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Review

A review of gastrointestinal manifestations of systemic lupus erythematosus

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Abstract

In this review, we analyse critically the effects of systemic lupus erythematosus (SLE) on the gastrointestinal (GI) tract from mouth to anus, attempting to distinguish the features that are most likely to be due to therapy. GI manifestations of SLE include mouth ulcers, dysphagia, anorexia, nausea, vomiting, haemorrhage and abdominal pain. GI vasculitis is usually accompanied by evidence of active disease in other organs. Early recognition of the significance of these symptoms offers the best opportunity to improve the symptoms and to aid long-term survival.

KEY WORDS: SLE, Ulcers, Dysphagia, Vasculitis, Abdominal pain.

Gastrointestinal (GI) manifestations are common in patients with systemic lupus erythematosus (SLE). William Osler, in 1895 [1], was the first to emphasize that the GI manifestations may overshadow other aspects of the disease and mimic any type of abdominal condition. Anorexia, nausea and vomiting are seen in ~50% of patients with SLE (see Table 1) [2–5]; however, they may be due to the disease, represent intercurrent processes (e.g. secondary to uraemia) or side-effects of medication. Studies reporting the frequency of these symptoms have not directly addressed this issue. We have excluded other causes of abdominal pain arising from the liver, spleen and pancreas, and those secondary to serositis and ascites, as these features are beyond the scope of this review.

The reported incidence of GI manifestations directly attributable to SLE in older literature varies widely (Table 2) [6–10]. For example, Fries and Holman [3] attributed most of their patients' abdominal complaints to the effects of medication and the intercurrent disease process rather than to the disease itself, and therefore the incidence of GI symptoms due to SLE was reported to be very low. While the most common GI manifestation of SLE occurs in the oral cavity, GI vasculitis may potentially contribute to greater morbidity and mortality, and early recognition and treatment are important if long-term survival is to be improved.

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Oral cavity and SLE

Bazin [11] first described oral manifestations of 'lupus erythemateux' in 1861, with a more detailed description in 1901 by Capelle [12]. Oral ulceration is one of the revised diagnostic criteria proposed by the American College of Rheumatology (ACR) for the classification of SLE [13].

The prevalence of oral lesions is reported to be 7–52% of patients with SLE [2, 3, 5, 7, 13–22] (Table 3). In our own experience, 29.2% of 266 patients under long-term follow-up complained of recurrent crops of mouth ulcers. This wide variation may in part be explained by demographic differences between study populations. Thus, one study reported that 46% of English patients with SLE, compared to 15 and 11% of patients in Brazil and Sweden, respectively, had mouth ulcers [23], whilst the highest proportion of SLE patients observed with oral lesions has been reported in Iraq [16].

Lesions due to the underlying disease process have been broadly classified into erythematosus, discoid (Fig. 1) and ulcerative type [17]. However, other factors such as associated Sjögren's syndrome and mucosal alterations occurring as a result of treatment or intra-oral infections need to be considered. The histo/immunopathology is summarized in Table 4.

Clinical features

Some studies have shown that up to 57% of mucosal lesions were painful [17], whilst other earlier observations made by Urman *et al.* [15] in 1978 stated that up to 82% of oral ulcers observed were painless. The disparity may be due to differences in the type of lesion, erythematous lesions being typically painless, whereas

TABLE 1. Gastrointestinal symptomatology in SLE (%)

	Dubois and Tuffanelli [2]	Fries and Holman [3]	Jessar *et al.* [4]	Harvey *et al.* [5]
No. of patients in study	520	184	168	105
Anorexia	49	36	–	71
Nausea and vomiting	53	63	13	25
Dysphagia	1.5	–	5	6
Abdominal pain	19.2	34	17	10
Diarrhoea	5.9	25	13	8
Haemorrhage	6.3	10	–	5

discoid lesions are more often painful. Earlier studies did not attempt to distinguish the two. It is accepted that a significant proportion of oral lesions are asymptomatic, thus necessitating a careful examination of the oral cavity in all lupus patients. The relationship of mucosal lesions to systemic disease activity is also disputed. One study specified an association of oral ulceration with clinical systemic activity according to defined guidelines on the basis of history and physical findings, although this did not correlate with significant changes in titres of serum complement (C3) or anti-DNA antibodies [15]. It has even been suggested that patients with oral ulcers have a higher mortality than those without oral ulcers [3], although this has not been confirmed by further studies. The most recent study addressing this issue, by Jonsson *et al.* in 1984 [17], showed that the overall prevalence of oral lesions was not related to disease activity as defined by an arbitrary scale from clinical and laboratory data; however, discoid lesions and ulceration were only seen in patients with active disease. In our own cohort utilizing the validated British Isle Lupus Assessment Group (BILAG) index [24], we found no evidence of increased lupus activity in those patients with recurrent mouth ulcers (S. M. Sultan, Y. Ioannou and D. A. Isenberg, unpublished observation).

The buccal mucosa, hard palate and vermilion border are the sites most frequently involved [17]. Discoid lesions appear as central areas of erythema with white spots surrounded by radiating white striae and telangiectasia at the periphery [17, 25]. Erythematous lesions are often accompanied by oedema and petechial reddening

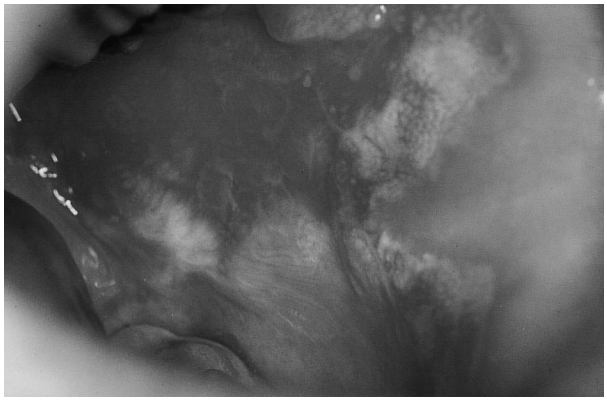

FIG. 1. Discoid lupus.

TABLE 2. Gastrointestinal disease directly attributable to SLE

	Total no.[a]	GI%
Couris *et al.*, 1964 [6]	231	1.3
Estes and Christian, 1971 [7]	150	16
Zizic *et al.*, 1978 [8]	140	8
Shapeero *et al.*, 1974 [9]	141	14
Matolo and Albo, 1971 [10]	51	27.5

[a]Total number of patients with SLE.

on the hard palate, although they are usually found incidentally as flat macular areas with poorly defined borders [17, 26]. Ulcers tend to occur in crops and are shallow. They are usually 1–2 cm in diameter and in one-third of patients may extend into the pharynx [15, 26]. All three lesions may co-exist [15] or merge into one another, leading to oedema and petechiae [17, 26].

Histo/immunopathology

The histology and immunopathology of oral lesions are well described, and tend to be similar to changes seen in the skin [15] (Table 4).

Oral lesions in SLE are often difficult to distinguish from lesions of lichen planus (LP) and other causes of leucoplakia (LPK) (Figs 1–3). Karjalainen and Tomich [27] have revised Schiodt's original five features that occur in oral lupus and help to distinguish them from LP on light microscopy (Table 5).

