CASE REPORT

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Systemic Lupus Erythematosus in a Patient with Ulcerative Colitis: Co-Existing or Drug-Induced?

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ABSTRACT

We report a 49-year-old lady with ulcerative colitis (UC) who subsequently developed systemic lupus erythematosus (SLE) ten years later. By reviewing the drug history and serum autoimmune panel, we hypothesize that systemic lupus erythematosus may occur in a patient with a history of inflammatory bowel disease as a coexisting disease, or triggered by drugs used in inflammatory bowel disease, such as disease-modifying anti-rheumatic drugs (DMARDs). This case raises the discussion that patients with Inflammatory bowel disease (IBD) may have a genetic predisposition for developing other autoimmune diseases, and explores the possibility of drugs used in the treatment of IBD as a trigger for SLE development. Being able to differentiate the two has important implications in management and prognosis.

***Keywords*:** Systemic Lupus Erythematosus; Ulcerative Colitis; Inflammatory Bowel Disease; Drug-Induced.

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a chronic inflammatory disorder of the gastrointestinal system and includes ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis. The disease may have different extents of gut involvement and is characterized by mucosal inflammation of the digestive tract, and usually with extra-intestinal manifestations such as arthritis and sacroiliitis. On the other hand, systemic lupus erythematosus (SLE) is a connective tissue disorder with widespread clinical manifestations including malar rash, small joint arthritis, nephritis, and other organ damage primarily affecting women of childbearing age. We report a case of SLE that developed in a patient with known UC which may be due to the coexistence of separate clinical entities or triggered by drugs used in ulcerative colitis, particularly disease modifying anti-rheumatic drugs (DMARDs).

CASE REPORT

A 49-year-old woman with a history of ulcerative colitis diagnosed 10 years ago was admitted to our hospital on 3 March 2019 presenting with 3 months of progressive symmetrical inflammatory polyarthritis, long term intermittent fever, and a sudden onset of dyspnea and pleuritic chest pain.

In 2009, she presented with tenesmus, mucus in the stool, and increased bowel opening from 2 to more than 20 times a day. There was no blood in the stool. She had previously been well, except for a right nephrectomy at the age of 9 for a congenital renal condition. Colonoscopy showed proctitis with haemorrhage, and a diagnosis of UC was subsequently made. Mesalazine suppository was prescribed, and her symptoms subsided. The most recent colonoscopy performed in September 2017 showed mild inflammation from the rectum up to 55 cm into the transverse colon. Biopsy found mild to moderate inflammation with no vasculitis. Treatment was changed to oral mesalazine.

In December 2018, she developed pain and swelling in the ankles and plantar regions. She was given multiple analgesics for symptomatic relief. However, a month later, she started to notice bilateral pain, swelling, and morning stiffness over metacarpophalangeal (MCP)

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and proximal interphalangeal (PIP) joints, wrists, shoulders, knees, and ankles. Bilateral finger dactylitis was also noticed. Anti-nuclear antibodies (ANA), rheumatoid factor (RF) and Human leucocyte antigen (HLA) B27 were negative. Due to her polyarthritis, the previous maintenance therapy of oral mesalazine for UC was switched to oral sulfasalazine by her gastroenterologist.

She developed low-grade fever after starting sulfasalazine. A patch of erythematous rash appeared over bilateral thighs and shins. It was neither painful nor itchy, and there were no vesicles. The patient had no exposure to excessive sunlight and was not on oral contraceptive pill. On 3 March 2019, she was admitted for a sudden onset of dyspnea with pleuritic chest pain and increased generalized joint pain. Investigations showed decreased hemoglobin of 10.8 g/dL, lymphopenia (0.92×10^9/L; normal range 1.06–3.61 $\times 10^9$/L), and low serum albumin of 25 g/L. Autoimmune workup showed raised ANA titre of >1/640 with a homogenous pattern, high anti-dsDNA antibodies of more than 300 IU/ml and positive anti-Ro antibodies. Anti-neutrophil cytoplasmic antibodies of p-ANCA was positive. There were also decreased complement C3 level at 90.7 mg/dL and C4 level at 10 mg/dL, increased C-reactive protein (CRP) of 8.74 mg/L (normal <3 mg/L) and erythrocyte sedimentation rate (ESR) of 93 mm/hr. Anti-histone antibody was not available in our Institute. Twenty-four-hour urine protein was 1.2 g per day. Septic workup including blood, urine and sputum cultures were negative. Chest radiograph showed blunting of the right costophrenic angle. Positron emission tomography computerized tomography (PET-CT) showed multiple small cervical lymph nodes with mild to moderate metabolic uptakes. While transthoracic and transesophageal echocardiogram failed to detect any pericardial effusion, mild pericardial (largest measurement 1.3 cm) and right pleural effusions were detected in the PET-CT.

