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Gastrointestinal Manifestations Associated with Systemic Lupus erythematosus

M. Witt, D. Zecher, H.-J. Anders

Medical Policlinic, Ludwig-Maximilians-University Munich, Germany

Abstract
Gastrointestinal symptoms are often difficult to interpret in patients with systemic lupus erythematosus. Symptoms can develop either from symptomatic autoimmune tissue injury, complications of lupus-related organ dysfunction, infections, thrombembolic manifestations of anti-phospholipid antibody syndrome, medication or unrelated disorders. We describe the gastrointestinal manifestations of lupus and discuss the diagnostic approach and therapy.

Key words: Systemic lupus erythematosus, gastrointestinal, intestinal vasculitis, therapy

Introduction

Gastrointestinal symptoms are often difficult to interpret in patients with systemic lupus erythematosus (SLE). Symptoms can develop either from symptomatic autoimmune tissue injury, complications of lupus-related organ dysfunction, infections, thrombembolic manifestations of anti-phospholipid antibody syndrome, medication or unrelated disorders (Table 1). Thus, physicians commonly face the problem that immunosuppressive therapy may either be unnecessary or urgently required for the patient. In this review we address this diagnostic dilemma by describing typical gastrointestinal manifestations of lupus.

Table 1. Causes for symptoms and findings related to the gastrointestinal tract in lupus patients.

Mechanism	
Autoimmune tissue injury	vasculitis or fibrosis of the affected organ (e.g. painful oral ulcers, abdominal pain from serositis)
Infections	Either due to disease- or drug-induced immunosuppression (e.g. oral candidiasis, infective diarrhea)
Anti-phospholipid-antibody syndrome	Thrombosis or embolism (e.g. intestinal infarction)
Complications of organ dysfunction	End-stage failure of solid organs affected by autoimmune tissue injury (e.g. nausea in uremia or congestive heart failure)
Medication	See Table 2
Unrelated disorders	"lupus does not prevent other diseases"

General Approach to Lupus Patients with Gastrointestinal Symptoms

A proper medical history is essential in the evaluation of gastrointestinal symptoms in lupus patients. Information about present and past patterns of lupus manifestations, anti-phospholipid antibody status, coincident medical disorders, new medications, and compliance to immunosuppressive or anticoagulant therapy are crucial to make a correct diagnosis. Helpful laboratory parameters include C-reactive protein, blood sedimentation rate, C3 and C4 complement levels, antiphospholipid antibody status, white blood count, hematocrit, platelets, liver function tests, lactate, clotting tests, serum creatinine, and urinary sediment. An abdominal ultrasound exam helps to rule out polyserositis, pancreatitis, intraabdominal lymphoma, and assists in determining liver and spleen size. In patients with acute abdominal pain a computed tomography may reveal signs of intestinal vasculitis or mesenteric thromboembolism [1, 2] or may rule out other intraabdominal pathologies.

Drug-related Manifestations

A number of gastrointestinal symptoms may develop secondary to medication commonly used in lupus patients (Table 2). Discontinuing the suspected drug should be

Table 2. Important drug-related manifestations of the gastrointestinal tract in lupus.

Drug	Manifestation
antimalarials	lichenoid lesions in the oral cavity, hepatitis, elevated liver enzymes
cyclosporine	gingival hyperplasia, Candida infection
NSAIDs	erosions, (peptic) ulcers, bleeding, perforation, elevated liver enzymes
methotrexate	mucositis, hepatitis with elevated liver enzymes, Candida infection
azathioprine	hepatitis with elevated liver enzymes, Candida infection
cyclophosphamide	mucositis, Candida infection
steroids	fatty liver, Candida infection
mycophenolat mofetil	abdominal pain, diarrhea
alendronate (oral biphosphonate)	ulcerative esophagitis

considered before the patient is given unnecessary or potentially harmful immunosuppressive therapy.