SLE and Sjögren's syndrome

Morgan [28] first described Sjögren's syndrome associated with SLE in 1954. Of 266 patients with SLE under long-term follow-up in our own unit, 13% have been diagnosed as having Sjögren's syndrome on the basis of meeting the European classification criteria [29]. The prevalence of secondary Sjögren's syndrome occurring in SLE is likely to have been overestimated by some studies due to the lack of specific diagnostic criteria for classifying patients. For example, in a prospective study of manifestations of Sjögren's syndrome in 50 patients with SLE, all were questioned for sicca symptoms, and tests performed included Schirmer's and Rose Bengal tests, parotid sialography, salivary scintiscans, isotopic excretion in saliva and lip biopsies [30, 31]. At least two abnormal test results were found in 49 out of 50 patients and were considered indicative of subclinical evidence of Sjögren's syndrome, despite the fact that 46.9% had

TABLE 3. Prevalence of oral lesions in patients with SLE

Author	No. of patients with SLE	% Reported with oral lesions
Jessar *et al.*, 1953 [4]	44	18
	168	15
Harvey *et al.*, 1954 [5]	105	14 (ulcers)
Dubois and Tuffanelli, 1964 [2]	520	9.1
Estes and Christian, 1971 [7]	140	18
Fries and Holman, 1975 [3]	193	18
Ropes, 1976 [14]	99	41 (ulcers)
Urman *et al.*, 1978 [15]	182	26
Tan *et al.*, 1982 [13]	177	27 (ulcers)
Al-Rawi *et al.*, 1983 [16]	67	52 (ulcers)
Jonsson *et al.*, 1984 [17]	51	45
Tsanios *et al.*, 1984 [18]	25	57
Hochberg *et al.*, 1985 [19]	150	23 (ulcers)
Pistiner *et al.*, 1991 [20]	464	19
Vitali *et al.*, 1992 [21]	704	20.7
		5.7 (ulcers]
Vitali *et al.*, 1996 [22]	61 centres worldwide	18.6 (ulcers)
Isenberg, 1998 (unpublished observation)	266	29.2

TABLE 4. Common histopathological and immunohistochemical findings of oral mucosal lupus erythematosus [15, 17, 27]

Interface mucositis
Hyperkeratosis
Keratotic plugging
Liquefactive degeneration
Inflammatory perivascular infiltrate—often lymphohistiocytic
Intra-epithelial microabscesses
Spongiosis
Civatte (colloid) bodies
Multinucleated epithelial cells
Deposition—IgM, IgG, complement and fibrinogen along the dermal–epidermal junction

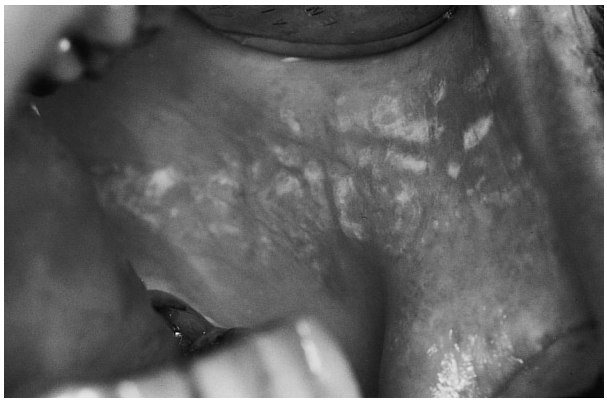

FIG. 2. Lichen planus.

no sicca symptoms. Studies that have used well-defined histological and objective clinical criteria have shown that Sjögren's syndrome occurs in ~20% of patients with SLE [32, 33].

Sjögren's syndrome may precede SLE by many years, although it most frequently appears late in the course of the disease and in elderly patients with SLE [34, 35]. Patients with SLE and secondary Sjögren's syndrome also tend to exhibit fewer systemic manifestations, particularly renal involvement, compared to those with SLE alone [36, 37].

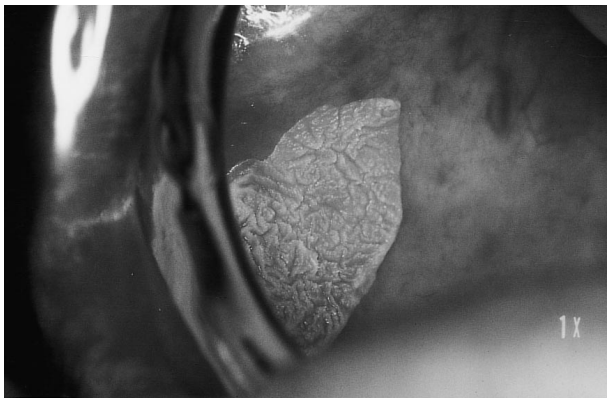

FIG. 3. Leucoplakia—traumatic hyperkeratosis.

TABLE 5. Distinguishing features of oral lupus lesions from lichen planus and leucoplakia on light microscopy [27]

Vacuolization of keratinocytes
Patchy periodic-acid Schiff (PAS)-positive deposits subepithelially
Oedema in the upper lamina propria
PAS-positive thickening of blood vessels
Severe deep/perivascular infiltrate

Dental considerations and other oral lesions

Drugs used to control disease activity can cause significant intra-oral pathology. Corticosteroids taken for many years can lead to root canal calcification [38] and, in children/adolescents, delayed primary and permanent tooth eruption with twisted root formation has been reported [39]. Steroids have also been shown to be associated with acute necrotizing gingivitis in a few SLE patients [40]. Non-steroidal anti-inflammatory drugs (NSAIDs) can induce bleeding gums by inhibiting platelet aggregation and exacerbating co-existing thrombocytopenia, seen at levels of $<100\,000 \times 10^9$/l in 17.4% of 266 patients under our long-term review (S. M. Sultan, Y. Ioannou and D. A. Isenberg, unpublished observation). These drugs have been implicated in the

interesting observation of improved periodontal health in patients with SLE [41], possibly because NSAIDs inhibit alveolar bone resorption [42]. Drug-induced lupus secondary to hydralazine can cause orogenital ulceration [43] and, when a patient develops erosive or keratotic lesions on the buccal mucosa, the possibility of a lichenoid drug reaction secondary to hydroxychloroquine should be considered [43]. Cyclosporin A, which may be of use for some patients with active lupus, and the antihypertensive nifedipine, are common causes of gingival hyperplasia. Methotrexate commonly causes a mucositis and should be taken in combination with folic acid. The above oral manifestations due to drug reactions are usually easily distinguishable macroscopically from primary lupus oral lesions, although occasionally a biopsy may be required to clarify equivocal cases.

Although SLE itself has major adverse effects on normal immune functioning [44], its immunosuppressive treatment undoubtedly facilitates intra-oral infections, particularly candida and herpes simplex virus.

Particular vigilance is necessary for patients with associated Sjögren's syndrome as lack of salivary secretion leads to a greater predisposition to tooth decay and to intra-oral infections such as oral candidiasis [45].

