Gastrointestinal involvement in systemic lupus erythematosus: A systematic review

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A B S T R A C T

Introduction: Gastrointestinal involvement is a common complain observed in 40–60% of systemic lupus erythematosus (SLE) patients. We performed a systematic review of clinically severe and potential life-threatening gastrointestinal manifestations and discuss clinical presentation, pathogenesis and treatment.

Methods: We performed a literature search in English literature using PubMed and Embase from 2000 to December 2020. The following MeSH terms: systemic lupus erythematosus, protein-losing enteropathy, ascites, pancreatitis, vasculitis, intestinal vasculitis, enteritis and diarrhea published in the English literature.

Results: We identified 141 studies (case reports, case series and cohort studies). The most frequent presenting symptoms were acute abdominal pain, nausea, and vomiting. Many of the manifestations were associated with disease activity. Histological features are rarely available, but both vasculitis and thrombosis have been described. There is no treatment guideline. The majority of patients were treated with corticosteroids and the most common immunosuppressive agents were azathioprine, cyclophosphamide and mycophenolate.

Conclusion: Vasculitis and thrombosis may be responsible for severe life-threatening manifestations such as pancreatitis, protein losing gastroenteritis, acalculous cholecystitis and enteritis.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with systemic inflammatory manifestations. Skin, kidney, central nervous system involvement, in addition to hematological abnormalities are most frequently observed [1].

Gastrointestinal involvement is a common complain observed in 40–60% of SLE patients [2]. A clinically recognized gastrointestinal manifestations have been described in 8–10% of patients [2,3]. Autopsy studies, on the other hand, report findings of gastrointestinal involvement in 60–70% of patients, suggesting that subclinical or unrecognized involvement is common [3].

Most gastrointestinal manifestations are usually mild [4]. Vasculitis and thrombosis may be responsible for life-threatening manifestations, leading to ischemia, perforation and infarction if not early diagnosed and adequately treated [5].

In this article we performed a systematic review of clinically severe and potential life-threatening gastrointestinal manifestations and discuss clinical presentation, pathogenesis and treatment.

2. Methods

We performed a systematic review of the literature and limited our search to articles published in the English literature from January 2000 to December 2020. The search of relevant references for the exploration of the electronic database in PubMed and Embase using the following MeSH terms: systemic lupus erythematosus, protein-losing enteropathy, ascites, pancreatitis, vasculitis, intestinal vasculitis, enteritis and diarrhea. The articles have been selected when presented this terms in Title/Summary. Bibliographies of articles were reviewed for additional literature not identified through the PubMed and Embase search.

An evaluation of the studies was made using as inclusion criteria: 1.

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Original articles; 2. Articles in English; 3. Patients with Systemic Lupus Erythematosus 4. Patients who presented gastrointestinal manifestations due to SLE.

Exclusion criteria: 1. Studies before to the year 2000; 2. Patients with manifestations not due to disease activity or other connective tissue disease knowingly responsible for gastrointestinal involvement were excluded from the analyses; 3. Articles using animal models; 4. Studies containing overlapping or insufficient data.

At the end of the analysis, 141 relevant articles were included in this study and the PRISM flowchart is shown in Fig. 1.

3. Results

3.1. Pancreatitis

We obtaining a total of 55 articles, including case report or case series and case-control studies of pancreatitis in SLE [4,6–59]. The most frequent presenting symptoms are acute abdominal pain, nausea and vomiting [6,15,17–21,23–33,35–50,52,55,58] (Table 1).

Fever and reduced bowel sounds were reported in 16 of the cases [15,17,20,25,30,38,40,42–44,48,50,52,55,59]. Pancreatitis was diagnosed within the first year of SLE in 24 studies [18,19,21,25–33,40,42,44–48,50,55–57,59] and concomitant SLE activity was identified in 34 studies [6,15,17–20,24–36,38–46,49,50,52,53,57,58]. Increased amylase and lipase were key laboratory features [6,14–16,18–20,23,26,27,35–57,43,45,46,52,55,57–59].

