SHORT REPORT

Infliximab and adalimumab-induced psoriasis in Crohn's disease: A paradoxical side effect

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Abstract

Treatment with antitumor necrosis factor-alpha (anti-TNF-α) offers a significant improvement in several immune-based diseases, including Crohn's disease (CD) and psoriasis. Different cutaneous side effects have been described for anti-TNF-α therapy such as psoriasis. Previous reports showed that inhibition of TNF-α can induce over expression of cutaneous IFN-α, which in turn caused a predisposition to psoriasis. We report a 31-year-old woman with extensive CD and perianal lesions, without response to conventional treatment. She paradoxically developed a cutaneous eruption with psoriasiform morphology and distribution during treatment with both anti-TNF-α approved in Europe for CD, infliximab and adalimumab. These lesions cleared after topical application of corticosteroids and cessation of the anti-TNF-α treatment. Due to ineffectiveness of pharmacological treatment on disease, the patient had to undergo surgery. TNF-induced psoriasis in patients with CD is rare and has been previously documented with infliximab or adalimumab. The reason for this apparently paradoxical effect of the therapy is still unclear. This is the first case of psoriasis induced first by infliximab and later by adalimumab in the same CD patient. We would like to review and to draw attention about psoriasis as a cutaneous side effect with anti-TNF-α treatments.

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1. Introduction

Anti-tumor necrosis factor-alpha (anti-TNF-α) therapy leads to significant improvement in several immune-mediated diseases as inflammatory bowel disease (IBD), rheumatoid arthritis, Behçet's disease, and psoriasis. Currently many new biological therapies are under development; however three anti-TNF therapies have demonstrated effectiveness in
Crohn’s disease (CD): Infliximab (a chimerical monoclonal antibody with 75% human and 25% mouse origin), adalimumab (antibody 100% human) and certolizumab (Fab fraction by IgG human monoclonal antibody). Only infliximab and adalimumab are authorized in Europe while certolizumab can only be administered by compassionate use. Those therapies can reduce inflammatory cell infiltration and TNF-α concentration but they are not free of side effects. The main side effects include potentially serious infections, optic neuritis, aplastic anemia, congestive heart failure and multiple cutaneous adverse effects such as eczema, erythema, urticaria, lupus-like syndrome and paradoxically even psoriasis.

A significant number of cases have been reported of psoriasis induced by anti-TNF therapy in CD; nevertheless the pathogenic mechanism of this contradictory side effect has not yet been explained. The management options of this phenomenon include continuing with the same anti-TNF-α therapy, switching to other biological therapy or changing to an immunosuppressant therapy, although the best option is still unclear.

2. Case report

We report the case of a 31-year-old woman with extended CD who paradoxically developed psoriasis during her first treatment with infliximab and later with adalimumab. Our patient was diagnosed with CD in March 2006 according to standard endoscopic, radiologic, and histologic criteria. She showed affected terminal ileum and right and transverse colon (A2 L3 and B1 Montreal Classification). She had no history of psoriasis and was otherwise healthy. At onset she started treatment with azathioprine but she developed gastrointestinal intolerance. For that reason, she began maintenance treatment with 6-mercaptopurine and she required episodic courses of antibiotic therapy and seton placement by the appearance of perianal lesions. The doses of 6-mercaptopurine were adjusted due to the development of leucopenia and she takes 25 mg/day. It was not possible to increase the dose during follow-up. In November 2007 we considered administration of anti-TNF-α treatment for continuous inflammatory disease and transesphincterian anorectal fistulas without abscess development. In January 2008 the patient received infliximab infusions (5 mg/kg) at weeks 0 and 2 according to the conventional procedure. Two days after the second infusion of infliximab the patient developed erythematous papulosquamous eruption in the proximal part of her extremities (soles and palms), her trunk and scalp, which became extensive and intense before the third dose of infliximab at the 6th week (Fig. 1). The patient showed no previous symptoms or infection causes that justified the skin lesions. The biopsy of skin lesions had histopathological features of psoriasis: psoriasiform epidermal hyperplasia with parakeratosis and a perivascular lymphocytic infiltrate in the dermis with neutrophils at the dermal papillae. The cultures of skin lesions and the pharyngeal swabs were negatives. Her perianal symptoms improved and had reduced inflammatory reactions. Infliximab was therefore suspended and topical corticosteroids (clobetasol) were started with subsequent disappearance of the lesions in 4 weeks.

