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Cutaneous Adverse Reactions during Anti-Tnf Alpha Treatment for Inflammatory Bowel Diseases: The Experience of the Dermatology Clinic of Cagliari (Italy)

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Abstract

Background

Anti-tumour necrosis factor alpha are a well-documented class of disease-modifying therapy for inflammatory bowel diseases, including Crohn's disease and ulcerative colitis. The monoclonal anti-TNFα antibody Infliximab and Adalimumab are the current approved drugs in Italy, showing high efficacy, but also variable clinically significant adverse effects.

Method

From 2012, an observational prospective study was activated at the Dermatology Clinic of Cagliari University, to screen all patients with inflammatory bowel diseases treated with Infliximab and Adalimumab for cutaneous adverse reactions and skin cancers. A basal visit, complete of melanocytic lesions digital image recording was performed in all patients referred from the Gastroenterology Unit of the same University Hospital. Subsequent visits were performed when new lesions or modification of the skin appearance occurred. All cutaneous adverse reactions associated with anti-TNF treatment were reported to the Italian Pharmacovigilance network.

Results

Ninety-one patients were included in the study: 58 (31 women and 27 men) patients affected by Crohn's disease, (the age range was between 16 and 69 years), and 33 patients with ulcerative colitis (15 women and 17 men; age range between 21 and 68 years). Proportion of patients treated with infliximab (52%) was similar to adalimumab (48%). Cutaneous adverse reactions were observed in 38 patients (42%): 20 were taking Infliximab (52%) and 18 Adalimumab (48%). Adverse reactions observed by frequency included: infections (32%), eczematous dermatitis (23%), infusion systemic reactions and at the injection site (5.7%), psoriasis paradoxical reaction (5.7%), followed by a mixture of different cutaneous reactions, including urticaria, photosensitivity, chronic lupus erythematosus, lichenoid eruption, alopecia areata, hypertrichosis. Benign skin tumors eruption (15%) and basal cell carcinoma (2.8%) occurrence were also noted. Patient with dysplastic melanocytic nevi (10%) at screening were regularly followed with digital dermoscopy, but no one showed changes in the study period.

Conclusion

Our sample of patients had a high rate of skin adverse reactions (42%), but considering severity, no case required definitive discontinuation of therapy. Dermatologist support might be critical to optimize biological agent management in inflammatory bowel diseases, performing a careful basal screening, strict monitoring of adverse reactions and prompt intervention, as well as educating the patient towards skin cancer prevention, considering the long-term drug exposure.

Keywords: Pharmacovigilance; Drug safety; Anti-tumour necrosis factor alpha; Anti- TNFα; infliximab; Adalimumab; Cutaneous adverse reactions

Introduction

Tumour necrosis factor alpha (TNFα) is a pro-inflammatory cytokine that plays a number of immunoregulatory and systemic effects, representing a key target for therapeutic intervention [1].

Although expressed predominantly by macrophages, it is also produced by other cells, such as lymphocytes, monocytes, keratinocytes, fibroblasts, and its receptors are expressed on almost all cells [2,3]. An overproduction of TNFα might affect inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis [3-6].

Impressive efficacy, with near-remission achievement and long-term functional improvement, has suggested the chance of altering the natural history of these diseases [7-9]. Overall, anti-TNFα biological agent therapy is well tolerated, but not devoid of side effects: infections, malignancies, demyelinating diseases, aplastic anemia, congestive heart failure and induction of autoimmune diseases [8-12].

Several recent studies and observations have shown that about 25% of patients treated with anti-TNFα biological agent develop cutaneous adverse reactions [13-15]. A wide range of skin manifestations has been described: infusion systemic reactions and at the injection site [16,17], infectious complications [18], eczematous dermatitis [13,19], psoriasis [20,21], and non-melanoma skin cancer [22,23].

More rarely, lupus erythematosus [24,25], acneiform eruption [26], sarcoidosis [27], anular granuloma [28], interstitial granulomatous dermatitis [29], lichenoid eruptions [30], erythema multiforme [31], leucocytoclasic vasculitis [32], purpura [33], dermatomyositis [34], eruptive benign lesions [35], and melanoma [36-38] are reported. In the present paper, we have focused on cutaneous adverse reactions to anti-TNFα agents and their proper management, comparing our data and results with those reported in the international literature.