Imaging studies [computer tomography (CT) or ultrasound (US)] were normal in a few; however enlarged pancreas, uniform enhancement of pancreas, peripancreatic fluid, calcification and cysts of the pancreas has been described [4,6–29,31–48,52,55,57,58].

In this review we did include only pancreatitis associated with SLE and excluded reports due to infections or mechanical causes. Most reported considered pancreatitis secondary to disease activity and treatment was based on prednisone [oral or intravenous] [15,17–20,23–32,36–39,41–50,52,55–59].

Some authors reported the association of cyclophosphamide, cyclosporine A, immunoglobulin, plasmapheresis or rituximab [6,18,20,26,39,46,48,50,52,55,57,58].

Concomitant antiphospholipid antibodies (aPL) was identified in the minority of the cases [33], however most studies did not report on aPL positivity.

Other associations reported were secondary Sjogren’s syndrome, anti-La, lower income, less private insurance, more disability and smoking [16], macrophage activation syndrome [18], increased D-dimer [40] and leukoencephalopathy [47]. Resolution of pancreatitis was reported in 24 articles [15,16,18–20,23,25–27,29–31,38,39,45,47,48,50,52,54–57,59]. Deaths, complications and chronicity were reported predominantly by case series [16–18,24,28,32,35–37,41,43,44,49,50,53,57,58] (Table 1).
3.2. Protein-losing enteropathy

We reviewed a total of 51 studies of protein-losing enteropathy [21, 55, 56, 60–107].

The most frequent symptoms observed were lower leg or generalized edema, ascites and diarrhea (Table 2). Laboratory abnormalities observed were low serum albumin, normal or low protein loss in nearly all patients [60–64, 66, 67–90, 96–100, 106]. Increased cholesterol level was also frequently observed [61, 66, 70, 72, 74, 81, 88] (Table 2).

Diagnosis was made by Technetium (Tc-99 m) albumin scintigraphy and/or increased α1 antitrypsin clearance in the stool [60–63, 67, 69–74, 77, 80, 99, 100, 102, 103, 105–107]. Additional imaging findings on CT scans revealed thickening of bowel wall [61, 63, 70, 85, 87, 90].

Biopsy performed in a few patients revealed unspecific inflammation and the absence of vasculitis in the lamina propria [63, 79, 86–88, 90].

Protein losing enteropathy was diagnosed at SLE onset [21, 62, 65, 71–74, 76–83, 85–87, 90, 98, 106] or concomitant with SLE flare [79, 84, 102, 103]. Patients with established SLE that presented with new onset gastrointestinal symptoms had the diagnosis of protein losing enteropathy made earlier than patients without SLE diagnosis [84].

Some larger studies observed an association with Raynaud’s phenomenon [21], CA-125 [81, 86] and Sjogren’s Syndrome [87] (Table 2).

In a retrospective case-control study the odds of an SLE patient with anti-SSA positivity developing protein losing enteropathy was 3 times higher than an SLE patient who were anti-SSA-negative [96].

In addition, the best combination of findings predictive of protein losing enteropathy were the simultaneous detection of serum albumin (<22 g/l) and 24-h urine protein levels (<0.8 g/24 h), with a sensitivity of 0.818 and specificity of 0.989 [96]. With adequate treatment, serum albumin is the first parameter to improve, followed by serum complement C3 levels [96].

Most patients reported were treated with corticosteroids [21, 60–107]. Additional immunosuppressant used were azathioprine [60, 65, 73–79, 81, 85–87, 96, 107], followed by cyclophosphamide [63, 70, 72, 88, 93, 96, 107], mycophenolate [65, 87, 92, 96, 103, 107], IVlg [64], anti-tumor necrosis factor (TNF) [63, 64], methotrexate [64, 65, 84, 96] rituximab [93, 107] and cyclosporine A [82] (Table 2).

