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Cutaneous side effects caused by treatment for inflammatory bowel disease

Neželjeni efekti na koži bolesnika prouzrokovani lekovima za inflamatorne bolesti creva

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Ključne reči:
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Introduction

Treatment of inflammatory bowel disease (IBD) has significantly changed the shape and efficiency over the last 20 years. Cutaneous lesions could be part of extraintestinal manifestations of these disorders (like erythema nodosum or pyoderma gangrenosum), can occur as consequence of specific vitamin and micronutrient deficiencies (zinc and iron deficiency), or as complications of the drugs that are used with the intention to control inflammation. In fact, treatment with these drugs can cause paradoxical inflammatory dermatoses.

This article suggests how to recognize and treat cutaneous lesions that can occur during the treatment of IBD, especially how to diagnose them early (particularly skin cancer) and how to treat them most effectively with an emphasis on the importance of very close cooperation of gastroenterologists and dermatologists in the approach to these patients.

Prebiologic era

Before the advent of medications from the biological group, the following drugs were the mainstay of IBD treatment: 5-aminosalicylic acid (5-ASA) and mesalazine, corticosteroids and immunosuppressants − azathioprine, methotrexate (MTX) and cyclosporine.

5-ASA

Cutaneous side effects of 5-ASA are various forms of nonspecific exanthemas, which occur rarely and with mild intensity not requiring interruption of therapy. Serious adverse reactions are even more rare, but can occur as exfoliative dermatitis (erythroderma), Stevens-Johnson syndrome, and toxic epidermal necrolysis, mainly during sulfasalazine treatment [1]. These reactions occur within the first month of treatment. In the event of such a severe reaction it is necessary to immediately stop further implementation of the drug.

Corticosteroids

Methylprednisolone, hydrocortisone and prednisone have great potential in the treatment of IBD and are used in inducing remission in moderate to severe form of the disease. Corticosteroids suppress immune system by decreasing the number of activated T lymphocytes which have very important role in pathogenesis of IBD. But corticosteroids also carry a risk of side effects. The skin is prone to the following adverse effects from prolonged courses or high doses of systemic steroids: skin infections such are bacterial (*eg cellulitis*) and fungal infections (*eg* tinea, candida), skin atrophy resulting in easy bruising (purpura), skin tearing after minor

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injury and slow healing; these effects are most prominent on sun exposed areas particularly the backs of the hands and the forearms. Also, stretch marks (*striae*) can occur, particularly under the arms and in the groin. Steroid acnes are very common side effect with clusters of small spots on the face, chest and upper back, but without the usual open and closed comedones that are typical of juvenile acne (Figure 1). However, aggravation of preexisting acne in the young patients is also frequent. Hirsutism and androgenetic alopecia are also a common side effect of a prolonged steroid use [2]. These adverse effects are just one of the several reasons for contemporary treatment corticosteroids to be no longer recommended for a prolonged use. Its use should be limited to no longer than 3 months and repeated episodes of their application should be avoided, especially now with a large selection of effective drugs of a much better safety profile.

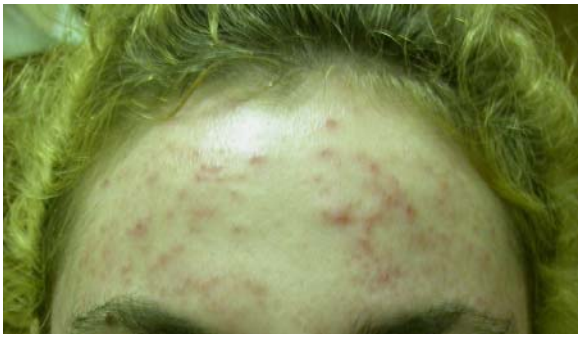

Fig. 1 − Steroid acne in a 19-year-old patient presented with severe form of ulcerative colitis. Treatment was started with 40 mg of methylprednisolone, and steroid acne developed thereafter, treated with topical antibiotic therapy. The lesions completely regressed after the discontinuation of systemic steroids.

Thiopurines

Thiopurine medications are used in the form of 6-mercaptopurine (not registrated in Serbia) and azathioprine. By blocking the synthesis of purines they represent antimetabolites which disrupt the synthesis of DNA and thereby block the differentiation and proliferation at the cell level, stimulate apoptosis of T lymphocytes, resulting in the reduction of the number of lymphocytes in peripheral blood and the number of natural killer cells [3].