Then, we planned to treat her by adalimumab. Initial dosing consisted of an 80 mg subcutaneous injection, followed by 40 mg subcutaneous injection 2 weeks later and then 40 mg subcutaneous injection every 2 weeks. Clinical improvement was maintained. After 4 months with adalimumab therapy, she subsequently developed a progressive palmoplantar eruption with pustules, pruritus and erythema in the same localization as before. The skin biopsy confirmed again psoriasiform dermatitis. We decided to treat the patient withdrawal adalimumab and with topical steroids. Complete resolution of cutaneous lesions occurred after 2 months but she required corticosteroid therapy for inflammatory symptoms. We offered to begin treatment with methotrexate intramuscular, but she rejected it due to intention of becoming pregnant. She preferred surgical intervention as opposed to pharmacological treatment.

3. Discussion

We present a case of new onset of psoriasis in an adult CD patient treated with infliximab and reappearance with
adalimumab treatment. In the literature, there is only a case reported in a pediatric patient with CD, who developed psoriasis with both drugs. Nevertheless, in the literature there are some reports of this side effect in dermatology and rheumatology.

Psoriasis usually has an incidence ranging from around 6% to just over 11% in patients affected by IBD, compared to 1.5% in the general population. The frequency of CD (11.2%) is greater than that of UC (5.7%).

The etiopathogenesis of psoriasis, like that of IBD, is still not completely clear. It is well established, however, that they are both multifactorial pathologies, where the inflammatory cascade involves various cytokines, including TNF-α. The dermal plasmocytoid dendritic cells (DPDC) produce IFN-α which has recently been shown to be an important cytokine for the early phase of induction of psoriasis. Moreover, there is an increase of IFN-α in the psoriatic lesions produced by anti-TNF-α therapy. TNF-α can inhibit the production of IFN-α by the DPDC. TNF-α antagonists induce cytokine imbalance: excessive inhibition of TNF-α, especially in subjects that are particularly predisposed, may induce local increase of IFN-α and induce the migration of T cells via IL-15 by the skin. Some authors have suggested an increase in certain chemokine receptors (CXCR3), which are upregulated by IFN-α, favoring the migration and activation of T lymphocytes (involved in the pathogenesis of psoriasis) into the skin.

This paradoxical side effect has been reported in nearly all diseases treated with anti-TNF-α and with all TNF antagonist therapies. The prevalence of this side effect is about 1.5 to 5%. The most of cases have been described in rheumatologic diseases, however onset of psoriasis for biological therapy in IBD is not rare (15% of the total number of all reported cases). There have been several previous cases in CD but only 3 cases in ulcerative colitis (UC).

Although the majority of cases have appeared after infliximab treatment, there are only four cases of new onset of psoriasis in adults CD patients treated with adalimumab, probably because infliximab is the main anti-TNF-α that has been used for IBD in the last years and adalimumab is more recent addition to the therapeutic strategies for the treatment of CD. In Table 1 are all identified cases reported in the literature.

According to the literature, this paradoxical reaction is more frequent in women and in patients often without a personal history of psoriasis. It is generally accepted that psoriasis lesions appear from days to years after drug initiation, but the most critical time is between the 3rd and 4th infusion of anti-TNF-α therapy. There is a predilection for pustular type and for palm and sole involvement.

