

Gastrointestinal Manifestations in Patients with Systemic Lupus Erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disorder of unknown etiology. Women of childbearing age are affected approximately nine times more often than men. Its presentation and course are highly variable, ranging from mild to fulminant systemic disease. Any organ can be affected by SLE. Although less common than in other systems, such as the skin, joints, and kidneys, 40%–60% of SLE patients have gastrointestinal (GI) involvement. SLE can affect any part of the GI tract, from the mouth to the anus. GI manifestations can be caused by SLE, medication-related side effects, or non-SLE causes including infection. This article reviews the most common types of GI involvement associated with SLE.

Keywords: systemic lupus erythematosus, gastrointestinal manifestations, oral ulcers, inflammatory bowel disease

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem inflammation, variable clinical manifestations, and a variable clinical course. A study noted that approximately 70% of SLE patients had relapsing-remitting disease, while the remaining 30% had either prolonged remission or persistently active disease.¹ Moreover, the etiology of SLE remains unknown. Epidemiological studies conducted between 1975 and 2000 have reported the incidence of SLE to be 1–10 per 100,000 person-years and the prevalence to be 20–70 per 100,000 person-years.² SLE can potentially affect nearly every organ, including the gastrointestinal (GI) system, which is not as common as musculoskeletal, cutaneous, renal, cardiovascular, hematological, and/or central nervous system involvement. GI manifestations are sometimes the initial presentation of SLE, and when this is the case, SLE diagnosis would likely be delayed.³ Furthermore, GI involvement associated with SLE is clinically significant since it can be fatal if not properly diagnosed and treated.⁴ Moreover, in an Australian population-based study, patients with SLE had an increased likelihood and risk of mortality associated with GI and hepatic diseases.⁵

The potential severity of SLE-related GI manifestations is concerning, considering that more than 50% of SLE patients develop GI symptoms at some point during the course of illness.⁶ The incidence and prevalence of GI involvement during the course of SLE disease vary widely. This could be due to less attention being paid to GI manifestations than other organ symptoms, such as lupus nephritis. According to an autopsy study, 60–70% of SLE patients had evidence of peritonitis, whereas only 10% showed clinical manifestations throughout their lives.⁷ In the majority of previous studies, the prevalence of GI symptoms in SLE patients has ranged from 15% to 75%.^{8,9}

SLE can affect any part of the GI tract, from the mouth to the anus. The liver can also be affected by SLE; abnormal liver function test results were obtained in 23%–79% of cases and hepatomegaly in 39%–40%.^{10,11} In terms of risk factors for GI involvement in SLE, Xu et al found that SLE patients with Raynaud's phenomenon, hypocomplementemia, and positive anti-neutrophil cytoplasmic antibody were at increased risk of developing GI complications.¹²

The most prevalent GI symptoms are non-specific and include nausea, vomiting, anorexia, and abdominal pain.⁷ Abdominal pain can present acutely, and its underlying causes can be mesenteric vasculitis, gastroenteritis, hepatobiliary disease, pancreatitis, or appendicitis.^{10,11} Most patients are being treated with steroids or immunosuppressive drugs,

which mask the physical features of perforation and ischemia. Delay in diagnosis should be avoided; according to Zizic et al, abdominal pain was experienced by two-thirds of SLE patients for an average of 34 days (range 11–66 days) before acute abdominal crisis,¹³ which has been associated with a high mortality rate of 9%–11%.⁹

The effect of GI involvement on SLE disease activity and damage accrual has been insufficiently researched. Additionally, the SLE Disease Activity Index (SLEDAI) does not weigh in GI manifestations; therefore, GI involvement may occasionally be underestimated. According to Fawzy et al, there was no significant difference in SLEDAI scores between patients with GI symptoms and those without GI symptoms. However, patients with GI symptoms had higher SLEDAI scores (mean 14.1 ± 4.7) compared with (mean 12.4 ± 4.7) for those without GI symptoms.³ Although patients with lupus enteritis, most commonly to have high SLEDAI scores. Furthermore, the development of GI symptoms without additional manifestations of active SLE is uncommon, as other organ systems typically exhibit signs of ongoing involvement.¹⁴

Regarding GI manifestations associated with SLE and damage accrual, a recent Spanish retrospective cohort study of 3658 SLE patients found that 3.7% developed GI damage.¹⁵ This low prevalence is consistent with the findings of previous cohort studies.^{16,17} Furthermore, they observed that GI damage is associated with poorer prognosis and clinical involvement of other target organs in SLE, such as vasculitis, renal disease, and serositis.¹⁶

This review provides an overview of common GI involvement in SLE.

