Diagnostic Challenge in Distinguishing Crohn's Disease from Lupus Enteritis in Systemic Lupus Erythematosus Patient: A Case Report

Eka Benhardi Layadi, Rabbinu Rangga Pribadi*, Anna Ariane**, Emiliana Kartika*, Diah Rini Handjari***, Irsalina Idzni*, Oemar Ichsan*, Megawati Ananda Hasbi Putri**

*Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy
Department of Internal Medicine, Faculty of Medicine
Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta
**Division of Rheumatology, Department of Internal Medicine
Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta
***Department of Anatomical Pathology, Faculty of Medicine
Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:
Rabbinu Rangga Pribadi. Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Pangeran Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-3153957; Facsimile: +62-21-3142454. E-mail: rabbinurangga@gmail.com

ABSTRACT

Diagnosing Crohn's disease in systemic lupus erythematosus patients with gastrointestinal symptoms poses a great challenge, due to its rare occurrence and similarity of clinical characteristics between its differential diagnosis. We herein present a rare case of a patient diagnosed with systemic lupus erythematosus, complicated by renal involvement and conspicuous gastrointestinal manifestations. The non-specific gastrointestinal findings in this patient led to challenge in differentiating lupus enteritis from Crohn's disease, as they share many similar aspects in clinical manifestations, endoscopic findings, and histopathological findings. We herein provide the clinical judgement in reaching Crohn's disease in concurrence with systemic lupus erythematosus as the final working diagnosis through scrutinizing and comparing data from similar case studies in the past.

Keywords: *Crohn's disease, systemic lupus erythematosus, differential diagnosis*

ABSTRAK

Penegakkan diagnosis Crohn's disease pada pasien systemic lupus erythematosus dengan gejala saluran cerna merupakan suatu tantangan karena insidensi komorbiditas kedua penyakit ini yang rendah dan manifestasi klinis Crohn's disease yang dapat menyerupai penyakit saluran cerna lain. Kami melaporkan sebuah kasus seorang pasien systemic lupus erythematosus dengan morbiditas keterlibatan ginjal yang memiliki gejala klinis sistem gastrointestinal yang prominen. Temuan gastrointestinal yang non-spesifik pada pasien ini mengakibatkan kesulitan dalam mencapai diagnosis akhir Crohn's disease dari lupus enteritis karena kedua entitas ini memiliki berbagai aspek klinis yang serupa dari segi manifestasi klinis, temuan endoskopi, dan temuan histopatologis. Dalam laporan ini, kami menyajikan temuan dan pertimbangan klinis dalam mendiagnosis komorbiditas Crohn's

disease pada systemic lupus erythematosus sebagai diagnosis akhir melalui analisis studi dan komparasi data klinis dengan laporan kasus serupa.

Kata kunci: *Crohn's disease, systemic lupus erythematosus, diagnosis banding*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is caused by autoantibody production, complement activation, and immune complex deposition.[1–3] Systemic lupus erythematosus has a wide range of clinical manifestations and the clinical picture varies greatly between patients as it affects multiple organ systems.[2,4,5] One of the organ systems affected with active SLE is the digestive system and gastrointestinal (GI) symptoms that are frequently reported by SLE patients.[6,7] Although some of the GI symptoms can be caused by adverse reactions to medication and infections, the most common cause is lupus mesenteric vasculitis (lupus enteritis). Other studies showed prevalence of other GI diagnoses related to SLE, namely intestinal pseudo-obstruction (2%), followed with protein-losing gastroenteropathy (1.9%), and acute pancreatitis (0.7–4%).[8,9] Other rare causes include celiac disease and inflammatory bowel disease (IBD).[8-]

Lupus enteritis was defined by the British Isles Lupus Assessment Group (BILAG) as vasculitis or inflammation of the small bowel with supportive image and/or biopsy findings.[9] The most common presenting symptom of lupus enteritis is abdominal pain (97%), followed by vomiting (42%), diarrhea (32%), and fever (20%).[10] There are no specific markers for lupus enteritis which can aid in diagnosis, but a recent study conducted by Aso et al has shown that anti-ganglionic nicotinic acetylcholine α3 subunit (anti-gAChRα3) could be a potential biomarker for lupus enteritis.[11,12] Other recent study has also shown that low levels of CH50 (total complement) at the start of treatment could portend a poor treatment response in patients with lupus enteritis.[13,14]