Additional treatment with octreotide [71, 75] or ingestion of medium chain triglyceride (MCT) diet [75, 85] may also be beneficial in this setting. Prognosis is generally good with full recovery; mortality is infrequently reported [21, 60–104].

3.3. Acute cholecystitis

We obtained a total of 8 reports/studies addressing acalculous cholecystitis [19, 108–114]. The patients usually present right upper quadrant pain and vomiting in the setting of active SLE features [19, 108–114].

Diagnosis was made by abdominal ultrasonography [19, 108–114], computed tomography scans [19, 112], histopathologic examination [108, 111] and laparotomy [19]. In some patients cholecystectomy was performed [19, 108–111].

Histopathology varies from medium-size vasculitis to thrombotic microangiopathy associated with aPL [19, 108–112]. Acalculous cholecystitis was diagnosed at SLE onset [19, 110, 111] or during the course of active disease [108-109,112-114].

Most patients were treated with IV or oral corticosteroids [19, 108–114]. Additional immunosuppressants used were cyclophosphamide [19,108,110,111], azathioprine [19,110,111] and cyclosporine [19]. Three studies reported treatment only with corticosteroids, without additional immunosuppressant [112–114].

3.4. Vasculitis

Vasculitis was described affecting the colon and/or the small bowel [19, 40, 46, 115–139].

Most patient present with abdominal pain [19, 40, 116–120, 122–125, 129, 131–133, 138, 139], nausea/vomiting [118, 122, 124, 126, 127, 129, 130, 132, 133, 138, 139].
139] and abdominal distention [117,120,130].

Fever [122], reduced bowel sounds [119,120,128,129] and acute surgical abdomen [19,117,128,134] may also be the presenting feature (Table 3).

Concomitant SLE disease activity has frequently been described [19, 117, 120–124,127,131–134,138,139].

Imagining studies described intestinal wall thickening [19,115,116,118–120,122–124,126–128,130] and mesenteric vessel engangement [115,116,124,134]. Some studies reported biopsy results with overt inflammation [115,118,122,125].

Oral or IV steroid was used in all patients [19,40,46,115–139]. Other immunosuppressants used were cyclophosphamide [19,116,117,119,120,132,134,138,139], IVIg [118], mycophenolate [117,134] and rituximab [130].

Although it is a potential severe manifestation, most patients had resolution of symptoms with adequate treatment [19,119,123–126,128–132,139]. Intestinal perforation [19,117,118,122] and death [122,138] were rarely reported (Table 3).

3.5. Diarrhea

We found four case reports [140–143] and two retrospective studies [144,145].

The most common associated symptoms described were abdominal pain [140–145] and vomiting [140–142,144,145]. Other signs and symptoms described were ascites [140,142–144], nausea [140,142,144,145], fever [142,143], colitis [142,143], mild hepatic dysfunction [143], pleuritis [141,143], abdominal sensitivity [145] and serositis [143] (Table 4).

In some studies, patients with diarrhea had active disease [140,141,143–145].

Imagining studies included CT scan [140,142,143,145], the main findings included: gastrointestinal thickening such as diffuse hypodense submucosal thickening of the stomach [140], extensive small bowel thickening from the antrum of the stomach through to the distal ileum [142] and wall thickening and trilayered enhancement of small bowel loops [143]. In addition, there were also abdominal ultrasonography [141], 99 mTc-HAS [144], radiography [144,145], gastroendoscopy [144] and colonoscopy [144] (Table 4).

Treatment described mainly included corticosteroids [140,141,143–145], cyclophosphamide [140,142,144,145], azathioprine, rituximab and mycophenolate mofetil [140,142] (Table 4).

Although clinical improvement was the most frequent reported outcome [140–145], there were also some cases of patient deaths [144,145].