Involvement by Location

Oral Cavity

Oral ulcers are one of the most common features of mucosal involvement in SLE, affecting 7%–52% of lupus patients.¹⁸ They are one of the diagnostic criteria for SLE.^{19,20} The most commonly involved sites are the buccal mucosa, hard palate, and vermillion border. In the majority of cases, they are painless. According to one study, 82% of patients had painless mouth ulcers,²¹ while several other studies had reported higher frequencies of painful ulcers.²² This disparity may be explained by differences between types of oral ulcer. Erythematous lesions are not typically painful, unlike discoid and ulcerative lesions.¹⁷ Oral ulcers can also be caused by aphthous stomatitis, infections, or medication side effects, which are factors other than SLE. Unfortunately, the majority of studies do not distinguish between subtypes of painful lesions, prompting the need to address this blind spot in future studies.

The risk factors of developing oral ulcer in SLE have been relatively unexplored as well. Raymond et al conducted a cross-sectional study of 99 patients with SLE, and they found that patients who smoked had increased odds of mucosal ulceration (OR 3.31, 95% CI 1.36–8.05; $p=0.008$).²³ Beyond behavioral factors, oral lesions and ulcers also seem to be more prevalent in individuals with severe disease, and their prevalence has been linked to the overall activity and organ-related processes of SLE.²¹ However, they are unrelated to systemic complement or autoantibody levels.⁷

Limited information is available about oral ulcers and lupus outcomes. Oral ulcers have been reported as potential predictors of systemic vasculitis and worse prognosis.²⁴ Unfortunately, there are currently no trials showing the effectiveness of systemic medications in the treatment of oral lesions. Treatment includes antimalarial medications as the first-line therapy, and corticosteroids and immunosuppressive medications such as azathioprine can be effective too. Other medications, such as thalidomide, dapsone, and cyclosporine, are alternatives if the ulcers are refractory.¹⁸

Esophagus and Stomach

Dysphagia, Esophageal Motility, and Gastroesophageal Reflux Disease

Esophageal involvement is less common in SLE than in mixed connective tissue disease. One study found that 1%–6% of SLE patients experienced dysphagia.⁸ Sultan et al estimated this frequency to be between 1% and 13%.¹⁸

There are numerous causes for dysphagia. One cause is esophageal dysmotility, experienced by 21%–72% of patients with SLE.⁹ Manometry studies have shown that 10%–32% of SLE patients had functional abnormalities of the esophagus.^{25–28} However, manometric findings of esophageal dysmotility have not been linked to overall clinical activity, disease duration, or treatment.²⁶ Another possible explanation for dysphagia is gastroesophageal reflux disease, which is

estimated to affect 11%–50% of SLE patients.¹⁸ Additional factors including drugs and reduced saliva production associated with Sjogren's syndrome may also play a role.

Dysphagia symptoms are associated with secondary Raynaud's phenomenon. According to Gutierrez et al, the presence of peristalsis dysfunction was strongly associated with Raynaud's symptoms in patients with SLE and mixed connective tissue disease,²⁵ though this disagrees with results of a more recent study.²⁹ Additional research is required to address this controversy.

