Coexistence of Crohn's disease and systemic lupus erythematosus: a case report and literature review

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Lupus enteritis and Crohn's disease are two common immune diseases involving the gastrointestinal tract. There are many similar clinical manifestations, therefore it is very difficult to distinguish between them. The digestive system is involved anywhere from 8 to 40% of patients with systemic lupus erythematosus (SLE) and up to 53% of these go on to develop lupus enteritis. In patients with Crohn's disease, 6–40% were presented with oral mucosa ulceration, nodular erythema of skin, arthritis, eye disease and other extraintestinal manifestations. The concomitant of Crohn's disease and SLE is extremely rare; however, here we described a case of concomitant Crohn's disease and SLE characterized by recurrent intestinal obstruction. A systematic literature review of lupus concomitant with Crohn's disease was then conducted. Eur J Gastroenterol Hepatol 32: 1256–1262

Introduction

Systemic lupus erythematosus (SLE) is a chronic and serious autoimmune disease, characterized by erythema discus, myalgia and arthralgias. It is a multisystem disease and can induce renal, digestive, neurologic and hematologic disorders. SLE tends to occur primarily in women aged 15–44. Gastrointestinal involvement in SLE appears almost regular. The digestive system is reported to be involved in 8–40% of patients with lupus and up to 53% of patients with SLE develop lupus enteritis [1]. Lupus enteritis is a disease of lupus that affects a wide range of intestinal tract. Lupus mesenteric vasculitis, protein-losing enteropathy and intestinal pseudo-obstruction (IPO) are collectively known as lupus enteritis.

Crohn's disease is a chronic intestinal granulomatous disease with unknown etiology. It tends to occur in young people around 30 years old and old people around 60 years old. It is characterized by abdominal pain, diarrhea, constipation and repeated intestinal obstruction. The lesion site is usually located in the ileum and colon. Many patients with Crohn's disease; however, still suffer from extraintestinal manifestations, including arthritis, spondylitis, sacroiliitis and erythema nodosum.

European Journal of Gastroenterology & Hepatology 2020, 32:1256–1262

Keywords: Crohn's disease, lupus enteritis, literature review, systemic lupus erythematosus

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Received 30 January 2020 **Accepted** 14 April 2020

The differentiation between Crohn's disease and lupus enteritis is difficult because both the two diseases can show similar clinical signs and symptoms such as abdominal pain, bloating, intestinal obstruction and so on. In addition, it is known that coexistence of SLE and Crohn's disease is very rare. Crohn's disease may occur before or after the diagnosis of SLE, but Crohn's disease prior to lupus is commonly seen in drug-induced cases during Crohn's disease treatment. Crohn's disease's presence after SLE is extremely rare. Below we describe a rare case of concomitant Crohn's disease and SLE.

Case presentation

A 50-year-old Chinese woman was admitted to our hospital because of fever and relapsing episodes of abdominal pain over the last 9 months. The patient was diagnosed with SLE (9 months ago) based on fever, relapsing episodes of abdominal pain, bloating, leucopenia [white blood cells (WBC) 2.24×10^9/L] positive antinuclear antibodies (ANA), anti-double-stranded (dsDNA) antibody, anti-Smith antibody, ribonucleoprotein (RNP)/Smith antibody and polyserositis (pleural effusion, ascites and pericardial effusion). The symptoms were relieved after she was treated with prednisolone and mycophenolate mofetil. However, symptoms of fever (38.5°C) and abdominal pain relapsed again, accompanied by hair loss, dry mouth, reduced defecation in the period of gradual prednisolone decrease.

When she was presented to our hospital, she had no other symptoms such as dry eyes, rampant teeth, photosensitivity, oral ulcer, joint pain or Raynaud's phenomenon, with only fever, abdominal pain, as well as reduced defecation. The physical examination was unremarkable, except where there was pain at the lower right abdominal quadrant. Her medical history included osteoporosis and tuberculous infection. The tuberculous infection was found 4 months ago, and had been treated by rifampicin and isoniazid for 3 months; however, the abdominal pain did not relieve. Her family history was unremarkable.