Table 3

| Signs and symptoms | Abdominal pain | Acute abdomen | Nausea, vomiting | Abdominal distension | Fever |
|--------------------|----------------|---------------|------------------|---------------------|-------|
| Associations       |                |               |                  |                     |       |
| Imaging findings   |                |               |                  |                     |       |
| Biopsy             |                |               |                  |                     |       |
| Treatment          |                |               |                  |                     |       |
| Outcome            |                |               |                  |                     |       |

3.6. Ascites

We identified a total of 33 studies reporting ascites in SLE [2–7,9–14,16–18,20–23,25–27,30,32,33,36,40,42,48,63,69,72,146].

Ascites is characterized by a non-normal fluid accumulation located in the peritoneal cavity, which can be acute or chronic in SLE, and may cause various symptoms such as abdominal distension [2,3,12,16–18,20–22,25,26,30] abdominal discomfort [14,30] or abdominal pain [2,3,12,14,20,22,25,36,63,146].

Marked ascites has also been attributed to chronic lupus peritonitis, characterized by the insidious onset of massive, painless ascites, and found to be unrelated to disease activity [3]. In SLE patients, ascites and/or effusions are more frequently a complication of nephrotic syndrome rather than SLE peritonitis [5].

The most common exams performed were computed tomography [3,6,9,12,18,20–23,25,27,32,36,40,42,48,63,69,72,146] followed by ultrasound [3,7,16,17,21,25,30] radiography [9,13,16,17,21,25,30] and colonoscopy [9,13,14,17,22,25,30].

Association with disease activity has been reported in most studies [3,6,12–14,17,18,20,21,32,36,40,48,63].

The most recurrent laboratory findings were positive anti-nuclear antibody (+) [140,143,144], proteinuria [140–145], i Serum level of C4 [140–143,145], i Serum level of C3 [140–143,144], anti-DNA (+) [140–145], serum albumin [144,145], anti-SSA antibody and anti-SSB antibody (+) [143,144].

Table 4

| Signs and Symptoms | Colitis | Diarrhea | Mild hepatic dysfunction | Abdominal pain | Enterocolitis | Enteropathy | Fever | Nausea | Abdominal sensitivity | Serositis |
|--------------------|--------|----------|--------------------------|---------------|--------------|-------------|-------|--------|---------------------|----------|
| Image exams        | CT scan | Ultrasound | 99 mTc-HAS | Radiography | Gastroendoscopy | Colosonoscopy |
| Main Laboratory findings | | | | | | |
| Medications | Corticosteroids | Cyclophosphamide | Azathioprine | Cyclosporine | Hydroxychloroquine | Mycophenolate Mofetil | Rituximab | Intravenous fluids | |
| Clinical progression | Clinical improvement | Death |
| Type of Study | Case report | Retrospective study |

Marked ascites has also been attributed to chronic lupus peritonitis, characterized by the insidious onset of massive, painless ascites, and found to be unrelated to disease activity [3]. In SLE patients, ascites and/or effusions are more frequently a complication of nephrotic syndrome rather than SLE peritonitis [5].

The most common exams performed were computed tomography [3,6,9,12,18,20–23,25,27,32,36,40,42,48,63] followed by ultrasound [3,7,16,17,21,25,30] radiography [9,13,16,17,21,25,30] and colonoscopy [9,13,14,17,22,25,30].

Association with disease activity has been reported in most studies [3,6,12–14,17,18,20,21,32,36,40,48,63].

The most recurrent laboratory findings were positive anti-nuclear antibody (+) [2,5,6,11–14,17,18,20,21,23,25–27,36,69], low level of C3 [5,6,12–14,16–18,27,30,36] low level of C4 [5,6,12,13,16–18,21,36] and increase of CA-125 [12,13,17,18,23,48,146].

Most SLE patients received corticosteroids [2,3,5,7,9,10,12–14,16–18,20–23,25–27,30,42,46], hydroxychloroquine [13–18,20,21,26], azathioprine [10,14,20–22,30], cyclophosphamide [2,5–7,17,20,26], mycophenolate mofetil [7,14,16,20,23] and rituximab [7,14,16].

Although clinical improvement was the most frequent outcome
Outcome of pancreatitis is difficult to determine due to many case reports that may have publication bias. Most studies confirm that it is a life-threatening manifestation. In a literature review, corticosteroids were shown to decrease mortality [14].

