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CASE REPORT

Dramatic improvement of severe acne pustolosa after adalimumab in a patient with ulcerative colitis

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Key clinical message

A 22-year-old male with extensive steroid-dependent/azathioprine-refractory ulcerative colitis and preexistent severe refractory acne pustolosa (AP) was successfully treated with adalimumab for both conditions. Severe AP could be considered a further indication, instead of a relative restriction, to anti-TNFα in steroid-dependent IBD patients needing therapy with this class of drugs.

Keywords

Acne pustolosa, adalimumab, inflammatory bowel diseases, infliximab, tumor necrosis factor alpha, ulcerative colitis.

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic complex inflammatory disorders of the gastrointestinal tract, often complicated by extraintestinal manifestations (EIMs), such as musculoskeletal, skin, eyes, liver, and biliary tract disorders. From this point of view, even if every organ system could be affected in IBD, the skin is one of the most frequently involved sites in this systemic inflammation [1]. Skin disorders occur in up to 75% of patients with CD and in 11% of patients with UC. According to pathophysiology, IBD related skin manifestations can be classified into four categories: (i) specific dermatological manifestations with the same histological features as the underlying IBD (noncaseating granulomas with multinucleated giant cells in the dermis surrounded by lymphocytes, plasma cells, and eosinophils); (ii) reactive cutaneous manifestations that share similar immunological mechanisms triggered by antigens presented in the gut and the skin (pyoderma gangrenosus, Sweet's syndrome); (iii) skin diseases classically associated with IBD (erythema nodosum, psoriasis); (iv) adverse effects of IBD treatment (psoriasis-like, eczema-like, lichenoid eruptions) [1].

Acne pustolosa (AP) is a subclass of acne vulgaris, a chronic inflammatory disease of the pilosebaceous follicles, characterized by comedones, papules, pustules, cysts, and nodules. Its pathogenesis includes follicular hyperkeratinization, sebaceous hypersecretion, follicular colonization by *Propionibacterium acnes*, immune, and inflammatory responses. AP is mainly considered as an adverse event caused by steroids or anti-TNFα drugs [2].

Interestingly and against current evidences, we report a case of a patient affected by ulcerative colitis (UC) and acne pustolosa (AP) which were both successfully treated with adalimumab.

Case Report

On February 2014, a 22-years-old male with a known extensive steroid-dependent and azathioprine-refractory UC attended our IBD Unit because of clinically moderate relapse of disease.

In 2013, the patient had presented bloody diarrhea (6–7 bowel movements/day) with diffuse abdominal pain. For this reason, he underwent ileocolonoscopy with the evidence of multiple ulcerations from rectum to ascending colon (Mayo subscore 3). The patient started high-dosage

steroids (methylpredisolone 60 mg) and mesalamine (3 g/daily), with clinical benefit. Unfortunately, being on steroid tapering, he presented a clinical relapse so that he started therapy with azathioprine (2.5 mg/kg/day).

Moreover, he was affected by a severe AP (Figs. 1A and 2A), which was preexistent the onset of UC, previously treated by several drugs (tetracyclines, clindamycin, isotreonina, sulfur derivates) without substantial response. In addition, our patient had reported a worsening of skin lesions after the introduction of steroids for the underlying UC (dosage range 10–15 mg of prednisone/day). AP had had a severe impact on the patient's quality of life, causing low self-esteem, anxiety, and difficulties in social relationship.

On February 2014, the patient attended our Unit because of clinically moderate relapse of his disease.

Differential Diagnosis, Investigations, and Treatment

On physical examination, the skin manifestation mainly involved the thorax region and the back.

Laboratory investigation showed no significant alterations except for a mild increase in fibrinogen and CRP levels. On March 2014, the patient underwent colonoscopy showing mucosal edema/erythema with diffuse erosions (Mayo subscore 2). In view of the steroid-dependent UC and the unsatisfactory response to conventional therapy (continuous oral and topical 5-ASA plus a course of 8 months of azathioprine), he started therapy with adalimumab (induction: 160/80 mg e.o.w.; maintenance: 40 mg/e.o.w.).

On the basis of the findings of comedones, papules, and, especially, pustules, the possibility of an AP was considered and the diagnosis of acne was fairly easy. However, we considered in differential diagnosis: rosacea, other dermatitis, flat warts, which were excluded by an expert dermatologist.

