Induction or exacerbation of psoriasis in patients with Crohn’s disease under treatment with anti-TNF antibodies

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Abstract: BACKGROUND AND AIMS: Paradoxically, psoriasis or psoriasiform skin lesions induced or exacerbated by anti-TNF antibodies have been described. Here, we report a series of 13 novel cases featuring exacerbation or occurrence of psoriatic skin lesions induced by anti-TNF antibodies in patients with Crohn’s disease (CD). METHODS: We performed a systematic analysis of exacerbation or occurrence of psoriasis or psoriasiform skin lesions induced by anti-TNF antibodies in an inflammatory bowel disease patient cohort at the University Hospital Zurich. RESULTS: We identified 13 CD patients who developed psoriasis or psoriasiform lesions while receiving anti-TNF therapy. 10 of the 13 patients were female with an average age of 26.9 years at diagnosis. 11 of the 13 patients had a complicated disease. The mean time of clinical latency between diagnosis and onset of psoriasis was about 9.4 years, and the time between the beginning of all biological infusions and the onset of psoriasis was about 7 months. 7 of the 13 patients received infliximab, 3 adalimumab, and 3 certolizumab pegol at onset of psoriasis. In most of the cases, anti-TNF therapy was changed or discontinued and skin lesions improved. CONCLUSION: Most of our described patients featured a complicated disease course of CD and had an improvement of the rash after changing the anti-TNF therapy.

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Induction or Exacerbation of Psoriasis in Patients with Crohn’s Disease under Treatment with Anti-TNF Antibodies

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Key Words
Inflammatory bowel disease · Crohn’s disease · Ulcerative colitis · Anti-TNF agents · Psoriasis · Infliximab · Adalimumab · Certolizumab pegol · Golimumab

Abstract
Background and Aims: Paradoxically, psoriasis or psoriasiform skin lesions induced or exacerbated by anti-TNF antibodies have been described. Here, we report a series of 13 novel cases featuring exacerbation or occurrence of psoriatic skin lesions induced by anti-TNF antibodies in patients with Crohn’s disease (CD).

Methods: We performed a systematic analysis of exacerbation or occurrence of psoriasis or psoriasiform skin lesions induced by anti-TNF antibodies in an inflammatory bowel disease patient cohort at the University Hospital Zurich.

Results: We identified 13 CD patients who developed psoriasis or psoriasiform lesions while receiving anti-TNF therapy. 10 of the 13 patients were female with an average age of 26.9 years at diagnosis. 11 of the 13 patients had a complicated disease. The mean time of clinical latency between diagnosis and onset of psoriasis was about 9.4 years, and the time between the beginning of all biological infusions and the onset of psoriasis was about 7 months. 7 of the 13 patients received infliximab, 3 adalimumab, and 3 certolizumab pegol at onset of psoriasis. In most of the cases, anti-TNF therapy was changed or discontinued and skin lesions improved.

Conclusion: Most of our described patients featured a complicated disease course of CD and had an improvement of the rash after changing the anti-TNF therapy.

Introduction
Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract which includes Crohn’s disease (CD) and ulcerative colitis (UC). While UC is restricted to the colon and reflects a continuous inflammation confined to the mucosal layer, CD is characterized by a discontinuous, granulomatous and transmural inflammation that can occur anywhere in the gastrointestinal tract. Environmental, genetic and immunological factors as well as the intestinal microbiota have been considered as the major etiology of IBD. Evidence suggests that an epithelial barrier defect, coupled with a
dysfunctional immune response of the innate as well as the acquired immune system to commensal microbiota, resulting in either excessive up- or impaired downregulation of inflammatory events, drives the development of chronic intestinal inflammation [1]. The predispositions are genetically determined and variations in about 160 gene loci have been associated with IBD [2, 3].

Current treatment strategies include steroids, immunosuppressants as well as biologicals, in particular anti-TNF antibodies. The introduction of anti-TNFs for IBD was in the late 1990s and these agents have proven efficacy in the induction and maintenance of remission in CD and more recently in UC. They are also routinely used in the management of rheumatologic conditions (e.g. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis) and psoriasis [4]. Infliximab (IFX) was the first biologic agent targeting TNF and was followed by other anti-TNF antibodies, such as adalimumab (ADA), certolizumab pegol (CZP) and golimumab [4–6].