Cohort studies show a higher frequency of chronic pancreatitis and complications. The overall mortality of pancreatitis in SLE is around 30% associated with other features of active SLE (macrophage activation syndrome, central nervous system manifestations), hypocalcemia, and pancreatic complications [18].

Comparing pancreatitis in childhood onset to adult onset SLE, the first group presents a higher prevalence, a higher disease activity score, more complications and greater mortality rate [17]. We previously reported a case series of acute pancreatitis (AP) and macrophage activation syndrome (MAS) in childhood (cSLE) patients [52].

Protein-losing gastroenteropathy is a clinical syndrome suspected in the presence of hypoalbuminemia without significant proteinuria, severe liver disease, malabsorption, or poor oral intake [5,60-64,66-71,74-86,88-99,103]. Protein-loss through the intestinal tract is usually diagnosed in an advanced stage with varying degree of edema and loss commonly with initially symptoms of diarrhea or abdominal pain [88]. Hypoalbuminemia is the characteristic laboratory finding, however serum cholesterol may be elevated, and lymphatic leakage may result in hypoglobulinemia, lymphopenia and steatorrhea [88].

Diagnosis can be made by dosage of fecal alpha-1 antitrypsin, a serum protein that is not digested in the gastrointestinal tract and is excreted mostly intact in stool but radioisotopic tests are usually more specific and sensitive [100]. Although α1-antitrypsin clearance is a reliable and easy test, it cannot detect the location of the leakage and results can be influenced by diarrhea or gastrointestinal hemorrhage [101]. False positives of 99 mTc HSA may result from active gastrointestinal bleeding and in vivo breakdown of 99 mTc HSA yielding free pertechnetate from radiolabeling [99,103].

Several mechanisms may underlie the pathogenesis of protein losing enteropathy in SLE, including intravascular activation and conversion of complement, non-necrotizing vasculitis, acquired lymphangiectasia and increased microvascular/endothelial permeability [64,84].

Since most of the studies are case report, and no systematic approach for the diagnosis protein losing enteropathy has been made, it is difficult to determine predominant causes in the literature. When performed, biopsy usually showed non-specific low grade inflammation [63,79,86-88,90]. Enterocytes regulate their own permeability and secrete cytokines [64]. The lamina propria contains nerves and T and B-lymphocytes, plasma cells, macrophages, mast cells, eosinophils, and neutrophils [64]. Antigenic stimulus results in expansion of resident immune cell populations and the release of chemotactic molecules or cytokines in reaction and attracts circulating immunocytes. Thus, in the presence of an altered immune system activity, such as in SLE flare, this mechanism may lead to increased permeability in the intestinal mucosa [21,62,64,65,71-74,76,79-87,90,98,102,103].

Literature review has shown response to corticosteroid and other immunosuppressants. Beneficial role of octreotide and microcomplement consumption test (MCT) has also been described [71,75,85]. Octreotide is potentially able to reduce microvascular intestinal blood flow, therefore decreasing local lymph formation and lymphatic flow. In addition, octreotide binds to somatostatin receptor SST2RA and exerts an immunomodulatory action [75]. MCT may be beneficial in protein-losing enteropathy because they are better absorbed than long chain fatty acids and they are transported by portal blood to the liver bypassing the lymphatic system [75].

There are only few reports of acalculous cholecystitis in SLE, making estimate prevalence difficult. It is a rare manifestation and usually associated with active SLE features. Histopathology varies from medium-size vasculitis to thrombotic microangiopathy associated with aPL in some articles, as written in the results. Corticosteroid and immunosuppressants have been used, but may not avoid cholecystectomy.