Features of SLE common to other organ systems may present with oral manifestations. For example, Raynaud's phenomenon may rarely affect the tongue [46] and mastication may be affected due to temporomandibular joint involvement [47].

Therapeutic options

No evidence-based guidelines exist regarding the systemic therapy for oral lupus lesions. A recent large international survey by Vitali *et al.* [22] found that mucocutaneous lesions are treated most frequently with antimalarials, with steroids and azathioprine reserved for more severe cases. Other studies show that thalidomide and cyclosporin are more often used as second-line agents in Europe, whilst American centres tend to prefer methotrexate [48]. Antileprosy drugs such as dapsone and clofazime have been shown to be effective [49, 50]; however, $<5\%$ of centres claim to have a great deal of experience in their use and 60% have never used these drugs [48]. Clearly, there is inconsistency in treatment regimens employed at national and international level, presumably due to the lack of evidence. In addition, interpreting these studies with direct relevance to the treatment of oral lupus lesions is difficult as 'mucocutaneous manifestations' also encompass a host of cutaneous manifestations such as malar rash and alopecia. What is required is a large multicentre prospective study specifically investigating the effects of various systemic therapies on oral lesions alone to resolve this issue.

Preventative dental care is important. Patients have a tendency to consume a diet that promotes dental decay because of impaired taste. The use of chlorhexidine mouthwashes will help to contain periodontal disease and infection [51]. Symptomatic local treatment of mucous membrane ulcers with hydrogen peroxide gargle, buttermilk gargle or steroid-impregnated gel may be of benefit. Intralesional injection of corticosteroids may be required [52]. Suspected or proven infections should be treated with antiviral, antifungal or antibacterial agents after a swab has been taken for culture and sensitivities. Evidence suggests that dentists should probably not undertake dental work during a lupus flare and should treat lupus patients with prophylactic antibiotics prior to dental procedures due to the high incidence of bacterial endocarditis [53].

The treatment of secondary Sjögren's syndrome includes sugar-free gum, artificial saliva and systemic therapy with pilocarpine hydrochloride which may increase salivary secretion [54]. Patients should receive oral hygiene instructions, prevention plans designed for people with oral dryness, and avoid antihistamines, tricyclic antidepressants and decongestants when possible.

SLE and the oesophagus

Clinical features

The reported prevalence of oesophageal symptoms in patients with SLE varies widely. Dysphagia occurs in 1–13% [2, 3, 5, 14] and heartburn in 11–50% [14, 55]. Oesophagitis with ulceration has been observed in 3–5% of patients with SLE, and mucosal bridging, which is occasionally seen in peptic oesophagitis, has been reported [5, 14, 56]. Rarely, oesophageal perforation may occur [57]. In these studies, it is unclear as to whether the observations were secondary to therapy, the underlying disease process or a combination of the two. In addition, the majority of the studies antedate the introduction of proton pump inhibitors and H_2 blockers, thus the relevance to modern day observations must be questioned.

Pathophysiology

Oesophageal symptoms do not correlate well with the results of oesophageal manometry. Oesophageal manometry abnormalities, particularly hypoperistalsis and aperistalsis, have been observed in up to 72% of patients with SLE [55]. No correlation has been observed between manometric findings of oesophageal dysmotility and overall clinical activity, duration or therapy [55, 58]. Ramirez-Mata *et al.* [58] observed oesophageal motility abnormalities in 16 out of 50 patients with SLE selected randomly. Abnormally low or absent contractions were mostly found in the upper one-third of the oesophagus. However, of the 34 normal studies, five patients had symptoms of heartburn or dysphagia. In more recent studies, Lapadula *et al.* [59] have confirmed the markedly decreased involvement of the lower oesophageal sphincter (LOS) in SLE. In patients with systemic sclerosis, 81.8% have abnormalities of the LOS, 30% of whom were classified as severe. In contrast to systemic sclerosis, none with SLE had severe involvement of the LOS, suggesting that this may discriminate between non-lupus autoimmune rheumatic disease and SLE.

Salivary gland dysfunction has also been linked to dysphagia. Prolonged pharyngeal transit times have been demonstrated using videofluoroscopy in patients with secondary Sjögren's syndrome and SLE compared to a normal control population. The abnormality in transit times was no different from patients with primary Sjögren's syndrome [60, 61].

The relationship of oesophageal dysfunction to Raynaud's phenomenon was originally recognized by Stevens *et al.* [62]. Gutierrez *et al.* [63] compared 14 patients with SLE and 17 patients with 'mixed' or undifferentiated connective tissue disease. The majority of patients in both groups complained of oesophageal symptoms and there was a good correlation between Raynaud's phenomenon and oesophageal aperistalsis in both groups. Montecucco *et al.* [64] demonstrated that the association of oesophageal dysmotility with Raynaud's phenomenon in patients with SLE is accompanied by an increased titre of antibodies to recombinant hn-RNP protein A1. There was no association between anti-A1 antibody positivity and other clinical findings, disease activity or therapy. It was postulated that antibodies to hn-RNP protein A1 may be associated with a subset of SLE patients with overlapping clinical features of scleroderma and are distinct from the group identified by anti-RNP antibodies. These observations contrast sharply with those findings made by Lapadula *et al.* [59], who reported poor correlation of Raynaud's phenomenon with oesophageal motor disorders not only in SLE, but also in other autoimmune rheumatic diseases including systemic sclerosis. This report suggests that oesophageal dysfunction and Raynaud's phenomenon may have different pathophysiology and constitute independent but parallel processes.

The aetiopathophysiological process by which oesophageal dysmotility arises in SLE patients is uncertain. Autopsy findings in 26 children with SLE showed two with upper oesophageal skeletal muscle fibre atrophy [57]. Castrucci *et al.* [55] postulated that an inflammatory reaction in the oesophageal muscles or ischaemic vasculitic damage of the Auerbach plexus leads to the hypoperistalsis/aperistalsis observed. Harvey *et al.* [5] reported arteritis of the oesophagus with associated ulceration in four out of 105 patients with SLE. Iatrogenic causes for oesophageal symptoms have been largely overlooked. For example, NSAIDs have been shown to cause oesophageal ulceration which may present as dysphagia and haloperidol has been reported to cause dysphagia in a patient with psychiatric features of SLE.

Therapy

There have been no randomized controlled clinical trials investigating the treatment of dysphagia and reflux in SLE patients. This fact, coupled with the uncertain aetiopathogenesis of oesophageal symptoms, makes tailoring therapy difficult. Patients should initially be given appropriate advice, such as taking small and frequent meals and avoidance of post-prandial recumbency [26]. Pharmacological agents may play a therapeutic role, such as antacids, proton pump inhibitors, H_2 blockers or pro-motility agents. These agents may be helpful if the oesophageal lesions are peptic in origin or have occurred as a result of NSAID or steroid therapy. Changing patients' conventional NSAID therapy to an (imminently available) specific COX-2-inhibiting NSAID may also be of benefit. However, treatment of lupus itself may help if the oesophageal lesions are proven on biopsy to be vasculitic in origin, particularly if coupled with clinical and serological evidence of active disease. Again, a prospective controlled trial in the treatment of oesophageal symptoms would resolve this issue.