The number of IBD patients being exposed to TNF inhibitors has dramatically increased in the last decade. Though clinical efficacy and safety of anti-TNF agents is well demonstrated, a significant number of patients exhibit side effects that often lead to discontinuation of anti-TNF treatment. This situation then displays a serious problem since further treatment options are limited and often fail.

A certain group of complications under the treatment with anti-TNF antibodies that gains more and more importance in the clinical management of IBD patients is the manifestation of psoriatic skin lesions. This phenomenon is seemingly paradoxical because of anti-TNF agents (e.g. IFX and ADA) are also effective in the treatment of psoriasis [5–7]. After publication of the first case series [8, 9], it nowadays appears that the magnitude of this problem has long been (and probably still is) underestimated.

Besides the unpleasant nature of this dermopathy, ranging from predominant cosmetic impairment up to severe pruritus and psychological, sexual as well as psychosocial affections, the severe impact of this side effect lies in the fact that a substantial number of patients need either to be switched to an alternative anti-TNF agent (with only limited efficacy) or completely be taken off (about 30% of patients) TNF inhibitors [4, 9–12], possibly resulting in acute IBD flares.

Here, we describe 13 new cases of CD patients developing psoriasis or psoriasiform skin lesions while being under anti-TNF therapy. This adds significantly to the described number of somewhat over 220 such cases to date. A further purpose of this study was to perform a systematic review of reported cases with this pathology.

Patients and Methods

We retrospectively identified 13 cases of anti-TNF-induced psoriasis or psoriasiform skin lesions in patients with CD in the IBD outpatient clinic at the Division of Gastroenterology and Hepatology, University Hospital Zurich, Switzerland, between 2007 and 2013. A detailed review of each patient’s medical record was undertaken, focusing on demographics, type of IBD, years from diagnosis of CD, presentation, location and behavior according to the Vienna Classification, personal and family history of psoriasis, time of onset of psoriasis, site of lesions, complications, therapy, and outcome. In each case, the tentative diagnosis psoriasis was diagnosed by the gastroenterologist and in most of the cases confirmed by a dermatologist who carried out a biopsy of the respective skin lesions, if deemed necessary.

Systematic Review

A comprehensive search was conducted using MEDLINE and PubMed databases from January 1946 to July 2013. The keywords used were: ‘Crohn’s disease’, ‘ulcerative colitis’, ‘inflammatory bowel disease’, ‘psoriasis’, ‘psoriatic skin lesion’, ‘anti-TNF’, ‘infliximab’, ‘adalimumab’, ‘certolizumab pegol’ and ‘golimumab’, either singly or in combination. Reports describing histological types of psoriasis or psoriatic skin lesions in patients who had not been on anti-TNF therapy at time of occurrence were excluded. The reference lists from the relevant articles were also searched manually to identify trials for possible inclusion. All available clinical and pathological variables from these reports were included.

Statistical Analysis

Qualitative variables were expressed as percentages with confidence intervals while quantitative variables were expressed as the mean and standard deviation or median and interquartile range, according to the presence or absence of a normal distribution.

Results

We identified 13 patients with the diagnosis of CD and a concomitant diagnosis of psoriasis or psoriasiform skin lesion while receiving an anti-TNF antibody (e.g. ADA, IFX, CZP or golimumab). Of note, no such cases in UC patients were found.

Demographic Aspects

All patients in this case series had CD. 10 of the 13 (77%) patients were female with the diagnosis of CD, a mean age of 26.9 (18–54) years at diagnosis and no personal and/or family history of psoriasis; 3 of them (23%) were males with a mean age of 22 (15–34) years and also without a history of psoriasis (table 1).

