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Gastrointestinal and Hepatic Disease in Systemic Lupus Erythematosus

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Summary

Gastrointestinal (GI) symptoms are common among patients with systemic lupus erythematosus (SLE) although only rarely are due to active organ system involvement from SLE itself. Rapid diagnosis and appropriate treatment of lupus enteritis and other GI manifestations of SLE are critical, due to the potential for organ and life-threatening complications. The three main variants of lupus enteritis are lupus mesenteric vasculitis, intestinal pseudo-obstruction, and protein losing enteropathy. These and other GI manifestations in patients with SLE are reviewed herein.

Keywords

lupus enteritis; enteral vasculitis; intestinal pseudo-obstruction; protein losing enteropathy

Introduction

Systemic lupus erythematosus (SLE) is a chronic, potentially severe, frequently disabling autoimmune disease with multi-organ involvement and a typically waxing and waning course. SLE is characterized by the production of a vast array of autoantibodies and is often considered the prototypical autoimmune disease. SLE has the potential to affect virtually every organ, including the gastrointestinal (GI) system, but most commonly presents with musculoskeletal, cutaneous, renal, cardiovascular, hematologic and/or central nervous system involvement. In contrast to other autoimmune diseases such as systemic sclerosis and inflammatory bowel disease (IBD), GI system disease activity is relatively rare among patients with SLE. But for that minority of patients, SLE activity involving the GI system can be severe and even life-threatening.

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Herein we review the types of GI system involvement associated with SLE. We include GI manifestations directly caused by SLE disease activity as well as those occurring in patients with SLE, but not directly attributable to active disease. This chapter is focused on the clinical manifestations of SLE-related GI involvement, with less emphasis on the therapies, which are covered in other chapters.

Who is at Risk for SLE GI Involvement?

The onset of SLE can emerge at any age, but most often occurs in young women between puberty and menopause. The incidence and severity of SLE is also disproportionately higher among certain racial and ethnic groups, such as people of African descent who live in North America or Europe.¹ In spite of its high impact on individual lives as well as high societal cost, little is known about the etiology of SLE.

The clinical symptoms and laboratory manifestations of SLE are extremely diverse. Early diagnosis can be difficult because of the insidious onset of predominantly nonspecific constitutional symptoms (e.g. fatigue, joint pains, and low-grade fever). This delay between symptom onset resulting from inflammation, subsequent diagnosis, and initiation of treatment can result in the development of organ system damage. The intent is to identify, when possible, and distinguish between active inflammatory features and features seen in long-standing disease due to damage.

GI symptoms are common and can occur in approximately half of people with SLE, often triggered by an underlying infection or by medication adverse effects.² The most prevalent GI symptoms are nonspecific, such as nausea and vomiting, anorexia, and abdominal pain.³ Other clinical clues are often needed to distinguish between GI manifestations stemming from an infection, medication side effects, active SLE, and/or a comorbid GI-related medical condition.

Defining Lupus Enteritis

By definition, lupus enteritis encompasses a wide spectrum of GI involvement. Lupus enteritis, as part of the British Isles Lupus Assessment Group (BILAG) disease activity index, is defined as either vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings.⁴ Abdominal pain is the most common presenting symptom of lupus enteritis, although presenting symptoms vary in character and severity (Figure 2). Studies show a range of 0.2 % to 5.8% of patients with SLE affected by lupus enteritis.⁵ The median age of onset is 34 years and it appears, on average, 34.3 months after the diagnosis of SLE; 85% of cases are females.

GI activity arising in isolation without additional manifestations of active SLE is highly unusual, as other organ system typically demonstrate evidence of ongoing involvement. Consequently, higher scores on disease activity measurements such as the BILAG or SLE Disease Activity Index (SLEDAI) are common for individuals affected by SLE enteritis. For example, 65% of SLE enteritis cases also carry a concomitant diagnosis of lupus nephritis, which contributes to the score on both instruments.