Stomach, duodenum and SLE

There has never been a large study directly addressing the actual incidence of peptic ulcer disease in patients with SLE. Previous reviews have quoted figures ranging from 5 to 20% [14, 65], but these studies antedate the present era of gastroprotective agents and routine endoscopy. Virtually all patients with SLE require treatment with NSAID therapy and/or corticosteroids. In our experience, the maximum therapeutic requirements included 21% managed with NSAID alone $\pm$ antimalarials, 8% with low-dose prednisolone (<0.2 mg/kg), 30% with moderate prednisolone (0.2–0.5 mg/kg) and 40% with high-dose prednisolone (>0.5 mg/kg) [66]. NSAID therapy is known to be strongly associated with gastroduodenal ulcer disease [67], but a much weaker association with corticosteroids exists [68]. The ulcerogenic effects of NSAIDs and corticosteroids used in combination are synergistic and put the patient at a high risk of serious ulcer disease. In addition, high-dose steroids may mask the early clinical signs of peptic ulcer perforation. There have been two recent studies reporting the prevalence of peptic ulcer perforation in a cohort of patients with SLE presenting with abdominal pain. Medina *et al.* [69] reported that, of 51 patients presenting with an acute abdomen, three had a perforated duodenal ulcer (5.8%), two of whom had significantly active disease as measured by the SLE Disease Activity Index (SLEDAI). Al-Hakeem and McMillen [70] reviewed a cohort of 88 lupus patients over a 15 yr period. Thirteen patients presented to hospital with abdominal pain, of whom one (7.6%) had a perforated peptic ulcer. In this study, no comment is made on the degree of SLE activity in these patients and both studies do not state whether patients were taking NSAIDs, steroids or gastroprotective agents prior to presentation. In our own cohort of 266 patients under long-term review for up to 20 yr, we have had no deaths attributable to peptic ulcer disease. Patients with rheumatoid arthritis are a different population of patients also taking long-term NSAIDs. Studies have shown in this group of patients that 1% of all deaths may be attributable to NSAIDs, of which two-thirds are as a direct result of peptic ulcer disease [71]. Musaev *et al.* [72] provided data suggesting that SLE itself may cause gastritis. In this study, 27 children with SLE and 12 with chronic

gastroduodenitis underwent biopsies of the stomach and duodenum. The inflammatory infiltrate from patients with SLE was found to contain higher levels of young and mature fibroblasts than those from patients with gastroduodenitis, and was associated with the progression of SLE. During disease exacerbation, immune complex deposition was observed in the arteriolar walls. Whether lupus disease itself confers an additional or even synergistic ulcerogenic effect with NSAIDs ± steroids is as yet undetermined. Only a multicentre study set up specifically to address this issue may yield the answer.

Patients on long-term NSAIDs may need to be maintained on a suitable gastroprotective agent such as a proton pump inhibitor, H_2 blocker [68] or misoprostol. Recent comparisons between these gastroprotective agents in patients on long-term NSAID therapy have shown omeprazole to heal and prevent ulcers more effectively than ranitidine [73]. Omeprazole, compared to misoprostol, showed a lower rate of relapse and was better tolerated [74]. The imminent introduction of specific COX-2 inhibitors which have potentially no or fewer gastric side-effects than conventional NSAIDs may also help.

Small and large intestine

Some of the more potentially dangerous GI complications of SLE occur in the small and large intestines secondary to small-vessel vasculitis. This may progress to ischaemic enteritis and eventually to bowel infarction with bleeding and/or perforation and peritonitis. Clinical presentation is variable and the incidence of symptomatology varies widely (Table 1). Symptomatology alone is not of great value in identifying patients with vasculitis [9]. The most common symptom arising from the intestine is abdominal pain, the aetiology of which has a lengthy differential diagnosis.

Abdominal pain

The acute abdomen in patients with SLE is a challenging diagnostic and therapeutic problem. Most patients are on steroids and/or immunosuppressive treatment, which mask the physical findings of perforation and ischaemia. Delay in diagnosis is common; Zizic *et al.* [75] noted that abdominal pain was present in two-thirds of patients with SLE for an average of 34 days before the acute abdominal crisis, ranging from 11 to 66 days. Symptoms may initially be attributed to medication such as NSAIDs, corticosteroids, hydroxychloroquine and azathioprine, any of which can cause GI upset.

The reported incidence of abdominal pain varies from 8 to 40% of patients with SLE [4, 5, 20, 75], with the lowest figure being reported in a series that excluded medication-related symptoms. The disease itself can also cause serositis or pancreatitis without bowel ischaemia or perforation, thus increasing the differential diagnosis.

The assumption that in active SLE most of the abdominal symptoms are due to vasculitis may lead to serious treatment errors and delays in surgical exploration. Medina *et al.* [69] looked at the aetiology of abdominal pain in patients with active and inactive SLE using the SLEDAI [76]. Fifty-one patients with signs and symptoms of an acute abdomen were studied. All patients received i.v. hydrocortisone during the first 12–24 h. After this, they underwent a surgical examination unless a complete resolution was seen. This study highlighted that the acute abdomen has a different significance in active and inactive SLE patients (Tables 6 and 7). A smaller study by Al-Hakeem and McMillen

TABLE 6. Patients with active SLE and acute abdomen [69] (reproduced with permission)

Final diagnosis	Number	Surgery	Mortality
Vasculitis (n = 19)			
Intestinal ischaemia	4	3	0
Intestinal necrosis	5	4	2
Ileal perforation	2	2	1
Colonic perforation	2	1	0
Necrotizing pancreatitis	2	1	1
Acalculous cholecystitis	2	2	1
Subtotal	19[a]	13	9[b]
Abdominal thrombosis (n = 13)[c]			
Mesenteric thrombosis	2	1	1
Hepatic arterial thrombosis	1	1	0
Subtotal	3	2	2
Non-SLE related (n = 14)			
Acute appendicitis	3	3	1
Lithiasic cholecystitis	3	3	0
Perforated duodenal ulcer	2	2	1[d]
Acute pancreatitis	2	2	0
Pyocholecyst	1	1	0
Retroperitoneal haematoma[e]	1	1	0
Pancreatic abscess	1	0	1
Negative laparotomy	1	1	0
Subtotal	14	13	3
Total	36	28	14

[a]Two patients did not undergo surgery due to a good response to steroid treatment.
[b]Surgery was not performed in four patients because of their critical condition.
[c]aCL antibody titres >5 S.D.
[d]Without evidence of vasculitis.
[e]Anticoagulant therapy.