IBD Characteristics

Multiple other organ systems can be affected in IBD patients, including bones and joints, skin and eyes. In our
review, 8 of the 13 patients (62%) with CD had extraintestinal manifestations. All 8 patients were suffering from arthritis and 2 (25%) additionally had a manifestation of their skin other than psoriasis (both had an erythema nodosum and a pyoderma gangrenosum). In 3 patients, IBD was associated with arthritis and perianal inflammation (37.5%) or in 2 patients with arthritis in combination with an association of their bones (25%). 5 (38%) CD patients had no extraintestinal manifestation. 6 (46%) CD patients featured a steroid-dependent disease course and 11 of the 13 (85%) CD patients received azathioprine at any stage during their disease.

**IBD Complications**

The major intestinal IBD complications include fistulae and stenosis either alone or in combination. In our case series, 11 of 13 patients (85%) had a complicated disease characterized either by stenosis or fistulae. Only 2 (15%) CD patients showed an inflammatory, meaning non-stricturing non-penetrating disease course, and 3 (23%) patients featured a structuring disease, while the majority of the 8 patients (62%) featured a penetrating disease. Of the 13 CD patients, 1 (8%) had inflammation restricted to the terminal ileum and 2 (15%) had colonic disease. 10 (77.0%) patients had ileocolonic disease and 2 also had upper gastrointestinal tract involvement (table 2). In our review, 7 of 13 (54%) CD patients had undergone surgery in their medical history. The mean time of clinical latency between the diagnosis and the first operation was about 7 (1–12) years.

**Clinical Manifestations**

For the treatment of the 13 CD patients, four different anti-TNF antibodies, namely IFX, ADA, CZP and golimumab, were used. 11 of 13 (85%) patients had IFX, 8 (62%) patients ADA, and 7 (54%) patients CZP in their medical history. Only 1 patient was being treated with golimumab after receiving IFX, ADA and CZP.

In our case series, three anti-TNF agents (IFX, ADA and CZP) were responsible for the induction or exacerbation of psoriasis or psoriasiform lesions in CD patients. At the onset of skin lesions, 6 (46%) patients with CD were being treated exclusively with IFX, 3 with ADA (23%) and 3 with CZP (23%). In 1 patient, IFX as well as CZP were responsible for the induction or exacerbation of the psoriasiform lesions. The mean time of clinical latency between the diagnosis and the onset of psoriasis or psoriasiform skin lesions was about 9.4 (1–19) years. The mean time of clinical latency between the beginning of all biological infusions and the onset of psoriasis or psoriasiform skin lesions was averaged about 7 (3–12) months (table 1).

Nine of the 13 CD patients (69%) who developed psoriasis or psoriasiform skin lesions being treated with anti-TNF agents saw a dermatologist and 8 (62%) received a skin biopsy. The skin biopsy results showed features consistent with psoriasis in 3 (37.5%) patients and psoriasiform skin lesions in 5 (62.5%) patients.

The most frequent sites of psoriatic or psoriasiform skin lesions were the limbs (54%) in 7 patients, followed by the scalp (31%) in 4, and the trunk (23%) in 3 patients. Most had more than one site of skin lesions (fig. 1).

### Table 1. Summary of data of 13 CD patients with psoriatic lesions induced or exacerbated by anti-TNF agents

<table>
<thead>
<tr>
<th>Gender</th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>26.9 (18–54)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>New onset of skin lesion</td>
<td>13 (100)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Previous history of psoriasis</td>
<td>No (de novo or induced psoriasis) 13 (100)</td>
<td>Yes (exacerbated preexisting psoriasis) –</td>
</tr>
<tr>
<td>Anti-TNF treatment used at the time of skin lesion</td>
<td>IFX 7 (54)</td>
<td>ADA 3 (23)</td>
</tr>
<tr>
<td>Time from diagnosis to onset of rash, years</td>
<td>9.4 (1–19)</td>
<td>7 (3–12)</td>
</tr>
<tr>
<td>Time from start of anti-TNF to onset of rash, months</td>
<td>IFX 8.7 (2–12)</td>
<td>ADA 6 (3–9)</td>
</tr>
</tbody>
</table>

Values represent n (%) or median (range).