The Lupus Patient with Symptoms Related to the Upper Gastrointestinal Tract

Oral Cavity and Esophagus

Autoimmune injury of the mucus membranes: The reported prevalence of oral lesions in lupus patients varies from 10-50% [3, 4]. Similar to the different lupus manifestations of the skin autoimmune injury of mucus membranes can be classified into a acute, subacute or chronic cutaneous lupus erythematosus (ACLE, SCLE, and CCLE) (Table 3). Erythematous lesions may be painless and only detected by careful inspection of the oral cavity. They are found as flat edematous macular areas with poorly defined borders. Petechial reddening may occur on lesions on the hard palate [4]. By contrast, discoid lesions are characterized by central white spotted erythema with surrounding white striae and teleangiectasia [4]. Discoid lesions of the oral cavity may be as painful as ulcers. Distinction from leukoplakia and Lichen planus may require an immunohistochemical examination of a biopsy [4-7]. Ulcers are usually shallow, commonly painful, and 1-2 cm in diameter [5]. Oral ulcers remain the only gastrointestinal manifestation comprised in the SLE criteria of the American Rheumatism Association (now: American College of Rheumatology) which allow to classify lupus patients when compared to patients with other types of rheumatic diseases [8]. However, different types of oral lesions may coexist and are most commonly located to the buccal mucosa, the hard palate, and the vermillion border [4]. All lesions may also extend to the pharynx and the esophagus. In rare cases ulcerative esophagitis can be complicated by perforation. Bullous epidermiolysis may rarely occur in the esophagus [9]. The presence of oral ulcers does not represent a reliable marker for lupus disease activity [3, 10], although being a criterion of the SLE disease activity index (SLEDAI). No evidence-based guidelines for the treatment of oral lupus lesions are available. Topical steroids, i.e. 0.05% fluocinoide or clobetasol gel placed on affected areas b.i.d. for 2 weeks may be effective [11]. Patients that do not respond to topical therapy may require more potent systemic therapy (Table 4).

Most centers use antimalarials [12] but antimalarials may also cause lichinoid lesions [13]. Systemic steroids or azathioprine are also used for severe ulcers. Cyclosporine, thalidomide, and methotrexate are preferred for second line therapy [14]. Dapsone and clofazime may be used but less than 5% of centers have experience in using these drugs [12]. Data on the efficacy of mycophenolat mofetil on mucocutanous le-

Table 3. Autoimmune and infectious causes for oral and esophageal lesions in lupus.

Mechanism	Type	Pain	Treatment
Autoimmune injury of mucus membranes	acute cutaneous LE	-/+	-
	subacute cutan. LE	-/+	antimalarials, steroids,
	chronic cutan. LE	+	azathioprine, cyclosporine, methotrexate
Infections	oral candadiasis	-/+	nystatin or fluconazole
	candida esophagitis	+	
	HSV 1	+	aciclovir
	CMV	+	ganciclovir, foscarnet

Table 4. Topical treatment for lupus-related oral lesions (adapted from ref. [11]).

	Directions for use
Topical steroids:	
0.05% fluocinonide gel	on affected area b.i.d. for 14 days
0.05% clobetasol gel	on affected area b.i.d. for 14 days
Dexamethasone solution 0.5mg/5 ml	Gargle and spit 4x/day for 14 days
Triamcinolone acetonide 5mg/ml	Intralesional injection
Topical antimycotics:	
0.12% chlorhexidine rinse	Gargle and spit b.i.d. until lesion resolves
Nystatin suspension (100,000 units/ml)	Gargle and spit 4x/day for 10 days

sions are not available at present. Another aspect of oral cavity ulcers is related to the high prevalence of valvular heart disease in lupus patients [15]. Lupus patients are at risk for infective endocarditis [16], thus antibiotic prophylaxis is recommended especially for patients with oral ulcers prior to dental procedures [11].