No renal biopsy was performed because of the single kidney. In view of the persistent fever, high dose steroid (prednisolone 60 mg per day), followed by pulse steroid (methylprednisolone 250 mg per day for 3 consecutive days) was started, and sulfasalazine stopped. Her symptoms gradually improved. No reassessment imaging was performed in view of the small lymph nodes and mild effusions. Oral mesalazine 1000 mg was restarted by the gastroenterologist after discharge.

DISCUSSION

We report a case of SLE in a patient who was diagnosed with UC 10 years earlier. Her presenting complaints (dyspnea and chest pain) were likely due to pleuritis with resultant pleural effusion and we had excluded pulmonary embolism as an important differential diagnosis by CT. Current understanding of pathogenesis suggests a prominent role of immune mechanisms in both diseases [1]. The coexistence of IBD and SLE is rare, with previously reported prevalence of 0.4% [2], mainly seen in case reports. Although it would be difficult to differentiate between SLE-related colitis and IBD as the two conditions share similar clinical, biochemical and imaging features [3]. Our patient's initial symptoms mainly involved the gastrointestinal tract, which was more suggestive of IBD. The recurrence of symptoms would provide further supporting evidence. Bowel vasculitis [4], mucosal thickening, mucosal edema, inflammatory cell infiltrates, lymphangiectasia, and mucosal atrophy have been reported to be the histological features of SLE-related colitis but majority of patients revealed no abnormalities [5]. Similarly, distortion of crypt architecture, basal plasmacytosis, lymphoid aggregates, granulomas, mucin depletion and paneth cell metaplasia have been reported to be the histological features of IBD. These features could also occur in other conditions [6]. Coexistence or overlap of autoimmune diseases is a widely acknowledged association, due to common genetic susceptibility and environmental factors [3]. Alleles contributing to susceptibility to autoimmune, systemic inflammatory disorders have been established. Jager et al. demonstrated in SLE patients' evidence of a gene region 16q12-13 containing the CARD15 alleles, which has been demonstrated to confer susceptibility to IBD [7]. Common genes (e.g. HLA DR3], shared autoantibodies (e.g. ANCA, antilymphocytotoxic antibodies) and good response to anti-inflammatory drugs and immunosuppressants give supportive evidence of the ways in which IBD and SLE may be related [1].

Drug-induced lupus may also explain the temporal onset of presenting symptoms. Medications for treating IBD such as sulfasalazine and anti-TNFα therapy may induce SLE or produce side effects that mimic a lupus-like syndrome [8]. The lack of initial lupus serology also made the diagnosis possible. Although anti-histone has been reported to be a serum marker for drug-induced lupus [9], the antibody was not available in our hospital. A previous study showed that a slow acetylator genotype

(enzyme N-acetyltransferase 2) and HLA haplotypes seem to predict disease induction in sulfasalazine induced SLE [1]. However, this is not likely the case as patients with drug-induced lupus often have less visceral involvement and usually remit after discontinuation of the offending agent [8]. Glomerulonephritis is uncommon but has been reported [10]. In addition, the positive ANA detected also makes the overlapping of SLE and IBD in our case more likely [11]. A 10 years' time-gap between onsets of the two diseases in our patient is also compatible with other reported overlaps of diseases [12, 13]. There is no case where both diseases are reported to have occurred at the same time. Reported treatments were similar to lupus alone [1]. There was lack of data to show the prognosis although the general understanding is worse than that of drug-induced lupus because of more visceral organ involvement.

It is important to recognize the discriminating features of drug-induced lupus and idiopathic SLE co-morbid with IBD, as each entity has different treatment and prognostic implications. The presence of low complement levels and different types of autoantibodies (such as anti-Ro, anti-La, anticardiolipin antibodies) are more indicative of idiopathic SLE. Genetic predisposition also plays a role, as HLA-DR3 predisposes to idiopathic SLE while HLA-DR4 occurs in drug-induced lupus [14].

CONCLUSION

In conclusion, SLE in a patient with UC may occur as a co-existing disease or as a drug-induced syndrome from sulfasalazine and anti-TNF used in the treatment of IBD. Our case report highlighted the importance of recognizing key distinguishing features in clinical manifestations, laboratory tests, and drug history of each disease. A high index of suspicion is essential for diagnosis and formulation of optimal treatment strategies.

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