Nevi, biologics for psoriasis and the risk for skin cancer: A real concern? (Case presentation and short review)

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Abstract. Psoriasis is a systemic inflammatory cutaneous disease that affects approximately 2% of the world's population. Systemic treatments and biologic treatment therapies are a powerful option for patients with moderate to severe psoriasis. Some studies from the literature indicate an overall small, but increased, risk of neoplasia in patients with psoriasis treated with phototherapy or systemic medication. The relationship between psoriasis and malignancy is not very well established; there are few studies with conflicting results. We present the case of a 31-year-old male patient, diagnosed with psoriasis, who was deemed eligible for systemic therapy. Treatment with methotrexate was initiated, but without a satisfactory outcome. Given the patient's resistant disease involving 15% of his body surface, his desire to have a clear skin, besides his being naïve to biologic therapy, he was proposed to start treatment with secukinumab 300 mg monthly. The patient experienced complete clearance of lesions and was followed-up on the basis of clinical and biological parameters. There are limited data concerning the relationship between melanocytic lesions, psoriasis and melanoma. Immunologic pathways implicated in psoriasis induce a reduction in the number of melanocytic nevi. Nevertheless, little is known concerning the association of melanocytic nevi with psoriasis. Thorough skin examination, meaning clinical and dermoscopic evaluation of melanocytic lesions, must be encouraged in patients treated with systemic therapies such as biologic agents.

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Introduction

Psoriasis is a chronic immune-mediated dermatological condition with potential systemic impact, predominantly associated with skin and joint damage (1). It affects about 2% of the world's population and can have a serious impact on the patient's quality of life. It consists of an abnormal inflammatory response characterized by an increase in proinflammatory cytokines consequent to keratinocyte hyperproliferation (2,3). Proper treatment can be selected according to disease severity. Psoriasis can develop into a debilitating disease that strongly impacts the quality of life and significantly contributes to health care costs (4).

In the case of mild and moderate forms, first-line treatment consists of topical corticosteroids, vitamin D3 analogues or a combination of the two. For more severe cases, phototherapy can be utilized. Systemic therapies, such as methotrexate or cyclosporine, may also be required (5). Phototherapy based on radiation in the UVB spectrum leads to apoptosis of T lymphocytes and immunosuppressive effects resulting in clinical improvement of immunologic skin diseases. Patients diagnosed with psoriasis may obtain clearance using the excimer laser technology rather than narrow-band UVB (3,5).

Currently, due to the long-lasting characteristic of the disease and frustration with conventional medical therapies, some psoriasis-diagnosed patients seek complementary and alternative treatments to help manage their symptoms (6). Some factors such as smoking, high body mass index (BMI), alcohol consumption, trauma, endocrine disorders, and of course, drugs are known to trigger psoriasis (7).

Certain drugs prescribed for other comorbidities are considered in the literature to be associated with the exacerbation of psoriasis; these include lithium, nonsteroidal anti-inflammatory agents, synthetic antimalarial drugs and β-blockers (8). Understanding the pathophysiology can provide clues to the treatment and management of drug-induced and drug-aggravated psoriasis, which may be indistinguishable from idiopathic psoriasis. Tumor necrosis factor (TNF)α inhibitors themselves can also trigger psoriasis, which leads to an interesting discussion (9). Since there is no standard therapeutic consensus for patients with moderate to severe forms of psoriasis, the benefits and risks of systemic therapy or phototherapy must be carefully assessed for each patient, and the treatment should be individualized accordingly (10).