The other disease entity juxtaposed with lupus enteritis in this case was inflammatory bowel disease (IBD), specifically Crohn's disease (CD), which may occur concurrently among SLE patients, exerting gastrointestinal distress. CD is a chronic relapsing inflammatory disease involving the GI tract, which manifested from a complex interaction between genetic susceptibility, intestinal flora dysbiosis, and environmental factors.[15–17] Although SLE is frequently observed with many other autoimmune and inflammatory diseases, concomitant diagnosis of IBD in SLE has been considered rare.[18,19] In addition to the rare occurrence, diagnosis of SLE with the coexistence of CD also poses a great challenge because lupus enteritis, shares similar symptoms, clinical signs, and radiographic findings with CD.[20] To the best of the authors' knowledge, there has not been any published case study regarding the coexistence of SLE and CD in Indonesia. Therefore, we reported this case study to exhibit how the final diagnosis of CD was obtained despite the diagnostic challenges.

CASE ILLUSTRATION

A 30-year-old woman was diagnosed with SLE with renal involvement in 2012, at the age of 22. Initially, the presenting symptoms reported by the patient were foamy urine and generalized swelling of the body. The urinalysis revealed granular renal casts, occult blood, and a 24-hour quantitative urinary protein of 6.029 gram/24 hours (normal value < 0.14 gram/24 hours). Further investigation was carried out to evaluate the possibility of SLE after the patient mentioned history of arthralgia, malar rash, recurrent oral ulcers, hair loss, relapsing fever for the past 12 months. The patient's blood panel results were suggestive of hemolytic anemia, thrombocytopenia, and leukopenia with Hb levels of 9.7 g/dL (12–14 g/dL), positive direct Coombs' test, thrombocyte count of 122,000/mcL (150–500,000/mcL), positive anti-platelet antibody, and leukocyte count of 3,350/mcL. ANA test revealed a value of 9.72 (normal value < 1). Elevation of anti-dsDNA levels was also documented with a value of 418.08 IU (normal value < 25 IU). Complement levels of C3 were decreased with a value of 81 mg/dL (normal value 90–180 mg/dL), while C4 levels were within reference range at 12 mg/dL (normal value 10–40 mg/dL). Antiphospholipid panels (anti-cardiolipin antibodies and anti-beta-2-glycoprotein) were non-reactive and lupus anticoagulants were negative.

The diagnostic criteria for SLE using Systemic Lupus International Collaborating Clinics (SLICC) 2012 were fulfilled with 6 clinical criteria and 3 immunologic criteria (ANA, anti-dsDNA, low complement levels). The patient also fulfilled the diagnostic criteria for SLE generated by the American College of Rheumatology

(ACR) in 2019 with cumulative the systemic lupus erythematosus disease activity index (SLEDAI) scores of 29, indicating high disease activity upon diagnosis. The patient was reluctant to undergo kidney biopsy, thus further definitive classification and extension of renal involvement could not be assessed. Even without the execution of kidney biopsy, the laboratory results and subsequent clinical findings of the patient met the diagnostic criteria for lupus nephritis according to ACR 2012. In terms of management, the patient was initially treated with mycophenolate mofetil 500 mg twice daily, chloroquine 250 mg twice daily, methylprednisolone 16 mg thrice daily, and losartan 50 mg once daily. The patient had achieved complete remission within two years, before the regimen was changed to azathioprine 50 mg twice daily and triamcinolone 4 mg twice daily for 3 years until 2017.

In 2017, the patient had a history of watery diarrhea, which had occurred for more than a month. The patient reported five passing liquid stools a day with occasional slimy mucus around the stools. She denied passage of fresh blood, black tarry stools, nausea, vomiting, abdominal pain, and weight loss. These episodes of diarrhea were initially suspected as infectious in origin and were relieved by antibiotics administration of ciprofloxacin 500 mg twice daily. The diarrhea was controlled for months, but relapsed continuously with periods of acute exacerbations and transient remissions for seven months. Stool analysis was performed and the result was within normal limits.

