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Cutaneous Manifestations in Inflammatory Bowel Diseases: Eight Cases of Psoriasis Induced by Anti-Tumor-Necrosis-Factor Antibody Therapy

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Key Words
Inflammatory bowel disease · Anti-tumor-necrosis-factor antibody · Psoriasis

Abstract
Background: Ulcerous rectocolitis and Crohn's disease are the best known forms of inflammatory bowel disease (IBD). Skin manifestations are not uncommon in IBD and may be divided into specific cutaneous signs, aspecific cutaneous signs, and cutaneous signs caused by drugs used for IBD therapy. The specific signs (fistulas, rhagades and ulcers) are the result of the diffusion of the intestinal inflammatory process into the skin. Aspecific cutaneous signs (stomatic aphthosis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, vasculitis, bullous diseases) are quite frequently found in those suffering from IBD, but also in apparently healthy subjects, and may sometimes be the first sign of the intestinal disease. Cutaneous manifestations due to drugs vary in clinical aspect and are the direct consequence of the therapies adopted, which in IBD patients can be quite numerous: steroids, immunosuppressants, 5-aminosalicylic acid, biological agents, antibiotics. ***Objective and Methods:*** Due to the frequent finding of cutaneous manifestations in patients affected by IBD, a collaboration was set up between the Dermatological Clinic of the University of Bologna and the Center for the Study of IBD of the same university hospital. The aim was to diagnose the cutaneous signs appearing during IBD and to establish their etiopathogenesis in order to assess whether they were the result of epiphenomena of the IBD or side effects of the therapies adopted. ***Results:*** The cutaneous manifestations we observed can be divided into three distinct groups: signs that were specific to the basic disease, aspecific signs and finally signs attributable to the drugs used for therapy. Particular attention was given to the aspecific signs and those consequential to therapy. The aspecific cutaneous signs seen in our clinic generally reflect those reported in the literature. The cutaneous manifestations due to drugs were further divided into three groups: rosacea, acneiform dermatitis and psoriasis-like dermatitis. The most notable aspect of our series is the high number of patients presenting psoriasiform-type dermatitides with a generally widespread diffusion. ***Conclusion:*** We would like to draw attention to the fact that all patients with psoriasis had been undergoing treatment with drugs inhibiting tumor necrosis factor α (TNF-α) as part of IBD therapy. In all cases, the cutaneous reaction started after the third or fourth infusion of the biological drug. Anti-TNF-α agents have also been successfully used to treat psoriasis in the last few years. The reason for this apparently paradoxical effect of the therapy is still unclear.

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Introduction

Ulcerous rectocolitis (UR) and Crohn's disease (CD) are the best-known forms of inflammatory bowel disease (IBD), and both fall into the category of 'idiopathic' IBD since their etiology is still unknown. UR normally affects the rectum and may partially or totally involve the colon, with a continuous extension without interposition of areas of undamaged mucosa. The inflammatory process is limited to the mucosa and submucosa without extending to the deeper layers.

On the other hand, CD can affect any area of the digestive tract from the mouth to the anus with lesions that have a characteristic segmentary distribution and can affect the whole thickness of the intestinal wall [1].

Skin manifestations are not uncommon in IBD and may be divided into: specific cutaneous signs, aspecific cutaneous signs and cutaneous signs caused by drugs used for IBD therapy.

The specific signs (fistulas, rhagades and ulcers) are the result of the diffusion of the intestinal inflammatory process into the skin.

Aspecific cutaneous signs (stomatic aphthosis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, vasculitis, bullous diseases) are quite frequently found in those suffering from IBD, but also in apparently healthy subjects, and may sometimes be the first sign of the intestinal disease.

Cutaneous manifestations due to drugs vary in their clinical aspect and are directly linked to the therapies adopted, which in IBD patients can be quite numerous: steroids, immunosuppressants, 5-aminosalicylic acid, biological agents, antibiotics [2]. The aim of our study is to identify the cutaneous manifestations seen in patients suffering from IBD and to understand whether they are the result of epiphenomena of the intestinal pathologies or side effects of the prescribed therapy, with a view to providing clinicians with further information which would allow a better therapeutic approach to the basic disorder. For these purposes we report the observations of 8 cases of psoriasis induced by the administration of tumor necrosis factor (TNF) α inhibitors.