The pathophysiology of esophageal motility abnormalities remains unclear. According to Castrucci et al, it could be caused by ischemic vasculitis, muscle atrophy, or an inflammatory response in the esophageal muscles.²⁶ Motility changes are most commonly observed in the upper one-third of the esophagus; however, the lower esophageal sphincter does not show any major functional alterations. This is unlike observations for systemic sclerosis.²⁹

Prospective controlled studies are essential for guiding the management of dysphagia and reflux symptoms in SLE patients. However, patients with SLE with esophageal dysmotility or reflux can be treated similarly to those with systemic sclerosis. Proton pump inhibitors, prokinetic medicines, and high-dose H₂-blockers are the mainstay of symptom management techniques. Immunosuppressive therapy is also required for esophageal lesions that are histologically determined to be vasculitic in origin.¹⁸

Gastric and Peptic Ulcer Disease

With regards to stomach involvement, gastritis and peptic ulcer disease are the most common gastric pathologies affecting lupus patients that can be induced by non-steroidal anti-inflammatory medications (NSAIDs) or corticosteroids.³⁰ The incidence of gastritis and peptic ulcer disease remains unknown. In one study including 51 lupus patients presenting with an acute abdomen, 6% had a perforated duodenal ulcer.³¹ In another study of 13 SLE patients, who had been hospitalized with significant abdominal discomfort, one patient also had perforated peptic ulcers (8%).³² In that study, the use of NSAIDs or gastroprotective agents was undocumented. The degree to which SLE itself played a role is also unknown. A Russian study compared the gastric biopsies of 27 children with SLE to those of 12 children with chronic gastroduodenitis. They found that the children with SLE had more inflammatory mucosal changes, including higher levels of fibroblasts and small vessel IgG immune complex deposition during disease flares.³³ This demonstrates how SLE affects gastritis.

Helicobacter pylori is a well-known risk factor for peptic ulcer disease, and the correlation between *H. pylori* infection and gastroduodenal ulcers with SLE has been insufficiently analyzed so far. A cross-sectional study, including 118 people with SLE from April 2017 to June 2018, concluded that *H. pylori* infection frequency in SLE patients was 39%. However, there was no difference between patients with and without *H. pylori* infection in terms of gastric ulcer or dyspeptic symptoms.³⁴ Similar findings were reported in another recent study featuring 65 SLE patients. Those who tested *H. pylori* positive in a polymerase chain reaction test had a lower frequency of gastric erosions.³⁵ Additional research is required to assess the relationship between *H. pylori* infection and the risk of gastroduodenal ulcers in lupus patients. Moreover, it remains to be clarified whether the use of NSAIDs has a positive or negative effect on *H. pylori*.

Pernicious Anemia

Although controversial, pernicious anemia has been reported in patients with SLE.^{36,37} In one study, while 23% of SLE patients had quite low cobalamin levels, anti-intrinsic factor antibodies were found in only 3 of 30 SLE patients and 0 of 45 controls.³⁶ Another study of 43 female SLE patients verified the rarity of pernicious anemia.³⁸

Small Intestine and Colon

Lupus Mesenteric Vasculitis

Lupus mesenteric vasculitis (LMV) has been described with a variety of terminologies, including lupus arteritis, lupus enteritis, GI vasculitis, intraabdominal vasculitis, and acute GI syndrome.³⁹ The global prevalence of LMV range from 0.2% to 9.7% among all SLE patients and 29% to 65% in SLE patients with acute abdominal pain.⁴⁰ LMV is associated with severe complications, such as perforation, infarction, and bleeding, which raise the mortality rate up to 50%.^{13,31} LMV commonly presents with acute abdominal pain and other associated symptoms, including nausea, vomiting,

anorexia, postprandial fullness, diarrhea, hematemesis, and melena.¹⁴ Multiple studies indicate that lupus patients with active disease, elevated SLEDAI, and acute abdominal pain are more likely to have LMV. Medina et al evaluated the link between the etiology of abdominal pain in 51 patients with SLE and the disease activity as measured using the SLEDAI. Patients presenting with GI vasculitis or thrombosis had higher scores than those with acute abdominal pain unrelated to SLE.³¹ Kwok et al showed that both SLEDAI score and mean prednisolone dose at the time of admission for acute abdominal pain were greater in patients with lupus enteritis (LE). This indicated a more active disease state.⁴¹ A recent study conducted outside of Asia by Buck et al further confirmed this. In their sample of 75 patients admitted with subacute abdominal pain, only those with a SLEDAI score of >8 developed LE.⁴²

The pathogenesis of LMV is unclear but has been attributed to immune complex deposition and complement activation, with subsequent submucosal edema.⁴³ According to a study assessing autoantibodies, SLE patients with LMV had considerably higher serum levels of anti-endothelial cell IgG than those with other SLE signs or healthy controls.⁴¹ The risk factors for LMV are still unknown. Proposed trigger factors included bacterial infections that alter intestinal flora, cytomegalovirus infection, eosinophilia, NSAIDs, chemicals, metallic particulates, animal viruses, helminth infection, caffeine, phosphodiesterase-4-inhibitors, adenosine diphosphate, certain foods, and herbal medicines.⁴¹ Future well-designed prospective cohort studies will provide further information on the factors triggering LMV.