While the wide differential diagnoses for SLE patients presenting with GI symptoms complicates matters, it is important to identify lupus enteritis in a timely manner, due to its rare but serious course. For instance, the mortality rate among SLE patients with acute abdominal pain is 11%.⁵ There may also be subclinical presentations that go undiagnosed, as suggested by an autopsy study showing 60-70% of SLE patients with evidence of peritonitis, despite the fact that only 10% were recognized clinically.⁶

Pathogenesis and Pathophysiology

Oral ulcers are a classic and common manifestation of SLE. The three principle pathologic and pathophysiologic components of lupus enteritis include: lupus mesenteric vasculitis, intestinal pseudo-obstruction, and protein losing enteropathy. Pancreatitis and hepatobiliary involvement are more rarely encountered.

Oral Ulcers

The characteristic oral ulcers of SLE are painless, involve the upper (hard) palate, and are unrelated to systemic complement levels or levels of autoantibodies.⁷ These affect 25-50% of SLE patients,⁸ and are a component of the classification criteria for SLE, both for the American College of Rheumatology 1982 Revised Criteria as well as the Systemic Lupus International Collaborating Clinics Criteria,^{9,10} assuming they occur in the absence of other causes of ulcers. Other oral manifestations include hyperkeratotic lesions and lichenoid inflammatory mononuclear infiltrates appearing as macules and plaques on direct visualization.¹¹

Lupus Mesenteric Vasculitis

The term lupus enteritis was initially used to distinguish true mesenteric vasculitis versus other causes of intra-abdominal manifestations of SLE associated GI complications. Typically, true mesenteric vasculitis involves small vessel arteritis or venulitis.¹² Variance in appropriate nomenclature of the disorder has led to some confusion in describing the condition. Lupus arteritis, lupus enteritis, GI vasculitis, intra-abdominal vasculitis, and acute gastro-intestinal syndrome have all been used to describe the same entity.¹³ Primary concern for untreated disease is for development of bowel wall infarction, ischemia, or perforation.¹³ These complications hold a high rate of associated mortality. The underlying etiology for the enteric vasculitis continues to be unknown.

Reports vary regarding the prevalence of elevated anti-phospholipid antibodies, incidence of thrombosis, as well as systemic disease activity during episodes of lupus enteritis. The current understanding of these thrombotic events relates inflammation of the blood vessels to immune complex deposition as well as complement activation, leading to endothelial cell and platelet activation.² Pathology reports from thromboses complicating lupus enteritis have been non-specific. These show findings of multi-segmental involvement in multiple vascular territories.¹⁴ Typically the jejunum and ileum are the most commonly GI tract locations involved. Macroscopic examination reveals edematous, hyperemic, or ischemic bowel wall with or without infarction.¹⁴ Microscopic (histologic) examination is consistent

with infiltration of the submucosal and muscular layers and necrotizing vasculitis with pan-mural predominant eosinophilic, neutrophilic, or mixed infiltrate.¹⁴

Intestinal Pseudo-Obstruction

Intestinal pseudo-obstruction is defined as ineffective propulsion in the intestinal tract. This entity may be a misnomer, as manometry studies reveal more frequent GI involvement in the esophageal and gastric portions of the GI tract.¹⁵ Pathologic processes featured with intestinal pseudo-obstruction include intestinal vasculitis leading to visceral smooth muscle damage. Typical involvement implicates not only the smooth muscle, but also involves the enteric nerves, leading to visceral autonomic nervous system dysfunction, further compromising GI motility.¹⁶ Patients are subject to an increased risk of developing urinary tract infections. However, urinary tract infections can also be associated with impaired gastric motility independently of intestinal pseudo-obstruction. Main areas of involvement include the lower third of the esophagus as well as the antrum and duodenum.