Materials and Methods

An observational study taking into account the cutaneous adverse reactions associated with anti-TNFα treatment for Crohn's disease or ulcerative colitis was conducted at the Dermatologic Clinic of Cagliari State University, from July 2012 to June 2015. The prospective design of the study recruited all consecutive patients attending the Gastroenterology Unit of the Surgical Department of the same University, hospitalized or outpatients, at the moment of screening before starting treatment (naïve patients), but also currently treated patients, during follow-up visits. Careful attention was paid not to duplicate cases.

Informed agreement was asked to the patients, although no additional ethical committee authorization was required, being the pharmacovigilance activities part of good clinical practice. A basal visit, complete of melanocytic lesions digital dermoscope image recording was performed in all patients (FotoFinder Systems GmbH; Deutschland), subsequent visits were performed when new lesions or modification of the skin appearance occurred. Clinical cutaneous findings were recorded on electronic worksheet in Excel format, including personal information, past and present medical history, with particular regard to skin cancers, type of regimen and treatment duration. Additional information for melanoma risk factors were investigated.

Among anti-TNFα, only Infliximab and Adalimumab are currently registered for chronic inflammatory bowel diseases (IBD) in Italy [39]. All documented cutaneous adverse reactions were electronically reported to the Italian Pharmacovigilance Agency. The diagnostic criteria for adverse cutaneous reaction followed the World Health Organization (WHO) Collaborating Centre for Drug Monitoring recommendations and the criteria for journal reporting, including clinical features, circumstantial evidence, time relationships between taking the drug and rash onset, and exclusion of alternative diagnoses [40]. For this purpose, accurate allergic and pharmacologic anamnesis, as well as a history of previous reactions to drugs was obtained from the patients and general practitioners.

A MEDLINE search of the reviews on cutaneous adverse events associated with anti-TNF treatment reported until 2015 was performed to compare our data with literature esteem. The search term used were Infliximab, Adalimumab, Crohn disease, ulcerative colitis, cutaneous adverse events, anti-TNFα drug reactions, skin cancer, melanoma.

Results

In a 3-year period, 91 (46 women (51%) and 45 men) patients with inflammatory bowel disease were referred to the Dermatology Clinic of the Cagliari State University for skin screening (Table 1). Fifty-eight patients (31 women and 27 men) had Crohn's disease (64%): the age range was between 16 and 69 years.

Inflammatory Bowel Diseases		Males	Females	Age range	Treatment duration	Infliximab	Adalimumab
Crohn's Disease	58 (64%)	27	31	16-69 years	2006-2015	21	37
Ulcerative colitis	33 (36%)	18	15	21-68 years	2008-2015	27	6
Total	91	45 (49%)	46 (51%)	16-69 years	2006-2015	48 (52%)	43 (48%)

Table 1: Anti-TNF alpha cutaneous adverse reactions: Patients' demographics from 2013 to 2015.

Thirty-three patients (15 women and 18 men) had ulcerative colitis (36%): the age range was between 21 and 68 years (Table 1). Proportion of patients treated with infliximab (52%) was comparable to those taking adalimumab (48%), considering that majority of ulcerative colitis patients have usually severe diseases, better responding to infliximab, while Cronh's patients are usually well managed with domiciliary subcutaneous injection of adalimumab.

During the study period, 4 patients had to shift from adalimumab to infliximab due to partial disease control or worsening; while by converse good clinical response allowed 2 patients to pass from infliximab to adalimumab.

Among melanoma risk factors investigation, a family history of melanoma (Table 2) was reported in only one patient (1.1%), none had a personal history of melanoma, one patient had more than 50 nevi

(1.1 %), two patients referred repeated sunburns in childhood (2.2%), and three patients showed a Fitzpatrick skin type I-II (3.4%), while the presence of clinically atypical nevi was detected in 9 patients (10.1%) (Table 2).