### Table 1 Case reports of new onset of psoriasis during treatment with anti-TNF-α therapy in adults IBD patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of IBD</th>
<th>N° of cases</th>
<th>Gender age</th>
<th>Type anti-TNF</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>11Thurber et al.</td>
<td>2004</td>
<td>UC</td>
<td>1</td>
<td>M/36</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>14Verea et al.</td>
<td>2004</td>
<td>CD</td>
<td>1</td>
<td>F/46</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>15Peramiquel et al.</td>
<td>2005</td>
<td>CD</td>
<td>1</td>
<td>F/29</td>
<td>IFX</td>
<td>Stop IFX+ TS+ PUVA</td>
</tr>
<tr>
<td>16Pirard et al.</td>
<td>2006</td>
<td>CD</td>
<td>1</td>
<td>F/19</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>17Glez-Lopez et al.</td>
<td>2006</td>
<td>CD</td>
<td>1</td>
<td>F/39</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>18Adams et al.</td>
<td>2006</td>
<td>CD</td>
<td>1</td>
<td>M/19</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>19Cohen et al.</td>
<td>2007</td>
<td>CD</td>
<td>3</td>
<td>F/32,53,56</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>20Angelucci et al.</td>
<td>2007</td>
<td>CD</td>
<td>1</td>
<td>F/28</td>
<td>IFX</td>
<td>Stop IFX</td>
</tr>
<tr>
<td>3Passarini et al.</td>
<td>2007</td>
<td>CD</td>
<td>6</td>
<td>18–54</td>
<td>7 IFX</td>
<td>Stop IFX</td>
</tr>
<tr>
<td>21Bruzzese et al.</td>
<td>2007</td>
<td>CU</td>
<td>2</td>
<td>M/29</td>
<td>IFX</td>
<td>Stop IFX</td>
</tr>
<tr>
<td>23Severs et al.</td>
<td>2007</td>
<td>CD</td>
<td>3</td>
<td>3 M/21–38</td>
<td>IFX</td>
<td>Stop IFX+ TS+ UVB</td>
</tr>
<tr>
<td>24Sladden et al.</td>
<td>2007</td>
<td>CD</td>
<td>1</td>
<td>F/37</td>
<td>IFX</td>
<td>Stop IFX+ TS+ AZA</td>
</tr>
<tr>
<td>25Takahashi et al.</td>
<td>2007</td>
<td>CD</td>
<td>4</td>
<td>1 M,3 F/29–42</td>
<td>IFX</td>
<td>Stop IFX+ TS+ PUVA</td>
</tr>
<tr>
<td>26Wollina et al.</td>
<td>2008</td>
<td>CD</td>
<td>8 Review</td>
<td>CD 1 New</td>
<td>M/22</td>
<td>Stop IFX+ O Steroids</td>
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<tr>
<td>27Ritchetta et al.</td>
<td>2008</td>
<td>CD</td>
<td>1</td>
<td>M/29</td>
<td>IFX</td>
<td>Stop IFX+ O CyA</td>
</tr>
<tr>
<td>15Harris et al.</td>
<td>2008</td>
<td>CD</td>
<td>1</td>
<td>F/29</td>
<td>ADA</td>
<td>Stop ADA+ TS+ MTX</td>
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<tr>
<td>28Collamer et al.</td>
<td>2008</td>
<td>IBD</td>
<td>17 Review</td>
<td>10 F,6 M/32</td>
<td>IFX</td>
<td>Stop IFX</td>
</tr>
<tr>
<td>29English et al.</td>
<td>2009</td>
<td>CD</td>
<td>1</td>
<td>F/20</td>
<td>IFX</td>
<td>Stop IFX+ TS</td>
</tr>
<tr>
<td>30Manni et al.</td>
<td>2009</td>
<td>CD</td>
<td>1</td>
<td>F/30</td>
<td>IFX</td>
<td>Stop IFX+ TS+ iv CyA</td>
</tr>
<tr>
<td>16Medkour et al.</td>
<td>2010</td>
<td>CD</td>
<td>1</td>
<td>M/32</td>
<td>IFX</td>
<td>Stop IFX+ TS+ AZA</td>
</tr>
<tr>
<td>11El Shabrawi-Caelen et al.</td>
<td>2010</td>
<td>CD</td>
<td>2</td>
<td>F/19,31</td>
<td>ADA</td>
<td>Stop ADA</td>
</tr>
</tbody>
</table>

IBD: Inflammatory Bowel Disease; CD: Crohn’s Disease; UC: Ulcerative Colitis; AS: ankylosing spondylitis; M: Male; F: Female; IFX: Infliximab; ADA: Adalimumab; TS: Topical steroids. IV: Intravenous; O: Oral; CyA: Cyclosporine; MTX: Methotrexate; AZA: Azathioprine.
The management of this side effect is not conclusive but the lesions of the majority of patients cleared after cessation of the therapy. A dermatologist should evaluate the possible skin infection and perform a skin biopsy to confirm the diagnosis and make a differential diagnosis of cutaneous symptoms in IBD. As a general rule, patients with these lesions have no previous personal or family history of psoriasis and Chlamydia infection has been associated in a small number of cases. Generally they should recommend treatment for psoriasis and suspend anti-TNF–α therapy. In cases of mild skin lesions with good response of topical therapy, we can try to keep anti-TNF therapy. Based on the literature review, some authors only recommending withdrawal of anti-TNF–α in case of severe (covering more than 5% of body surface), intolerable lesions or if the patient prefers discontinuation. If psoriasis is tolerable and the patient agrees, we can reintroduce the biological therapy or consider alternative anti-TNF treatment (e.g. immunosuppressant therapy such as methotrexate). The switch to another biological agent can be considered if the patient has general skin disease and IBD is aggressive as our patient. In our case, the patient was treated with topical steroids. The previous studies indicate that the development of a paradoxical side effect does not always require treatment discontinuation and can switch to another TNF antagonist, but in our case it was not possible. Of course, we should make a decision case by case. Even though we think that it is important to try to switch anti-TNF therapy, because the gains can be greater than the risks. We would like to draw attention to the fact that it is not possible to continue with biological therapy in all patients and ultimately, in many occasions, we clinicians are obliged to perform surgery. Though the new biological therapies allow us to delay surgery, it is not always possible because the therapeutic possibilities are limited. Further studies with similar cases are necessary to interpret the clinical significance of this paradoxical condition and increased knowledge of the patients pathophysiology can help to treat conditions adequately.

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