Sjögren's syndrome: Published data on the prevalence of Sjögren's syndrome in lupus suffers from the different classification criteria for the primary and secondary type of the disease [3, 17]. Xerophthalmia has been reported in 8-13% of lupus patients [3, 18]. Xerostomia compromises patients by sensitivity to acids, difficulty eating dry foods, sensitivity to spicy foods, and dryness of the lips and the tongue [19]. Xerostomia due to either primary or secondary Sjögren's syndrome is associated with cervical or atypical caries in 83%, fissured erythematous tongue in 70%, and oral candidiasis in 74% [19]. Treatment is notoriously difficult [20]. Sugar free chewing gum, artificial salivary or systemic pilocarpin hydrochloride may improve symptoms [21-23].

Infections: Erythematous oral lesions in lupus patients can also represent Candida infection which does not always present as oral thrush (Table 2). Coincident Candida infection and mucocutaneous lupus is common [24], but Candida usually responds immediately to topical antifungal therapy (Table 4). Dysphagia and retrosternal pain are symptoms of candida esophagitis which may require systemic therapy with fluconazole. Oral ulcers can also arise from systemic infection with human herpesviruses, i.e. herpes simplex viruses (HHV1, HHV2) or cytomegalovirus (HHV5). Both viruses can be effectively treated with systemic aciclovir (HHV1/2) or ganciclovir/valganciclovir (HHV5).

Gastroesophageal reflux: Lupus patients report about dysphagia and heartburn in up to 13-50% [3, 25]. Decreased mobility of the esophagus with low or absent contractions on manometry is common in lupus patients [26]. The most specific disorder is an isolated abnormal peristalsis of the esophagus whithout affection of the lower sphincter [27]. However, reported symptoms poorly correlate with manometry findings [26, 28]. An assumed association to the presence of Raynaud's phenomenon was not confirmed in a study involving 129 patients with various connective tissue diseases including lupus. Proton pump inhibitors and prokinetic drugs may provide relief of symptoms. In addition, non-steroidal anti-inflammatory drugs (NSAID) should be avoided. The role of Cox-2 inhibitors in this setting remains unclear, but potential disadvantanges regarding the cardiovascular risk profile need to be considered.

Stomach and Duodenum

Peptic ulcer disease: No prospective study concerning the incidence of peptic ulcer disease in patients with SLE exists until today. In one retrospective study, 3 out of 51 patients presenting with abdominal pain had a perforated duodenal ulcer (5.8 %), two of whom had significantly active disease as measured by the SLE Disease Activity Index [29]. In another cohort, 13 out of 88 lupus patients presented with abdominal pain, of which one had a perforated peptic ulcer (7.6 %) over a period of 15 years [30]. Both studies do not comment on NSAID or gastroprotective medication. The lack of published data suggests symptomatic peptic ulcer disease or gastric vasculitis to be rather uncommon in SLE. However, bleeding gastric ulcers may occasionally be caused by veno-occlusive disease in anti-phospholipid antibody syndrome [31].

The Lupus Patient with Abdominal Pain

Abdominal pain is a common symptom in lupus patients with a reported incidence ranging from 8-40%, and can be caused by a broad spectrum of underlying pathologies [3]. Most commonly, abdominal discomfort is associated with the start of a new drug, e.g. NSAIDs, mycophenolate mofetil, azathioprine, and hydroxychloroquine. Abdominal pain as a manifestation of autoimmune tissue injury can be caused by e.g. serositis, intestinal vasculitis or pancreatitis. In a retrospective study, abdominal pain was preceding acute surgical abdomen for an average of 34 days in 15 out of 150 SLE patients [32]. Among 11 patients (73%) explored by laparotomy, nine had signs of abdominal vasculitis and two had peritonitis without signs of overt vasculitis. 8 (53%) patients died as a consequence of the abdominal crisis. Other studies, however, found the majority of lupus patients presenting with abdominal pain and requiring surgical intervention to have conventional illnesses such as appendicitis, diverticulitis or adhesions [30]. Patients with peripheral vasculitis, circulating rheumatoid factor, central nervous system disease and thrombocytopenia seem to be more at risk of developing an acute abdomen [33]. In patients that present with abdominal pain there is a strong association between lupus activity measured by SLEDAI and mortality, and mortality is also increased by delaying time to laparotomy [29]. Pneumatosis intestinalis on radiographic studies as well as new-onset of leucopenia and thrombocytopenia were identified as indicators for urgent invasive exploration [34]. In conclusion, early imaging studies as well as an early surgeon's opinion are mandatory in the context of abdominal pain in a lupus patient.