Materials and Methods

Due to the frequent finding of cutaneous manifestations in patients affected by IBD, a joint investigation was set up between the Dermatological Clinic of the University of Bologna and the Center for the Study of IBD of the same university hospital. The aim was to diagnose the cutaneous signs appearing during IBD and establish their etiopathogenesis in order to assess whether they were the result of epiphenomena of the IBD or side effects of the therapies adopted.

So far 47 patients have been observed in our clinic, ranging in age between 18 and 54 years (mean age 35.2 years), made up of 31 females and 16 males, 32 suffering from CD and 15 from UR. All patients underwent extensive laboratory and instrumental examinations at the unit for the study of IBD and were then referred to our clinic for dermatological assessment. Clinical examination involved bioptic sampling and subsequent histological testing to obtain a more accurate diagnosis.

Results

The cutaneous manifestations observed in the 47 subjects can be divided into three distinct groups: signs that were specific to the basic disease, aspecific signs and finally signs attributable to the drugs used for therapy. Particular attention was given to the aspecific signs and those consequential to therapy.

The aspecific cutaneous signs seen in our clinic (table 1) generally reflect those reported in the literature [8–14].

The cutaneous manifestations due to drugs were further divided into three groups (table 2); although rosacea and acne are both extremely common in the general population, the 7 cases of rosacea (5 in patients with CD and 2 in patients with UR) and the 6 of acneiform dermatitis (3 CD, 3 UR) can certainly be attributed to side effects of the prescribed therapy, especially when the treatment involved steroids.

The most notable aspect of our series is the high number of patients presenting psoriasiform-type dermatitis with a generally widespread diffusion (8 cases, 6 with CD and 2 with UR). In all these cases, histological tests confirmed the diagnosis of psoriasis (fig. 1).

Finally, mention should be made of other aspecific cutaneous manifestations that according to the literature are rarely associated with IBD. For example, herpes zoster, condylomata acuminata and erysipelas quite frequently develop in apparently healthy subjects. More predictable is their appearance in immunocompromised patients, especially those undergoing immunodepressive therapy.

Disussion and Conclusions

The aspecific cutaneous manifestations observed in our series of patients affected by IBD do not differ greatly from those reported in the literature [8–14]. They occur

Table 1. Aspecific cutaneous manifestations (our cases) and percentage foreseen in the general population

Cutaneous manifestation	Cases	Patients with CD	Patients with UR	Percentage observed	Cases foreseen in the general population
Pyoderma gangrenosum	6	5	1	12.8	1/1,000,000 p.a. [3]
Erythema nodosum	5	4	1	10.6	2.4/1,000 p.a. [4]
Bullous pemphigoid	2	2	–	4.3	0.17–0.26/1,000,000 p.a. [5]
Sweet's syndrome	1	–	1	2.1	2–6/1,000,000 p.a. [6]
Leukocytoclastic vasculitis	1	1	–	2.1	15/10,000,000 p.a. [7]

Table 2. Cutaneous manifestations and correlations with drug administration (our cases)

Cutaneous manifestation	Cases	Patients with CD	Patients with UR	Percentage observed	Incidence in the general population	Drugs involved
Acneiform dermatitis	6	3	3	12.8	extremely frequent	steroids
Rosacea	7	5	2	14.9	extremely frequent	steroids
Psoriasis	8	6	2	17	1.5% [15]	anti-TNF-α agents?

much more frequently than would be expected in the general population. This should come as no surprise, considering that such pathologies are often the first signal of serious internal disorders (e.g. enteropathies or malignant neoplasias). For instance, pyoderma gangrenosum is nearly always associated with a more serious underlying pathology. It is therefore not easy to provide precise percentages for the incidence in the general healthy population of the so-called idiopathic cases, where a correlated internal pathology is not evident.

The first two groups of manifestations due to drug administration (acneiform dermatitis and rosacea) can be attributed to adverse reactions to the prescribed therapy, especially where steroids are involved. Although acne and rosacea are observed on a daily basis by the dermatologist, the assumption of steroids as a trigger factor seems clear: such lesions are also frequently seen in patients treated with steroids for pathologies other than IBD.

The most notable aspect of our series is the high number of patients suffering from chronic inflammatory intestinal diseases who were also affected by psoriasis. Of the 8 patients in question, 5 presented a cutaneous picture that was so characteristic that a clinical examination alone would have been sufficient to arrive at a diagnosis of psoriasis (fig. 2). The 3 remaining cases, however, presented a less evident picture (fig. 3).