Protein Losing Enteropathy

Protein losing enteropathy is defined as profound edema with hypoalbuminemia secondary to excessive protein loss from the GI tract. There are three main pathophysiologic mechanisms that have been proposed, and all three revolve around impairment of the permeability of the gut wall. The first mechanism is vasculitis leading directly to increased intestinal vessel permeability.¹⁷ The second mechanism is complement conversion leading to cytokine-mediated damage and vasodilation. The third proposed mechanism is intestinal lymphangiectasia. In order to establish the diagnosis of protein losing enteropathy, decreased dietary protein intake and excessive urinary losses must be ruled out.¹⁸

Association with Inflammatory Bowel Disease

Case reports and case series from around the world indicate an infrequent association between inflammatory bowel disease and SLE. However, overlapping symptoms can make differentiating the two diagnoses challenging.¹⁹ Observational studies have shown a prevalence of ulcerative colitis in SLE at 0.4%, which is comparable to general population controls.²⁰ In regards to Crohn's disease, the prevalence has been estimated at 0.7% to 0.3% of SLE patients,²⁰ which, in contrast to ulcerative colitis, suggest a possible association between SLE and Crohn's.

Reports of SLE among patients with IBD are confounded by the possibility of tumor necrosis factor inhibitor (TNFi)-induced lupus reactions. Since TNFi are the most common class of biologic used for IBD, it is difficult to discern whether characteristics of SLE represent drug-induced lupus/lupus-like syndrome or the systemic inflammatory disease unrelated to therapy. The pathophysiologic mechanism of drug-induced lupus is thought to invoke dysregulation of apoptosis and exposure of nuclear antigens.²¹ Elevated antinuclear antibodies (ANA) are commonly found in this patient population, however, symptoms of drug-induced lupus correlate more strongly with the presence of anti-dsDNA antibodies. A review found that 11-26% of adalimumab-treated IBD patients had a positive ANA, while 45% of infliximab treated patients had a positive ANA.²²

Association with Celiac Disease

Prior investigations have revealed a possible association between SLE and celiac disease. Celiac disease has an approximately 1% prevalence in the general population,²³ and has a tendency to coexist with other autoimmune conditions, including rheumatoid arthritis and type 1 diabetes, among other diseases.²⁴ There appears to be overlap in disease presentation as well as autoantibody positivity, as manifest through high ANA titers and HLA serotypes. There is also similar immune system activation in the form of elevated soluble interleukin-2 receptor and soluble intercellular adhesion molecule-1.²⁴ These clinical and biomarker overlaps feed the speculation of an association between SLE and celiac disease. Results from an epidemiologic study identified an increased prevalence of celiac disease in a SLE population, compared with age- and sex-matched controls (0.8% compared to 0.2%).²⁴ However, continued exploration on a verifiable clinical association is ongoing.

Lupus Associated Pancreatitis

Rates and definitions of pancreatitis among SLE cohorts vary across studies. Variations in laboratory assays may produce elevation of pancreatic enzymes without clinical symptoms compatible with pancreatitis. Estimates of prevalence range from 0.7% to 4% of SLE patients. Interestingly, some authors report that in up to 22% of the SLE population, pancreatitis is the initial presentation of SLE.² It is typically more prevalent in the first few years following the onset of SLE symptoms. Vasculitis leading to tissue necrosis, anti-phospholipid-associated thrombosis of pancreatic arterioles and arteries, and intimal thickening with immune complex deposition in the wall of the pancreatic arteries are possible underlying pathophysiologic causes of pancreatitis related to SLE.² Other causes of pancreatitis, including azathioprine-induced pancreatitis, must be ruled out prior to diagnosis. Some suggest a possible correlation between the presence of anti-La antibodies and the risk of pancreatitis.