Outcome and Follow-up

After 2 months of therapy with adalimumab we verified a significant improvement of intestinal symptoms with a reduction of both the endoscopic activity (Mayo subscore 1) and the need for steroids (5 mg of prednisone/day). Interestingly, and quite surprisingly, we also recorded a dramatic improvement of the dermatological lesions (Figs. 1A–B and 2A–B), with a relevant benefit for our patient in terms of quality of life. After 8 months of ADA treatment, our patient was still on steroid-free clinical remission and, at the same time point, he was considered in remission even about AP: no comedones/papules/pustules were seen with only residual scars of the previous severe AP. These relevant dermatological results were not

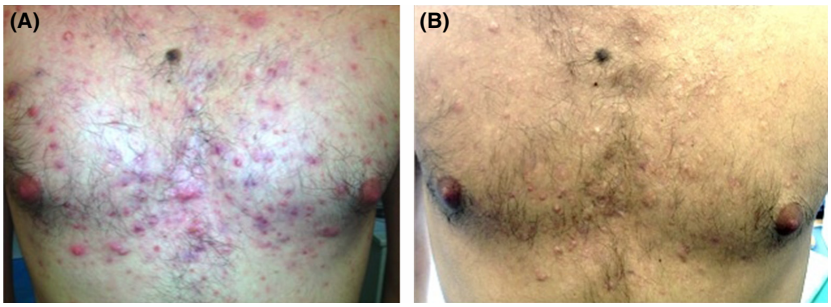

Figure 1. Acne pustolosa before (A) and after 2 months of therapy with adalimumab (B) (Chest).

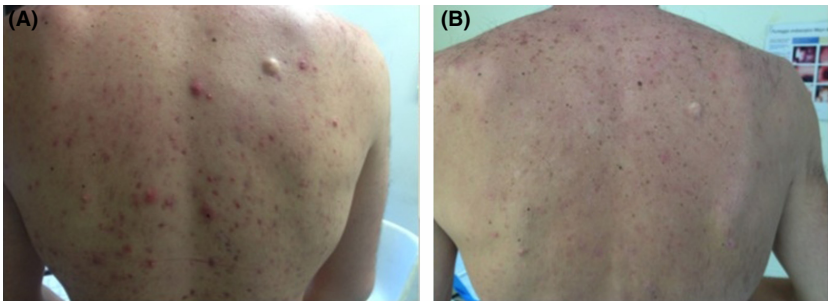

Figure 2. Acne pustolosa before (A) and after 2 months of therapy with adalimumab (B) (Back).

evident at previous attempts of reducing the dosage of steroids, so underlying the pivotal therapeutic role of the anti-TNF alpha treatment.

Discussion

Although it is well-known that several extraintestinal dermatological manifestations (e.g., pyoderma gangrenosum, erytema nodosum, Sweet's syndrome) can be associated with UC [1], AP is not included in this group of skin disorders, being mainly considered as an adverse event caused by steroids [2]. According to this opinion, also our patient had reported a worsening of skin lesions after starting steroids for the active UC.

The main outcome of our case was the clear improvement of the severe and therapy-resistant AP after only 2 months of therapy with adalimumab. Even if the pathogenesis of AP remains quite complex and debated, the role of TNFα in inducing and worsening skin inflammation appears to be relevant [3]. Some reports have already highlighted the efficacy of anti-TNFα agents in treating the dermatological manifestations of the SAPHO syndrome (Synovitis, Acne, Pustolosys, Hyperostosis, Osteitis), supporting the potential role of anti-TNFα agents in treating AP [3–5].

To our knowledge, only few case reports have been published to establish the efficacy of anti-TNFα drugs as monotherapy in patients with therapy-resistant AP. *Campione* et al. [6] previously reported a patient with facial acne conglobata responded rapidly to treatment with etanercept; *Shirakawa* et al. [7] reported another patient suffering from acne conglobata and rheumatoid arthritis responded to infliximab plus oral isotretinoin; *Schuttelaar* et al. [8] showed a patient with severe nodular inflammatory acne and ulcerative colitis, which was in complete remission with azathioprine treatment, and was treated successfully with infliximab.

As mentioned above, acne is an inflammatory condition sustained by cytokines, including tumor necrosis factor α (TNFα), interleukin 1β, and granulocyte-macrophage colony-stimulating factor (GM-CSF), where follicular colonization by *Propionibacterium acnes* has been suggested as a trigger of this inflammation by stimulating production of TNFα from keratinocytes. Therefore, the upregulation of TNFα in AP hypothetically supports the use of anti-TNFα for this skin disorders.

In fact, *Holland* et al. [9] showed that *Propionibacterium acnes* stimulated in vitro the secretion of TNFα from keratinocytes: so a suppression or a reduction in *Propionibacterium acnes*-induced inflammation by blocking TNFα might be an additive effect of infliximab in inflammatory acne.

Currently, acne has been reported as a paradoxical adverse reaction to treatment with anti-TNFα in IBD or rheumatic patients [10]. Moreover, the "switch" from another anti-TNFα might not improve these adverse effects. These remarks indicate that TNFα has a complex role in the induction of skin disorders, which needs to be still investigated.

In conclusion, the presence of severe AP could be considered a further indication, instead of a relative restriction, to anti-TNFα agents in patients with steroid-dependent inflammatory bowel diseases needing a course of therapy with this class of drugs.

Conflict of Interest

None declared.

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