After starting thiopurine medications, maculopapular rash can occur and lead to discontinuation of the treatment. Thiopurines also increases the risk of viral infections, such as herpes simplex (Figure 2) or herpes zoster. These infections are usually mild, although the presentation in immunocompromised patients may have an aggressive form [4, 5]. Regarding the patient presented to our clinic it is clear how a banal infection under the immunosuppressive therapy can take a more severe form which is harder and takes longer to treat.

This is the reason when under treatment with thiopurine with this type of skin changes, chemoprophylaxis is recommended for such patients with acyclovir 400 mg 2 times *per* day. In Serbia, the vaccination against varicella (chickenpox) is optional and according to the European Crohn's and Colitis

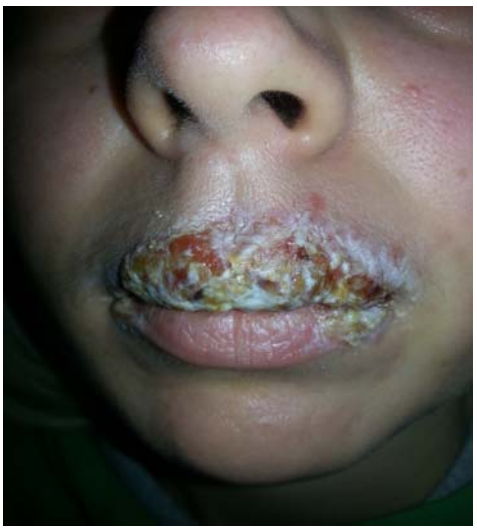

Fig. 2 − Labial bilateral herpes simplex in a 20-year-old patient with Crohn's disease treated with azathioprine and mesalazine. Oral and topical acyclovir were started and continued for 10 days, since the regression of the lesions was slow and prolonged. Azathioprine treatment was interrupted during the infection.

Organisation (ECCO) recommendations it is advised that nonvaccinated patients who are planned for application of immunosuppressive therapy are screened for susceptibility to primary varicella zoster virus (VZV) infection. Those without a clear history of chickenpox, shingles or receipt of two doses of varicella vaccine should be tested for VZV IgG. Where possible, seronegative patients should complete the two-dose course of varicella vaccine at least 3 weeks prior to commencement of immunomodulatory therapy [6].

Hypersensitivity skin reactions to thiopurine occur in about 12% of patients, most commonly manifested in the form of urticaria or maculopapular rash. Sweet syndrome (SS) (Figure 3) represents an eruption of painful erythematous plaques or nodules, accompanied by fever.

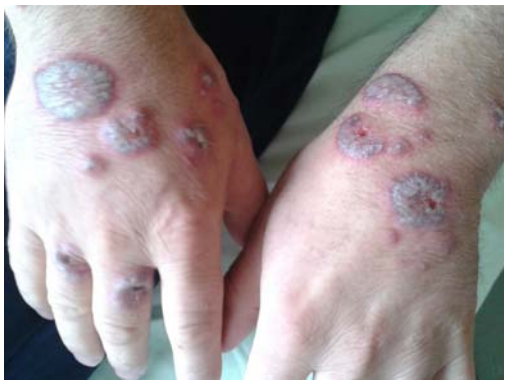

Fig. 3 − Neutrophilic dermatosis of the dorsal hands (localized form of Sweet's syndrome) in a 48-year-old patient with fistulized Crohn's disease treated with azathioprine and antibiotics. Skin changes presented as erythematous and edematous livid plaques, with ulcerations on the dorsal hands. Corticosteroid therapy (topical and oral) was started and complete resolution of the skin was achieved. Azathioprine was excluded and the treatment continued with anti-tumor necrosis factor (TNF) therapy.

Changes of this type occur in the first two weeks after starting thiopurine medication. It is important to emphasize that SS is also described as cutaneous extra-intestinal manifestation of IBD, but nevertheless there is sufficient evidence for the existence of azathioprine-induced SS that exists independently of confounding factors [7, 8].

Erythema nodosum (Figure 4) also occurs, although these changes may be a manifestation of an underlying IBD [9]. Common to all of these dermatoses is that after the cessation of drug administration, regression of skin lesions is evident. If cutaneous reaction to azathioprine is suspected, reintroduction of the drug can be dangerous because it can lead to more severe manifestations, so it should be avoided.