Serositis

In a retrospective study of 52 lupus patients with abdominal pain, 63% had signs of serositis on CT scan [35]. Ascites, as a sign of abdominal serositis, can be found in 8-11% of patients with SLE [36], but has rarely been reported as the single initial presentation of the disease [37, 38]. Abdominal serositis in lupus occurs either in an inflammatory or non-inflammatory as well as as in an acute or chronic form [39]. Acute serositis can present with nausea, vomiting, abdominal wall tenderness and severe pain, but chronic serositis is usually painless. Chronic ascites may also be a sign of hypoalbuminemic states (nephrotic syndrome, liver

cirrhosis, protein loosing enteropathy), hepatic congestion (veno-occlusive disease, right heart failure) or malignancy. On paracentesis, low complement levels and high dsDNA antibody titers together with an exsudative type of the ascitic fluid are indicative of lupus peritonitis [40]. Serositis in SLE ususally responds well to high doses of steroids [40]. In resistant cases cyclophosphamide may be effective [41].

Intestinal Vasculitis

According to the Chapel Hill Consensus classification for vasculitides, vasculitis in SLE is classified as a secondary vasculitis of small vessels including both arteries and venules [42]. Histologic hallmarks include an inflammatory infiltration with polymorphonuclear leukocytes, macrophages, and eosinophils. Other findings are fibrinoid necrosis, disruption of the elastic laminae, and thrombosis. The vasculitic lesions tend to be segmental or focal. Immunofluorescence may show IgM and complement C3 deposition [43]. Vasculitis can present as ischemia or thrombosis either affecting small vascular beds (e.g. enteritis, pancreatitis, appendicitis, cholecystitis) or large vascular beds (mesenteric vasculitis). Intestinal vasculitis preferentially involves the superior mesenteric artery [1, 2]. Vascular thrombosis in lupus-related antiphospholipid antibody syndrome can mimic intestinal vasculitis, but a decision for either immunosuppressive therapy or anticoagulation based on the presence or absence of anti-phospholipid antibodies and other criteria for lupus disease activity may be misleading [2]. Computed tomography may contribute to the distinction of thrombembolic disease or vasculitis [1], because mesenteric vasculitis is commonly associated with asymmetric multifocal thickening of the small bowel wall and mesenteric vascular engorgement or haziness [44-46]. No prospective data on treatment efficacy for intestinal vasculitis is available. Retrospective analyses and case reports suggest that enteric vasculitis in SLE usually responds to high doses of steroids [2, 46, 47]. In resistant cases cyclophosphamide may be effective [48].

Vasculitis of the Gall Bladder

The incidence of gall bladder disease in lupus patients appears to be the same as in the general population [36], but case reports have documented acute acalculous cholecystitis in lupus patients secondary to vasculitis of the gall bladder wall [49, 50]. In such cases steroid therapy can avoid unnecessary cholecystectomy [49, 50]. However, surgery should not be delayed in patients with septicemia [51] or presumed gall bladder necrosis as a manifestation of antiphospholipid antibody syndrome [52, 53].