Risk factors	N° cases (%)
Family history of melanoma	1 (1.1%)
Personal history of melanoma	0
More than 50 nevi	1 (1.1%)
Presence of dysplastic nevi	9 (10.1%)
History of childhood sun-burns	2 (2.2%)
Fitzpatrick Skin type I-II	3 (3.4%)
Use of tanning bed	0
Chronic immunosuppression	89 (100%)

Table 2: Anti-TNF alpha cutaneous adverse reactions: melanoma risk factors investigation.

All patients should be considered at risk for skin cancer due to the chronic immunosuppression (100%). The nine patients with clinical and dermoscopy dysplastic nevi underwent a 6 and 12-month videodermoscope follow-up, and none required surgical treatment. A reassessment was recommended to all patients at the appearance of any new skin lesions or changes of the pre-existing condition.

Cutaneous adverse reactions were documented in 38 patients (42%) (Table 3), 20 patients (52.6%) taking Infliximab and the remaining 18 Adalimumab (47.4%). Frequency in respect to disease was similar: 43% of Crohn's patients experienced a kind of skin reaction, and 42% of the Ulcerative colitis affected patients.

Considering the rate of reaction for each disease in respect to the number of patients treated with the same drug, no differences were detected, neither peculiar differences related to the sex (52% females/48% males).

Inflammatory Bowel Diseases		Total patients with ADR (%)	Infliximab ADRs/total exposed	Adalimumab ADRs/total exposed
Crohn's Disease	58 cases	24 (43%) 15 females 9 males	9/21 (43%) 4 females 5 males	15/37 (40%) 11 females 4 males
Ulcerative colitis	33 cases	14 (42%) 5 females 9 males	11/27 (41%) 5 females 6 males	3/6 (50%) 0 females 3 males
Total	91 cases	38 (42%) 20 females (52%) 18 males (48%)	20/48 (42%) 9 females (45%) 11 males (55%)	18/43 (42%) 11 females (61%) 7 males (39%)

Table 3: Anti-TNF alpha cutaneous adverse reactions: frequency in respect to the disease and type of drug administration.

The total number of cutaneous adverse reactions seen (69) was greater than the number of affected patients (Table 4), as several patients experienced more than one adverse event during the study period.

Clinical adverse events observed by frequency were (Table 5): infections (32%), eczematous dermatitis (23%), infusion systemic reactions and at the injection site, paradoxal psoriasis onset or worsening (5.7%), followed by a mixture of different cutaneous reactions, including urticarial reactions, chronic lupus erythematosus, lichenoid eruption, erythema nodosum, alopecia areata.

All eczematous dermatitis were moderately itching, causing valuable discomfort to the patients. Benign skin tumors were included in the study when occurring and increasing rapidly in numbers (eruptive) after treatment initiation (15%).

Only two cases of basal cell carcinoma were diagnosed (2.8%), respectively in a 50 and 40 year-old Caucasian man, after 26 and 38 months of adalimumab administration (data not shown on tables).

Reaction categories	Etiology/Clinical form	N° cases	Infliximab	Adalimumab
Infection 22/69 ADRs (32%)	Viral • Herpes simplex • HPV infection • Molluscum contagiosum	13 10 2 1	7 0 1	3 2 0
	Bacterial • Folliculitis (medium deep) • Deep follicular infection (boil) • Whitlow	5 3 1 1	2 1 0	1 0 1
	Mycosis • Candida infection (intertrigo) • Dermatophyte (tinea manum)	3 2 1	1 1	1 0
	Parasites • Cutaneous leishmaniosis (hand)	1	1	0
Eczematous dermatitis 16/69 ADRs (23%)	• Moderate xerosis • Severe xerosis (ictyosiform; pytiriasis rosea like) • Periflexural and neck (atopic dermatitis like) • Hand contact dermatitis	11 2 2 1	6 1 0 1	5 1 2 0
Infusion/injection 4/69 (5.7%)	Injections site reactions Infusion reaction	3 1	0 1	3 0
Psoriasis 4/69 (5.7%)	Patients with previous history of psoriasis • Pustular palmo-plantar psoriasis • Psoriasis invertita De novo diagnosis	3 2 1 1	2 1 1 0	1 1 0 1
Miscellanea of Autoimmune Auto-inflammatory dermatitis 10/69 (14.4%)	• Urticaria/symptomatic dermographism • Photosensibility • Chronic Lupus Erythematosus • Lichenoid eruption • Erythema nodosum • Areate alopecia • Hypertrichosis	3 2 1 1 1 1 1	1 0 0 0 1 0 1	2 2 1 1 0 1 0
Benign skin tumors (onset/increasing after drug initiation) 11/69 (15%)	Seborrheic keratosis Eruptive ruby angiomas Fibropapillomas	4 4 3	1 1 2	3 3 1
Skin cancer 2/69 (2.8%)	Basal cell carcinoma	2	0	2
	Total cutaneous ADRs	69	31 (45%)	38 (55%)