Radiologic evaluation with computed tomography (CT) showed pneumatosis lumen, accompanied by air-fluid level and mesangial exudation. Laboratory tests were within normal limits except for leucopenia (WBC 2.56×10^9/L) and anemia (hemoglobin of 102 g/L). Erythrocyte sedimentation rate, C-reactive protein and procalcitonin were all normal, and blood culture for fungi and bacteria was negative. Immunological tests showed positive rheumatoid factor 153 IU/mL, decreased complement components C3 0.71 g/L (normal 0.85–1.93), positive ANA 1/320, as well as positive anti-Smith antibody, anti-dsDNA and anti-RNP antibodies. Tuberculosis (TB)-spot test was positive. The PET-CT found no abnormality. After the infection, intestinal tuberculosis and cancer were excluded, and SLE, mesenteric vasculitis and intestinal obstruction were considered. After treatment with methylprednisolone (120 mg/day *11d), cyclophosphamide (0.2 g/q2qod), gastrointestinal decompression and enteral and parenteral nutrition support, the patient's fever subsided, and WBC returned to normal. However, the incomplete intestinal obstruction, with reduced defecation, still existed. Abdominal X-ray examination still showed the air-fluid level (Fig. 1). Enteroscopy revealed a small intestinal ulcer with intestinal cavity stenosis, and the biopsy showed that intestinal mucosa had moderate chronic inflammation, with mild acute inflammation and erosion, except for granulation tissue formation (Fig. 2). Small intestine simulation CT revealed that part of the intestinal cavity was slightly expanded, with wall enhancement and multiple air-fluid planes (Fig. 3). Further laparoscopy, partial appendectomy and small intestine resection were performed after a comprehensive disease evaluation. Pathological examination showed longitudinal ulceration, stenosis and dilatation were observed in the intestinal canal and a lymph node was detected in the pericentric adipose tissue by gross observation. Microscopically, it could be seen that transmural inflammation, local erosion and ulcer formation. Inflammatory granulation tissue formation occurred at the ulcer site. Adipose tissue hyperplasia of the whole intestinal wall and outside the serous membrane, multiple lymphoid hyperplasia and reduce mucosal crypt could be seen. Besides, the submucosa of the surrounding intestinal wall was widened and swollen, and the blood vessels were dilated and congested. One lymph node was seen around the intestine (Fig. 4). It was diagnosed as multiple autoimmune diseases, SLE concomitant to Crohn's disease. The treatment regimen was adjusted to add cyclophosphamide (800 mg/month), thalidomide (75 mg/day) and metronidazole 0.4 g two times a day. Symptoms improved significantly and after 5 months, simulated small intestine-enhanced CT showed no stenosis in the lumen. The enteroscopy showed the ileum anastomosis was smooth and there was no ulcer stenosis.

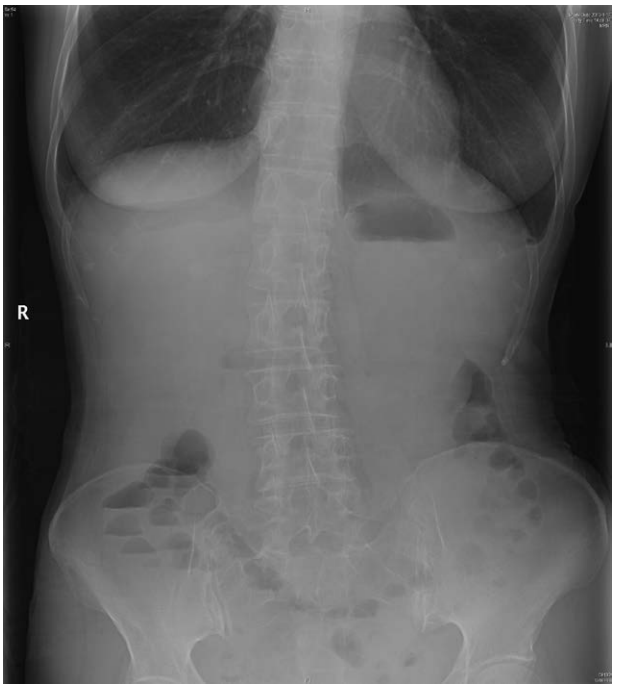

Fig. 1 Abdominal X-ray showed pneumatosis lumen, accompanied by air-fluid level.