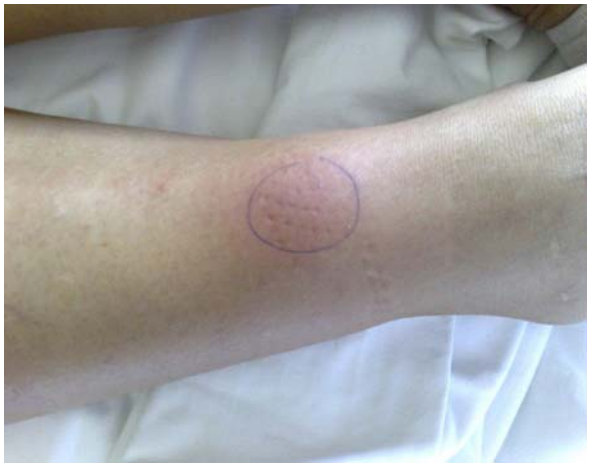

Fig. 4 − *Erythema nodosum* in a 27-year-old patient with first presentation of ulcerative colitis. At the onset of disease the patient was presented with barely raised, painful, tender, reddish nodules, below the knees, and treated with local and systemic steroids. While reaching clinical remission, skin changes completely disappeared.

Although thiopurine has been known for more than 30 years in the treatment of IBD it has been only recently noted that a prolonged use of this drug is associated with the appearance of skin cancer. It was originally observed in transplant patients. It is believed that patients who receive the drug for a prolonged period of time have a much higher risk of getting non-melanoma skin cancer (NMSC) than people in the general population [10]. NMSC is the most common cancer in industrialized world, and it presented as basal cell carcinoma (BCC) (Figure 5) and squamous cell carcinoma (SCC), usually in the ratio 1 : 4 and most commonly in the sun-exposed areas (face, lips, and backs of hands and forearms). Skin cancer develops as a consequence of accumulated 6-thioguanine (6-TG) that absorbs UV rays causing damage and instability formation of DNA and generates reactive oxygen species that can cause mutagenic and irreversible DNA damage [11].

A retrospective study on 53,377 patients found a positive correlation between exposure to azathioprine and NMSC after the minimum drug exposure of 90 days. The study points to the increased risk of incidence of NMSC (IRR, 1.64; 95% CI, 1.51−1.78), based primarily on the occurrence of immunological function disturbances which represent the basis of disorder in patients with IBD, as well as the use of immunosuppressive drugs. The risk is further increased if the exposure is prolonged over a year [12].

A French study (CESAM) on 19,486 patients with IBD showed an increased tendency of getting NMSC in Caucasians, over 65 years of age, with the hazard ratio (HR) of 5.9 for patients still in treatment phase and the HR of 3.9 in patients who discontinued the drug [13].

Information about the tendency of getting melanoma in these patients is still very scarce. Only 3 cases of melanoma on combined immunosuppression (azathioprine plus corticosteroids) have been described so far [14].

Clearly, for patients treated with thiopurines there is the need for regular dermatologic examination once a year. Rigorous sun protection (avoidance of direct sun exposure, especially between 11 a.m. and 4 p.m.; sun protective clothes and the use of broad spectrum sun protection factor (SPF) 50 sunscreens is also mandatory and should be emphasized [15].

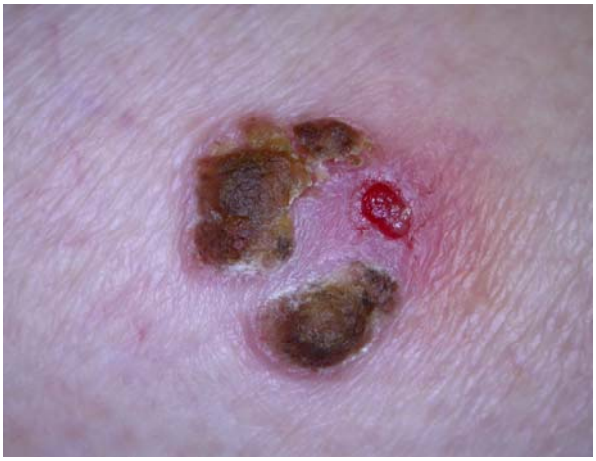

Fig. 5 − Basal cell carcinoma in a 48-year-patient with ulcerative colitis treated with mesalazine and azathioprine for 3 years. The patient was presented with erythematous patch with ulcerations and crusting on the left shoulder. Complete excision was done.