Table 4: anti-TNF alpha cutaneous adverse reactions: clinical manifestations ordered by frequency of observation. Several patients underwent more than one episode and/or different type of reactions during the study period.

The reactions observed were mainly mild to moderate in severity (Table 5), treated with symptomatic general and local options. Temporary discontinuation of anti-TNF alpha therapy was performed in more severe conditions (10%), but in no case definitive discontinuation of therapy was required.

Skin manifestation	Treatment without drug withdrawal	Temporary drug withdrawal	Definitive withdrawal
Viral infection	10	3	0
Bacterial infection	4	1	0
Mycosis	3	0	0
Cutaneous leishmaniasis	0	1	0
Eczematous dermatitis	16	0	0
Injections site reactions	3	0	0
Infusion reaction	1	1	0
Psoriasis	4	1	0
Urticaria/symptomatic dermographism	3	0	0
Photo sensibility	2	0	0
Chronic Lupus Erythematosus	1	0	0
Lichenoid eruption	1	0	0
Erythema nodosum	1	0	0
Areate alopecia	1	0	0
Hypertrichosis	1	0	0
Benign skin tumors	11	0	0
Basal cell carcinoma	2	0	0
TOTAL cutaneous ADRs	69	7 (10%)	0 (100%)

Table 5: anti-TNF alpha cutaneous adverse reactions: frequency of cases requiring temporary or definitive drug dismission.

Discussion

Cutaneous adverse reactions associated with anti-TNFα therapy are subject of several reviews and meta-analysis, considering randomized controlled trials, and open label studies [12-15]. Besides, observational studies are more representative of daily clinical practice. Our survey recruited patients reporting even very mild skin modifications, which do not require treatment modification, but slightly affect the quality of life, and which might have worsen if not promptly recognized and treated. Dermatologist's consultation is important to suggest preventive measures, collect precise anamnestic information and recognize minimal skin findings, especially before the biologic treatment is administered to avoid eventual over-esteem of drug responsibility. Minimal skin disorders observed at the screening visits were excluded from the study, representing specific and non-specific findings related to the chronic immune activation and saline/nutritional depletion of active inflammatory bowel diseases, as well as other immunosuppressive therapy side effects [41-44]. In our biologic "naïve" patients, history of herpes infections, steroidal acne and diffuse folliculitis, striae distensae, skin fragility with capillarity, and one case of leucocytoclasic vasculits were recorded and excluded from the study if further presenting under biologic treatment in that patient. Thus, association specificity to drug exposure of the present case collection should be considered reliable. Each type of reaction observed in our experience is discussed thoroughly below, compared with literature reported evidence.

Infectious complications

Skin infections were the most frequent adverse event observed (32%), as well as reported in current literature findings [13-15,18]. Viral etiology is by far the most common observation, although bacterial infections were clinically more severe, as well as the occurrence of a dermatophyte infection and a cutaneous leishmaniasis might be worth of note in the present survey (Figure 1). A slight increased association with the administration of Infliximab was noted (14/8 cases; 63%), further in agreement with literature, reporting an increased risk of 2.51 times compared to naive subjects [18]. In contrast with literature, reporting several life-threatening infections associated with anti-TNF alpha therapy [10,32,45-47], our patients experienced mild to moderate diseases, mostly self-resolving and/or successfully treated with specific systemic and topical therapy (90%). A peculiar exception is the cutaneous leishmaniasis, occurring on the left hand of a Crohn's patient under Infliximab, in which the drug was withdrawn for two months, to consent meglumine antimoniate (Glucantim) intralesional administration (1 ml weekly for 5 weeks), following our previous experiences in similar infections [48]. After infection recovery, the biologic treatment was re-introduced, but the

decision to shift to Adalimumab was judged more prudential by the gastro-enterologist.