TABLE 7. Non-SLE related acute abdomen in inactive SLE [69] ($n = 15$; events = 18) (reproduced with permission)

Final diagnosis	Number	Surgery	Mortality
Acute appendicitis	3	3	0
Acute pancreatitis	3	1	0
Lithiasic cholecystitis	2	2	0
Mucinous ovarian cystadenoma	1	1	0
Polycystic ovarian	1	1	0
Perirenal abscess	1	1	0
Retroperitoneal abscess	1	1	0
Hepatic amoebic abscess	1	1	0
Tubo-ovarian abscess	1	1	0
Tubular pregnancy	1	1	0
Perforated colonic diverticulum	1	1	0
Perforated gastric ulcer	1	1	1
Appendicitis followed by retroperitoneal abscess	1	1	1
Total	18	16	2

[70] reviewed the charts of all patients with SLE who had presented with abdominal pain. Of the 13 patients with abdominal pain, nine required surgery: for cholecystitis (one patient); diverticulitis (three patients); perforated peptic ulcer (one patient); colonic perforation (one patient); adhesions (three patients). They had no cases of bowel oedema, polyserositis, ascites or mesenteric infarction. Those not operated on had a diagnosis of gastroenteritis, duodenitis, cholecystitis and inflammatory bowel disease. Neither the degree of SLE activity nor the concurrent therapy of these patients presenting with abdominal pain was commented upon. In general, patients with SLE presenting with abdominal pain may have conventional illnesses and an early surgical opinion is warranted.

Vasculitis

The prevalence of intestinal vasculitis has been reported to range from 0.2–53% of patients with SLE [9, 69, 77, 78] (Table 8). However, on closer analysis of these figures, the higher figure in this highly diverse range has been reported in patients with active SLE with abdominal pain. This higher figure is thus very unlikely to represent the true incidence of vasculitis in SLE patients in general. A recent large study of 540 patients with lupus by Drenkard *et al.* [78] found that the incidence of GI vasculitis was 1/540 (0.2%). In our cohort of 266 patients, we have had one patient with SLE (0.4%) who developed iron deficiency anaemia (in the absence of NSAID), but associated with an increase in her lupus activity as shown by a raised erythrocyte sedimentation rate (ESR), rising anti-double-stranded (ds) DNA antibody titre and low serum complement. Clinically, she had abdominal pain associated with a vasculitic rash and worsening arthralgia. The patient presented with an acute drop in haemoglobin concentration of 3 g/dl. Gastroscopy demonstrated numerous small areas of angiodysplasia in the duodenum and jejunum, and angiography confirmed bleeding from these areas. There was a good response to high-dose i.v. pulsed methylprednisolone and the patient was subsequently maintained on oral prednisolone.

Clinical features

Abdominal pain, nausea and vomiting are frequent manifestations of GI vasculitis (Table 1). The symptomatology varies from non-specific bloating, anorexia, post-prandial fullness and diarrhoea to abrupt and massive GI haemorrhage or presentation with acute abdominal pain. Unexplained acidosis, hypotension, abdominal distension or bowel dilatation on X-ray should alert the clinician to the possibility of a perforated viscus. Many of these patients are taking corticosteroids and immunosuppressive agents, and overt signs of peritonitis may not fully develop. In three recent studies, there was no description of therapy prior to the onset of the acute episode, whether there was a difference between the active and inactive groups or if therapy prior to the onset of the acute abdominal crisis influenced the outcome [69, 70, 78]. The absence of bowel sounds and the presence of guarding are not reliable signs, and usually present late in the course of the disease [79, 80]. Patients with peripheral vasculitis, circulating rheumatoid factor, central nervous system disease and thrombocytopenia appear to be more at risk for developing an acute abdomen [77, 78], although others dispute this [80]. In general, GI vasculitis is almost always accompanied by evidence of active disease elsewhere, such as the skin, kidneys, cardiovascular system, nervous system or bone marrow.

Pathophysiology

Macroscopically, there are no pathognomic findings suggestive of SLE and the appearance varies from segmental oedema to discrete ulceration [81, 82], gangrene and perforation. Histologically, both small-vessel arteritis and venulitis have been described. Associated findings include atrophy and degeneration of the media of small arteries, fibrinoid necrosis of vessel walls, old thrombosis, phlebitis and monocyte infiltrate in the lamina propria. Immunohistochemistryes of adventitia and media may demonstrate immune complexes, C3 and fibrinogen deposition.

Acute and chronic inflammatory infiltrate is seen in the mucosa and may occasionally be transmural. Colonic ulcers are seen as punched out ulcers with oedematous mucosa on colonoscopy [82]. Rarely, pneumatosis cystoides intestinalis may occur. Although this condition is usually a benign incidental finding in other conditions, e.g. in systemic sclerosis, it may be associated with necrotizing enterocolitis in patients with SLE [83–86] and can occasionally cause perforation. These cases appear to be related to disease activity in other organ systems and respond to high-dose pulsed methylprednisolone. The perforation is likely to be secondary to vasculitis at the site as in conditions such as scleroderma

TABLE 8. Incidence of vasculitis in patients with SLE

Author	No. of patients	% with vasculitis
Shapeero *et al.*, 1974 [9]	141	14
Zizic *et al.*, 1978 [8]	140	6
Medina *et al.*, 1997 [69] All patients with abdominal pain	51	37
Medina *et al.*, 1997 [69] Patients with abdominal pain and active disease	36	53
Drenkard *et al.*, 1997 [78]	540	0.2

they are not associated with an increased incidence of perforation.

Investigations and diagnosis

Patients presenting with abdominal pain require a thorough investigation starting with biochemical and haematological screening including antiphospholipid antibody measurements. Of note is that new-onset leucopenia and thrombocytopenia or significantly worsening leucopenia appears to correlate with active SLE in those patients presenting with an acute abdomen [77, 78].

Plain abdominal radiographs may not be useful early in the course of the disease. Radiographs reflect the underlying pathological process of ischaemia and are similar to those in other causes of ischaemic bowel disease. They may show intraperitoneal free air, pneumatoses cystoides intestinalis, ileus or pseudo-obstruction pattern which may be due to ischaemia, sepsis, uraemia or electrolyte imbalance. If progression of ischaemia occurs, then bowel wall oedema manifests with oedematous haustra, valvulae conniventes and thumbprinting. Thumbprinting represents submucosal oedema or haemorrhage on a barium enema; this finding is fairly specific for ischaemic bowel. These changes can be recognized by a radiologist on a plain abdominal film or an upper GI series such as a barium meal, and in a patient with SLE mesenteric vasculitis would be the most probable diagnosis. Shapeero *et al.* [9] looked at 141 patients with SLE, 68 patients had abdominal symptomatology at some stage during their disease. Symptoms varied from nausea and vomiting to abdominal pain and haemorrhage. Of these, 20 had reversible ischaemic disease (14.2%). Perhaps GI vasculitis is more common than generally recognized and many patients are misdiagnosed as having gastritis, ulcers or gastroenteritis. Further studies are necessary to correlate GI symptoms with radiographic changes. Serial X-rays for pneumoperitoneum and paracentesis, even when the radiographs are normal, may be useful.