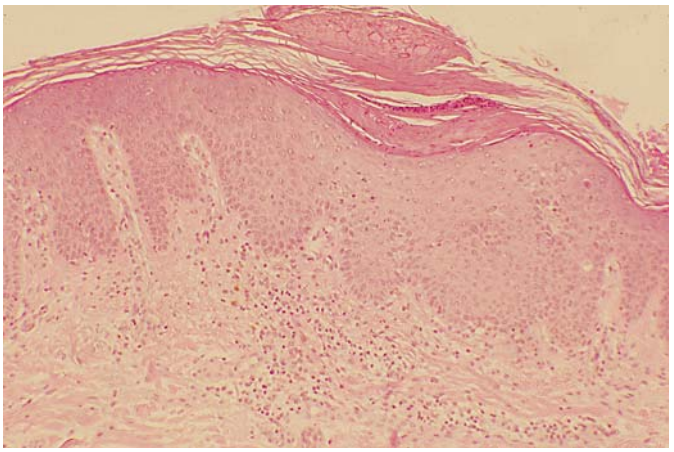
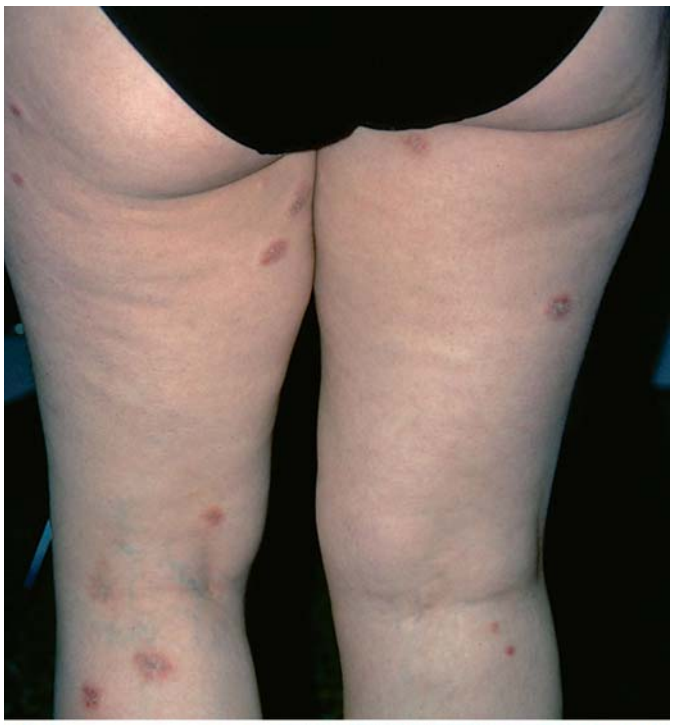
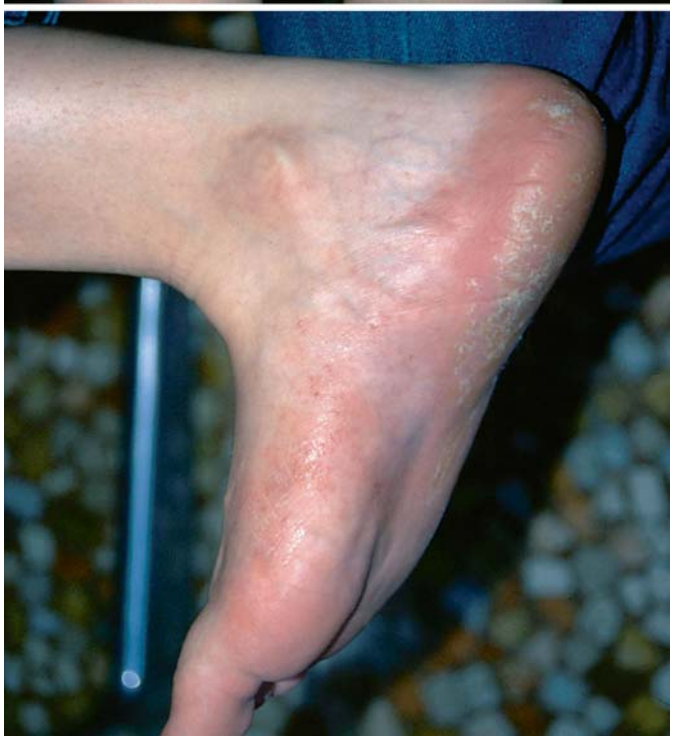


Fig. 1. Epidermis with psoriasiform acanthosis and focal parakeratosis induced by intracorneal pustule.