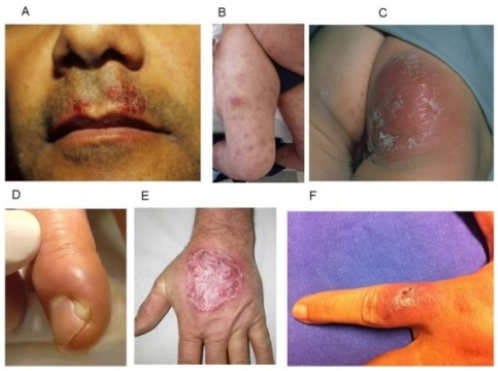

Figure 1: Example of some infections associated with anti-TNF alpha treatment: recurrent herpes infection (inset A), diffuse leg folliculitis (inset B), a gluteal boil (inset C), a whitlow case (inset D), a dermatophyte infection of the hand, misdiagnosed and treated with corticosteroid cream (inset E), the cutaneous leishmaniasis case.

A possible explanation of the absence of severe events, in our sample, is the prospective nature of the survey, with strict patient vigilance, and prompt recognition and infection treatment. Moreover, patients were mostly young adults, without significant comorbidity. There is ample evidence that factors such as advanced age, concomitant disease and a long-lasting disease greatly increase the risk of developing a sepsis, whereas the young age and early detection of the underlying disease are protective factors [45].

Eczematous dermatitis

Moderate to severe xerosis, with some exudative patches and itching lesions (Figure 2) appeared in 16 patients (23%), second in frequency only to infections, corresponding to literature datum of a 18% incidence rate [16]. No differences were noted in respect to the administered drug. In agreement with the literature the events are generally mild to moderate [15], not requiring biologic treatment modification, and responding to daily moisturizing with emollients and keratolytic agents in the majority of patients. Beside, all patients complained for itching, sometimes impairing night sleeping, and ameliorated by short curses of systemic antihistamine therapy. The most severe cases were also supported with local medium potency corticosteroids. A personal and /or familiar history of atopy has been suggested as the only factor predictive of eczematous complications during anti-TNF treatment [15], due to a certain Th1/Th2 imbalance, with a prevalence of Th2 activity, worsening clinical conditions just as atopic dermatitis [49]. The eczematous findings appear generally after the first month of therapy. None of our case reported previous atopic dermatits or a family history of atopy.

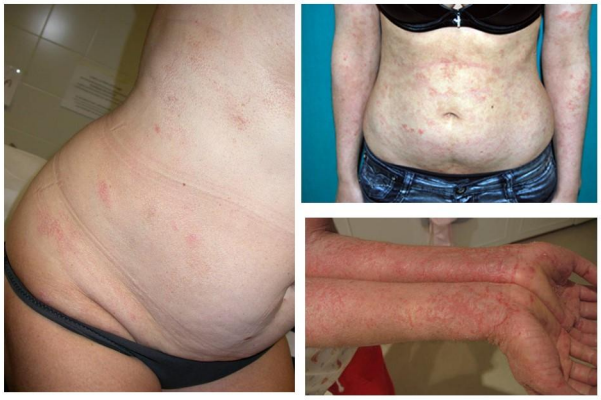

Figure 2: Some examples of the most severe eczematous dermatitis during anti-TNF alpha therapy.