Although considered a type of visceral or serosal vasculitis, LMV is rarely verified histologically, making computed tomography (CT) the diagnostic gold standard. Patients with LMV frequently exhibit focal or diffuse intestinal wall thickening, dilated intestines, mesenteric edema, ascites, the comb sign (which indicates engorgement of the involved vessel), and abnormal wall enhancement.^{44,45} CT scans have been shown to be more effective in detecting areas of intestinal thickness and vascular engorgement, both of which may be signs of vasculitis. In lupus, the superior mesenteric artery (especially in the jejunum and ileum) is most frequently affected by vasculitis.^{41,42,44}

After diagnosis, an effective treatment for LMV involves corticosteroids used in high doses, which are then lowered gradually.^{41,46} Immunosuppressive agents are requested in some cases; however, there have been no controlled trials yet to advise this treatment. On the other hand, cyclophosphamide (CYC) has been used in several cases with success, and there is also a trending idea that CYC can prevent recurrences.^{47,48} Surgical intervention should be considered when no rapid response to immunosuppressive agents is observed to prevent potential complications like intestinal perforation or significant bowel ischemia. According to Medina et al, all 33 LMV patients who received surgery between 24 and 48 h survived, while 10 of 11 LMV patients who underwent surgery after 48 h died.³¹ Large multicenter trials are required to evaluate the outcomes of those who receive medicinal therapy against those who undergo surgery early.

Intestinal Pseudo-Obstruction (IPO)

IPO is an uncommon condition characterized by intestinal hypomotility and symptoms resembling mechanical bowel obstruction in the absence of a mechanical or organic etiology.⁴⁹ Cacoub et al described the first lupus patient with a confirmed IPO case in 1993.⁵⁰ IPO can develop as the initial manifestation of SLE, which makes diagnosis challenging. It can also develop as a complication of diagnosed SLE. In a case series from Hong Kong, 2 of 6 patients exhibited IPO symptoms for about 2 years prior to the onset of additional SLE symptoms and subsequent lupus diagnosis.⁵¹ According to a recent study, 2% of SLE patients were admitted to the hospital with SLE IPO.⁵² The incidence of IPO was 1.96% among SLE patients and in-hospital mortality was 7.1%. Additionally, 57.6% of patients with SLE IPO presented with this disease as the first sign of SLE.⁵²

However, the pathophysiology of IPO in SLE remains unclear. Possible pathogenic mechanisms include vasculitis of visceral smooth muscles, which causes muscle injury and hypomotility.^{4,52,53} The pathogenic mechanism of IPO may also be related to those of genitourinary complications such as ureterohydronephrosis, which may be caused by either intrinsic myopathy or neurogenic pathology (attributable to either vasculitis or circulating smooth muscle autoantibodies).^{51–53} Other findings, such as gallbladder wall thickening, biliary tract dilatation, and pancreatic duct dilatation, have also been previously reported in association with IPO.^{52,53} Furthermore, SS-A/Ro autoantibodies are present in approximately two-thirds of SLE IPO patients.⁴⁷ According to a few case reports, there was also an association between the presence of anti-SSB antibodies in lupus patients and IPO.^{51,54}

