall thickening and intraluminal distention, especially in the terminal ileum. There was wall thickening of the descending colon to the splenic angle, without dilatation or obstruction. Moderate ascites was also present. Colon biopsy result was unspecific for vasculitis but allowed the exclusion of other differential diagnosis (tuberculosis, CMV colitis and Whipple disease among others). She received prednisone 1 mg/kg/day with no response. Nasogastric intubation and parenteral nutrition were required, and treatment with IV MPDN 1g pulses was started, followed by oral azathioprine. She fully recovered and remains symptom and relapse-free until today, after a 3-year follow-up.

PATIENT 7

An 18-year-old female with a recent diagnosis of SLE based on hematological, articular, mucocutaneous and immunological features, presented with fever, diffuse abdominal pain, nausea, vomiting and bloody diarrhea in the emergency room. At physical examination, she had a tender abdomen and severe peripheral edema. Laboratory tests revealed anemia, increased CRP, low complement fractions and positive anti-dsDNA. Proteinuria was identified for the first time at this point (2.4g/24h). Abdominal US showed moderate parietal thickening of the left colon and rectum walls, mild as-

cites and slight hepatosplenomegaly. It was also evident the presence of bilateral pleural effusion and minimal pericardial effusion. Kidney biopsy revealed mesangial proliferative glomerulonephritis and thrombotic microangiopathy. She was immediately started on IV MPDN 1g pulses for 3 days followed by cyclosporine 100 mg/day. She was discharged from the hospital 10 days later, after total symptom resolution. At one-year follow-up the patient remains symptom-free, with complete kidney response (proteinuria 0.8 mg/24h).

DISCUSSION

Many GI conditions can mimic LE. The differential diagnosis can be rather challenging since some of these conditions, despite being nonspecific for SLE, are more prevalent in these patients, such as infectious colitis (parasitic, bacterial or viral), peritonitis, acute pancreatitis, autoimmune hepatitis, primary biliary cirrhosis, mesenteric thrombosis (more commonly associated with the presence of antiphospholipid antibodies) or even GI toxicity of drugs.^{4,6,7}

Several predisposing factors for LE have been proposed, such as simultaneous peripheral or central nervous system vasculitis, thrombocytopenia and serum rheumatoid factor.⁸ None of them were present in our series. All of our patients presented with acute onset abdominal pain, mainly diffuse, with associated nausea and vomiting. Three patients suffered from concomitant lupus cystitis, characterized by urinary bladder wall edema and thickening and, in one case, hydronephrosis. This association was previously described in the literature and was even proposed as risk factor for recurrence.^{9,10}

Patients 5 and 6 had LE as inaugural manifestation of SLE. In both cases, SLE was suggested by the concomitant presence of arthritis and positive immunological markers of the disease (antinuclear and anti-Smith antibodies, high anti-dsDNA and low complement), although both ESR and CRP were within their normal range.

In our case series, all patients but two underwent abdominal CT scan and all of them fulfilled the criteria proposed by Byun for LE.¹¹ The widespread use of abdominal CT allowed higher diagnosis accuracy, early screening for complications, treatment planning and disease follow-up. However, CT findings in LE, despite its high sensitivity, carry a low specificity since they can be found in other GI conditions, mainly pancreatitis,

mechanical bowel occlusion, peritonitis and inflammatory bowel disease.^{5,12}

Patients 5 and 6 were submitted to intestinal biopsy. In patient 5, histological findings were indeed suggestive of mesenteric vasculitis. In patient 6, on the other hand, the result was inconclusive for vasculitis but allowed the exclusion of other possible conditions, such as CMV colitis, Whipple disease and other granulomatous diseases. Janssens *et al.* conducted a literature review and concluded that in the 150 cases already published of LE, 25 had been submitted to endoscopic studies. Of these, in 15 cases there was no macroscopic changes. The histological examination presented a low sensitivity, with only 55,6% of the cases showing necrotizing vasculitis and/or fibrinoid necrosis.³

US is an underestimated diagnostic tool in LE, but in our case series, it has been shown to be a valuable screening tool for early diagnosis (Figure 1). It is likely to be the most readily available imaging method, and a valuable alternative to CT scan when the later is not available or is contraindicated. Patient 3 is a good example of the potential role of US where hemodynamically instability and acute renal failure precluded the use of CT scan. It also performed better than any serological marker, including CRP and ESR which were frequently normal. Although this may seem odd considering lupus enteritis is a vasculitis, CRP and ESR are poor serological markers for many other SLE manifestations including arthritis and even nephritis.

Being a more accessible technique, it was the first imaging exam in all our patients when they present at the emergency room. In all of them US showed thickening of the intestinal wall, dilation of intestinal segments, increased reflectivity of mesenteric fat and mild ascites. CT scan subsequently confirmed these features, suggesting that both methods have similar sensitivity for the diagnosis of LE. Regarding specificity, US has the same limitations as CT scan, but with advantages already mentioned. Considering the demographic characteristics of these patients (young women of child-bearing age), US is likely the best screening exam for suspected LE diagnosis.

CONCLUSION

Despite being rare, LE must always be considered in any SLE patient presenting with GI symptoms. US proved to be a reliable first line diagnostic tool for LE

and a reasonable alternative to CT scan in selected patients.

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