### Table 2. Vienna Classification in 13 CD patients

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
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<tr>
<td></td>
<td>B1</td>
</tr>
<tr>
<td>L1</td>
<td>1</td>
</tr>
<tr>
<td>L2</td>
<td>1</td>
</tr>
<tr>
<td>L3</td>
<td>2</td>
</tr>
<tr>
<td>L3/4</td>
<td>1</td>
</tr>
</tbody>
</table>

Vienna Classification: A (age at diagnosis): A1 <40 years, A2 >40 years; L (location): L1 terminal ileum, L2 colon, L3 ileocolon, L4 upper GI; B (behavior): B1 non-stricturing, non-penetrating, B2 stricturing, B3 penetrating.
Management

In 4 of 13 (31%) CD patients, the current anti-TNF treatment was stopped and switched to a different medication (e.g. methotrexate, steroids or azathioprine). All had a topical treatment and in 3 cases an improvement of their skin lesions was observed. In 4 (31%) patients the current anti-TNF agents were switched to another one. All of them also featured an improvement. One patient (8%) was switched first to another anti-TNF agent, but as the dermatopathy recurred, the patient was switched to an experimental drug (interleukin-6 antibody) and anti-TNF treatment was stopped. In 2 (15%) patients the medication with anti-TNF agents was continued and not suspended; they had an improvement of their skin lesions under topical treatment with corticosteroids. In another 2 patients (15%) the final decision about how to continue with anti-TNF therapy was not decided. Topical treatment was the anti-psoriatic therapy most often used (85%), with a topical corticosteroid resulting in improvement of skin lesions in nearly in all cases.

Discussion

Since their introduction in the late 1990s, anti-TNF agents have acquired a prominent place in the treatment of IBD and psoriasis [4]. Paradoxically, numerous reports of new onset or exacerbation of psoriasis under treatment with anti-TNF agents have been observed in patients with IBD. Although the first case of anti-TNF agent (IFX)-induced psoriatic lesions was described in a patient with CD [13], most of the skin lesions concerned were obtained from the rheumatologic literature [14]. An increasing number of IBD patients developed a psoriatic skin lesion as described in numerous reviews [15–17] and the latest overview in patients with IBD mentions more than 220 cases [18].

In our case series representing 13 new cases, we found that all of the patients with anti-TNF agent-induced psoriasis or psoriasiform skin lesions were patients with CD without a personal history of psoriasis. This observation is in good accordance with previous data in the literature where CD patients are also described to be mainly affect-
In our experience, CD patients developing psoriasis or psoriasiform skin lesions were mainly female with CD (77%), while in the literature the male:female ratio seems to be mainly equivalent. In the literature it is recommended that patients developing psoriasis or psoriasiform skin lesions while receiving anti-TNF therapy should be evaluated by a dermatologist [20, 21]. In our case series, 9 patients (69%) saw a dermatologist and 8 (62%) had a skin biopsy. Their histopathological assessments revealed the diagnosis of a psoriasiform lesion in 5 (62.5%) patients as the most reported form of skin lesion and the diagnosis of psoriasis in the biopsy of 3 (37.5%) patients. In the other cases the skin lesions were described as a psoriasiform lesion. Because there is no exact and clear definition of psoriasiform or psoriasis-like lesions, many of these cutaneous reactions may actually be the classic type of psoriasis. However, to classify and diagnose the respective skin lesions accurately and to initiate adequate treatment, it might be the best option that patients who developed psoriasis or psoriasiform skin lesions while undergoing anti-TNF therapy should be evaluated by a dermatologist [20, 21].

Our observed sites of psoriasis or psoriasiform skin lesions by patients with CD were the limbs in 7 patients (54%), followed by the scalp (31%) in 4, and the trunk (23%) in 3 patients. This is also in accordance with other reviews [16, 19].

Multiple other organ systems can be affected in IBD patients, including bones and joints, skin and eyes [22, 23]. In our case series, 8 of 13 (62%) patients had extraintestinal manifestations; all had IBD-associated arthritis/arthropathy. Two patients (25%) also had a manifestation of their skin (both had an erythema nodosum and a pyoderma gangrenosum) and 2 patients a manifestation of their bones (25%). This is also well in line with previous findings [24, 25].