In those patients with insidious onset of symptoms, non-invasive investigations such as ultrasound (US) and abdominal computed tomography (CT) should be considered first. CT and magnetic resonance imaging may identify intra-abdominal abscesses, lymphadenopathy, serositis, bowel wall thickening, oedematous and distended loops of bowel, pancreatic pseudocysts and hepatosplenomegaly in patients with SLE [87, 88]. Abdominal US can show bowel wall thickening [89]. Barium studies (or gastrografin when perforation is suspected), gastroscopy and colonoscopy may show signs of ischaemia and ulceration appearing as 'punched out' areas of mucosa. Colonoscopy is a useful technique, particularly as a biopsy may confirm the diagnosis of vasculitis.

Other highly specialized investigations such as gallium and indium-111 white cell scanning can highlight areas of inflammation and sepsis, and may be useful in difficult cases. Visceral angiography is not useful routinely as the pathology in lupus vasculitis lies in the small vessels. However, it may highlight areas of GI bleeding and rule out other differential diagnoses such as polyarteritis nodosa. If there is evidence of altered gut motility with ileus or diarrhoea, or progressive clinical symptoms, laparoscopy or open laparotomy to rule out ischaemia should be considered [70].

Treatment

If paracentesis and X-rays are negative, then these patients have potentially reversible ischaemia [77]. The treatment of severe systemic vasculitis is well established with pulsed methylprednisolone at a dose of 1–2 mg/kg/day in addition to complete bowel rest. There are numerous case reports of successful treatment of intestinal vasculitis with high-dose prednisolone only [3, 8, 69, 84, 90]. Owing to the paucity of patients with GI vasculitis, there have been no randomized clinical trials investigating the optimum treatment for these patients. Further large multicentre studies are required to evaluate the significance of acute abdominal pain in patients with active and inactive SLE in order to assess the difference in outcome comparing early medical intervention with i.v. methylprednisolone and cyclophosphamide against early surgical intervention in those who have failed to response to pulsed steroid alone. Intravenous pulsed steroid therapy is best employed for short-term management, given slowly over a 3–4 h period as with a rapid infusion over 15–20 min there is a danger of reactive arthropathy. We use pulsed therapy: up to 1 g of methylprednisolone on three consecutive days.

Today, treatment with i.v. cyclophosphamide is widely used in the management of systemic vasculitides [91]. There have been three recent case reports of successful treatment of GI vasculitis with i.v. methylprednisolone and cyclophosphamide in patients with SLE [82, 85, 90]. In those that do respond to i.v. steroids, then conversion to oral steroids with the addition of azathioprine as a steroid-sparing agent can be used [92]. To date, there have been no trials looking into the use of agents such as azathioprine, cyclosporin and methotrexate. The therapy needs to be tailored to the individual patient, coupled with the experience of the managing physician in treating patients with the above severe systemic manifestations of SLE. Global assessment of SLE disease activity to differentiate patients with active and inactive SLE, and early laparotomy (i.e. within 24–48 h), may improve the prognosis of patients with SLE who have abdominal pain. Medina *et al.* [69] noted that in their group of 33 patients (both active and inactive groups) who were operated on within 24–48 h, none died. However, in those operated on after 48 h, 10 out of the 11 patients died. In general, the outcome in patients with perforation is dismal with death occurring in more than two-thirds of cases [79].

Small intestinal ischaemia and intestinal infarction and perforation of both the small and large intestine require emergency surgery.

Large bowel ischaemia may be treated conservatively with antibiotics and resuscitation when appropriate. However, a low threshold of suspicion should be present for recommending diagnostic laparoscopy for all these

patients as it is less invasive and is followed by fewer complications than with open laparotomy [69].

Intestinal infarction

This may occur due to underlying vasculitis or hypercoagulability from secondary antiphospholipid syndrome [69, 81]. Medina *et al.* [68] found that in 51 SLE patients with signs and symptoms of an acute abdomen, three developed abdominal thrombosis (mesenteric thrombosis in two patients and hepatic arterial thrombosis in the other) in the subgroup with active disease. All three had high levels of anticardiolipin antibodies and two had the lupus anticoagulant. Two out of three patients died, the third responded to thrombectomy and high-dose steroids. Pathological examination may reveal thrombus in the branches of the inferior mesenteric artery without any evidence of vasculitis. High levels of antiphospholipid antibodies, thrombocytopenia and prolonged prothombin time can coincide with an episode of intestinal ulceration and infarction [81]. Diagnosis and therapy are similar to those for intestinal vasculitis, in addition to treatment with oral aspirin and anticoagulation after surgery. At our centre, we have had no cases of intestinal infarction in a cohort of 266 patients despite 24.4% being positive for anticardiolipin antibodies and 14.8% having lupus anticoagulant.

Inflammatory bowel disease

Ulcerative colitis (UC)

Persistent diarrhoea resulting from UC has been reported to be associated with SLE. UC has been described with other autoimmune diseases and appears to have an increased association in patients with autoimmune diseases.

Two unequivocal cases of UC reported occurring in association with SLE were in patients who had developed SLE prior to the onset of colitis and then subsequently developed primary sclerosing cholangitis (Table 9). We also report a male Indian patient whose renal lupus was successfully treated with prednisolone and azathioprine, and who subsequent to stopping the immunosuppression developed unequivocal biopsy-proven ulcerative colitis (D. Isenberg, unpublished observation) (Table 9). In our centre, the incidence in a cohort of 266 patient under long-term review is 0.4%. The incidence in the general population is not accurately available, but is $\sim 6.5/10^5$.

Multiple case reports describe colitis preceding the onset of SLE with symptoms and signs frequently beginning after the administration of sulphasalazine for the treatment of inflammatory bowel disease [93–95]. In most cases, the symptoms from drug-induced lupus have been reversible after the discontinuation of the offending drug. Of interest is that antibodies to dsDNA, which are not detected in drug-induced/SLE-like syndromes caused by hydralazine and procainamide, have been reported in the majority of patients with sulphasalazine-induced SLE. Gunnarsson *et al.* [95] found that four out of 11 patients with sulphasalazine-induced lupus had persistent clinical symptoms and positive anti-dsDNA 3 yr after withdrawal of the drug. The underlying mechanism by which sulphasalazine induces SLE or lupus-like syndromes is not clear. Gunnarson *et al.* suggested that slow acetylator status of the patient and HLA haplotype associated with idiopathic SLE were seen to predict induction.

Features which may discriminate between sulphasalazine-induced lupus (in a patient with UC) and the association of UC with idiopathic SLE are the presence of low complement levels (as drug-induced lupus is only rarely associated with low complement levels), presence of different types of autoantibodies which occur in idiopathic SLE [antibodies to the collagen-like region CLR of C1q (which occur in 47% of patients with SLE) [96], anticardiolipin antibodies (which occur in 10–30% of SLE patients), anti-Ro and anti-La antibodies] and HLA status as HLA DR3 is associated with idiopathic disease, whereas DR4 occurs in drug-induced lupus [93].

Regional ileitis (Crohn's disease)

The concurrence of SLE and regional ileitis is rare. There are very few case reports of the co-existence of these two diseases. Details of one reported case are shown in Table 9 [97]. Other reported cases in the literature presume the co-existence on clinical and radiological grounds as pathological material was not available. In our cohort of 266 patients, we have not had a patient with Crohn's disease.