Associated Hepatobiliary Manifestations

Elevated transaminases / transaminitis have been found among SLE patients with a frequency of between 15-55% .²⁵ As has been noted in a number of chapters in this volume, many of the medications used for SLE therapy can affect the liver and involve routine monitoring of liver enzyme tests as standard of care. Medications such as NSAIDs, methotrexate, azathioprine, mycophenolate and corticosteroids are possible culprits.²⁵ Other SLE-associated conditions include viral hepatitis, hemolysis, myositis, venous congestion, and veno-occlusive disease, especially in the setting of antiphospholipid antibody syndrome. Autoimmune hepatitis and primary biliary cirrhosis should be considered if anti-mitochondrial antibodies and elevated alkaline phosphatase are present.

In regards to biliary pathology, two main associated disorders are typically considered for the SLE patient: primary sclerosing cholangitis (PSC) and autoimmune cholecystitis. The underlying mechanism is thought to be subclinical vasculitic damage of the intramural capillary network.³ This may eventually progress to acute acalculous cholecystitis.

Serositis

Abdominal serositis (lupus peritonitis) is seen in 10% of SLE patients, though the 1982 Revised Criteria for Classification of SLE limits consideration of serositis to pleural and pericardial surfaces.⁹ In the vast majority of cases, SLE is simultaneously active in other organ systems.²⁶

Diagnostic Evaluation

The main modality for diagnosis of SLE-associated mesenteric vasculitis revolves around imaging. Typically, computerized tomography (CT) of the abdomen is the test of choice, with a recent study describing 98% of images showing bowel wall edema, and 71% percent demonstrating abdominal bowel wall enhancement (termed the “double halo” or “target sign”). Another 71% of images associated with study showed engorgement and increase visibility of the mesenteric vessels (Comb’s sign).¹⁴ (Figure 3) In addition, attenuation of the mesenteric fat can also be a feature. Serology and inflammatory markers in SLE-associated mesenteric vasculitis are typically non-specific. The mean C-reactive protein (CRP) has been reported as 2.0 mg/dl with low complement levels noted in 88% of the study population.² ANA was positive in 92% with a positive dsDNA antibody present in 74% of the study population. Anti RNP, anti-SSA, and anti-Sm was positive in 28%, 26%, and 24% respectively.² Proteinuria (greater than 0.5 g/24 hours or 2+ on dipstick) was found in 47% of SLE patients. An association with antiphospholipid antibodies (of concern due to concurrent mesenteric thrombosis) remains in dispute.¹⁴

For intestinal pseudo-obstruction, a combination of imaging and manometry may clarify the diagnosis. Imaging, in the form of abdominal plain radiographs, are usually sufficient to reveal evidence of intestinal obstruction. Follow-up endoscopy frequently does not reveal a specific structural cause of the obstruction.¹⁶ As was mentioned above, the lower third of the esophagus, the gastric antrum, and duodenum are particularly susceptible to pseudo-obstruction.

The diagnostic evaluation for protein losing enteropathy is most definitive when based upon 99 m Tc-HAS scintigraphy and fecal alpha-1-antitrypsin assays. A low serum albumin should be attributed to protein losing enteropathy only after the clinician has ruled out excessive urinary losses (which may be present in SLE glomerulonephritis) or decreased protein intake. Firm laboratory cutoffs for classifying the source of protein loss do not exist, however, levels of serum albumin below 22 g/L and urinary protein of less than 0.84 g/dl demonstrate high specificity and positive predictive value for identification of protein losing enteropathy.¹⁷ Correlations with anti-SSA positivity, and hypercholesterolemia have also been described. However, the evidence for 99 m Tc-HAS scintigraphy and fecal alpha-1-antitrypsin, is more specific than the aforementioned biochemical tests. In a study of 67 cases with 99 m Tc-HAS scintigraphy, protein leakage was identified in all cases with 58 cases revealing the anatomical location of the leakage¹⁸. In 49 of the cases, the area of leakage occurred in the small intestine. The investigators also subjected 24 of the participants to a 24 hour stool collection, and in all cases, a positive fecal alpha-1-antitrypsin clearance was present.¹⁸ Ultrasound and CT studies are also useful for identifying bowel wall obstruction and ascites.

