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Ulcerative Colitis and Systemic Lupus Erythematosus: An Unusual Association with Diagnostic and Therapeutic Difficulties

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Abstract **Case Report**

Background: Although patients with systemic lupus erythematosus (SLE) may experience various gastrointestinal disorders, SLE and ulcerative colitis (UC) rarely coexist. The gastrointestinal (GI) manifestations of these two diseases may be quite similar. Without a definite diagnosis, the physician may confuse the two diseases. We present the case of a patient with SLE and UC who developed abdominal pain and recurrent bloody diarrhea that was initially treated as SLE-related colitis to little effect. ***Case Presentation:*** A 33-year-old Moroccan woman with systemic lupus erythematosus (SLE) developed abdominal pain and diarrhea mixed with blood and mucus since the patient was aged 28 years that was initially treated as SLE-related colitis. Although a diffuse erythema and two superficial ulcerations in the descending colon were observed every examination, biopsy revelated only mild inflammation with no signs of specificity. Colonoscopy was performed again when the patient was 30 years because of the persistence of the bloody diarrhea with tenesmus. The transverse and descending colon and rectum showed diffusely Inflamed hyperemic colonic mucosa with multiple active ulcers. Macroscopic examination highly suggestive for UC. Histopathological examination revealed an aspect consistent with UC and no evidence of vasculitis. Introduction of specific treatment of the UC has considerably relieved the patient's symptoms. ***Conclusion:*** Diagnostic criteria for UC and SLE overlap, making them difficult to diagnose correctly. It is important to consider UC for patients who have SLE with gastrointestinal.

Keywords: Ulcerative colitis - systemic lupus erythematosus - autoimmune diseases – Treatment – diseases.

BACKGROUND

Systemic lupus erythematosus (SLE) and ulcerative colitis (UC) are both considered systemic diseases with an abnormal immune response that depends on interactions between susceptibility genes and environmental factors [1-3]. Although many autoimmune disorders tend to coexist in one patient, these two diseases are rarely associated with each other. Patients with SLE may have gastrointestinal involvement, mostly due to vasculitis of intestinal blood vessels [4, 5] and patients with UC may share common manifestations with SLE [6, 7]. This makes the diagnosis of both diseases in one patient a real challenge. There are, in fact, few report suggesting an association between these diseases [8-13].

We present the case of a patient with SLE and UC who developed abdominal pain and recurrent bloody diarrhea was initially treated as SLE-related colitis to little effect.

CASE PRESENTATION

A 33-year-old woman, hospitalized at the age of 19 years old rash and arthralgia when she was 23 years old for a fever, malar rash, arthritis for both ankles and biological inflammatory syndrome. The antinuclear, -antibody (ANA) were positives (1/320), the antibodies to double-stranded (DNA) were positives, anti cardiolipin antibodies were also positives (30U GPL/ml), and the serum complement was low. SLE was diagnosed according to American Rheumatism Association criteria for SLE. Treatment with prednisolone 30mg/day (PSL) and chloroquine led to remission. The treatment was well tolerated and there was control of the symptoms in following 4 years with continuous prednisolone at 10mg daily and chloroquine 200 mg/day.

Abdominal pain accompanied by bloody diarrhea began to occur intermittently when the patient was aged 28 years. Although colonoscopy revealed a

diffuse erythema and two superficial ulcerations in the descending colon, the biopsy showed only mild inflammation in the descending colon, with no specific signs of specificity (neither granuloma, nor crypt abscess). Her PSL dose was increased to 60 mg/day during each of these hospital visits, because her symptoms were assumed to result from exacerbation of lupus enteritis. However, remission was not achieved. GI symptoms were exacerbated whenever the PSL dose was reduced to 15 mg/day.

At the age of 30 years old, the patient come to medical attention because of persistence of bloody diarrhea and appearance of tenesmus. Laboratory results were as follows: complete blood count (CBC): hemoglobin (Hb) 8.1 gm/dl microcytic hypochromic anemia; white blood cell count (WBC) was 14,000, and platelets count was 310,000. The erythrocyte sedimentation rate (ESR) was 120 mm/hour, C-reactive protein (CRP) was 96 mg/dl, Urine analysis was normal, serum albumin was 34g/l and total protein was 62 g/l, C3 complement was normal, antinuclear antibody (ANA) by immunofluorescence was 1/320 speckled, anti-DNA were positive, lupus anti- coagulant (LA) was positive 82 IU/l, ASCA were also positives.