Methotrexate

MTX is anti-metabolite drug which inhibits DNA, RNA and protein thymidylate synthesis. The mechanism of immune suppression induced by MTX is accumulation of adenosine, which inhibits the activation of T lymphocytes. Cutaneous reactions to MTX are nonspecific maculopapular exanthems, (15%), alopecia (8%), photosensitivity (5%) and urticaria (4%). Erosions, ulceration, hemorrhagic bullae of the oral and vaginal mucosa, the knees and the back are the result of the MTX cytotoxic effect the regions with the fast epithelial turnover [16].

Only 10 cases of cutaneous lymphomas induced by MTX have been described so far, Epstein Barr virus (EBV) associated multifocal B lymphomas being the most frequent. In the majority of cases, they spontaneously regress with MTX treatment discontinuation [17]. Also, a case of cutaneous lymphoma at the site of intramuscular injection, which spontaneously regressed after discontinuation of MTX has been described [18].

There are several case reports on melanoma developed while on MTX treatment, most commonly in rheumatologic patients. Also, in a study a 3-fold increased risk for melanoma was described in these patients. Similar results, however, have not been published for IBD patients. Further investigations in this filed are needed, until then yearly dermatological checkups are recommended [19].

Cyclosporine

Cyclosporine is still used in Serbia in treatment of the most severe forms of ulcerative colitis, although in most countries after advent of drugs from the group of anti-tumor necrosis factor (TNF), its use has been drastically reduced. Cyclosporine inhibits translocation of nuclear transcription factor [nuclear factor of activated T lymphocytes (NFAT)] which leads to reduced secretion of proinflammatory cytokines by T cells [20]. Cutaneous lesions develop in 7% of patients and are manifested as hirsutism, acne and gingival hyperplasia. Also, cases of cutaneous T-cell lymphoma are described, especially in prolonged use in transplant patients. Since cyclosporine is used in IBD for a short period of time (usually 3 months) these side effects have not been described in IBD patients [21].

Biologic era

For the last 15 years in Serbia, biological therapy of IBD primarily involves the use of monoclonal antibodies to TNF, which is one of the dominant secreting proinflammatory cytokines in the pathogenesis of IBD. Although these drugs are also used in the treatment of psoriasis and other dermatoses, inflammatory dermatoses can appear as a paradoxical side-effect of these class of drugs. New drugs called antiadhesive antibodies have not yet been registered in Serbia, and hereby were not reviewed.

Anti-TNF drugs

TNF-α is a proinflammatory cytokine, and one of the main inflammatory mediators involved in the pathogenesis of IBD. TNF-α inhibitors led to the revolutionary advance in the treatment of patients with IBD. Today there are 4 products of this group on the market: infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®) and certolizumab (Cimzia®). TNF inhibitors lead to the fast control of IBD symptoms with a maximum mucosal healing, reduce the need for hospitalization and surgery, and the cost of treatment of these patients [22, 23]. Combination of anti-TNF inhibitors with thiopurine or with MTX is considered the most effective therapy in the treatment of IBD. Treatment with TNF inhibitors is, however, accompanied with frequent cutaneous side effects, including the occurrence of skin infections and inflammatory dermatoses in about 12−20% of patients.

Local site reactions (Figure 6) with the application of anti-TNF drugs are frequent and are described in the form of erythema and edema at the site of the injection. These changes are observed only during the application of adalimumab.

Skin infections are also described in the literature as common side effects of TNF inhibitors: *cellulitis*, herpes simplex infection and reactivation, staphylococcal skin infection, *tinea corporis*, *pityriasis versicolor*. Infections are not related to the particular TNF inhibitor, and are specific for the entire class of these drugs. Overall, they do not exceed 1.5% in biologics exposed patients, and are second most common after acute respiratory infections. However, coadministration of anti-TNF with thiopurine is leading up to 3−4 times higher incidence of opportunistic infections. The risk is highest for the simultaneous administration of at least two of immunosuppressants and in patients older than 50 years. They are mostly milder infections as oral candidiasis but life-threatening infections are also possible [24].