The chronic relapsing nature of the patient's GI symptoms warranted a colonoscopy assessment for further evaluation. The colonoscopy revealed hyperemic and edematous mucosa of terminal ileum and colon. Biopsy of the lesions confirmed an active chronic ileocolitis with crypt destruction, with additional findings of atrophic villi and deposition of chronic inflammatory cells along with lymphoid aggregates in the lamina propria. From the standpoint of predilection sites and histopathological findings, the involvement of terminal ileum and chronic inflammatory cells deposition can be observed in both CD and lupus enteritis. Granuloma formation which could gravitate the working diagnosis towards CD was not visualized as well, expanding the gray area that obscured the diagnosis. However, the absence of ischemic changes on histopathological findings favored the diagnosis of CD. Thus, the patient treated for CD and was given a regimen ciprofloxacin 500 mg twice daily for one week and mesalazine 500 mg twice daily for two months. The patient's azathioprine regimen was switched back to mycophenolate mofetil 360 mg twice daily. Complaint of diarrhea was resolved with mesalazine and antibiotic administration, and the second colonoscopy showed improvement two months later with mucosal healing of the terminal ileum.

After a two-year period of remission, complaint of diarrhea relapsed again in 2019 and another colonoscopy evaluation was scheduled. The colonoscopy at the time revealed multiple circular, clean-based ulcers on the descending colon with some hyperemic regions of mucosa surrounding the ulcers. The results of biopsy indicated non-specific ileitis and active chronic colitis, with crypt distortion and chronic inflammatory cells deposition in the lamina propria, and absence of ischemic changes. The mesalazine regimen was replaced with sulfasalazine 1000 mg twice daily and the symptoms of CD resolved since the administration of sulfasalazine. The patient stayed in remission until current examination with the regimen of mycophenolate mofetil 360 mg twice daily and sulfasalazine 500 mg thrice daily.

DISCUSSION

The coexistence of CD and SLE has been perceived as a rare occurrence, especially when SLE is also complicated with renal involvement (lupus nephritis).[21] A prior multivariate logistic regression study by Shor et al showed a strong positive association between SLE and CD (OR = 2.23; 95% CI: 1.46–3.4; $p < 0.001$), which can be explained by the fact that SLE and CD share some of genetic loci that are exclusive between the two entities, namely TNSF15, CCNY, ICOSLG, and UBE2L3.[22] These genes are essential for several cytokine ligands expression and immune cells activation.[18] A recent case study has also discovered the presence of ring chromosome 18 in a patient with SLE and CD, which may have a role in the concurrent development of the two diseases on genetic level.[23] Studies have also shown that patients with IBD tend to have higher prevalence of reactive ANA levels than healthy population, which supports the association between the two entities.[24]

The prevalence of lupus enteritis ranges from 0.2–5.8% from studies, and 65% of lupus enteritis cases were discovered to be attributed to lupus nephritis.[6,25] A recent article review regarding the coexistence of CD and SLE conducted by Jin et al showed fifteen documented case studies from 1985–2019 with variable characteristics and clinical findings. There was only one out of fifteen case studies which reported the

coexistence of CD and SLE with renal involvement as in this case.[26] The need to differentiate between the two entities is essential because lupus enteritis is generally reversible and steroid-responsive, while CD requires more aggressive treatment in order to prevent complications such as perianal abscess, strictures, and fistula which would often require surgical intervention.[10]

The combined results of studies concerning the characteristics of patients with the coexistence of SLE and CD indicated that the majority of patients were women (82%) and both concomitant diagnoses were made between 15 and 56 years of age. The diagnosis of SLE preceded the diagnosis of CD in 65% of cases.[21] In this case, the patient fitted the typical characteristic profile. She was diagnosed with SLE complicated with renal involvement at the age of 22. Lupus nephritis as the initial presentation of SLE only occurs in about 35% of SLE patients.[27] The diagnosis of CD was confirmed 5 years following the SLE diagnosis in this patient. The time duration between two concomitant diagnoses varies greatly, especially when SLE precedes the CD diagnosis, with the shortest duration of 2 years and the longest duration of 36 years.[26] When CD precedes SLE, the administration of drugs to control CD such as sulfasalazine, infliximab, and adalimumab can play a role in the development of drug-induced lupus erythematosus.[28–30]

There are multitudes of conditions that have similar manifestations to CD, aside from the most similar entity, lupus enteritis. Therefore, a complete work-up to exclude differential diagnoses, such as infectious origins, lupus-like reactions, and visceral vasculitis needs to be carried out in order to reach the final diagnosis.[16] In the case when SLE is complicated with concomitant antiphospholipid syndrome (APS), ischemic enteritis is also one diagnosis which should be priorly excluded. In addition to that, approximately 22% of CD patients also have positive anti-cardiolipin antibodies.[31] Since the anti-cardiolipin antibodies were not reactive in this patient and there was no history of thrombosis, ischemic enteritis could be properly excluded in this case. The stool analysis findings also showed no leukocytes, occult blood, nor parasites, which did not support inclination toward ongoing infection processes.