Discussion

Although the patient's history is short, the diagnosis is extremely complicated, covering the differential diagnosis of three acute abdomens, which is one of the most valuable points of this case report. Second, the treatment of this case is extremely clever in the selection of immunosuppressants, which quickly stabilized the condition without the selection of biological agents.

Patients with SLE presenting with gastrointestinal symptoms account for about 50% of patients with SLE

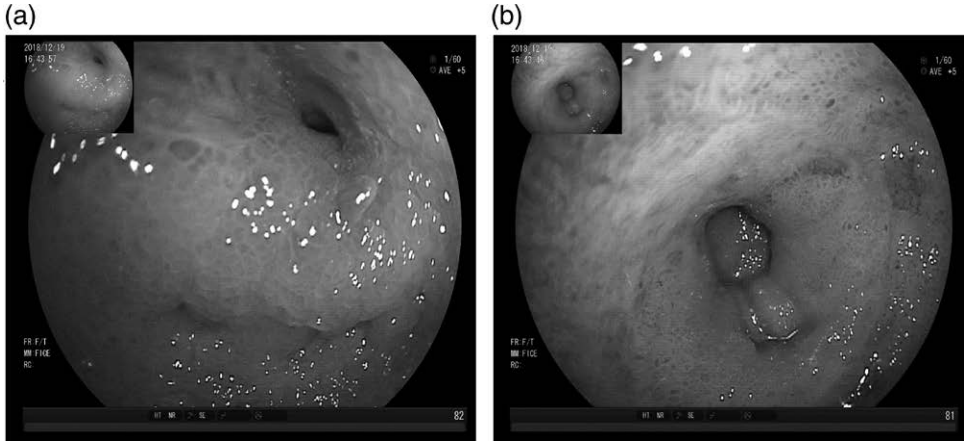

Fig. 2 Enteroscopy revealed small intestinal ulcer (b) with intestinal cavity stenosis (a).

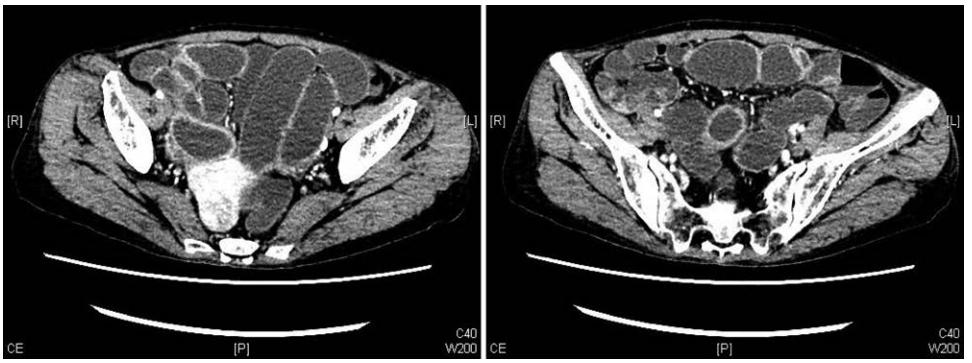

Fig. 3 Small intestine simulation CT revealed that part of the intestinal cavity was slightly expanded with wall enhancement and multiple air-fluid planes.