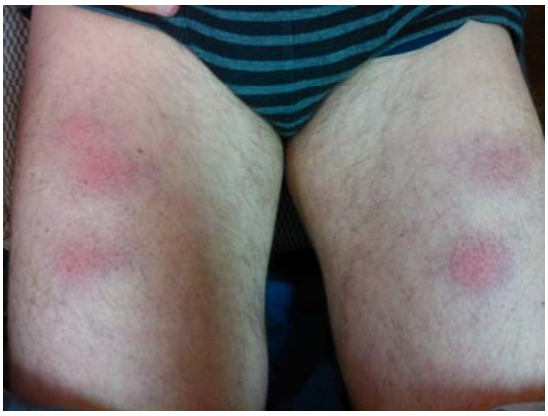

Fig. 6 − Injection site reaction in a 26-year-old patient with small bowel Crohn's disease on treatment with adalimumab. Skin reaction presented immediately after starting adalimumab therapy. The patient was treated with topical corticosteroids until resolution. Therapy was switched to infliximab.

Development of anti-nuclear antibodies (ANA) and lupus-like syndrome are rare, and they are most frequently described in rheumatologic patients. In IBD patients it is described as case reports. In a study that analyzed 105 drug-induced lupus erythematosus cases on anti-TNF therapy, ten of them were patients with Crohn disase [25], so the literature is scarce. Malar rash and photosensitivity are the most common presentation, followed by discoid cutaneous lesions, while lupus nephritis is rare. TNF itself prevents the formation of autoantibodies and its blockade creates the opposite effect. Also, treatment with TNF inhibitors decreases clearance of antibodies, enables the shift from Th1 to Th2-type cytokines, leading to the production of ANA [26].

Psoriasis is a chronic inflammatory skin disease with different manifestations. In about 10% of cases it is associated with other inflammatory diseases, and IBD is one of them. TNF inhibitors are used for the treatment of psoriasis and psoriatic arthritis, but paradoxically the use if these drugs can be associated with *de novo* psoriasis onset, irrespective of the type of TNF inhibitor. The frequency of psoriasis in TNF inhibitor treated patients is about 3%, it is more often in women (70%) and it usually develops after 2−6 months from the application of this type of treatment. It was shown that anti-TNF-alpha therapy induces higher levels of

interferon (IFN)-alpha, that is known as a factor capable of inducing or aggravating existing psoriasis, through the induction of proinflammatory cytokines, such as IL-12 and IL-23 [27]. That is why it is recommended to switch the patients with anti-TNF induced psoriasis to ustekinumab anti IL-12/23 antibody [28].

A number of patients also show exacerbation of previously existing psoriasis, while the highest number gets *de novo* changes. The changes are most frequently manifested in the form of palmoplantar pustulosis which is nowadays considered as a separate entity from psoriasis (Figure 7). Also, it can be manifested in the form of guttate (Figure 8) and pustular psoriasis. Scalp lesions with infiltration and thickened scale, sometimes in the form of *tinea amiantacea* can also be present [29], as frequently as the palmoplantar lesions. Completely atypical lesions are also described, where psoriasiform reaction was confirmed by histopathological analysis. These cutaneous lesions quickly regress after discontinuation of TNF inhibitor [30].

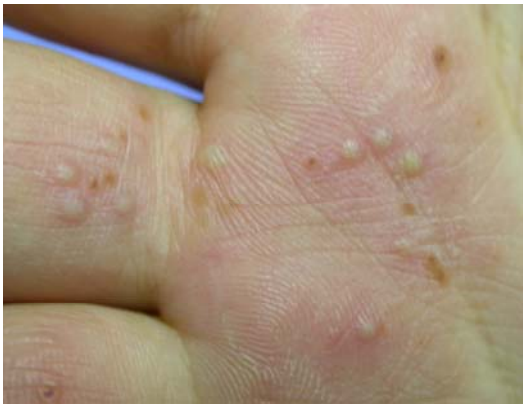

Fig. 7 − Palmoplantar pustulosis in a 35-year-old patient with inflamatory bowel disease on infliximab/azathioprine therapy. After a year of the therapy the patient presented with sterile pustules on erythematous background on the palms and soles, and was successfully treated with acitretin 25 mg a day without interruption of the biologic therapy. Trough levels were checked, at that point that were high, so optimisation with lowering the infliximab dose was done.

