SHORT REPORT

Anti-tumor necrosis factor-α induced systemic lupus erythematosus in a patient with metastatic Crohn's disease—what is the role of anti-TNF antibody?

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Received 11 May 2012; received in revised form 30 May 2012; accepted 25 June 2012

KEYWORDS
Crohn's disease; Infliximab; TNF-α antagonist-induced lupus-like syndrome; Autoantibodies; Cross reactivity

Abstract

Biological therapies are supposed to trigger the development of autoimmune diseases. We report a case of a 27-year old woman presenting with drug induced systemic lupus erythematosus (SLE) associated with infliximab therapy. The development of paradoxical inflammation in immune-mediated inflammatory diseases patients treated with anti TNF-α suggests that an unknown inflammatory pathway may be provoked by inhibiting TNF-α. We suppose that in our case a cross reactivity between anti-infliximab antibodies and autoantibodies may lead to the development of TNF-induced immune disease.

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1. Introduction

Drug induced lupus erythematosus like syndrome is a rarely described condition in Crohn's disease; however patients treated with biological therapy are slightly more susceptible for developing such an adverse reaction.1 The use of anti-TNF agents has been associated with an increasing number of autoimmune diseases, mainly lupus, vasculitis, and intestinal lung disease.2 Biological therapies are supposed to trigger the development of autoimmune diseases, although allergic reaction or loss of response due to the production of antibodies against the TNF blockers may also play role in the development of these complications. From another point of view, the mechanism in the background of this effect may be stimulated humoral immunity: production of autoantibodies due to the neutralization of TNF-α or inhibition of cytotoxic T lymphocytes by TNF blockade.3,4 Although the development of autoantibodies is common during infliximab therapy; drug induced lupus erythematosus like syndrome is still rare. A study of 500 Crohn's disease patients from the Mayo Clinic revealed only three patients who developed drug induced lupus during the

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doi:10.1016/j.crohns.2012.06.016
therapy. In Hungary infliximab was approved for the treatment of moderate to severe Crohn's disease in 2001. We report a case of a 27-year-old woman presenting with drug-induced systemic lupus erythematosus (SLE) associated with infliximab therapy. In the past 10 years, the present is the only case of the more than 230 patients who have been on biological therapy when anti-TNF-α therapy provoked the occurrence of SLE at our center.

2. Case report

Crohn’s disease of our female patient was diagnosed in 2007 at age 22 years when she was presented with fever, diarrhea, aphthous stomatitis and a painful mass in the preauricular region requiring surgical intervention. Ileocolonoscopy identified aphthous lesions in the ileum, the right side of the colon and the transverse colon. After initiating the treatment with mesalazine and corticosteroids her symptoms gradually improved. Two years later she developed active symptoms and perianal abscess. Mesalazine was stopped because of loss of efficacy. After adding azathioprine and draining the abscess the patient shortly achieved remission. However, in January 2010 she presented with recently activated 2 × 1-cm abscess the patient shortly achieved remission. However, in January 2010 she presented with recently activated 2 × 1-cm discharging preauricular and perianal fistula; therefore infliximab therapy was started (Fig. 1). The histology of discharging preauricular and perianal fistula reduced significantly. However, at the end of the one-year treatment period, the patient presented with swelling and pain in her fingers, wrists, elbows, knees and ankles and her walking became difficult. Her bowel symptoms were still in remission, although the perianal fistula started to discharge again.