The similarities in clinical characteristics between CD and lupus enteritis exhibited the difficulty of distinguishing both entities.[22] The pooled data indicated that IBD associated with the diagnosis of SLE, diagnosis was determined primarily through endoscopic and histopathological findings as in this case, while an additional abdominal CT-scan may be considered to find for the target sign that is highly associated with lupus enteritis.[10,21] Lupus enteritis has two phenotypes, shown by perforated blood vessels (type 1) or nonspecific ulcers, accompanied by granulomatous colitis (type 2). Among both phenotypes, type 2 was known to be barely perceptible from CD.[24]

The clinical feature of lupus enteritis ranges from oral ulcer, dysphagia with/without anorexia, nausea and/or vomiting, abdominal pain with/without abdominal distension; while CD is associated more with weight loss, diarrhea, hematochezia, mucus in the stool, perianal lesions, and systemic manifestations, such as joint pain and skin disease.[32] Abdominal pain is one of the most common symptoms of lupus enteritis, which occurred in 80–97% of patients.[33] The initial symptom of this particular patient was unresolving chronic diarrhea without any abdominal pain, which progressed into significant weight loss, and thus based on the scope of symptoms, the diagnosis was inclined toward CD rather than lupus enteritis. Additionally, similar case reports also documented diarrhea and hematochezia as the main presenting symptoms of CD with concomitant SLE, supporting the notion.[24] No extraintestinal manifestations of CD were observed in this case. However, some studies did report several extraintestinal manifestations such as arthralgia, joint swelling, and keratitis in CD patients with concomitant SLE.[20,29,34,35]

To date, there are no specific diagnostic examinations that can differentiate CD from lupus enteritis, as these two entities cannot be solely diagnosed by laboratory findings alone. A study by Janssens et al revealed that the laboratory findings discovered in lupus enteritis were anemia (52%), leukocytopenia and/or lymphocytopenia (40%), and thrombocytopenia (21%), with median C-reactive protein (CRP) value of 2.0 mg/dL, and hypocomplementemia was reported in 88% of cases. From the serology studies, ANA was positive in 92% of patients and dsDNA was positive in 74% of patients.[10] All of the documented case reports regarding SLE concomitant with CD showed positive ANA and dsDNA, and there is one study showing positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA), which is specific for CD.[36] However, the possibility of using p-ANCA in differentiating lupus enteritis and CD has not been explored.

The endoscopic findings of lupus enteritis and CD are similar, although some findings such as longitudinal

ulcers, cobblestone changes, and segmental jumping lesions are strongly associated with CD, and the findings of multiple round- or oval-shaped ulcers are strongly associated with lupus enteritis.[37] The other features of lupus enteritis are segmental, local irregular, spacious, and clean ulcers which can often be found in the colon.[24] Moreover, similar to the predilection sites for CD ulcers, some studies have also documented lesions of lupus enteritis in ileum (85% of cases) and jejunum (80% of cases) as well.[38] In addition to the classic finding of the cobblestone appearance in concurrent CD and SLE, the findings documented in other similar case reports were multiple ulcers in terminal ileum, pseudopolyps, deep pleomorphic ulcers in the colon with skip lesions.[20,37,39] The endoscopic findings of this patient were initially a hyperemic terminal ileum, which progressed into multiple ulcers with surrounding hyperemic areas in the descending colon two years after. The ulcers were circular and clean based, and no mass was observed. (Figure 1). However, the attributes found in the colonoscopic evaluation of this patient were non-specific and could not overtly discern CD from lupus enteritis.

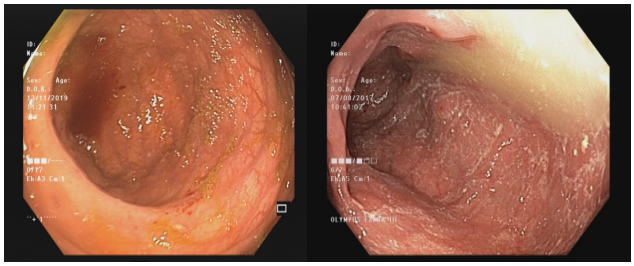

Figure 1. Colonoscopy findings showed hyperemic terminal ileum (left, taken in 2017) and multiple ulcers with surrounding hyperemic regions in descending colon (right, taken in 2019)