Treatment depends on the severity of skin lesions, mainly does not require discontinuation of anti-TNF preparations and is well controlled with application of topical corticosteroids, keratolytics, vitamin D analogs. In severe cases, addition of MTX, retinoids or cyclosporine is necessary. Also, phototherapy can be very useful in most cases. If there is no success in treatment it should be discontinued with the implementation of anti-TNF preparations or possibly replace one anti-TNF preparation with another, although it is accompanied with a large (52%) percentage of relapse [31]. Consultation of dermatologist to diagnose psoriasis, psoriasiform eruption or other inflammatory dermatosis is necessary in order to choose the appropriate and most effective treatment combination.

Localized or generalized eczema, sometimes typical of atopic dermatitis is well-known in IBD patient on anti-TNF therapy. However, in a case control study [32] it was shown that atopic manifestations, particulary eczema were more frequently reported in patients with Crohn's disease in comparison to control patients. Anti-TNF therapy can aggravate atypical form dermatitis manifestations, with erythema, desquamation and itching usually manifested in popliteal and antecubital fossa, but more severe erythema, oozing and severe itching can occur on other flexural areas, and can progress to erytroderma (Figure 9). Treatment involves application of local therapy, but if the lesions are generalized systemic corticosteroids are necessary with intensive local treatment with emollients, topical corticosteroids and topical calcineurin inhibitors. In the most severe cases, discontinuation of therapy with a possibility to switch to another form of biological therapy is necessary. Close collaboration with the dermatologist is mandatory to diagnose and adequately treat these patients.

More rare changes observed in the application of these therapies involve alopecia which may occur shortly after the start of treatment, or after a few months/years of anti-TNF treatment. Alopecia areata, androgenetic alopecia and diffuse alopecia were all described. Discontinuation of the drug is generally sufficient for withdrawal symptoms but the reintroduction of these products can repeatedly induce alopecia [33]. Vasculitis is present in 5% of gastroenterology patients treated with anti-TNF therapy over 30 years, but this percentage

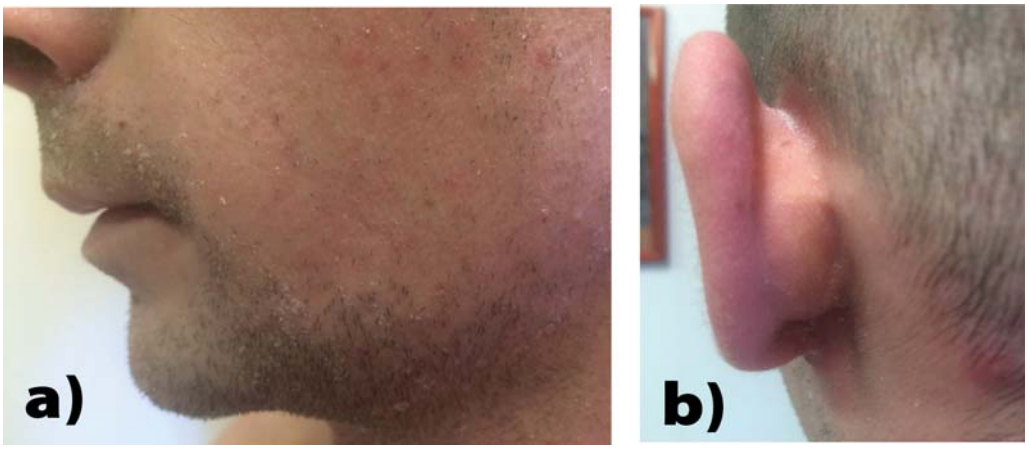

Fig. 8 − Psoriasiform reaction during treatment with infliximab: a) Guttate papules on the face; b) Slightly indurated plaques with whitish adherent scales in the retroauricular region in a 24-year-old patient with Crohn's colitis presented with skin lesions 8 months following starting the therapy. The patient was treated with topical corticosteroids and a combination of calcipotriol/betamethasone.