Injection/infusion reactions

Although these reaction are very frequently reported in clinical trials, with an incidence rate of 13.4% [18], requiring drug discontinuation in 1% of cases; our experience was reassuring (5.7%), with only one infusion reaction, although quite severe, and 3 injection site reactions (Figure 3). They are considered a direct manifestation of the drug immunogenicity [8,14], generally more frequent during infusion therapy with Infliximab [17]. Conversely, in our sample the reactions involved more patients receiving Adalimumab. Temporary withdrawn of the treatment was needed in the infusion reaction, but subsequent re-exposure after antihistamine and steroids premedication was well tolerated. One possible explanation of the increased tolerability of both treatments in our experience could result from the improved use of administration protocols, such as delivery of premedication therapy, heedful control of the infusion rate, and the careful monitoring of vital clinical parameters. Appropriate education of patients about the correct use of the device to subcutaneous Adalimumab injections is also crucial. All patients in our experience received first 2-4 injections under nursing surveillance, only when absolutely confident with the device being allowed to make it at home. In patients with allergic diathesis it had also been planned prophylactic therapy with corticosteroids and antihistamines two days before and the infusion day.

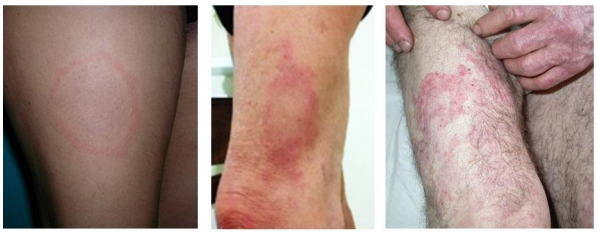

Figure 3: The three injection site reactions occurred in adalimumab treated patients.

Psoriasis

A paradox effect of anti-TNF inducing psoriasis onset is significantly reported in the literature, with rates between 12%-18% [19-21,50] in patients treated with Adalimumab and 6.6% in those taking Infliximab [50]. Incidence of such events in our sample was quite lower, without differences among drugs, all patients affected with Crohn's disease. Three of them had a pre-existing diagnosis of psoriasis vulgaris, that changed to pustular palmoplantar lesions in 2, and inverse psoriasis in the other patient after the biologic agents introduction (Figure 4).

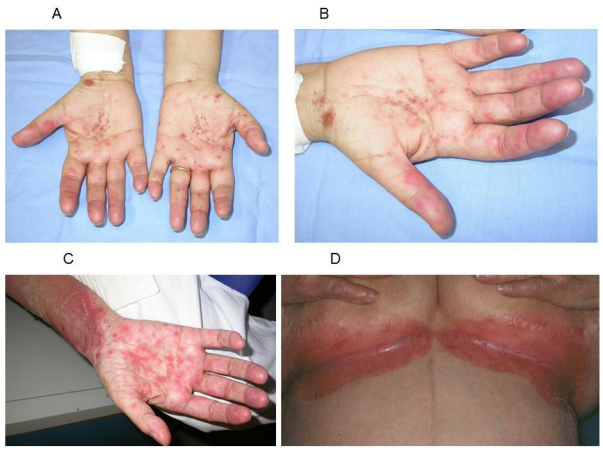

Figure 4: The two pustular palmar psoriasiform eruptions, and the inverted psoriasis case occurred in patients treated with anti-TNF alpha for inflammatory bowel diseases.

Only one patient developed a newly diagnosed psoriasis, with pustular lesions on palms and soles, but also a diffuse sub-erythrodermal psoriasis. The majority of literature reported patients present a negative personal medical history for psoriasis [51]. Both in our sample and in the literature lesions are pustular, the events usually occurring at the third or fourth administration [3,50]. Topical therapy was based on specific two-compound combination (Calcipotriol and Betamethasone gel). In the most severe reaction, adalimumab was discontinuated and the decision to switch to Infliximab better controlled the disease, with complete remission after 2 months. The pathophysiologic mechanism underlying this paradoxical effect has not yet been clarified: a claimed hypothesis is that the cytokines imbalance might lead to excessive dendritic cells production of IFN, in genetically predisposed individuals [19]. It is also possible that genetic polymorphisms play a role in blocking TNFα: future genomic study of patients with such events could clarify the mechanisms triggering these reactions [51].