Pancreatitis

Pancreatitis is a rare complication in lupus patients, and, as in the general population, the most common underlying mechanisms are biliary calculi and alcohol. A recent retrospective study evaluated 49 episodes of acute pancreatitis in 35 SLE patients and found 14 cases to be related to calculi, 10 toxic, 13 drug-related and 17 to be idiopathic with a higher incidence of idiopathic pancreatitis in patients with a high disease activity assessed by SLEDAI [54]. What is the role of immunosuppressive drugs in inducing pancreatitis in lupus patients? The low incidence of pancreatitis in non-lupus patients on steroids, the evidence of vasculitis on histologic findings as well as recent retrospective data argue against steroids being a causative agent in the disease. In fact, symptoms improve in the majority of lupus patients with acute pancreatitis after either increasing or continuing the maintenance dose of steroids [55-58]. Thus, having ruled out other common causes, treatment of pancreatitis in the lupus patient should include steroids in addition to intravenous fluid resuscitation, complete bowel rest and antibiotics, if there are signs of necrosis on computed tomography.

Infective Diarrhea

Non-typhoid salmonella are a common pathogen that causes infective diarrhea in lupus patients [3]. Blood cultures have a higher sensitivity as compared to stool cultures for the recognition of Salmonella enteritidis. Patients with Salmonella infection occurring with the first presentation of SLE and patients with SLE re-infected with Salmonella species are at higher risk of death [59]. Risk factors for bacterial infection include steroid or other immunosuppressive therapy, low complement, functional hyposplenism and haemolysis [60]. Another pathogen that can cause severe intestinal infection in lupus patients includes amobeiasis. Early endoscopy to collect intestinal fluid specimen and proper antibiotic therapy are crucial as steroid therapy in this setting may result in a fatal course [61].

The Risk for Gastrointestinal Malignancy

Older studies with small numbers of lupus patients revealed conflicting data on the incidence of non-Hodgkin's lymphoma and other malignancies compared to the general population [3, 62-64]. A recent international cohort study comprising data of more than 9000 lupus patients observed 431 cancers within an eight year period of follow up and confirmed an overall increased risk of malignancy, with an especially increased risk for developing non-Hodgkin's lymphoma [65]. In view of the gastrointestinal tract, the incidence of colorectal, gastric and pancreatic cancer was found to be that of the general population. Hepatobiliary malignancy, however, occurred more than twice as much. Additionally, cases of hepatocellular carcinoma in patients with lupoid hepatitis have been reported [66, 67]. Notably, paraneoplastic antinuclear antibody production, cytopenia, fever, rash or arthralgias, misinterpreted as SLE, can precede malignancy [68-70].

The Lupus Patient with Elevated Liver Enzymes

Elevated liver enzymes are found in 15-55% of lupus patients [71-73]. Jaundice, hepatomegaly, and ascites are less common [74]. Elevated liver enzymes are

commonly related to prescribed medication, e.g. NSAIDs, azathioprine, methotrexate, steroids or antimalarials. However, a number of conditions that can cause liver damage in lupus patients need to be considered (Table 5). Viral hepatitis, cardiac congestion, lupus-related hemolysis or myositis can usually be ruled out clinically or by appropriate blood tests. The patient should also be checked for the presence of anti-phospholipid antibodies. Budd-Chiari syndrome and possibly veno-occlusive disease are rare complications of secondary anti-phospholipid antibody syndrome [75]. But when do elevated liver enzymes indicate autoimmune liver disease? Hepatic autoimmune injury may occur e.g. as a hepatic manifestation of SLE, autoimmune hepatitis or primary biliary cirrhosis (Table 5, ref. [76]). The presence of antimitochondrial antibodies and elevated serum levels for alkaline phosphatase strongly argue for primary biliary cirrhosis. The distinction between lupoid hepatitis, chronic active autoimmune hepatitis, nodular regenerative hyperplasia, and veno-occlusive disease may require a liver biopsy. Lupoid hepatitis is found in 30% of lupus patients with elevated liver enzymes and was found in 3% of lupus patients [77]. Lupoid hepatitis histology is characterized by lobular lymphocytic cell infiltrates [72, 78]. Ribosomal P protein antibodies have been reported to be associated with lupoid hepatitis [77]. A pathologic analysis of 51 Japanese autopsy cases found hepatic arteritis in 11 cases, indicating that autoimmune vasculitis may occur more often as previously suspected [79].

