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Systemic lupus erythematosus in Crohn's disease: drug-induced or idiopathic?

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Abstract

Coexistence of Crohn's disease (CD) and idiopathic systemic lupus erythematosus (SLE) is very rare. On the other hand, drug-induced lupus erythematosus (DILE) due to anti-tumor necrosis factor (TNF) agents is a relatively more common entity. DILE due to anti-TNF agents and idiopathic SLE share common serologic and epidemiologic characteristics making the differentiation between those two entities difficult. We present a case of a 35-year-old woman with CD who developed SLE after treatment with adalimumab and denosumab and persisting symptoms eight months after discontinuation of those agents.

Keywords Crohn's disease, SLE, DILE, adalimumab, denosumab

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder, affecting predominantly young females [1]. It is characterized by skin lesions, polyarthritis, multiorgan involvement, hematologic disorders, and typical autoantibodies [1]. There have been some case reports of coexisting idiopathic SLE and Crohn's disease (CD) reported in current literature [1,2]. However, drug-induced lupus erythematosus (DILE) also represents a possible complication of anti-tumor necrosis factor (TNF) treatment for CD, and may lead to a serious diagnostic dilemma [1].

Case report

We report a case of a 35-year-old woman with CD who developed SLE after anti-TNF treatment. The patient was hospitalized during 2009 for abdominal pain, diarrhea, fever, weight loss, and oral aphthous ulcers. CD diagnosis was based on the endoscopic findings of long irregular ulcers in terminal ileum with highly suggestive histology (focal crypt irregularity, focal inflammatory infiltration and pyloric metaplasia). Her medical history was negative, but she reported a family history of antiphospholipid syndrome and SLE. Prednisone was successfully administered as induction therapy and remission was maintained with azathioprine (125 mg/day). In May 2013 adalimumab (40 mg s.c. every 2 weeks) was initiated and azathioprine was withdrawn, to manage recurrent episodes of type II arthropathy. The patient fully responded after the two induction doses. In September 2013, bone density measurement revealed osteoporosis, and oral biphosphonates were initiated. Due to intolerance, in January 2014, denosumab (60 mg s.c. every six months) was introduced.

Five months after the first dose of denosumab, the patient developed severe debilitating polyarthritis and a photosensitive rash of the interphalangeal spaces. Serologic workup revealed antinuclear antibodies (ANA): 1/640 (negative <1/160), C3: 0.795 g/L (normal range 0.825-1.8), p-ANCA: 1/80 (negative <1/20), anti-double stranded (ds) DNA: 20.4 IU/mL (normal <7 IU/mL), rheumatoid factor: negative, lupus erythematosus cell test (Le test): positive, anticardiolipin antibodies IgM: 38.0 (negative <12.5), partial thromboplastin time - lupus anticoagulant screen (PTT-LA): 46 sec (normal <45), erythrocyte sedimentation rate: 15 mm/h (normal <20 mm/h) and C-reactive protein: 0.48 mg/L (normal <5 mg/L). The patient was diagnosed with SLE and antiphospholipid syndrome. Adalimumab and denosumab were withdrawn to manage the possibility of DILE, and methotrexate 15 mg/week s.c was initiated for both CD and SLE. Folic acid (5 mg, 48 h following methotrexate), prednisone 7.5 mg/day, hydroxychloroquine 200 mg/day, and acetylsalicylic acid 100 mg/day (as antithrombotic prophylaxis against antiphospholipid syndrome) were also administered. Eight months after this episode, the patient is in clinical and serological remission for CD, with no photosensitive rash, but the polyarthritis has only slightly improved.

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Conflict of Interest: None

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Discussion

There are only 12 cases of coexisting idiopathic SLE and CD in the literature, typically in young patients and usually with the first diagnosed disease in remission when the second develops [1]. Differentiation between the two diseases, when they coexist, is difficult as they share common symptoms [1]. CD can cause arthropathy and skin lesions, while reversibly SLE may cause symptomatic mesenteric vasculitis presenting with diarrhea, abdominal pain, and bowel infarction [1,2]. Imaging can be identical in both diseases, with segmental thickening of bowel wall, enhancement of mesenterial fat and comb sign [2]. Endoscopic findings in SLE with diminished vascular pattern, friability and diffuse or focal ulcerations may also mimic CD [1]. Although ANA and anti-ds DNA antibodies are typical for SLE, these antibodies may be present in up to 53% and 35% respectively of CD patients under anti-TNF treatment [3].

A second important and more common entity is DILE, which can be caused by a variety of drugs. In the case of CD treatments, sulphasalazine and anti-TNF agents have been implicated [4]. Symptoms involve polyarthralgia, myalgia, serositis, fever, fatigue and non-specific skin lesions with commonest symptom symmetric polyarthralgia [4]. DILE can occur within months or even years after exposure, and involves patients with mean age of 50-70 years. Usually full remission of symptoms follows the discontinuation of the inciting drug within weeks [4]. Although DILE has some specific characteristics that may differentiate it from SLE, anti-TNF-associated DILE shares common serological and epidemiological characteristics with SLE making differentiation difficult [5-7]. Anti-TNF-associated DILE may occur in 0.6-1.6% of IBD patients under infliximab [1]. In Table 1 the characteristics of idiopathic SLE, DILE and anti-TNF-associated DILE are presented. Perhaps the most important clues for differentiation between these two entities arise from clinical observations such as the temporal association between anti-TNF therapy and lupus symptoms, and, importantly, from the rapid resolution of symptoms after the discontinuation of the anti-TNF agent.

Denosumab, a fully human monoclonal antibody directed to the receptor activator of nuclear factor κB-ligand (RANKL), is used in the treatment of osteoporosis [8]. RANKL is a cytokine molecule member of the TNF family and a major mediator of osteoclastic activity but it is also involved in the immune system, mainly in dendritic cell maturation and in T-cell-dependent immune response [8]. There are no reported cases of DILE associated with denosumab and no data regarding interactions between denosumab and anti-TNF agents.

Family history of idiopathic SLE has been recognized as a risk factor for development of idiopathic SLE, but its role in development of anti-TNF-associated DILE has not been defined [9].

We live in the era of biologics, there are dozens of monoclonal antibodies used in clinical practice and even more are under development. Although many patients may use more than one of these highly potent drugs, there are limited data regarding the interactions between those medications.

Table 1 Characteristics of SLE, DILE and DILE due to anti-TNF[a]

	Idiopathic SLE	DILE	DILE due to anti-TNF
Sex (female to male)	9:1	1:1	4:1
Skin lesions	54-70%	<5%	67%
Arthritis	83%	20%	51-93%
ANA	99%	>95%	79-100%
Anti-ds DNA	90%	<5%	72%
Low complement	48%	<5%	17-59%

SLE, systemic lupus erythematosus; DILE, drug-induced lupus erythematosus; TNF, tumor necrosis factor; ANA, anti-nuclear antibodies; ds-DNA, double stranded-DNA. a: compiled from articles by Vasoo [5], Ramos-Casal [7], Costa [8], Wetter [9]

In our case, the serologic profile as well as the gender and the age of the patient could indicate either idiopathic SLE or anti-TNF-associated DILE. However the fact that there was no complete resolution of symptoms eight months after the discontinuation of adalimumab and denosumab and the positive family history indicate that it may be a case of idiopathic SLE. There is one question regarding the possibility that this is a case of a more protracted DILE, due to the combination of the two biologics. The hypothesis that this could be attributed to the effects of denosumab in immune tolerance through influence in T-regulatory cells and to its longer half life cannot be proven.

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