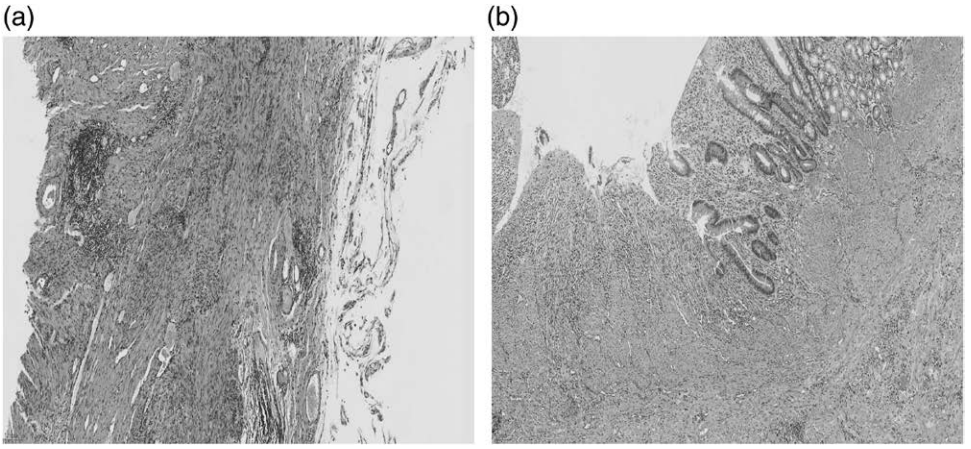

Fig. 4 Pathological examination showed transmural inflammation, local erosion and ulcer formation. Inflammatory granulation tissue formation occurred at the ulcer site (×10).

[2], mainly including lupus enteritis (including lupus mesenteric vasculitis, protein-losing enteropathy and IPO), acute pancreatitis and peritonitis [3]. The prevalence of lupus enteritis in SLE is up to 53% [1]; however, only 2% of patients with SLE usually have clinical symptoms of bowel vasculitis [4]. Patients with lupus enteritis are also prone to occur ischemic enteritis, bleeding or perforated peritonitis. It can present as a variety of gastrointestinal symptoms such as oral ulcer, dysphagia, anorexia, nausea, vomiting, bleeding, abdominal distension, abdominal pain, etc. Early radiographic manifestations of lupus enteritis were thumb-printing, targeted sign, comb sign, pseudo-obstruction and segmental bowel dilatation, and 'collar button types' when involving the colon by barium enema [5,6]. Ultimately, lupus enteritis is divided into two types: type 1 with perforated blood vessels and type 2 with nonspecific ulcers and granulomatous colitis [7,8]. The type 2 lupus enteritis is the one easily confused with Crohn's disease.

Crohn's disease is a chronic granulomatous inflammatory bowel disease (IBD) of unknown etiology. It is a type of IBD with diverse clinical manifestations and no clear diagnostic criteria. Crohn's disease can also present with abdominal segmenting colic, abdominal distension, and even ulceration of the oral mucosa, skin nodular erythema, arthritis, eye disease as well as other extraintestinal manifestations [9,10]. Crohn's disease is difficult to distinguish from lupus enteritis when it presents as extraintestinal manifestations involving the skin, eyes and joints. Therefore, pathological examination is the key to identifying and further distinguishing between the two diseases, by revealing the presence of inflammatory epithelial-giant cell granuloma. Lupus enteritis is more prone to perforation, which may occur even if the disease is well controlled [4]. Therefore, clinical treatment needs to be more active, and large doses of prednisolone or cyclophosphamide shock therapy is preferred. The patient had repeated intestinal obstruction under the definitive diagnosis of lupus, and lupus enteritis was initially considered. Though, after treatment involving large doses of prednisolone, the obstruction symptoms were not alleviated. According to the 2016 European Crohn's and Colitis Organization (ECCO) consensus and the 2018 consensus of IBD in China, the intraoperative pathological results were consistent with the pathological diagnostic criteria of Crohn's disease (Table 1). This did not support autoimmune enteropathy, and thus lupus enteritis was excluded.

Intestinal tuberculosis is a chronic and specific infection caused by the invasion of *Mycobacterium tuberculosis* into the intestinal tract, which can involve the upper and lower digestive tract, causing abdominal pain and intestinal obstruction. In addition, it can be accompanied by systemic symptoms such as low fever, night sweats and weight loss. Crohn's disease is an autoimmune disease; however, the clinical manifestations of abdominal pain, diarrhea, weight loss, fever and nutritional disorders, are clearly similar to the clinical symptoms of intestinal tuberculosis. Hence, it is easy to confuse the diagnosis of Crohn's disease with intestinal tuberculosis. The tuberculin test was strongly positive, and the gastroscopy showed