Colonoscopy revealed (Figure-1) diffusely Inflamed hyperemic colonic mucosa with multiple active ulcers in the transverse and descending colon and rectum, with pseudo polyps (pancolitis), Macroscopic examination strongly suggested UC. Histopathological examination revealed (Figure-2) multiple surface ulcerations, crypt abscesses, loss of goblet cell, the lamina propria was congested, edematous with infiltration by chronic inflammatory, consistent with UC. The diagnostic of UC was made and treatment with PSL 50mg daily, azathioprine 75 mg/day, chloroquine 200 mg/day. This was followed by significant improvement. As of April 2019, remission is maintained with azathioprine, PSL 10 mg/day and chloroquine.

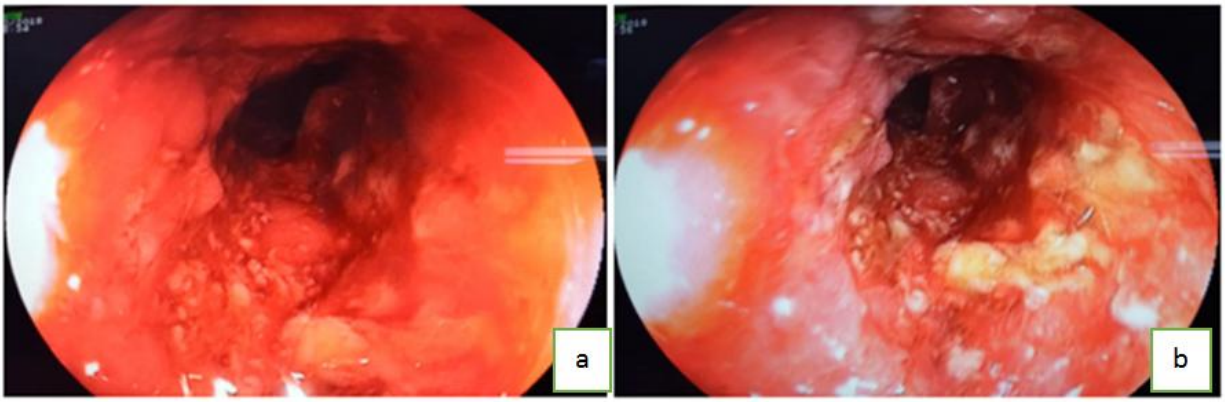

Fig-1: Colonoscopy: [a] Diffusely inflamed hyperemic colonic mucosa with multiple active ulcers in the transverse and descending colon; [b]with pseudo polyps (pancolitis)

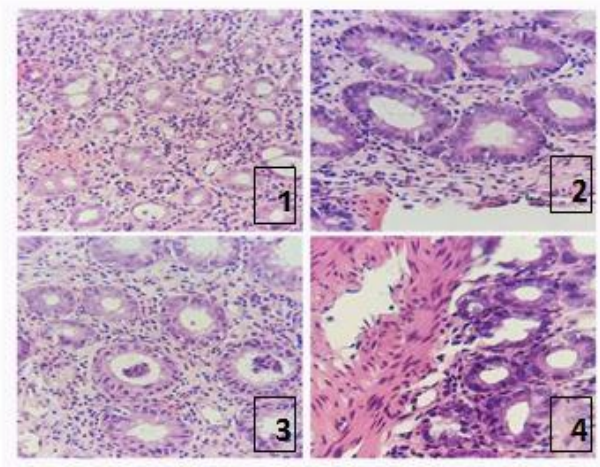

Fig-2: Histopathological features of Ulcerative Colitis: 1) Architectural distortion loss of goblet cells; 2) Cryptitis; 3) Crypt abscesses; 4) Basal plasmacytosis

DISCUSSION

SLE may manifest in the entire gastrointestinal tract [14] SLE and UC are chronic autoimmune diseases with the characteristic of relapse and remission episodes [5, 15]. The presence of SLE with inflammatory gastrointestinal disease is a frequently questioned phenomenon, but is rarely associated [4]. The

relationship between SLE and UC is very rare and has only been documented in several case reports [8-13]. Table I lists reports of the combination of SLE and UC. Except in Case 4, UC developed a mean of 10.0 years after the onset of SLE symptoms. In the case reported here, the patient developed regular UC more than 5 years after onset of SLE. All cases were positive for anti- dsDNA antibodies or anti-DNA antibodies. Polyarthritis occurred as an SLE symptom in five of the seven cases. The frequency of peripheral arthritis among UC patients is 1–22% and symptoms similar to those of collagen disease may develop [6-16]. Therefore, a causal relationship between SLE and UC cannot be excluded.