IPO can be diagnosed based on clinical manifestations, physical findings, and radiological examinations such as abdominal radiography and CT. Clinical manifestations of SLE IPO include abdominal pain and distension, nausea, vomiting, constipation, and/or diarrhea.⁵⁵ On plain abdominal radiographs, there are multiple air-fluid levels, dilated bowel loops (often of the small bowel), and possibly thickened bowel walls. CT would show dilated bowel loops with air-fluid levels, bowel wall thickening, and ascites.⁵⁶ Manometry frequently reveals abnormalities across the GI tract including aperistalsis of the esophagus, as well as hypomotility of the stomach and small intestine.⁵¹ Because the disease is deep within the smooth muscle layer, intestinal mucosal biopsies may come back normal or demonstrate non-specific edema.⁵⁷ High-dose corticosteroids are usually effective in treating IPO caused by SLE.^{8,51,58} In some instances, immunosuppressive drugs such as azathioprine, cyclosporin A, and cyclophosphamide are required.^{51,59–62}

Protein-Losing Gastroenteropathy (PLE)

PLE is an uncommon clinical syndrome characterized by significant hypoalbuminemia and substantial edema due to excessive serum protein loss from the GI tract, in the absence of nephrotic syndrome, liver disease, malabsorption, and low protein intake.^{6,12,17} According to a large Chinese study, the prevalence of PLE in lupus patients was 3.2%, but in another series, the frequency of PLE was reported to be 7.5%.^{63,64} A smaller case series also previously reported prevalence of SLE-related PLE as 1.9%.⁶⁵ PLE may also be an initial manifestation of SLE, while affecting women more frequently than men.^{63,65,66} PLE has been commonly reported in patients with severe SLE and multiple organ involvement.^{65,67}

Although the pathogenesis of PLE is unclear, several theories of its etiology have been proposed. One theory is that mesenteric and intestinal artery vasculitis increased intestinal vascular permeability to proteins. Other proposed causes included cytokine-mediated mucosal injury from intravascular complement conversion and activation, as well as intestinal lymphangiectasia.^{63,65,68,69}

The main clinical features of PLE include peripheral pitting edema, ascites, pleural effusion, and pericardial effusion. GI symptoms associated with PLE are infrequent and include nausea, vomiting, and diarrhea.^{63–65,70} PLE diagnosis depends mainly on the exclusion of other causes of hypoalbuminemia. Recently, Tc-99m albumin scintigraphy has become the diagnostic tool of choice for patients with PLE. It is the most commonly used diagnostic approach for detecting protein leakage and has a high sensitivity of 95.7%. Tc-99m albumin scintigraphy can also localize protein leakage and track treatment effectiveness.^{4,64,70} However, a negative result cannot exclude PLE. In a previous study, two SLE patients had negative scans, but fecal alpha-1- antitrypsin clearance (AATC) tests subsequently confirmed a PLE diagnosis.⁶⁴ In terms of treatment, the majority of patients respond well to corticosteroids, but when these are ineffective, immunosuppressive medications may be added to the treatment plan.^{63,65} In addition to steroids, the majority of patients responded to treatment with azathioprine, cyclophosphamide, or both.⁷⁰ Mok et al believed that long-term maintenance therapy with low-dose prednisolone and azathioprine could decrease the recurrence rate.⁶³ However, there has yet to be a controlled study regarding the optimal immunosuppressive drug or even the duration of treatment.

Inflammatory Bowel Disease (IBD)

It is uncommon to concurrently diagnose IBD and SLE. Case reports and case series account for the majority of data on the relationship between the two. Diagnosis is challenging because these two illnesses have similar clinical and immunological characteristics. Observational studies indicate that the prevalence of ulcerative colitis (UC) among patients with SLE is 0.4%, while the prevalence of Crohn's disease (CD) ranges from 0.3% to 0.7%.^{71,72} IBD can be diagnosed at any time during the SLE course; however, according to published data, SLE has usually been diagnosed first.⁷³ Drug-induced lupus after IBD treatment with sulfasalazine or TNF inhibitors should also be considered.