As with UC, drugs used in the treatment of Crohn's disease, e.g. tetracycline and trimethoprim–sulphur, may cause drug-induced lupus and result in difficulty in determining which is the primary disease [98].

Collagenous colitis

This is a distinct disorder that is characterized by watery diarrhoea associated with thickening of the subepithelial collagen of the colon. It usually occurs as an isolated phenomenon and is rarely associated with autoimmune rheumatic disorders. There are a few reported cases of collagenous colitis in association with SLE (Table 9) [99]. Collagenous colitis has rarely been associated with seronegative polyarthritis [100], discoid lupus [101] and scleroderma [102]. There does not appear to be an association with concurrent therapy or SLE disease activity and all patients respond to low-dose prednisolone.

Coeliac disease

There have been a few case reports (Table 9) of non-specific inflammatory changes with villus blunting on small bowel biopsy specimens which correlate to features seen in coeliac disease [103]. HLAB8 and DR3 are found in 70–90% of patients with gluten-sensitive enteropathy (GSE). These markers are also found more frequently in patients with SLE [104]. Thus, Rustgi and Peppercorn [105] postulated that this genetic haplotype predisposes patients to acquiring both diseases. A gluten-

TABLE 9. Case history summaries of SLE patients with associated ulcerative colitis (UC), Crohn's disease and coeliac disease

Clinical features	Investigations	Management
Diagnosis of UC aged 10 yr. Treated with sulphasalazine. Aged 22 yr developed generalized lymphadenopathy, multiple ulcers and a purple plaque on his thenar primary eminence [93]	UC confirmed on rectal biopsy. Lymphopenia, low C4, ANA 1:100, antibodies to dsDNA >300 IU/ml. Anticardiolipin IgG antibodies 24 IU. ERCP demonstrated sclerosing cholangitis (PSC)	Sulphasalazine stopped. ANA and dsDNA antibodies remained positive 9 months after diagnosis of SLE. Treatment with prednisolone and azathioprine
Diagnosed with SLE aged 21 yr. Bloody diarrhoea 3 yr later [94]	ANA 1:200, dsDNA antibodies positive. Colonoscopy consistent with UC. [a]ERCP consistent with PSC[b]. No evidence of active SLE disease at onset of diarrhoea	SLE treated with chloroquine and prednisolone. Good response to sulphasalazine
SLE diagnosed aged 44 yr. Arthritis and glomerulonephritis. Bloody diarrhoea after reducing dose of azathioprine and prednisolone (D. Isenberg, unpublished observation)	ANA 1:80, dsDNA negative, complement normal. Colonic biopsy confirmed UC	SLE treated with azathioprine and prednisolone. Good response to sulphasalazine with resolution of symptoms
SLE diagnosed aged 36 yr. Six months later developed bloody diarrhoea and acute abdominal pain. Concurrent therapy with indomethacin [97]	Severe anaemia, lymphopenia. ANA 1:1280, anti-DNA antibodies 1:40. Complement levels normal	Crohn's disease confirmed at subtotal colectomy. Symptoms resolved with oral prednisolone
Intermittent diarrhoea since childhood associated with iron deficiency anaemia. SLE diagnosed aged 33 yr (D. Isenberg, unpublished observation)	Lymphopenia. ANA speckled. Anti Jo-1 positive. Complement levels normal	Jejunal biopsy confirmed coeliac disease. Good response to gluten-free diet. SLE responded well to prednisolone and chloroquine
SLE diagnosed aged 48 yr. Treated with oral prednisolone. Watery diarrhoea 18 months later [105]	ANA 1:320, lymphopenia. Small bowel biopsy confirmed total villous atrophy. Coeliac disease diagnosed	Resolution of symptoms on gluten-free diet. Prednisolone stopped after 6 months with no flare of SLE
SLE aged 47 yr with myositis and interstitial lung disease. Diarrhoea 6 months [99]	Low C3 and C4, lymphopenia. Rectal biopsy revealed thickened subepithelial collagenous band. Negative stain for amyloid	Collagenous colitis confirmed on biopsy with resolution of symptoms with oral prednisolone and sulphasalazine

[a]Endoscopic retrograde cholangio-pancreatography.
[b]Primary sclerosing cholangitis.

free diet, as in primary cases of GSE, is usually sufficient treatment, although steroids may be useful in resistant cases. A further case report documented a patient with SLE who developed skin eruptions similar to those seen in dermatitis herpetiformis, which is known to have an association with coeliac disease [106]. This suggests the possibility of coincident SLE and GSE in these patients. Others have reported vesiculobullous eruptions in sun-exposed areas in patients with active SLE, resembling dermatitis herpetiformis histologically, which have improved on treatment of the underlying disease rather than diet manipulation. In these patients, recurrence was associated with exacerbation of the underlying systemic disease [103]. We have also had one patient with SLE who subsequently developed coeliac disease (Table 9).

Organ-specific autoimmune diseases have an increased incidence in SLE compared with the general population e.g. autoimmune thyroid disease and type I diabetes. The overlap of SLE with both the organ-specific and non-organ-specific autoimmune diseases would be expected from the finding that HLA B8 and DR3 occur more commonly in both groups. Further large studies are required to assess the true frequency of UC, Crohn's disease and coeliac disease in patients with SLE. One explanation for the low reported frequency could be that the immunosuppressive therapy for lupus may be inadvertently rendering the above diseases subclinical as steroids are effective treatment for UC, Crohn's diseases and coeliac disease in resistant cases.

Other conditions of the small bowel associated with SLE

Protein-losing enteropathy (PLE) in SLE

Hypoalbuminaemia in SLE is most commonly due to excessive loss through the kidney causing nephrotic syndrome. Much less frequently, it can be secondary to decreased synthesis (deficient protein intake, liver disease) or rarely due to a PLE. Other causes include those secondary to constrictive pericarditis. There have been over 20 case reports of PLE in patients with SLE [107, 108]. The main features are the presence of severe diarrhoea and marked hypoalbuminaemia without proteinuria. In some cases, this may be the first manifestation of SLE [109]. Radiography demonstrates a prominent mucosal pattern because of oedema, spiculation, fragmentation and clumping of barium. Pathologically, villous atrophy with inflammatory infiltrates and submucosal oedema are seen without evidence of vasculitis.

Increased faecal excretion of i.v. radiolabelled albumin is the best quantitative study for following disease activity, although one report has suggested that 24 h clearance of stool alpha 1-antitrypsin can also monitor

response to therapy. This is a glycoprotein synthesized by the liver, with a molecular weight similar to albumin. When leaked into the GI lumen, it is digested minimally by intestinal proteases and then excreted in the stool. Thus, its excretion can serve as a measure of albumin loss into the GI tract [110]. Specific serological features appear to be present in a subset of patients with SLE in whom PLE is a major manifestation, including ANA positive (speckled pattern), anti-dsDNA negative, anti-RNP positive and low serum complement levels [111, 112].