It has been noted that patients with chronic inflammatory conditions such as psoriasis, psoriatic arthritis, Crohn's disease and rheumatoid arthritis (RA) may have an increased risk of malignancy due to impaired immune support and stress management (immunosurveillance) resulting from the effects of chronic inflammation and immunosuppressive agents (11-13). Due to exposure to immunosuppressive agents, methotrexate (MTX), biologic therapies, cyclosporine, and UV light therapies, there may be an increased cancer risk in patients with psoriasis (14,15). MTX is a structural analogue of folic acid that reversibly inhibits dihydrofolate reductase, thereby preventing DNA synthesis. Its mechanism of action in psoriasis has not been fully understood yet, but MTX is believed to act primarily as an immunosuppressant and reduces the rate of epidermal proliferation in psoriasis (16).

A retrospective study by Scott *et al* (17) on RA and inflammatory bowel disease (IBD) patients with non-melanoma skin cancer (NMSC) history showed that the MTX use was associated with an increased risk of a second NMSC in RA. The risk particularly increased with an exposure duration longer than one year or when other medications for other diseases were associated (17,18). The addition of an anti-TNFα agent caused a risk increase, but there was no increased risk with rituximab or abatacept (17). An analysis of 130,315 RA patients suggested no significantly increased risk of melanoma in patients treated with TNFα inhibitors. There was also no significant risk in this same group of patients for tocilizumab and abatacept exposure (19).

Small-molecule (apremilast, tofacitinib) and biologic therapies such as anti-TNFα (infliximab, etanercept adalimumab), anti-IL-12/23 (ustekinumab), anti-IL-17 (secukinumab, ixekizumab, brodalumab) and anti-IL-23 (guselkumab, tildrakizumab) can be effective in severe forms of psoriasis or psoriatic arthritis, but they can have significant side effects and require close follow-up (5,20). Biologic therapies are a powerful treatment option for those with moderate to severe psoriasis. According to current guidelines regarding the use of biologics, they are contraindicated in those patients with proven malignancy or premalignancy states, which means that adequately treated NMSC, as well as malignancies diagnosed and treated earlier than 20 years previously should be excluded (21). Patients with psoriasis are at a far greater risk of malignancy as they receive UV therapy such as 311-nm narrowband phototherapy, PUVA (Psoralen plus UVA), and excimer laser therapy (3,22). Furthermore, some of the patients suffering from psoriasis receive retinoids (which increase their sensitivity to UV radiation) and MTX further increasing the risk of skin cancer occurrence (23).

The relationship between psoriasis and malignancy is not very well established; there are few studies that have led to conflicting results (24). Studies referring to psoriasis patients highlighted an increased risk of (NMSCs and lymphoma, whereas the results regarding other solid malignancies are inconsistent (25). Chiesa Fuxench *et al* (26) suggested that there is an overall small increased risk of neoplasia in patients with psoriasis treated with phototherapy or systemic medications, and that they were shown to have a higher risk for malignant neoplasms compared with controls. Future studies should be focused on a better knowledge of the disease severity effect and exposure to treatment separately on cancer risk in this population.

Dermatologists who treat patients with psoriasis should consider appropriate cancer screening guidelines and counseling in their daily practice (26-28). Another study also confirmed that were was no increased risk for melanoma, but non-melanoma skin cancer was associated with PUVA, cyclosporine and anti-TNFα treatment in psoriasis. It also suggests taking into consideration the incidence of cancer in a patient's history before using biologic or immunosuppressive therapy because of the lack of studies on these patient groups (29). Pérez Ramírez *et al* presented one psoriasis patient suffering from metastatic melanoma with spontaneous regression without any treatment. His psoriatic disease was associated with HLA Cw6 (human leukocyte antigen). The authors draw their attention on a possible relationship between psoriasis, HLA Cw6, and spontaneous melanoma regression, and that psoriasis is considered an immune-mediated disease that can play a protective role against melanoma (30).