Coexistence of SLE and UC is difficult to diagnose because both diseases have several similar gastrointestinal symptoms and some drugs used to treat UC may cause drug-induced lupus particularly sulfasalazine, 5-ASA, and infliximab [17]. Diagnosing UC in SLE is quite challenging due to several factors. First, almost between 15% et 75% SLE patients have gastrointestinal symptoms (18,19). Second, UC may happen before or after the diagnosis of SLE [17]. However, there are some differences(15); compared to SLE, UC presents more frequently as bloody diarrhea, abdominal pain, and tenesmus. All seven patients described in table I experienced diarrhea, whereas for experienced abdominal pain, and two had tenesmus. UC has greater colon involvement with a more segmented distribution than SLE, and radiographs show pancolitis was demonstrated with diffuse erythema, and friability of colonic mucosa and superficial ulcerations as well as the macroscopic colonoscopy findings.

The most common pathological lesions in the GI tract of patients with SLE are chronic, non specific mucosal inflammation and ischemic changes due to vascular lesions. However, vasculitis was not confirmed in any of the cases presented in table I. Therefore, the abdominal symptoms experienced by patients with both SLE and UC can be attributed to UC alone. Additionally, perforation rarely occurs in IBD, but is often observed in lupus enteritis, and may be helpful in differential diagnosis [20].

Plain film radiographs of SLE-related mesenteric vasculitis usually show non specific indications of disease, such as segmental bowel dilatation in a thumb-print pattern and an air–fluid level. CT scans reveal the characteristic features of IBD (e.g., a double halo sign and comb-like appearance of the supplying vessels). Angiography of the mesenteric arteries may also provide evidence of vasculitis.

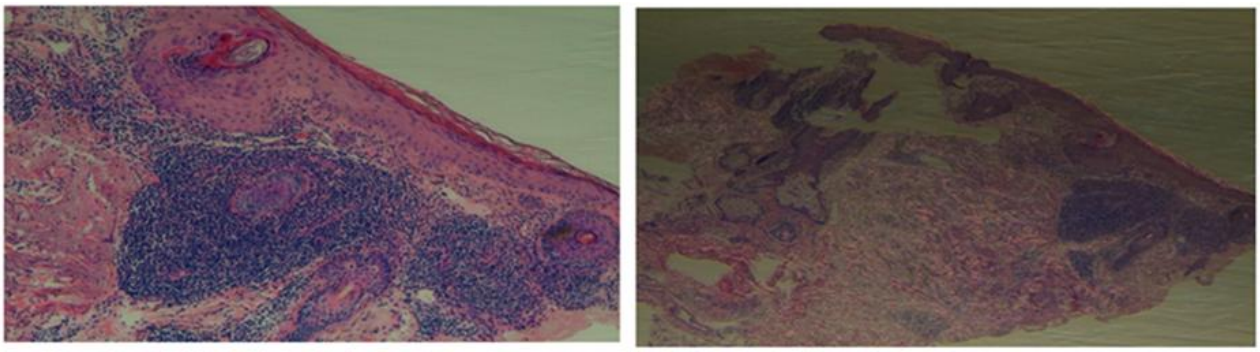

Fig-3: Cutaneous lupus erythematosus, inflammatory cells infiltrate pilosebaceous folliles, keratotic follicular plugging

The factors described above might, in fact, lead to an under estimation of cases of coexisting IBD and SLE. The association of these two diseases seems more than casual. Both SLE and IBD have a genetic autoimmune basis that combines with environmental factors in the pathogenesis of these diseases, although this is more established in SLE [21, 22]. HLA DR2 is more prevalent in both SLE and UC. Antineutrophilic cytoplasmatic antibodies are found in 60–70% of UC patients [15, 23], as well as in a minority of SLE patients [24]. Antilymphocytotoxic antibodies are found in both SLE and IBD [25]. Finally, both diseases respond to treatment with similar anti-inflammatory and immunosuppressive drugs, such as sulfasalazine, steroids, methotrexate, and azathioprine [26, 27]. All of these findings would seem to indicate that SLE and UC may be related autoimmune diseases.

Patients with IBD that is treated with sulfasalazine can, in rare cases, develop drug-induced lupus syndrome [28, 29], Antibodies to double-stranded DNA are usually present in idiopathic SLE, but absent in drug-induced disease. HLA types B8 and DR3 are associated with idiopathic disease, whereas DR4 occurs in drug-induced disease. Drug-induced lupus is only rarely associated with low complement levels. Steven *et al.*, [9] describe a patient with UC, treated by sulfasalazine, ten years later, he developed SLE, ANA and anti dsDNA, HLA type DR3 was found in this patients, drug-induced lupus syndrome was unlikely.