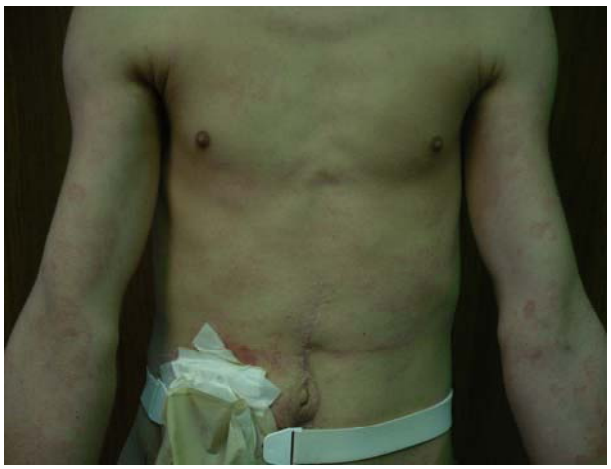

Fig. 9 − Generalized eczema developed during the treatment with adalimumab. A 36-year-old patient with small bowel Crohn's disease treated with adalimumab presented after the 3rd dose with generalized eczema. The patient was treated with systemic corticosteroids and intensive topical corticosteroid and emollient therapy. Skin lesions resolved and biologic therapy was switched on infliximab. At follow-up no further skin lesions developed, and the disease was in stable remission.

also includes patients with vasculitis as a manifestation on the underlying disease. Cutaneous vasculitis usually starts as palpable purpura, hemorrhaagic bullae and skin ulcers can further develop [34]. Erythema nodosum is one of the most common extraintestinal manifestations of IBD, but in IBD patients it was described as a complication of infliximab and certolizumab treatment [2]. Non-melanoma skin cancer develops in 0.3−1.4% on mono anti-TNF therapy [35]. These skin tumors were specific for the application of thiopurine medications but given that in practice the most common use is the combination therapy of thiopurine/anti-TNF, it can sometimes lead to a confusion of which of administered medicationsis a specific cause of these complications.

More recent meta-analysis, including patients with mono application of anti-TNF preparations, have established HR for development of NMSC of 2.02, indicating that these cancers are rare but clearly possible consequence during anti-TNF treatment [12]. It is important to familiarize patients with complications and refer them to implement preventive actions (protection and covering of the skin, avoiding open exposure to UV radiation, regular control), thereby reducing the incidence of NMSC. Regular self-skin examination every month is advisable and dermatological consultation if new or changing lesions appear is necessary. If NMSC is suspected, surgical excision is advised, and there is no need to discontinue the therapy. The risk of lymphoma is also present during anti TNF treatment and HR is approximately 4.4, with or without concomitant use of thiopurine medications and usually manifests itself in the form of systemic lymphoma, without cutaneous manifestations, but one case report of cutaneous lymphoma on infliximab therapy was described [36].

The risk of melanoma in IBD patients and relation to the used anti-TNF medication at least more than 1 year conveyed with almost 2-fold risk for getting this malignancy [37]. Long et al. [38] in a retrospective nested case control study reveal that IBD patients have an increased risk for melanoma, and that therapy with biologics further increases the risk. Risk was significant for Crohn's disease but not for ulcerative colitis [12]. Therefore, regular and rigorous sun protection, self skin examination and dermatologic consultations for new and changing lesions are necessary. Patients on combination therapy have the greatest risk of NMSC with the HR of 5.85 while the HR, in application of only thiopurine medications, is 3.56 and the lowest one in mono therapy with anti-TNF preparations, 2.07 [38]. This clearly indicates the synergistic effect of a combination, where the risk is particularly increased with thiopurine combination with corticosteroids or anti-TNF medication. Similar associations were seen in the incidence of skin lymphoma in IBD population. In thiopurine monotherapy the risk of developing cutaneous lymphoma is 1.4, in anti-TNF monotherapy 1.7, but in combination with anti-TNF preparations the risk is substantially increased and the HR is 6.6. [39]. Contrary to these published results are those from study of Soh et al. [40] where the most significant observation is that the concomitant use of AZA/6 MP at the time of introducing anti-TNF agents decreases the risk of adverse skin lesions in both univariate ($p = 0.008$) and multivariate ($p = 0.006$) analysis. Moreover, the cumulative probability of the incidence of adverse skin lesion was the lowest in the group with concomitant use of azathisprine/6 mercaptopurine at the start of anti-TNF treatment. Further studies and careful statistical interpretation of results are necessary to draw the final conclusion. Meanwhile, regular skin check-ups are necessary in these patients.