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 UR (5.7%) [15]. A higher prevalence of psoriasis among IBD patients might therefore be considered as normal. However, in our series the percentage of patients with psoriasis (17%) is almost double the percentage expected in IBD and much greater than that of the general population. The high in-





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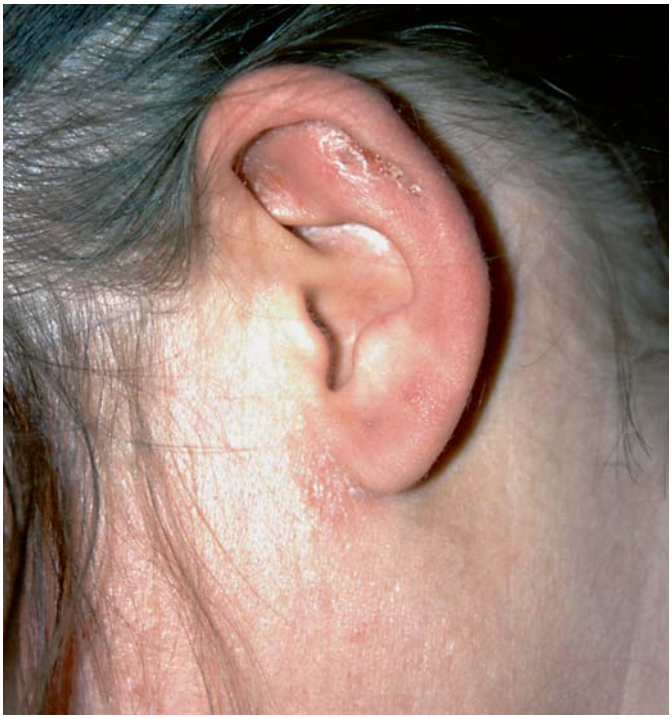

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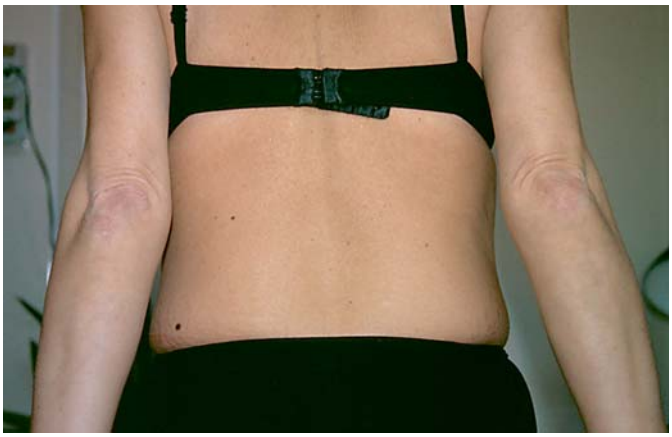

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Fig. 2. Roundish red scaly patches with clear margins of the lower limbs and of the plantar region.
Fig. 3. Red scaly patches with diffuse margins and crusted lesions of the auricular region.
Fig. 4. Small red scaly patches with clear margins of the elbows.

cidence of psoriasis among our patients cannot be solely attributed to a genetic or immune imbalance or alterations associated with the basic disease. Some other factors must surely be involved that bring about an increase in this cutaneous pathology by adding to or interfering with the intestinal disease.

Significantly, all 8 patients with psoriasis had been undergoing treatment with drugs inhibiting TNF-α as part

of the IBD therapy; 7 had been given infliximab and 1 adalimumab (the latter during an experimental study). In all cases, the cutaneous reaction started after the third or fourth infusion of the biological drug.