The multitude of perianal complications in CD patients includes fissures, fistulae, abscesses, and stenosis, either alone or in combination. In our case series, 85% patients had a complicated disease characterized either by stenosis or fistulae. The medical therapy is considered to be the treatment modality of choice for most IBD patients while operative management is reserved for individuals who fail medical treatment or develop potentially life-threatening complications. However, most patients with IBD ultimately require one or more operations over their lifetime. In our review, 7 of 13 (54%) CD patients had undergone surgery in their medical history with a mean time of clinical latency between the diagnosis and the first operation of 7 (1–12) years. Previous studies have shown similar results [26–31].

In our case series, 13 patients with CD had been treated with four different anti-TNF agents, IFX, ADA, CZP or golimumab, and three of them (except golimumab) were responsible for the induction or exacerbation of psoriasis or psoriasiform lesions in our case. Most of the patients (54%) received IFX. This observation is in good accordance with other literature [16, 18, 19]. The majority of the IFX therapy likely reflects the fact that it was the first biological agent available on the market and because of that the drug has been used longer than the other anti-TNF agents.

The duration of anti-TNF therapy prior to the onset of the rash is highly variable suggesting that an environmental trigger may also be involved [16, 18]. The mean time of clinical latency between the diagnosis and the onset of all biological infusions was about 9.4 (1–19) years and the mean time between the beginning of the biological therapy and the onset of psoriasis or psoriasiform skin lesions in our case series was about 7 (3–12) months.

At this time, no guideline exists for treating psoriasis or psoriasiform skin lesions in patients with IBD under treatment with anti-TNF agents. There is a wide range of therapeutic approaches, but there is a disagreement whether discontinuation of the biological is needed to achieve an improvement or complete resolution of the lesions [16, 18].

In our patient collective, anti-TNF treatment was either stopped and the patient was switched to a different, non-anti-TNF medication (e.g. methotrexate, steroids or azathioprine), anti-TNF agents were switched to another one, or the anti-TNF agents were continued and not suspended. Of note, all three approaches were successful, at least in some of the patients and/or in combination with specific psoriasis treatment. Topical steroids are the treatment of choice for skin lesions alone or in combination with other topical drugs or phototherapy. In our case series, 85% had a topical treatment, mostly with topical steroids and most of our patients showed an improvement of skin lesions.

Although psoriatic lesions that are induced or exacerbated by anti-TNF agents in patients with IBD have been reported, their immunopathogenetic mechanism has not yet been elucidated [15, 18]. It is known that T cells play a key role for the development of chronic inflammatory conditions such as IBD, psoriasis, rheumatoid arthritis or systemic lupus erythematosus.
Due to the surprising nature of this induced dermopathy, as anti-TNF agents are also largely and successfully used in the treatment of psoriasis, the term paradoxical psoriasis has been coined. To date, the pathogenesis of such psoriatic lesions occurring under anti-TNF therapy still largely remains obscure. All in all, the direct mechanism of action of these agents, namely neutralization of TNF, most likely is a key element in the pathogenesis. A dysbalance between TNF and interferon-α seems to be of great importance [32]. Interferon-α is produced in dermal plasmacytoid dendritic cells, is negatively regulated by TNF [33] and is known as a key driving factor in the pathogenesis of psoriatic skin lesion development [34, 35]. However, other cytokine and T-cell pathways were also identified as potential key players and this was mainly driven by the recognized overlap of candidate genes in IBD on the one hand and psoriasis as well as eczema on the other [36, 37]. Nevertheless, the rising number of IBD patients developing psoriatic skin lesions under anti-TNF therapy makes the need for further investigation about the pathogenetic mechanisms of these complications obvious. A better pathogenetic understanding would clearly help to define and improve treatment strategies for this complication.

All in all, we show that psoriatic skin lesions in CD patients under anti-TNF therapy occur mainly in females featuring a complicated disease course. Since these patients are obviously difficult to treat anyway, the onset of psoriatic skin lesions makes their treatment even more difficult. Therefore, our study might contribute to better characterization of such patients.

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Disclosure Statement

The authors have no conflicts of interest to disclose.