The cause of PLE is unknown, but several theories have been postulated, including vascular damage, bacterial overgrowth [113, 114], fat malabsorption, alteration in bile salt metabolism, thrombosis and mesenteric venulitis as possibilities [115]. Intestinal permeability is altered in most patients, as measured by Cr-51-labelled ethylenediaminetetraacetic acid (EDTA) resorption tests [116]. The reported cases responded to low-dose steroid therapy; however, some patients may require a gluten-free diet [105, 117]. In cases with bacterial overgrowth, antibiotic therapy with tetracycline or metronidazole should be added for 7–10 days [110] as well as using oral steroids.

Fat malabsorption

Patients with SLE may also develop diarrhoea due to the malabsorption of fat. This may occur with or without carbohydrate malabsorption. It causes voluminous, oily, foul-smelling stools and weight loss. Investigations reveal positive staining of stool sample with Sudan black and increased fat content of stool on a 3 day collection. Pathologically, blunting of the villi and immune complex deposition have been described [114]. In addition to treatment with antibiotics and steroids as above, patients may require a low-fat diet, cholestyramine and supplementation with fat-soluble vitamins (A, D, K).

Colonic involvement

This is well recognized and may present as perforation secondary to arteritis [77] or colonic diverticulae [118]. Colonic diverticulae are present in 23% of all barium enemas. They are rare in the age group under 30 yr, but occur in $>50\%$ of those over 70 yr of age. They do not appear to occur more frequently in patients with SLE.

Zizic *et al.* [77] documented five patients (out of 107) with large bowel perforation, four of whom died, making colonic perforation the commonest cause of death in their series. At presentation, one patient was not receiving any corticosteroids, two were on a dose of 15 mg/day and one was on a reducing dose. All patients had clinical manifestations of active SLE in addition to the acute abdominal pain. It was noted that the most striking feature was evidence of active arteritis in all patients in other organ systems; either central nervous involvement (demonstrated by increased CSF pressure and protein), ulcerative skin lesions, signs consisting of mononeuritis multiplex and splinter haemorrhages. There are case reports of corticosteroids causing an apparent increase in perforations from colonic diverticulae. However, only two out of the five patients in Zizic *et al.*'s series had any diverticulae. One of these patients had no evidence of diverticular disease on barium enema 2 months prior to the terminal event when perforation of a diverticulum occurred. At autopsy, no other diverticuli were found, although there was evidence of diffuse arteritis in multiple organs. The second patient had a perforated sigmoid diverticulum with very severe arteritis at the site of the diverticulum and at other sites of the bowel. This patient was not on prednisolone. This suggests that arteritis probably plays a primary aetiological role in the perforation.

Anorexia, nausea and vomiting are common features. On examination, all patients had fever, tachycardia and tenderness in the lower quadrants of the abdomen. The abdominal pain was not well localized, becoming generalized only at the time when free air was demonstrated radiographically. Bowel sounds were normal in two out of the five patients with perforation.

Treatment and management are as for those with intestinal vasculitis.

Infective diarrhoea in SLE

Owing to the early diagnosis and treatment of renal and central nervous system disease, infections have become the leading cause of mortality and morbidity among patients with SLE [119, 120]. The recognition of infection in SLE may be delayed, partly because of their similar manifestations and partly because steroids mask its symptoms. Bacterial infections are the commonest type of infection. There are numerous case reports of non-typhoid *Salmonella* infections in patients with SLE, virtually all of whom presented with fever and only half had symptoms of gastroenteritis. Blood cultures usually grew *Salmonella enteritidis*, but stool cultures were positive in only 30% [121]. This observation is striking, since bacteraemia complicates $<5\%$ of all *Salmonella* gastroenteritis in healthy adults. Risk factors for this susceptibility appear to include concomitant steroid and/or cytotoxic therapy, low complement levels (resulting in decreased opsonizing activity), functional hyposplenism and haemolysis [122, 123].

Infections such as invasive amoebic colitis should also be considered in the differential diagnosis, especially if the patient gives a history of overseas travel [124]. Early endoscopy and specimen collection are important in diagnosis. Radiology is usually non-diagnostic with dilatation of the colon on films and thumbprinting on barium enema with loss of haustrations. Colonoscopy shows discrete ulcers surrounded by a ring of swollen mucosa and covered with white or yellow exudate. These findings are very similar to those found in ischaemic colitis. It is important to differentiate between ischaemic colitis due to SLE and fulminant colitis due to amoebiasis as the former requires high-dose corticosteroids, which can be fatal in amoebic colitis [125]. Again, GI manifestations due to the disease will be associated with evidence of disease activity in other organ systems.

TABLE 10. Gastrointestinal manifestations of major rheumatological diseases

	SLE	Rheumatoid arthritis	Adult dermato-myositis	Systemic sclerosis	Sjögren's syndrome
Oral lesions	++	+	–	–	+++
Oesophageal dysmotility	++	+	++	+++	+++
Small bowel	+	+	–	++	+
Large bowel	+	+	–	++	+

+++, occurs in >50% of patients; ++, occurs in 5–49% of patients; +, occurs in <5% of patients; –, occurs rarely if ever.

Gastrointestinal malignancy in SLE

There has been a case report of rectal and anal carcinoma in a series of 96 patients with SLE [132]. Three studies have shown increased risk of malignancy [126–128], although there was no increased risk of GI malignancy. Various solid tumours have been documented, including uterine, breast and cervical, as well as an increased risk of lymphomas. These contrast with other studies in which the frequency of malignancy was noted less often [129–131]. Abu-Shakra *et al.* [132] noted that there was a significant increased risk of haematological cancers, but there was a lower risk of all cancers. In our own group of 266 patients under long-term review with a follow-up period of 1695 patient-years, 15 malignancies were diagnosed in 14 patients (5.3%). Only one malignancy originated from the gut with a patient presenting with metastatic disease from a colonic primary tumour. As may be expected in a predominantly female population, the commonest was breast carcinoma (D. Isenberg, unpublished observation). Eighteen per cent of our patients have been treated with cyclophosphamide and 3% with cyclosporin—none of these patients have developed malignancies. We have found no evidence that treatment with cytotoxic agents conferred an increased risk of developing malignancies in patients with SLE.

Conclusion

GI manifestations of SLE are common; however, they are frequently overlooked in the presence of renal, pulmonary and cerebral complications. SLE is a great mimic of many GI conditions. The most common GI manifestation is involvement of the oral mucosa and a careful examination of the oral cavity is mandatory in all patients presenting with SLE. In assessment of a patient with a GI symptom, the effect of medication should always be considered first as the most common cause before embarking on intensive investigations. Once this has been excluded, then further investigations should be performed. However, it is often difficult to separate treatment-caused GI manifestations and those due to the disease itself, but disease activity in other organ systems is suggestive that the symptoms are due to lupus.

The most serious GI complications in SLE are those associated with abdominal pain. If initial investigations are negative and infection has been excluded, then patients should be promptly treated with high-dose steroids and immunosuppressive agents. If any patient fails to respond or deteriorates, then early rather than late surgery may improve the prognosis in these patients.

SLE is only one of the autoimmune rheumatic diseases and the others too may be complicated by GI manifestations. In Table 10, we summarize the more frequent of these manifestations in the other autoimmune rheumatic diseases.

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