Clinically, patients can present with abdominal pain, diarrhea, and other known IBD symptoms. Regarding SLE features, patients with both IBD and SLE have no neurological involvement, and are less likely to have photosensitivity, arthritis, and serositis than patients with SLE alone. Patients with both diseases commonly have positive antinuclear antibody (ANA) and anti-dsDNA.^{74–76}

The pathogenesis of the two autoimmune diseases in the same patient might be explained by genetic factors, along with exposure to environmental triggers. HLA DR2 is more prevalent in patients with SLE and UC.^{77,78} In fact, whether

genetic susceptibility links SLE and CD is debatable. A pooled study of released and unpublished data on 1305 SLE cases analyzed genotyped CARD15 risk alleles; results show that only the CARD15 (908R) IBD risk allele may significantly enhance the risk of SLE.⁷⁹ Another study from 2003 found no proof that CARD15 mutations increased susceptibility to SLE, despite being linked to Crohn's disease.⁸⁰

Diagnosis of IBD in lupus patients requires imaging and endoscopic studies, in addition to histological findings, to confirm the diagnosis and to rule out other differential diagnoses.⁷⁶ Treatment includes steroids, hydroxychloroquine, and azathioprine, with the majority of patients showing good responses and relatively favorable prognoses for both SLE and IBD.⁷⁴

Pancreas

Pancreatitis is a rare complication of SLE. Its prevalence is estimated to range from 0.7% to 4% in SLE patients,^{81,82} with a reported incidence of 0.4 to 1/1000.^{83,84} It may occur at any time during the SLE course, commonly a few years after diagnosis, or it might be the first sign of SLE as observed in several cases.^{85,86} It is more prevalent in women and in younger individuals.⁸³ According to Breuer's study, 88% of the 27 lupus patients with pancreatitis were women, and their median age was 27.82 years.⁸³ In addition, many of these patients had a lengthy history of active SLE with extra-organ involvement and prolonged intensive medical treatment.⁸⁷

The underlying pathophysiology of SLE-related pancreatitis remains unclear. It could be secondary to vasculitis, which leads to tissue necrosis and antiphospholipid antibodies, resulting in thrombi or microthrombi occluding the pancreatic arteries and arterioles. Another possible underlying etiology could be immune complex deposition, complement activation in the pancreatic arterial wall, and intimal thickening.^{74,81} Furthermore, medications such as azathioprine, which is commonly used to treat SLE, are predisposing factors. Steroid use is thought to play a role in inducing pancreatitis in SLE patients.^{88,89} However, the relationship between pancreatitis and glucocorticoid administration is controversial because pancreatitis has been reported in both patients who used and did not use steroids.^{90–92} Regarding autoantibodies, the presence of anti-La antibodies is associated with an increased risk of pancreatitis as well.⁹³

Clinically, patients commonly present with abdominal pain, which is seen in approximately 90% of cases. Other features include nausea and vomiting, fever, absent bowel sounds, and abdominal distension.^{4,83,93} Diagnosis of SLE-related pancreatitis is based on clinical features, laboratory evidence of high serum amylase and lipase levels, and radiological findings. However, potential causes of pancreatitis other than SLE should be ruled out first, such as infection, diabetes, and drugs. Treatment includes immunosuppressive agents such as cyclophosphamide in combination with corticosteroids. Early administration of steroids has been associated with a 67% reduction in mortality.⁸³ Likewise in support of steroid use, another study observed a significant reduction in mortality among patients administered glucocorticoids (20%) versus those who were not (61%).⁸⁴ In serious cases, plasmapheresis and intravenous gamma-globulin infusion could also be useful.

Pancreatitis with SLE can have serious consequences on patient health. The overall mortality of pancreatitis in SLE is 27%, associated particularly with central nervous system and cardiac involvement, hypocalcemia, low complement levels, and pancreatic complications.⁸⁴ Additionally, approximately 22% of patients experience recurrent acute pancreatitis attacks, 12% develop complications such as pancreatic pseudocysts, and 5% to 14% become chronic.^{84,93} Just as with acute pancreatitis due to other causes, SLE-induced pancreatitis is treated with intravenous fluids, pain management, and electrolyte balance.