When evaluating the differential diagnosis for GI symptoms in an SLE patient, endoscopy is commonly employed to complete a thorough diagnostic evaluation. Endoscopy with pathologic biopsy evaluation assists in the diagnosis of IBD as well as celiac disease. Direct biliary evaluation is typically at the discretion of specialist. Initial abdominal imaging in the emergency department typically consists of either abdominal ultrasound or CT of the abdomen, as these modalities can narrow down the broad differential posed by nonspecific GI symptoms.

Physical Exam Findings

Very few physical exam findings are specific to GI disease among patients with SLE. For example, mucocutaneous ulcerations involving the nose and mouth are common in the general population. In SLE, however, as noted above, the ulcerations tend to be painless and frequently involve the hard palate, buccal mucosa, or vermillion border. (Figure 1) Erythematous lesions often have edema and petechia of the hard palate.⁸ Most GI conditions present with traditional signs and symptoms of biliary and hepatic disease, and without features unique to SLE. Patients with peritonitis as a manifestation of SLE-related serositis can present with findings mimicking an acute abdomen and rarely may have evidence of ascites on exam.

GI Aspects Related to Treatment of SLE

The pharmacologic therapies for SLE are recognized for their potential to induce GI and hepatobiliary adverse drug reactions. These are summarized below.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used in SLE, particularly for symptomatic management of inflammatory joint pain, pericarditis and pleuritis. They are usually taken as needed, however, some patients may take them on a daily scheduled basis. NSAIDs, particularly non-selective COX-2 inhibitors, can lead to gastritis as well as ulcerations in the mucosa of the stomach and subsequent GI bleeding. In addition these medications can lead to a reversible elevation in hepatic enzymes.²⁹

Corticosteroids are also used for early bridging therapy in SLE, as well as flares. Prolonged administration necessitates monitoring for hyperlipidemia, fatty liver disease, and complications of central obesity.²⁹

Hydroxychloroquine is generally a well-tolerated first line therapy for patients with SLE, though it, too, has the possibility of producing GI adverse effects. These include abdominal cramping, nausea, vomiting, and diarrhea.²⁹ Azathioprine may cause similar GI adverse effects as hydroxychloroquine, and has been associated with pancreatitis. Methotrexate for SLE can occasionally cause hepatotoxicity and very rarely, cirrhosis. Bloodwork for toxicity monitoring is described in a companion chapter. Its administration is contraindicated in most forms of chronic hepatitis.³⁰ Patients on methotrexate should be cautioned regarding alcohol intake.

Cyclosporine and cyclophosphamide are both associated with GI intolerance. Patients on cyclosporine require routine liver enzyme measurement to monitor for hepatotoxicity. Both medications may benefit from antiemetic co-administration for improved tolerance.²⁹

Management of the Digestive/Hepatic Manifestations

Gastrointestinal manifestations primarily related to SLE activity follow the general tenants of SLE medical management: immunosuppressive therapy should be tailored to the severity of organ involvement. For potentially organ-threatening or life-threatening GI involvement, high dose corticosteroids are indicated. The dose and duration required for control of GI disease have never been examined through a randomized controlled trial, so current practice is governed by observational data and expert opinion.

For SLE-related mesenteric vasculitis, glucocorticoid therapy can range from 40 mg/day to 1 mg/kg/day. Dose and delivery is based on severity of symptoms as well as tolerance of oral intake. Case reports vary dramatically in their reported duration of glucocorticoid use, from 1-34 days.¹⁴ In cases with concomitant systemic disease (neurologic involvement, nephritis), cyclophosphamide has been used successfully with dosages ranging from 500 mg/m² to 750 mg/m² intravenously. Time to symptom resolution averaged around 7-10 days.¹⁴ Maintenance therapy has consisted of varying regimens of azathioprine, mycophenolate mofetil, and (less frequently) hydroxychloroquine. Other maintenance therapeutic considerations include tacrolimus and rituximab. Tacrolimus was also shown to be effective in recurrent refractory lupus enteritis in a case study.³¹

As is the case for mesenteric vasculitis, first line medications for intestinal pseudo-obstruction are also glucocorticoids. Dose and duration of therapy from case reports have varied, ranging from 5 mg/day of prednisone to 1 mg/kg/day of methylprednisone. Symptoms typically improved in 7-10 days with improvement in manometry between 3-8 weeks.¹⁵ Four out of 5 cases reported in a case series showed complete remission at 48 months.