Histopathology examination has not been commonly used as the sole method to differentiate lupus enteritis from CD as they can share similar features, especially when characteristic findings of CD are not present. Lupus enteritis manifests as chronic, nonspecific mucosal inflammation or vascular ischemic changes, while CD typically manifests as inflammatory epithelial-giant cell granuloma.[24] However, granuloma is not always observed in CD, and only some cases of vasculitis can be confirmed histologically.[10] The biopsy result of this case illustrated active chronic ileocolitis with crypt destruction which suggested either IBD or chronic infection (atrophic villi, lamina propria was occupied by chronic inflammatory cells and lymphoid aggregates). A similar case report reported transmural fibrosis and inflammation with lymphocyte aggregation, without evidence of vasculitis in a patient with concurrent CD and SLE.[40] In contrast to the histopathological findings illustrated in this case, the most common findings in similar case reports were non-caseating granuloma.[24] The endoscopic and histopathologic findings in this study were not specific to both diseases, as chronic ileitis could be caused by either CD or SLE, yet the absence of vascular ischemic changes gravitated our clinical judgement toward Crohn's disease (Figure 2).

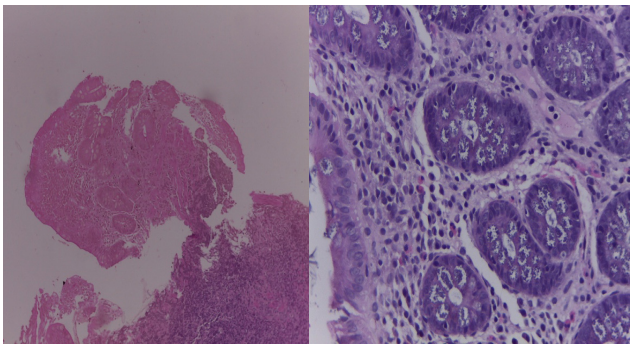

Figure 2. Histopathological examination showcasing active chronic ileitis with crypt destruction with absence of ischemic changes (left) and chronic inflammatory cells deposition (mainly histiocytes) within the lamina propria of colonic mucosa (right)

Some studies used the results of abdominal CT scan findings as a primary justification of lupus enteritis diagnosis.[41,42] The features of lupus enteritis that can be found through CT scan are the target sign, comb sign, pseudo-obstruction, increased mesenteric fat attenuation, and segmental bowel dilatation.[37,43] However, comb sign and segmental bowel stenosis are not specific signs because they can also be found on CD.[37] The characteristic target sign in lupus enteritis is documented in 71% of patient through imaging studies.[10] In this patient, unfortunately, the abdominal CT scan was not performed at diagnosis and this fact highlights the limitation of this study .

The patient was introduced to sulfasalazine and symptoms were finally improved. Similar case reports have shown that prednisolone was the most commonly used medication in treating CD with concurrent SLE.[24] Mesalazine was also used in two related studies, with one case similar to the current case, and the other one was used to treat infliximab and adalimumab-induced SLE in a patient with CD.[20,30] Another two studies combined prednisolone with azathioprine for the treatment.[32,35] The use of infliximab in treating CD with concurrent SLE are also highly encouraged, due to its rapid effect on alleviation of symptoms and mucosal healing.[31,34] JAK inhibitors can also be used as second-line treatment as some studies have shown that they exhibited some beneficial effects for both diseases.[44]

Along with the treatment regimens, the pooled clinical findings of this case were tabulated in tandem with the common clinical findings found in lupus enteritis and CD for comparison in Table 1 below (Table 1).

According to ACR 2012, the patient met diagnostic criteria for lupus nephritis and achieved remission with consumption of mycophenolate mofetil, but the kidney biopsy could not be conducted because of the patient's reluctance. The coexistence of lupus nephritis and CD is very rare. Up to date, there are only four published reports regarding the coexistence of lupus nephritis and CD, to the best of the authors' knowledge. One study was written in Japanese and published in 1989, and the authors could not explore the findings further.[45] Another study by Principi et al reported a case of CD with concurrent lupus nephritis that was unresponsive to corticosteroids and immunosuppressants, but showed a favourable response with infliximab administration.[46] A study by Magalhães et al also reported a similar case of CD concurrent with lupus nephritis with presenting symptoms of diarrhea and weight loss, which showed dramatic improvement with the administration of infliximab.[39] Another study by Somaï et al reported a case of lupus nephritis complicated with CD and Sjögren syndrome, which showed remission with the administration of mycophenolate mofetil.[19] Previously published similar case studies were evaluated for comparison as shown in Table 2 below (Table 2)

This study shows a rare case study of patient with CD and concurrent SLE with renal involvement in Indonesia. However, the diagnosis was met with prior diagnostic examinations according to the guidelines, as authors appreciated the patient involvement towards decision-making in invasive interventions and complied to current regulations based on the Indonesian national healthcare system. This limitation created challenges on effectively justifying the final diagnosis, and therefore adding insight to the best practice. With this case study, authors encourage practitioners to diagnose as the state of the art.