Miscellaneous skin reactions

Several inflammatory conditions are reported in anecdotal association to anti-TNF treatment, such as the lupus erythematosus, lichenoid dermatitis, urticarial reactions we also observed [13,24-30,52]. Peculiar findings were the occurrence of a symptomatic photosensitivity, requiring active photo protection in two subject with IV to V Fitzpatrick phototype; an alopecia areata, and a hypertrichosis case, which are rarely reported controversial events [53-57].

In addition to the above clinical manifestations, the literature reports a wide range of events, which may be included among these miscellaneous adverse reactions, and that we have not been able to appreciate given the limited sample of patients.

Eruptive benign lesions

In our series, the eruptive growth of benign lesions was also recorded (15%), mainly seborrheic keratosis and ruby angiomas, followed by neck and groins fibropapillomas. These events are considered rare, closely associated to adalimumab [35]. Underestimation is plausible, pharmacovigilance focusing on more severe and debilitating adverse reactions, but the eruptive appearance is usually considered a clue to immunosuppression, and it is also an alarming events for patients, educated to advise the physician of any new skin proliferating lesion. Being totally benign tumors, further investigation was not needed and physical therapy indicated only for aesthetic purposes.

Skin cancers

Large scale studies reported a non-melanoma skin cancer (NMSC) incidence rate of 3%, a low degree of association, without significant differences according to the employed biological agent [22,23]. Thus, the occurrence of two basal cell carcinomas (2.8%) is an expected event. Lesions (Figure 5) were small in size and surgical excision performed without complications.

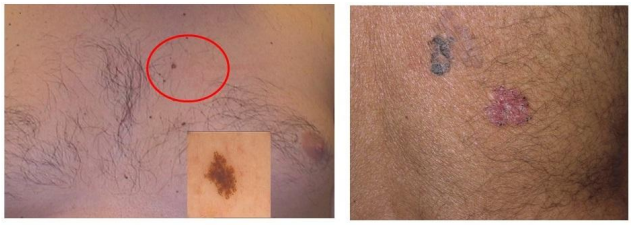

Figure 5: Two basal cells carcinoma case, respectively occurred on the chest of 40-year old Caucasian men, with peculiar dermoscopy findings, suggestive of a malignant melanocytic lesion, and a more typical basal cell carcinoma on the back of a 50-year old man, also carrying several seborrheic keratosis.

Other malignancies

None of our patient developed systemic malignancies, particularly hematologic and/or solid tumors: a review of the literature does not provide a unanimous consensus. Several Authors deny the existence of a risk related to treatment with anti-TNFα [23], while other Authors reported a risk with an incidence rate of 1% [58]. A longer period of observation may provide more complete and statistically significant data.

Special consideration should be reserved to melanoma, as concern about the possible occurrence of primary lesions, as well as more aggressive course and activation of dormant lesions are controversial issues [22,23,37]. Two recent studies reported a significant degree of association, confirming the need for further studies in order to establish the actual existence of a risk [36,38]. Thus, a special attention was paid to the nevi control, with global photography and videodermatoscopy recording of all melanocytic lesions with notable

features. None of our patients required more invasive investigations, such as surgical excision and histological examination. Besides, melanoma occurrence seems to be correlated with the duration of anti-TNF administration, with a suggested meantime of 47.6 months from treatment beginning [43]. Long-term follow-up and patient education about skin pigmentary lesions changes are necessary to avoid any delay in diagnosis.

Conclusion

Overall, our sample of patients had a high rate of adverse reactions (42% of patients; 69 total events), but less severe than literature reports, in no case requiring definitive discontinuation of ant-TNF alpha therapy. Clinical findings were somewhat surprising, with less infusion reactions and paradoxical psoriasis compared to clinical trials experiences, and observation of much more rare events, such as photosensitivity, alopecia areata, hypertrichosis. Data are preliminary, and enrollment of more patients is warrant, as well as increasing long-term follow-up under treatment to detect more rare events, such as skin cancer and melanoma. The experience of the dermatologist can be invaluable in early recognition of adverse reactions and set proper treatment, which might avoid worsening, as well as interruption of biological administration.

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