There is limited data regarding the association between systemic treatments for psoriasis and cancer recurrence, since patients with a history of malignancy are usually excluded from participating in clinical trials, and dermatologists hesitate to initiate immunosuppressive agents in cancer survivors. The possibility of collision skin lesions, nevi located at the border of psoriatic plaques, or even nevi found within psoriatic plaques is considered to be worth exploring. The potential effects of treatments in such situations and the existence of possible differential diagnoses, such as the Meyerson phenomenon are

also worth studying. The Meyerson phenomenon is described as the development of a halo or eczematous patch over another skin lesion. Topical treatment with corticosteroids is effective in many cases (31). Some authors suggest that melanoma may occur as a component of Meyerson phenomenon, and that careful dermoscopic examination is useful to differentiate between pigmented lesions with peripheral erythematous halo (32). Nevi located within a psoriasis plaque may appear to decrease in pigment. This aspect, however, should not necessarily be interpreted as regression. Some nevi may be observed to lighten as they are covered by psoriatic scale, and will subsequently darken when exposed to sunlight.

Case report

We present the case of a 31-year old male patient, non-smoker, non-alcoholic, who was referred to the Dermatology Department of 'St. Parascheva' Clinical Infectious Diseases Hospital of Galati in the Fall of 2019 due to the presence of widespread, sharply demarcated erythemato-squamous, irregularly shaped lesions, ranging from 2 to 4 cm, located on the trunk and lower extremities. The patient reported the onset of cutaneous lesions as early as childhood. He underwent various topical treatments, including topical corticosteroid creams, ointments and calcipotriol without significant changes. The initial management with topical agents and narrow-band UVB phototherapy did not prove to be of any success. Laboratory tests were within the normal range. A punch skin biopsy was taken from a plaque situated on the trunk. The histological examination revealed parakeratosis, marked hyperkeratosis Munro's microabscesses, agranulocytosis, and acanthosis.

Based on the clinical and histological findings, the diagnosis of psoriasis vulgaris was made. After a thorough clinical-biological assessment, the patient was deemed eligible for systemic therapy, and MTX treatment starting with 15 mg per week was proposed. After about 4 weeks, the response to the treatment was encouraging with clearance of the skin, but the outcome was inadequate, despite adherence to treatment (Fig. 1).

Unfortunately, after a 4-month treatment with MTX, the lesions reappeared, becoming refractory to treatment; therefore, MTX treatment would later prove to be unsuitable. Given his recalcitrant disease covering up to 15% of his body surface, the patient's desire to have a clear skin, and based on the fact that the patient was naïve to biologic therapy, he was started on secukinumab 300 mg monthly. Secukinumab, a fully human monoclonal IL-17A antibody which binds to IL-17A inhibiting the inflammatory cascade, has been shown in several clinical trials to be safe and effective for the treatment of psoriasis. The patient is being followed-up for clinical and biological parameters, with complete skin clearance. He also presented some 1-3 mm brown and black macules that involved the arms and trunk. He recalls that they were not present at birth, but that he has had them for many years. Our hypothesis was that they appeared after the patient's repeated sun exposure during the summer holidays in order to obtain a clear skin.

A particularity observed in this patient was his strong desire for cosmesis that led him to seek out tattooing as a solution to mask his psoriatic lesions. Tattooing has been identified as a possible trigger for the Koebner phenomenon occurring in psoriasis patients (33). Stress provoked by a negative self-image can be both an initiating and sustaining factor in psoriasis through the increased release of cytokines, hormones, and neuropeptides that combine to cause overall proinflammatory and immunomodulatory effects in what is now referred to as the Brain-Skin connection (34).

Figure 1. Anterior aspect of the patient including sharply demarcated erythemato-squamous, irregularly shaped lesions, some of them covered by tattoos.

The Ethics approval was obtained from the Ethics Commission of the 'St. Parascheva' Clinical Hospital of Infectious Diseases, Galati (approval no. 24/26.02.2021) and written informed consent was obtained from the patient.