Table 1 Differential diagnosis

	Lupus enteritis	Crohn's disease	Intestinal tuberculosis
Clinical feature	Oral ulcer, dysphagia, anorexia, nausea, vomiting, bleeding, abdominal distension, abdominal pain	Diarrhea, hematochezia, perianal lesions, parenteral manifestations (joint pain, oral sores, skin diseases)	Fever, night sweats, weight loss
Microbiome	N/A	N/A	Acid-fast bacilli smear/culture positive
Image examination	Fingerprint sign, false obstruction, dilatation of intestinal segment	Bowel involvement/ comb sign/ jumping lesion	Lymph node necrosis/adjacent ileocecum involvement
Endoscope	Colon involvement, segmental, local irregular ulcer, spacious, clean and no moss ulcers, which discontinuous involved all gastrointestinal tract	Colon, sigmoid colon involvement, longitudinal ulcers, mouth sores, cobblestone lesions, lumen stenosis and jumping lesions/aphthous oral ulcer	Cecum involvement, transverse ulcer/ dilated ileum valve
Pathology	Chronic, nonspecific mucosal inflammation or vascular ischemic changes	Inflammatory epithelial-giant cell granuloma	Caseous necrosis

Table 2 Pathological diagnosis of Crohn's disease

1. Transmural inflammation
2. Distribution of aggregated inflammation, permeable lymphocyte hyperplasia
3. Submucosal thickening (caused by fibrosis – fibromuscular tissue destruction and inflammatory edema)
4. Fissures (fissuring ulcers)
5. Noncaseous granuloma (include lymph node)
6. Abnormalities in the gut nervous system (submucosal nerve fiber hyperplasia and ganglionitis, intermuscular nerve fibers proliferate)
7. Relatively normal epithelial-mucus secretion is preserved (Goblet cells are usually normal)

It has been suggested that a diagnosis of Crohn's disease should be made when three features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature provided that specific infections are excluded.

transverse ulceration around the cecum, ileocecal flap, as well as openings. Also, pathological features showed typical caseous necrotizing granuloma, which clearly identified intestinal tuberculosis [11]. The identification points between the three diseases are shown in Table 2. During the course of the disease, tuberculosis infection was found in this patient, but the symptoms did not relieve after 3 months of anti-tuberculosis treatment. According to the report by Kedia *et al*. [11], when the diagnosis of intestinal tuberculosis and Crohn's disease is uncertain, it is recommended to try to fight tuberculosis for 3 months. Crohn's disease is considered if endoscopic or radiological reexamination shows the disease is still active after 2–3 months of anti-tuberculosis treatment. In conclusion, intestinal tuberculosis was excluded and Crohn's disease was considered.

Studies have shown that SLE concomitant with Crohn's disease is extremely rare. In this study, the concomitant cases of Crohn's disease and SLE since 1985 were summarized, and a total of 15 cases were found [7,12–25]. Table 3 shows comparisons of reported patients with SLE complicating Crohn's disease. A total of nine cases of SLE prior to Crohn's disease have been reported. SLE often occurs after the diagnosis of Crohn's disease, which is mostly caused by drugs involved in treatment. The use of sulphapyridine [26,27], 5-aminosalicylic acid (5-asa) agents [28,29] and anti-tumor necrosis factors [20] used in the treatment of IBD may, therefore, lead to drug-induced lupus. There are four relevant case reports, including three cases of SLE induced by treatment with tumor necrosis factor and 1 case of Crohn's disease merged with lupus encephalopathy. The incidence of SLE coexistence with Crohn's disease is even more rare, and only two cases have ever been reported. This patient was diagnosed with Crohn's disease 9 months after the diagnosis of lupus. During the course of the disease, the patient was mainly manifested by repeated intestinal obstruction. Except for the specific antibodies found for lupus, there were no extraintestinal manifestations, so we considered the SLE as co-occurring with Crohn's disease. We found that among the 15 patients with SLE concomitant with Crohn's disease, 7 patients were less than 30 years old and 4 patients were more than 50 years old. Consequently, we speculate that SLE concomitant with Crohn's disease may occur more frequently in people less than 30 years old or more than 50 years old. It was noted that this patient was just in the high-risk group. All of these patients were treated with steroids or immunosuppressants and ended up in remission. Only one male was untreated for economic reasons and eventually died. Perhaps we can speculate that SLE with Crohn's disease has a better prognosis.