CONCLUSION

The coexistence of SLE, particularly with renal involvement and CD as in this case is very rare. Furthermore, the challenge in diagnosing CD in patients with SLE stems from the fact that CD shares many similar clinical features, endoscopic findings, and histopathological findings to the most common GI comorbidity of SLE patients, lupus enteritis. Some specific findings for CD, such as cobblestone appearance from endoscopy, and the absence of ischemic changes in histopathologic findings can help clinicians in reaching CD the final diagnosis.

Table 1. Comparison of common lupus enteritis and Crohn's disease findings with the case study

	Lupus enteritis	Crohn's disease	Current case
Clinical symptoms (in order of frequency)	Abdominal pain Nausea Vomiting Diarrhea Fever Dysphagia, oral ulcer, anorexia	Weight loss Abdominal pain Diarrhea Anorexia Mucus in the stool Hematochezia Fever Nausea Perianal lesions Vomiting	Diarrhea Mucus in the stool Weight loss Vomiting
Endoscopic findings	Segmental, local, round or oval-shaped, discreet irregular ulcers	Longitudinal ulcer, cobblestone lesions, skip lesion	Hyperemic terminal ileum, multiple circular, clean-based ulcer on descending colon with surrounding hyperemic region
Histopathologic findings	Chronic inflammation with ischemic changes	Non-caseating granuloma	Chronic ileocolitis with focal crypt destruction, chronic inflammatory cells deposition in lamina propria, and lymphocyte aggregates without ischemic changes
Radiologic findings	Target sign, comb sign, pseudo-obstruction, segmental bowel dilatation, increased mesenteric fat attenuation	Comb sign Segmental bowel stenosis	N/A
Treatment	Corticosteroids Immunosupressants	Mesalazine, corticosteroids Immunosupressants, biologic agents	Sulfasalazine Mycophenolate mofetil

Table 2. Comparison of reported patients with the diagnosis of systemic lupus erythematosus (SLE) with renal involvement and concurrent Crohn's disease (CD)

Case	Age/ gender	SLE/CD duration (years)	Symptoms	Endoscopic findings	Histopathological findings	Kidney biopsy	Treatment	Publication date
1	24/F	SLE 8 years with lupus nephritis + CD	Abdominal pain, hematochezia, edema of lower limbs (hypoalbuminemia)	Not specified, but involving terminal ileum and colon	N/A	Diffuse glomerulonephritis with active necrotizing sclerosing lesions	Unresponsive with steroids, cyclophosphamide and tacrolimus, later switched to infliximab	2004 (46)
2	34/F	SLE 21 years with lupus nephritis + CD	Abdominal pain, diarrhea, weight loss > 10%	Several deep pleomorphic ulcers, some confluent, with sparse normal mucosa between them, from the rectum to the cecum	Compatible with CD	N/A	IV corticosteroid , later switched to infliximab	2015 (39)
3	56/F	SLE 3 years, with lupus nephritis, Sjögren syndrome + CD	Non-bloody liquid diarrhea	Congestion and ulceration in colon with a stenosis of the ileocecal valve	Moderate inflammatory infiltrate, polymorphous abundance, with some lymphoid nodules but no obvious epithelioid granuloma	Class III + V	Mycophenolate mofetil	2019 (19)
4	30/F (current case)	SLE 8 years with renal involvement + CD	Significant weight loss (> 10%) watery diarrhea	Hyperemic terminal ileum, multiple circular, clean-based ulcer on descending colon with surrounding hyperemic region	Chronic ileocolitis with focal crypt destruction, chronic inflammatory cells deposition in lamina propria and lymphocyte aggregates without ischemic changes	N/A	Sulfasalazine Mycophenolate mofetil	2020

AUTHORS' CONTRIBUTION

EBL and RRP conceived the study. EBL and EK conducted the literature research. EBL, EK, II, OI, and MAHP drafted the manuscript. RRP, AA, and DRH supervised the study and revised the drafted manuscript critically. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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