Table 5

| Symptoms            | Acute abdomen [20] | Diarrhea [1,7,13,17,19,20,22,26,30] | Abdominal distension [10,14,15,18,19,21,25] | Abdominal pain [1,7,13,14,18,20,22,25,36,63,146] |
|---------------------|--------------------|--------------------------------------|---------------------------------------------|--------------------------------------------------|
| Laboratory findings| Positive anti-nuclear antibody [10,14,17,18,20,21,23,25,27,30,36,66] | Anti-dsDNA [10,14,17,18,20,21,23,25,27,30,66] | Low level of C4 [10,14,17,18,20,21,23,25,27,30,66] | Increase of Ca [12,13,17,18,23,46,146] |
| Exams              | Magnetic resonance imaging (MRI) [10,12,13], Computed Tomography (CT) [18,19,20,21,23,25,27,32,36,40,42,72,146] | Color Doppler [10,12,13,17,18,20,23,25,27,30,36,40,42,72,146] | Ultrasound [10,12,13,17,18,20,23,25,27,30,36,40,42,72,146] | Radiography [10,12,13,17,18,20,23,25,27,30,36,40,42,72,146] |
| Changes found by imaging exams | Intestinal edema [10,13] | Pleural effusion [10,12,13], Serositis [10,12,13,16,18,22,25,42,69] | Lupus enteritis [10,13] | Peritonitis [64,65,12,13,16,42] |
| Main Treatment     | Corticosteroids [10,12,13,16,18,20,23,25,27,30,42,146] | Azathioprine [10,14,20,22,23] | Cyclophosphamide [10,12,13,16,20,23] | Mycophenolate mofetil [10,12,13,16,20,23] |
| Disease progression| Death [91,11,26,73,146] | Clinical improvement [10,17,12-20,14,18,20,23,25,26,30,13,146] | Reported [7,3,10,12-14,16,18,20-23,25,26,33,146] | There were some cases of patient deaths reported [91,11,26,73,146] |

4. Discussion

The association of SLE with gastrointestinal autoimmune diseases is common, however mostly mild. Although severe gastrointestinal manifestations are uncommon, they are potentially life-threatening and have to be diagnosed timely to allow adequate treatment [5].

Acute pancreatitis has described to occur in 0.8% of patients screened for pancreatitis and 8% of patients with abdominal pain [7,14,16]. Common clinical symptoms as shown findings include nausea, vomiting, fever, absent bowel sounds and abdominal distension. In most studies pancreatitis may be associated with a history of active SLE, suggesting vasculitis as possible etiology [18,19,21,25-33,40,42-48].

This hypothesis is further corroborated with the improvement or resolution with corticosteroid or other immunosuppressant use. In a few cases associations with aPL have been made and thrombosis as etiology cannot be excluded, however it is important to remember that we included only studies with pancreatitis due to SLE and other causes such as mechanical, infections (e.g CMV) and drug related (corticosteroid, azathioprine) have to be always excluded [7,16].
prevalence of this manifestation difficult. Large studies report an overall prevalence of enteritis in SLE patients ranging from 0.2 to 9.7% and from 29% to 65% in patients who had acute abdominal pain [121, 133, 135, 122–120]. Marked ascites has been attributed to chronic lupus peritonitis, characterized by the insidious onset of massive, painless ascites and unrelated to disease activity [72].

Most studies are case reports and case series, making adequate prevalence of this manifestation difficult. Large studies report an overall prevalence of enteritis in SLE patients ranging from 0.2 to 9.7% and from 29% to 65% in patients who had acute abdominal pain [121, 133, 135, 136]. Imaging findings and biopsy help adequate diagnosis in most patients [115, 118–120, 122–124, 126, 128, 130, 134]. Although the above reviewed gastrointestinal manifestations are rare they have a potential for severe complications and even death. A high index of suspicions is necessary to differentiate disease activity from infection or other secondary causes. Corticosteroids (oral or intravenous) is still the first line treatment. Responses to cyclophosphamide, cyclosporine A, azathioprine, mycophenolate, methotrexate, IVlg, rituximab and anti-TNFα have been described, however no randomized control trial exist up to date to determine the most adequate immunosuppressant medication.

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Data sharing statement

Not applicable

Declaration of competing interest

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