Liver

Liver involvement in SLE is common, although often asymptomatic or subclinical. However, this is usually uncorrelated with lupus activity. The presence of oral ulcers, cytopenia, double-stranded DNA antibodies, and thyroid disease have all been associated with increased risk of liver involvement in lupus patients.⁹⁴

Hepatomegaly has been observed in 39% of lupus patients, according to Runyon et al.⁹⁵ A review by Abraham et al in 2004 observed hepatomegaly rates of 12–55%.⁹⁶ Liver function abnormalities are also common in lupus patients, with a reported frequency of 25–50%.^{97,98} Numerous causes can be attributed to this, including the use of aspirin, NSAIDs, azathioprine, methotrexate, fatty liver infiltration brought on by corticosteroid therapy, diabetes mellitus, obesity, viral

hepatitis, and alcoholism. Takahashi et al identified liver dysfunction in 123 (59.5%) of 206 patients, with the following causes: drug-induced (30.9%), SLE-related (28.5%), fatty liver (17.9%), AIH (4.9%), PBC (2.4%), cholangitis (1.6%), alcohol (1.6%), and viral hepatitis (0.8%).⁹⁹ When secondary causes are excluded, lupus can be attributed as the underlying cause.

Previous reports have identified various frequencies of liver dysfunction in lupus patients and different underlying causes; for example, a retrospective study conducted by Runyon et al found that 124 out of 238 individuals showed abnormal liver function tests, with 43 matching the criteria for existing liver disease.⁹⁵ A randomized survey of 193 patients with SLE was further conducted by Suzuki et al, who found 78 patients (40.4%) with elevated transaminase levels; abnormal liver enzymes also indicated identifiable liver disease in 35 patients of the 78.¹⁰⁰ However, according to Suzuki and et al, the disease process was frequently less severe in the 9 discovered cases of lupus-induced liver inflammation than in patients with other underlying diseases such as fatty liver disease, AIH, and PBC.¹⁰⁰ In a prospective analysis, Miller et al also observed high liver enzyme levels in 23% of 260 patients with SLE who were followed up for 12 months.¹⁰¹ Fluctuations in alanine transaminase levels corresponding to SLE activity have been reported in some patients with SLE as well.^{102,103} Abnormal liver enzymes are discovered accidentally or incidentally in most patients with lupus. In such patients, detailed serial examinations, full laboratory, radiography work, and even liver biopsy in some cases are needed to identify whether the underlying cause is lupus itself or something else. Treatment is adjusted according to the cause.

Lupus hepatitis is a liver dysfunction related to lupus characterized by hypertransaminasemia owing to fluctuations in alanine transaminase levels, which is consistent with disease activity.¹⁰² Zheng et al found that the incidence of lupus hepatitis, according to the exclusion of all other liver etiologies, was 9.3%, and they noticed that lupus hepatitis was more prevalent in active SLE than in quiescent SLE (11.8% vs 3.2%).¹⁰⁴ The presence of serum anti-ribosomal P antibodies was also correlated with the occurrence of lupus hepatitis in 44% of patients with lupus hepatitis.^{105,106} Nonetheless, according to previous reports, the lupus hepatitis progression rate to end-stage liver disease is low.^{105,107}

Regarding diagnosis, histopathological findings further included mild portal infiltration (with lymphocytes, neutrophils, and plasma cells), hydropic degeneration of liver cells, steatosis, mild cholestasis, focal necrosis, and nodular cirrhosis with deposits of complement 1q.¹⁰¹ Deposits of complement 1q, visible with liver immunohistochemistry, correlate strongly with the diagnosis of lupus hepatitis and have been considered useful for differentiating lupus hepatitis from other associated liver diseases. Most patients with lupus hepatitis respond well to glucocorticoid therapy.¹⁰²

Conclusion

This review focuses on important GI manifestations that occur in SLE patients. GI involvement is common in lupus patients and ranges from mild and non-specific to severe and life-threatening. It could be caused by the disease itself or by other disease-related factors, such as medications. Physicians should be aware of those GI manifestations since early detection and treatment are crucial for better outcomes.

Although the GI symptoms of SLE are well-described in the scientific literature, their prevalence and severity are likely grossly underestimated. Insufficient research has been conducted on the effect of GI involvement in SLE patients in terms of disease activity and damage accumulation. In addition, treatment strategies for GI and hepatic disease in SLE are still based on limited data and inferences from other connective-tissue diseases. Controlled trials are thus required to inform and optimize treatment plans.

Disclosure

The author reports no conflicts of interest in this work.

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