Discussion

In summary, the risk of new or recurrent systemic malignancies is similar between patients with biologic and non-biologic treatments. The risk of additional non-melanoma skin cancer occurrences in patients with a history may be increased, and data concerning additional primary melanomas and melanoma recurrence are inconclusive in melanoma survivors. Despite evidence suggesting the short-term efficacy and safety of biologic therapy as compared to classic conventional systemic therapies, there are concerns regarding the long-term risk of developing cancer in patients treated with biologic therapy as compared to those treated by conventional systemic therapies (35-37). Based on high-level evidence, therapies for psoriasis appear to be safe. Additional long-term data are warranted for newer treatments and for their use in cancer survivors (38).

Long-term studies focused on safety guidance are still lacking for these newer treatments, including biologic agents targeting IL-12/23 (ustekinumab), IL-23 (guselkumab), IL-17 (ixekizumab, secukinumab), phosphodiesterase-4 (apremilast), and small-molecule inhibitors of Janus kinase (tofacitinib), as well as data for their use in cancer patients and cancer survivors. An increased risk of squamous cell carcinoma (SCC) has been confirmed by several studies, but there is conflicting evidence regarding the risk for melanoma (39,40).

Nevi are considered to be an independent marker of overall melanoma risk. Most nevi in adults range from 2 to 6 mm and are estimated to be composed of thousands of melanocytes depending on the size and type of the nevus (41). They have a uniform color and clinically symmetric architecture. They are classified into one of three major categories: Junctional (melanocytes confined to the epidermis only), intradermal (confined to the dermis only) and compound (both a dermal and an epidermal component) (42). Microscopically, nevi are well circumscribed, symmetric, and are composed of melanocytes with a banal cytology. They have two main histopathological features: nesting and maturation (43). The clinical importance of dysplastic nevi resides in their association with melanoma risk. In these patients, the risk of melanoma increases with the presence of melanoma in their personal or familial history and with the number of nevi (44,45).

Patients with multiple atypical lesions are known to have an increased risk of developing melanoma. It is considered that periodic cutaneous assessment is a generally accepted procedure (46). Dermoscopy, also called epiluminescence microscopy, is an *in vivo* non-invasive technique that aids visualization of the otherwise invisible morphology of a pigmented lesion, thereby improving the clinical diagnosis. Currently, dermoscopy is considered to be one of the most efficient tools for the early diagnosis of melanoma. It reduces the frequency of having to biopsy benign lesions (as excisional biopsy is difficult to perform on each and every lesion in patients who develop multiple melanocytic lesions) and is efficient for monitoring nevi. Biopsy should be performed when differential diagnoses are difficult (47,48). Thorough skin examination, meaning clinical and dermoscopic evaluation of melanocytic lesions, must be encouraged in patients treated with systemic therapies such as biologic agents. Melanoma is a skin cancer with high immunogenicity. There are concerns for patients treated with TNFα inhibitors, since the melanoma risk is increased when the suppression of the immune system occurs (49,50).

There are limited data concerning the relationship between melanocytic lesions, psoriasis and melanoma. Immunologic pathways implicated in psoriasis induce a reduction in the number of melanocytic nevi. Nevertheless, little is known about the association of melanocytic nevi with psoriasis (51). Di Cesare *et al* demonstrated that psoriatic patients have fewer melanocytic nevi than control subjects without psoriasis, which suggests that the immune pathogenic background of psoriasis may play a protective role against the development of melanocytic lesions. It was also observed that patients treated with biologic agents are more likely to have more nevi than patients treated with other methods, and that no cases of melanoma development were reported during biological treatment (52). The use of sun protective creams was significantly reduced in patients with psoriasis probably because of the 'therapeutic' use of UV exposure by the patients. Therefore, it is not surprising that more psoriatic patients than control subjects displayed solar lentigines (52). Cengiz *et al* developed a study to investigate the number of melanocytic nevi in psoriatic patients as compared with control subjects, and whether there is any relationship between the disease severity and the type of treatment. They detected a very low proportion of clinically atypical nevi and no cases of melanoma in either patients or controls. In addition, they found that psoriatic patients had significantly fewer nevi than the control group (53) and their results are consistent with other studies in the literature (52,54). This suggests a protective role of the cytokines involved in psoriatic disease and an increased secretion of IL-17, TNFα, and IL-6 against the development of melanocytic lesions (52).