What gastroenterologists have to know?

Gastroenterologists are not trained to identify early premalignant skin lesions or even NMSC and are not trained to stratify patients based on their risk factors. Evidence based guidelines for primary and secondary prevention are lacking in IBD population. Torres et al. [41] propose the algorithm for all the patients who are starting on azathioprine/anti-TNF in an attempt to avoid the adverse effects of this drug on the skin and to timely recognize skin lesions that may be malignant, and it is presented in Figure 10. It is recommended that all patients starting with immunosuppressive therapy must be examined by the dermatologist, which would reduce the risk of serious skin lesions. At the same time it is recommended that the control and monitoring continues even after cessation of immunosuppressive therapy.

Conclusion

Inducing effective immunosuppression as early as possible is a goal of effective treatment in IBD, since it will beneficially affect the course of the disease and prevent development of severe disease and its complications. But this immunosuppression and immune modulation, could, on the other hand, lead to diverse dermatologic manifestations which could severely affect the quality of life of patients and compromise further treatment. Although some of the cutane-

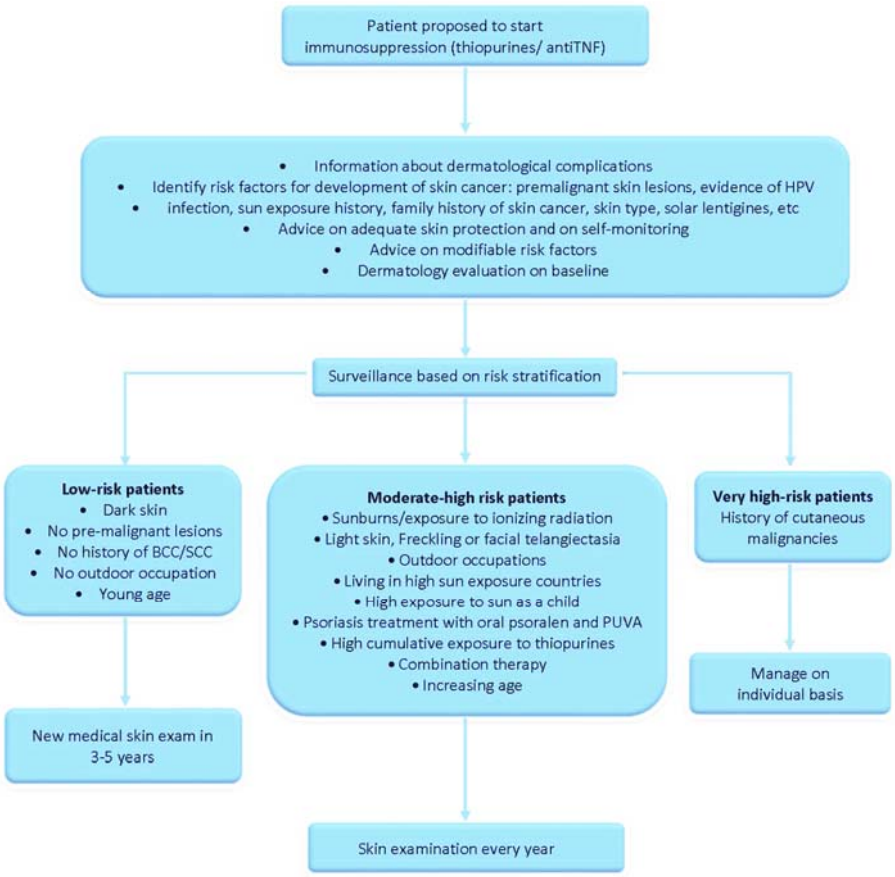

Fig. 10 − Modified algorithm [41] where yearly skin exams were recommended.
TNF – tumor necrosis factor; HPV – human papilloma virus; BCC – basal cell carc inoma; SCC – squamous cell carcinoma; PUVA – psoralen and ultraviolet A.

ous manifestations are not frequent, it is necessary to know their pathogenesis, prevention, and how to treat them.

The most important suggestion is that these changes should be seen and treated by a team, where the role of dermatologist is very important and unavoidable. Recommendations and adequate approach in this field is necessary to be established at the international level and make them available to the physicians from the primary care level to high-end subspecialists.

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