Table-1: Comparison of reported patients with SLE complicating ulcerative colitis

Pt	Age/ Sex	SLE disease duration	Immunological findings	Symptoms	ESR (mm/hr)	Colonoscopy findings	Result of biopsy	Treatment	Reference
1	21F	5years	ANA 1/200, Anti-DNA positive	Bloody Diarrhea, Abdominal pain	N/A	friable mucosa, ulceration, pseudo polyps,	Sparse glands, Poorly differentiated cells, chronic inflammation	Sulphasalazine/ prednisolone	[8]
2	10M 1/2000	10 years after UC	ANA Anti-DNA> 3000 pANCA+	Bloody diarrhea Tenesmus	73	pancolitis	Infiltration of chronic inflammatory cells in the lamina propria mucosa with marked depletion of goblet cells without vasculitis	Sulphasalazine	[9]
3	48F	31years	ANA 1/256, Anti- DNA 1/160	Abdominal pain, bloody diarrhea	35	diffuse erythema and hemorrhage on the rectal mucosa	Neutrophilic micro abscess in the crypt and loss of goblet cells with infiltration of mononuclear cells and plasma	Sulphasalazine	[10]
4	54F	11years	ANA 1/160 Anti- DNA 70 IU/ml pANCA positive	Abdominal pain Bloody diarrhea mucosa	21	diffuse erythema Friable Superficial Ulcerations	Neutrophilic micro abscesses in the crypte, infiltration with mononuclear cells and plasma cells in the lamina propria	Prednisolone Mesalazine	[11]
5	40F	Concomitant Diagnostic positive	ANA 1/640 Anti- DNA	Bloody Diarrhea	35	diffuse erythema	Crypt abscesses, loss of goblet cells and chronic inflammation in lamina propria	Prednisolone Mesalazine	[12]
6	27F	10 years	ANA + AntiDNA +	Diarrhea Massive bloody stool	68	Vascular pattern, superficial ulcerations Many ulcers from the rectum to caecum	Cryptitis, infiltration with lymphocytes and neutrophils	Prednisolone Azathioprine	
7	30F	concomitant	AAN 1/160	Bloody Diarrhea hyperemic,	48	Many ulcers from the rectum to caecum	active colitis Without vasculitis	prednisolone, 5 ASA	[13]

M, *male; F, female; ANA, antinuclear antibody; Anti-DNA, antinative deoxyribonucleic acid antibody; mPSL, methylprednisolone; N/A, not available; Anti-dsDNA, antinative double-stranded antinative deoxyribonucleic acid antibody.*

Concomitant diagnosis of IBD and SLE is rare and IBD may occur either before or after SLE diagnosis. Although a chance occurrence cannot be excluded it is possible that both conditions share some genetic or immunological defects. According to a referral center study the overall prevalence of concomitant ulcerative colitis (UC) diagnosis is 0.4% of SLE patients [30], most patients with reported concomitant diagnosis of IBD and SLE have adequate response to steroids combined with hydroxychloroquine and/ or azathioprine. The prognosis of SLE–related IBD is generally good [31]. Glucocorticosteroids is an effective treatment for UC, and can be used to treat severe cases or disease that does not respond well to mesalazine therapy. However, long term treatment with glucocorticosteroids should be avoided. In case of steroid dependency or steroid refractory TNF-alpha blockers are an effective treatment to induce and maintain remission [32]. The role TNFalpha plays in SLE is controversial and data on the likely effects of blocking TNFalpha on anti-DNA autoantibody production is always of interest [33]. But those antibodies are not generally associated with clinical signs of autoimmunity and there is no indication for monitoring in patients who have no symptoms [30]. There is no clear explanation for this high prevalence of those autoantibodies [34].

Patients on anti-TNFα therapies may rarely present cutaneous lupus [35] or lupus-like syndrome [36, 37]. A logical clinically relevant approach is necessary before treating patients with UC and SLE.

CONCLUSION

In conclusion, the diagnostic criteria for UC and SLE overlap, making them difficult to diagnose correctly. Physicians should bear in mind the possibility that a patient may be afflicted with both of

these diseases simultaneously. If a patient known to have SLE develops gastrointestinal symptoms such as abdominal pain or diarrhea, it is prudent to rule out UC. The status of UC as an autoimmune disease is becoming clear and the pathology of lupus enteritis should be clarified through the accumulation of cases of SLE combined with UC.

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