Dosages of 1 mg/kg/day of IV glucocorticoid or prednisone oral equivalent have also been used in protein-losing enteropathy. Cyclophosphamide, mycophenolate mofetil, and methotrexate have also been used with some success.¹⁷ In addition, diets high in protein and medium chain triglycerides have been thought to be helpful in protein-losing enteropathy.¹⁸ Resolution was considered complete if serum albumin was greater than 35 g/dl and partial if greater than 30 g/dl.¹⁷

Surgical emergencies should be ruled out at the time of acute presentation. This includes bowel infarction, perforation, or ischemia. In addition, specialty care should be considered for advanced hepatobiliary manifestations.

Conclusion

GI disease may complicate SLE and is an important cause of morbidity and mortality. Oral ulcers are a cardinal feature of SLE. Distinguishing GI involvement from active SLE versus other causes is critical since therapy ranges from aggressive immunosuppression for lupus

enteritis, to lowering immunosuppression while starting antimicrobial therapy in settings where infection is the culprit. Treatment strategies for GI and hepatic disease in SLE are based on limited data (primarily small, uncontrolled series and case reports) and the experience from other connective-tissue disorders.

Continued investigations into the pathogenesis and treatment of SLE-related GI and hepatic involvement are needed to improve morbidity and mortality outcomes for patients with SLE.

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Key Points

- Lupus associated enteritis is a rare feature of SLE but has morbidity and mortality implications.
- Pathophysiology of lupus enteritis involves a vasculopathic process in the bowel wall with extension to the mesenteric plexus.
- Presenting signs and symptoms of lupus enteritis are often non-specific, but rarely present without other evidence of active SLE.

Figure 1.
Patient with SLE having painless oral ulcerations apparent on the upper palate.

Figure 2.
Incidence of symptoms at presentation with lupus enteritis ¹⁴

(Combs Sign) Engorgement and increased visibility of the mesenteric vessels ¹⁴

(Target Sign) Enhancement and thickening of bowel wall ¹⁴

Figure 3.
Abdominal CT findings of lupus enteritis.

Table 1

Anatomic distribution of GI involvement among patients with SLE

Organ	Involvement	Evidence	Citation
Mouth/Pharynx	Oral Ulcers	Review Article	8
Esophagus	Dysphagia Esophageal Dysmotility Gastric Reflux Bullous Epidermolysis Ulcerative Esophagitis	Review Article	25, 3, 27
Stomach	Peptic Ulcer Disease Gastric Enteritis Dyspepsia	Review Article	3,27
Pancreas	Acute Pancreatitis	Review Article	2,27
Liver	Hepatomegaly Type One Autoimmune Hepatitis Steatosis Nodular Regenerative Hyperplasia	Review Article	2,3
Gall bladder	Primary Sclerosing Cholangitis Autoimmune Cholangiopathy Acute Acalculous Cholangitis	Review Article	3
Small Intestine	Celiac Disease Mesenteric Vasculitis Protein Losing Enteropathy CMV Enteritis Intestinal Pseudo-obstruction	Case-control	2,3,24
Colon	Crohn's Disease Bowel Perforation Pneumatosis Cystoides Intestinalis Benign Pneumoperitoneum	Review Article	3,20
Rectum, Anus	Ulcerations	Case Study	28
Other	Appendicitis Primary Lupus Peritonitis Splenomegaly Ascites	Review Article	3