Furthermore, only 2 subjects (both suffering from CD) already had minor, stable psoriatic lesions (fig. 4) that spread after the administration of anti-TNF-α agents; the other 6 had no signs of the disorder before treatment with a TNF-α inhibitor and had no family history of psoriasis. The possible concomitance of underlying infections was excluded in all patients at the moment of prescribing therapy with biological drugs, as recommended in the guidelines, as well as after the revelation of the cutaneous pathology. Possible causes of a psoriasiform cutaneous rash such as Reiter's syndrome [16] were excluded due to the absence of correlated characteristic signs: none of our patients had eye involvement, nor showed any articular or urogenital disturbances. Moreover, the cutaneous manifestations never began acutely but appeared slowly and progressively. Finally, tampons used in the only case of palmoplantar pustular psoriasis (patient treated with adalimumab) were negative.

Very recently there has been a series of reports in the literature of psoriasiform lesions in patients who had been given TNF-α inhibitor drugs [17–22]. Grinblat and Scheinberg [23] reported a case of psoriasis with plaques induced by infliximab; a case of pustular psoriasis associated with infliximab was described by Thurber et al. [18]; Flendrie et al. [24] observed 3 cases of psoriasis triggered by adalimumab; 2 patients with psoriasis induced by biological drugs were reported by Dereure et al. [20]; Beuthien et al. [22] described a case of palmoplantar pustular psoriasis in a patient treated with adalimumab; 8 cases of psoriasis correlated with anti-TNF-α inhibitors were documented by Kary et al. [25] and another 4 by Haibel et al. [26]; Baeten et al. [27] reported 3 observations of palmoplantar pustular psoriasis following the administration of infliximab; another case was described by Verea et al. [28]; finally, 5 cases of psoriasis triggered by biological drugs were reported by Sfikakis et al. [21], 2 by Michaëlsson et al. [29], 1 by Peramiquel et al. [30] and 3 by Pirard et al. [17].

Our study would seem to support the hypothesis of psoriasis induced by anti-TNF-α agents and confirm an apparent paradox. Not only have these drugs been authorized for around 10 years in the treatment of CD, rheumatoid arthritis and ankylosing spondylitis, but they have also been widely adopted in the dermatological field to treat moderate or severe psoriasis and psoriatic arthritis not responding to other therapies. Recent studies appear to confirm the beneficial effects of infliximab in psoriatic lesions [31–33].

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, which involves various cytokines (including TNF-α), appears to play an essential role.

There is little doubt that the psoriasiform cutaneous manifestations observed in several of our patients were triggered or worsened by the administration of TNF-α inhibitor drugs. This is confirmed by the fact that after the withdrawal of the drug the clinical picture improved progressively and sometimes completely resolved.

We believe that there is a clear temporal link between the administration of the drug and the appearance of the cutaneous signs. In the cases described in the literature, the interval of time between the administration of the drug and the appearance of cutaneous manifestations seems, when mentioned, to be quite varied. In our series, though, the period of time appears to be constant for all patients and can be easily checked, given that the therapeutic regime for the administration of infliximab is very strict and involves endovenous infusion of the drug at well-defined intervals (at weeks 0, 2, 6 and thereafter every 8 weeks for maintenance). This enabled us to calculate that the latency time in our patients varied between 1.5 and 3.5 months. There were, in fact, no obvious dermatological problems after the first 2 administrations. The critical moment appears to be after the third or fourth administration (i.e. between the sixth and fourteenth week of protocol). The interruption of therapy with anti-TNF-α agents and a modification of the treatment prescribed for IBD brought about a regression of the lesions in all 8 patients and an evident improvement in their cutaneous clinical picture. So far, after the cessation of the biological drug therapy and several routine checkups, none of the patients has shown any signs of relapse.

The reason why drugs potentially used to resolve a cutaneous pathology could be the cause of the same pathology is still largely unknown. A particular consideration can nevertheless be made: the TNF seems to be fundamental to the normal development and functioning of the immune system. Excessive inhibition of this factor, especially in subjects that are particularly predisposed, could be just as damaging as its overactivation. The greater tendency for certain individuals to develop psoriasis during treatment with biological drugs could be linked to particular genetic or immune conditions, irrespective of the basic disorder. Some authors, on the other hand, have suggested that the appearance of psoriasis

may be related to the increase in certain chemokines (CXCR3), thus favoring the migration and influx of T lymphocytes (involved in the pathogenesis of psoriasis) into the cutis [34]. The complexity of the pathogenetic mechanisms involved in psoriasis, as well as the tests currently being carried out on anti-TNF-α drugs and the recent observation of patients presenting psoriasis after the administration of these drugs, all point to the urgent need for further investigation in order to clarify this apparent discrepancy.

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