Physical examination revealed swollen and tender shoulders, fingers, knees and toes without cutaneous symptoms. Laboratory investigation showed elevated C-reactive protein (24.5 mg/l) and erythrocyte sedimentation rate (66 mm/h), a positive serum anti-nuclear antibody, significantly elevated anti-Sjögren’s syndrome A antibody (181 U/ml) and anti-Sjögren’s syndrome B antibody (> 200 U/ml). Anti-double-stranded (ds)DNA, anti-ribonuclear protein/anti-Smith antibody and anti-histone antibodies were also positive. C3 and C4 levels were normal. The patient was negative for anti-cardiolipin antibodies (IgG, IgM, IgA) and anti Beta-2-glycoprotein-1 (IgG, IgM, IgA). She did not have any sign of renal involvement; urea and creatinine levels were in normal range. The pharmacokinetic examinations revealed low infliximab trough levels (2.75 ng/ml) and high levels of antibodies against infliximab (ATI-3194 ng/ml). On the basis of the clinical symptoms, the autoimmune and pharmacokinetic measurements the diagnosis of infliximab induced SLE was established. Infliximab was stopped and low dose oral methylprednisolone (8 mg daily) was administered. Her symptoms resolved completely within 2 months after stopping infliximab and her gastrointestinal symptoms also remained in remission with azathioprine monotherapy. Methylprednisolone was gradually tapered and stopped after 4 months of therapy. Because of her discharging perianal fistula, Seton placement was performed in January 2012.

3. Discussion

Metastatic Crohn’s disease presents as cutaneous manifestation of Crohn’s disease characterized by ulcerative lesions. The skin lesions may precede the diagnosis of Crohn’s disease and usually show simultaneous activity with the clinical course. The presence of granulomas in MCD is the most prominent histopathologic finding, and Langerhans giant cells are frequently seen along with epithelioid histiocytes and an accompanying lymphoplasmacytic infiltrate. Biopsies of these lesions show noncaseating granulomas that are characteristic of Crohn’s disease. In our case, the simultaneous appearance of preauricular fistula and the intestinal symptoms suggested the diagnosis of metastatic Crohn’s disease, although metastatic Crohn’s disease on the face is a rare entity. Infliximab has not only proven its efficacy in the treatment of metastatic Crohn’s disease; furthermore, it seems to be the most beneficial in the management of mucocutaneous manifestations.

In the last two decades anti-tumor necrosis factor (TNF)-α has been extensively used for the treatment of immune-mediated diseases. However, with the increasing use of anti TNF-α therapy, the number of anti TNF-α related side effect is also increasing. Paradoxical inflammatory reactions have been described in patients with immune-mediated inflammatory diseases receiving biological therapy. The review of Fiorino et al. revealed the onset of psoriasis in 18 cases of patients with inflammatory bowel disease treated with anti-TNF-α therapy.
TNF therapy. In the majority of the patients, psoriatic lesions resolved after cessation of biological therapy. The development of paradoxical inflammation in immune-mediated inflammatory diseases patients treated with anti TNF-α suggests that an unknown inflammatory pathway is provoked by inhibiting TNF-α. According to the hypothesis of Florino et al. interferon (IFN) α may play an important role in the development of TNF-α induced psoriasis. Withdrawing biological therapy or switching to another anti TNF agent may be considered in these very rare conditions.

The least rigorous criteria for diagnosis of drug induced lupus need one or more symptoms compatible with lupus erythematosus, ongoing exposure to a drug known to cause drug induced lupus, no prior history of lupus erythematosus, and resolution of symptoms when the offending drug is discontinued. In our case, the patient suffered from arthritis, had antibodies to dsDNA and ANA positivity (three symptoms compatible with SLE) was also detected; she received infliximab which had been shown to provoke drug induced lupus, never had SLE before and her symptoms resolved after discontinuing anti TNF therapy.

Treatment with infliximab can cause immunogenicity and the formation of ATI. Detectable infliximab in the serum predicts higher rates of remission and endoscopic improvement, while ATI positive patients are associated with lower response to infliximab and with the development of adverse reactions. Infliximab-treated patients also develop autoantibodies in some cases, including ANA and anti-dsDNA antibodies that may be associated with SLE. Patients with ANA positivity before infliximab therapy are more susceptible to develop dsDNA antibodies and drug induced lupus. Compared to drug-related lupus, dsDNA is more susceptible to develop dsDNA antibodies and drug induced lupus.

References