It is believed that immunosuppression may induce melanocyte-stimulating hormone or melanoma growth-stimulatory activity, two endogenous growth factors specific for melanocytes. Therefore, the growth and development of melanocytes could be stimulated under these circumstances. Genetic factors may also be involved. The role of immuno-surveillance in tumoral genesis is therefore essential, and can prevent the appearance of malignant lesions and malignant transformation of benign lesions (55).

Melanocytic proliferation may be benign, like in eruptive melanocytic nevi, or malignant, as in melanoma (56). The literature available suggests that patients undergoing biologic treatment should be encouraged to monitor their pre-existing nevi and to observe the appearance of new ones (56-58). Paradoxically, exacerbation of psoriasis has been observed with the introduction of monoclonal antibody therapies such as ipilimumab, nivolumab and pembrolizumab for advanced stage melanoma (59).

We discovered a case report of a young lady with arthritis who developed halo nevi at the site of every nevus while being treated with tocilizumab. When describing the development of halo nevi, vitiligo and diffuse alopecia areata in this patient, cellular and humoral immunity were considered to be causative factors. Tocilizumab blocks IL-6R, leading to an increase in serum IL-6 that can have direct effects on melanocytes. The presented case describes the pathogenesis and development of halo nevi, diffuse alopecia areata and vitiligo associated with tocilizumab therapy. The regression of melanocytes during the treatment with tocilizumab provides evidence for IL-6 as a potential future target in the treatment of melanoma (60,61). Continuous monitoring for invasive features of pigmented lesions is a reasonable alternative to excision (62,63).

The newer biologic and non-biologic agents appear to be promising and effective, but additional studies are needed to evaluate the malignancy risk in these agents. We should also remind patients of the importance of prophylaxis and the use of sunscreen products among patients of this group.

To conclude, the risk of new or recurrent systemic malignancies is similar between patients on biologic and non-biologic treatments. Recent research concerning the development of new melanocytic lesions in patients under immunosuppressive therapy showed that the treatment with biologic agents was associated with increased nevi count and the appearance of dermoscopic changes in existing nevi, but none of the changes, or any of the subsequently excised nevi, were malignant. Based on high-level evidence, psoriasis therapies appear to be safe.

Any clinical or dermoscopic changes in existing melanocytic nevi in patients undergoing biological treatment or other immunosuppressive therapies should be carefully monitored as alternative to excision. As in other dermatological conditions, temporization and follow-up with both clinical and dermoscopic monitoring of pigmented lesions are an alternative to surgical excision. Additionally, reflectance confocal microscopy or optical coherence tomography could

be used. Further long-term data are warranted for novel treatments and for their use in patients with malignancies.

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Availability of data and materials

Further information regarding the case study can be obtained from the corresponding author upon reasonable request. All information in the short review is documented by relevant references.

Authors' contributions

ALT contributed to the conception, design, and drafting the study. VA, CB, DSJ, SAM and MC, contributed to the interpretation of the data, and to the revision of the manuscript critically for important scientific content. FCB, LB and DSR made substantial contributions to the conception and design of the work and were responsible for the clinical management of the patient, while TN, LCN and EN supervised and substantially revised this work. All authors agreed on the final manuscript and contributed equally in all the stages of the study. They reached an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The Ethics approval was obtained from the Ethics Commission of the 'St. Parascheva' Clinical Hospital of Infectious Diseases, Galati (approval no. 24/26.02.2021) and written informed consent was obtained from the patient prior to publication.

Patient consent for publication

Written informed consent was obtained from the patient for the use of all data and graphical images for publication.

Competing interests

The authors declare that they have no competing interests.

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