However, autopsy studies may be subject to a strong bias towards severe cases of lupus. Although, chronic active autoimmune hepatitis shares the presence of antinuclear antibodies and other clinical characteristics with lupoid hepatitis, a distinction can usually be made on clinical grounds, additional laboratory findings, and liver histology (Table 6). Autoimmune hepatitis is characterized by chronic persistent hepatitis with periportal lymphocytic and plasma cell infiltrates in the presence of liver-specific protein and smooth muscle antibodies [74]. Thus, elevated liver enzymes in SLE may be caused by different disorders. Drug interactions are common, but persistent laboratory abnormalities may require a liver biopsy to make a diagnosis.

Summary

Gastrointestinal manifestations are common but may be asymptomatic in lupus patients. A careful inspection of the oral cavity is mandatory on each patient's visit. In symptomatic patients the medical history helps to distinguish between autoimmune tissue injury, complications of lupus-related organ dysfunction, infections, anti-phospholipid antibody-related thrombembolic complications, medication side-effects or unrelated disorders [80]. A pragmatic approach seeks for causative pathogens, discontinues possible causative drugs, and does not withheld surgery or immunosuppression, if initial treatment does not result in immediate improvement of symptoms.

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Table 5. Causes for elevated liver enzymes in lupus.

Condition	Rule out by
Mistaken for hepatopathy	
Myositis	serum creatine kinase
Hemolysis	serum haptoglobin
Common hepatopathies	
Drug toxicity (see also Table 4)	discontinue medication
Viral hepatitis	serology for HAV, HBV, HCV, HDV, CMV, EBV
Fatty liver	abdominal ultrasound and/or liver biopsy
Manifestations of autoimmunity	
Chronic active hepatitis (AIH)	liver biopsy and serum sm/LKM-antibodies
Lupoid (lobular) hepatitis	liver biopsy
Hepatic arteriitis/vasculitis	liver biopsy
Primary biliary cirrhosis	liver biopsy and serum anti-mitochondrial antibodies
Thrombotic events	
Budd-Chiari syndrome	liver ultrasound and serum antiphospholipid antibodies and lupus anticoagulans
Veno-occlusive disease	liver biopsy
Others	
Nodular regenerative hyperplasia	liver biopsy and serum antiphospholipid antibodies and lupus anticoagulans
Cardiac congestion	clinically or serum proBNP or echocardiogram

Table 6. Lupoid hepatitis and autoimmune hepatitis, modified from ref .[76]

	Lupus	Autoimmune hepatitis
ARA criteria (ref.[8])		
Malar rash	+++	±
Discoid rash	+	±
Photosensitivity	+	±
Oral ulcers	++++	±
Arthritis	+++++	+++
Serositis (Pleuritis/Pericarditis)	+++/+	+/±
Proteinuria, cellular casts	+++	±
Seizures or psychosis	++	±
Hemolysis/leukopenia/thrombocytopenia	+/+++/++	±/+/+
Autoantibodies: APA/dsDNA	+/+++++	++/±
Antinuclear antibodies	+++++	++++
Other clinical findings		
Raynaud's phenomenon	++	±
Fever	++	+
Other laboratory markers		
Smooth-muscle antibodies	+-++	++++
Liver-kidney-microsomal antibodies	±	+
Liver-specific protein antibodies	±	+++++
Ribosomal P protein antibodies	+++++	±
Hypocomplementaemia	+++	±
Liver histology		
Lobular hepatitis	+++++	++
Periportal hepatitis	+	+++++

±: 0-5%, +: 6-20%, ++: 21-40%, +++: 41-60%, ++++: 61-80%. +++++: 81-100%

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Address for correspondence:
PD Dr. med. H.-J. Anders
Lupus-Ambulanz
Medizinische Poliklinik
Klinikum der Universität München – Innenstadt
Pettenkoferstr. 8a
D-80336 München, Germany
Tel.: ++49-89-51603583
Fax.: ++49-89-51603719
Email: hjanders@med.uni-muenchen.de