According to the response of Crohn's disease to steroid treatment, it can be divided into three categories: steroid dependence Crohn's disease, steroid-refractory Crohn's disease and steroid intolerance Crohn's disease. In this case, the symptoms were relieved after treatment with high-dose steroids and enzymatic phenolic esters at the onset of the disease, and the recurrence of symptoms during the course of steroid reduction was considered to be related to steroid reduction. Since lupus was assessed as mildly active according to the systemic lupus erythematosus disease activity index score in 2000, the diagnosis of SLE combined with steroid dependence Crohn's disease was considered. For steroid dependence Crohn's disease, steroids are the first line of treatment, and although steroids contribute to Crohn's disease remission, they are not effective for maintenance treatment. The ECCO Guideline proposed that steroids contribute to the maintenance therapy of immunosuppressants such as methotrexate, azathioprine and cyclophosphamide in patients with recurrent Crohn's disease [30,31]. After treated with methylprednisolone and cyclophosphamide, the intestinal obstruction was not completely relieved. Thus, it may be transformed into steroid-refractory Crohn's disease, and at this condition, tumor necrosis factor-α (TNF-α) was recommended by the guidelines. However, the patient had a history of tuberculosis infection, and TNF-α may induce TB activity, so the final choice of surgical treatment was reasonable.

Table 3 Comparison of reported patients with systemic lupus erythematosus complicating Crohn's disease

Case	Age/ gender	SLE/Crohn's disease duration (years)	Symptoms	ESR (mm/h)	Immunological findings	Endoscopic findings	Histopathological examination biopsy	Treatment	Publication date
1	28/M	SLE 7 years	Diarrhea, pyoderma, gangrenosum	89	ANA 1:1280 dsDNA 1:160	Deep linear and ulceration, pseudopolyps, skip lesion	Acute and clonic inflammation	Prednisolone	1985 [12]
2	15/F	SLE 3 years	Abdominal pain, diarrhea, blood-stained stool	68	ANA 1:1280 dsDNA 1:50	Multiple ulcers with linear ulcer, skip lesion, pseudopolyps	Infiltration of chronic inflammatory cells in the lamina propria mucosa with marked depletion of goblet cells without vasculitis	Salicylazosulfapyridine	1989 [13]
3	55/F	SLE 12 years	Intermittent hematochezia, tenesmus and loose bowel movements	35	ANA 1:80 dsDNA 1:80	Multiple ulcers with linear ulcer, diffuse aphthous ulcers	Active colitis with noncaseating granulomas	Prednisolone	1995 [14]
4	25/F	Crohn's disease 4 years	Watery diarrhea, lower abdominal, pain, perianal, abscess	N/A	ANA 1:160 dsDNA 800 IU/mL pANCA (+)	Longitudinal ulcers and mucosal erosion	Focal cryptitis with noncaseating granuloma	Salicylazosulfapyridine	1998 [15]
5	37M	SLE 9 years	Diarrhea, Hematochezia	65	ANA 1:320 dsDNA 1:320	Longitudinal ulcers, linear ulcer, cobblestone appearance, pseudopolyps	Nonspecific colitis without vasculitis	Salicylazosulfapyridin, azathioprine	1999 [16]
6	49F	SLE 5 years	Diarrhea, abdominal pain, massive bloody stool	N/A	ANA (+) dsDNA 234 IU/mL	Emergent operation with a right hemicolectomy was performed.	Transmural fibrosis and inflammation with lymphocyte aggregation, but no evidence of vasculitis.	Prednisolone	2008 [17]
7	19/F	Crohn's disease 5 years (SLE induced by infliximab and adalimumab)	Swelling in her fingers, wrists, elbows, knees, and ankles	N/A	ANA 1:5120 dsDNA 1:40	N/A	N/A	Mesalazine	2009 [18]
8	18/F	Crohn's disease 4 years	Abdominal pain, diarrhea, keratitis	N/A	ANA (+) dsDNA (+)	Segmental colonic ulcer	Epithelial granuloma	Prednisolone, azathioprine, chloroquine	2001 [19]
9	53/F	Crohn's disease 6 years (lupus encephalopathy induced by Adalimumab)	Nuchal headache, dizziness, a visual, defect in her right eye, chest pain, pleuritic pain	N/A	ANA 1:320 dsDNA 1:320	N/A	N/A	Prednisolone	2011 [20]
10	27/F	Crohn's disease 5 years (SLE induced by infliximab)	Multiple joint swelling and pain, abdominal pain	66	ANA (+) dsDNA (+)	N/A	N/A	Prednisolone, azathioprine	2012 [21]
11	55/F	SLE 36 years	GI bleeding, diarrhea	48	ANA (+)	,	Noncaseating granuloma and no evidence of vasculitis	Infliximab	2012 [7]
12	40/F	SLE 2 years	Abdominal pain, diarrhea, upper and lower extremities arthralgias	32	ANA1:640 dsDNA1:40	Colonic inflammation with ulcers and pseudopolyps	Supportive of Crohn's disease	Prednisolone, azathioprine, hydroxychloroquine, mesalazine	2013 [22]
13	34/F	SLE 21 years (lupus nephritis and Crohn's disease)	Abdominal pain, diarrhea, weight loss	N/A	N/A	Several deep pleomorphic ulcers, some confluent, with sparse normal mucosa between them, from the rectum to the cecum.	Supportive of Crohn's disease	corticosteroids	2015 [23]
14	22/F	Concurrence of Crohn's disease and SLE	Fever, arthralgia, diarrhea, vomiting	73	ANA 1:160 dsDNA 7.5 IU/mL	A discontinuous cobblestone appearance and longitudinal ulcers	A noncaseating granulomatous lesion in the colonic mucosa	Prednisolone, cyclosporine, infliximab	2017 [24]
15	71/F	Concurrence of Crohn's disease and SLE	Abdominal pain, diarrhea,	130	ANA1:320	Multiple ulcers in the terminal ileum	Tended to Crohn's disease (there were ganglion cell and crack shape ulcer)	Prednisolone	2019 [25]

ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; N/A:Not available; SLE, systemic lupus erythematosus.

The patient's symptoms were relieved after the operation. Maintenance therapy included the application of cyclophosphamide to control SLE and thalidomide to prevent Crohn's disease recurrence. Thalidomide has a similar effect to TNF-α) and has a lower risk of inducing TB activity. Finally, the patient's symptoms were well controlled, and Crohn's disease and SLE did not recur.

We hypothesized that the concurrent occurrence of SLE with Crohn's disease was not accidental. SLE and Crohn's disease are similar to other immune-mediated inflammatory diseases, but their etiology and pathogenesis are unknown. Currently, it is believed that they are produced by microorganisms and genetic/immune/environmental factors [32]. Autoimmune diseases are known to cluster in families, and studies have found that SLE, Crohn's disease and certain alleles on major histocompatibility complex-II are related. For example, the alleles of DR2 and DR3 in the human leukocyte antigen region are susceptible to SLE, and these loci genes are also closely related to Crohn's disease [33,34]. In addition, data from 1305 published and unpublished SLE patients with the Computer Aided Reliability Date (CARD) risk allele showed that only patients with IBD with CARD (908R) gene were at high risk of SLE. Dana *et al*. used linear regression to analyze 5018 patients with SLE in the CHS database and 25 090 patients excluding SLE and confirmed the correlation between SLE and Crohn's disease [35].

The coexistence of SLE (subsequently lupus enteritis) and Crohn's disease in a patient represents a diagnostic challenge, as they have many similar clinical manifestations and signs. In some cases, Crohn's disease may satisfy the classification criteria of SLE. Therefore, repeated gastrointestinal symptoms in patients with SLE should be considered as Crohn's disease after infectious and visceral vasculitis are excluded. It is difficult to distinguish lupus enteritis from Crohn's disease by laboratory tests and imaging, which is where endoscopy and biopsy become key in diagnosis. Especially for patients resistant to methylprednisolone, it is recommended a biopsy is conducted as soon as possible to make a clear diagnosis. Although corticosteroids and immunosuppressive drugs are equally effective for both, they have a different emphasis on the selection of immunosuppression, as well as different treatment intensities. As an example, lupus enteritis is more effective on steroids, cyclophosphamide, enzymatic phenolate esters and calcineurin preparations. Whereas Crohn's disease patients see more positive results when using hormones, thalidomide and TNF-α. So as a result, early diagnosis is very important for the prognosis of patients with these conditions.

Acknowledgments

The patient signed a written informed consent form for the purpose of publication of the results of this case study.

Conflict of interest

There are no conflicts of interest.

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