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

FLORIN CIPRIAN BUIOREANU1-3*, LAURA BEZMAN4-5, DIANA SABINA RADASCHIN1-2, ELENA NICULET5*, CARMEN BOBEICA5, MIHAELA CRAESCU5, THOMAS NADASDY1, DANIELA STAN JICMAN6, VALERIU ARDELEANU7-9, LAWRENCE CHUKWUDI NWABUDIKE10, SILVIU ADRIAN MARINESCU11 and ALIN LAURENTIU TATU1,2,12

1Department of Dermatology, ‘Sf. Cuvioasa Parascheva’ Clinical Hospital of Infectious Diseases, 800179 Galați; 2Clinical Department, Faculty of Medicine and Pharmacy, ‘Dunărea de Jos’ University of Galați; 3Department of Dermatology, Doctoral School of Biological and Medical Sciences, ‘Dunărea de Jos’ University of Galați, 800010 Galați; 4Ophthalmology Department, ‘Sf. Apostol Andrei’ Clinical Emergency Hospital, 800578 Galați; 5Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, ‘Dunărea de Jos’ University of Galați, 800010 Galați; 6ENT Department, ‘Sf. Apostol Andrei’ Clinical Emergency Hospital, 800578 Galați; 7Surgery Department, Arestetic Plastic Surgery Clinic, 800908 Galați; 8Faculty of Medicine, Doctoral School, ‘Ovidius’ University, 900533 Constanța; 9Surgery Department, CFR General Hospital, 800223 Galați; 10Outpatient Dermatology Department, ‘Prof. N. Paulescu’ National Institute of Diabetes, 011233 Bucharest; 11Department of Plastic and Reconstructive Surgery, ‘Carol Davila’ University of Medicine and Pharmacy, 020021 Bucharest; 12Research Center of Medical and Pharmaceutical Sciences, ReFORM-UDJ, 800010 Galați, Romania

Received July 2, 2021; Accepted August 2, 2021
DOI: 10.3892/etm.2021.10789

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.

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 dermatoscopic 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 erythematous-squamious, 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 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).

The Ethics approval was obtained from the Ethics Commission of the ‘St. Parascheva’ Clinical Hospital of Infectious Diseases, Galati (approval no. 24/26.02.2016) 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 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 sipilimunab, 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.

Acknowledgements

Not applicable.

Funding

No funding was received.

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 of 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 Clín Dermatol 28: 88-92, 2010.

Patient consent for publication

Written informed consent was obtained from the patient prior to publication.

Competing interests

The authors declare that they have no competing interests.

References

1. Griffiths CE and Barker JN: Pathogenesis and clinical features of psoriasis. Lancet 370: 263-271, 2002.
2. Gedjimson JE and Elder JT: Psoriasis: Epidemiology. Clin Dermatol 25: 535-546, 2007.
3. Ardeleanu V, Sabina Radaschin D and Tatu AL: Excimer laser for psoriasis treatment: A case report and short review. Exp Ther Med 20: 52-55, 2020.
4. Kruger G, Koo J, Lebwohl M, Menter A, Stern RS and Rolstad T: The impact of psoriasis on quality of life: Results of a 1998 national psoriasis foundation patient-membership survey. Arch Dermatol 137: 280-284, 2001.
5. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, et al: Guidelines of care for the management of psoriasis and psoriatic arthritis: Section I. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 58: 826-850, 2008.
6. Nwabudike LC and Tatu AL: Using complementary and alternative medicine for the treatment of psoriasis: A step in the right direction. JAMA Dermatol 155: 636, 2019.
7. Baseeraj KH, Ashok NM, Rashmi R and Praveen TK: The role of drugs in the induction and/or exacerbation of psoriasis. Int J Dermatol 49: 1351-1361, 2010.
8. Tatu AL, Elisei AM, Chioncel V, Miulescu M and Nwabudike LC: Immunologic adverse reactions of β-blockers and the skin. Exp Ther Med 18: 955-959, 2019.
9. Li SJ, Perez-Chada LM and Merola JF: TNF inhibitor-induced psoriasis: Proposed algorithm for treatment and management. J Psoriasis Psoriatic Arthritis 4: 70-80, 2019.
10. Naldi L: Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: Facts and controversies. Clin Dermatol 28: 88-92, 2010.
11. Chen YJ, Chang YT, Wang CB and Wu CY: The risk of cancer in patients with rheumatoid arthritis: A nationwide cohort study in Taiwan. Arthritis Rheum 63: 352-358, 2010.
12. Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V and Jewell D: Cancer in patients with ulcerative colitis, Crohn’s disease and coeliac disease: Record linkage study. Eur J Gastroenterol Hepatol 20: 297-304, 2008.
13. Chen YJ, Wu CY, Chen TJ, Shen JL, Chu SY, Wang CB and Chang YT: The risk of cancer in patients with psoriasis: A population-based cohort study in Taiwan. J Am Acad Dermatol 65: 84-91, 2011.
14. McKenna KE, Patterson CC, Handley J, McGinn S and Allen G: Cutaneous neoplasia following PUVA therapy for psoriasis. Br J Dermatol 134: 639-642, 1996.
15. Mordaca G, Colombo BM, Cagnati P, Gulli R, Spanò F and Puppo F: Update upon efficacy and safety of TNF-α inhibitors. Expert Opin Drug Saf 11: 1-5, 2012.
16. Patel RV, Clark LN, Lebwohl M and Weinberg JM: Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 60: 1001-1017, 2009.
17. Scott FI, Mamtani R, Brensinger CM, Haynes K, Chiesa-Fuxench ZC, Zhang J, Chen L, Xie F, Yun H, Österman MT, et al: Risk of nonmelanoma skin cancer associated with the use of immuno-suppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol 152: 164-172, 2016.
18. Nwabudike LC and Tatu AL: Response to-chronic exposure to tetracyclines and subsequent diagnosis for non-melanoma skin cancer in a large Mid-Western US population. J Eur Acad Dermatol Venereol 32: e159, 2018.
19. Mercer LK, Asking J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, Strangfeld A, Zink A, Mariette X, Finckh A, et al: Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: Results from a collaborative project of 11 European biologic registers. Ann Rheum Dis 76: 386-391, 2017.
20. Badiani E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mauzac C, Droitcourt C, Hughes C, Ingram JR, Naldi L, et al: Systemic pharmacological treatments for chronic plaque psoriasis: A network meta-analysis. Cochrane Database Syst Rev 12: CD011553, 2017.
21. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, et al: Association of dermato-gologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol 153: 486-497, 2005.
22. Wong T, Hsu L and Liao W: Phototherapy in psoriasis: A review of mechanisms of action. J Cutan Med Surg 17: 6-12, 2013.
23. Gross RL, Schwartzman-Morris JS, Krathen M, McGinn S, Fisher MC, Greenberg JD, Putterman C, Maese PJ, et al: A comparison of malignancy incidence among psoriatic and rheumatoid arthritis patients in a large US cohort. Arthritis Rheumatol 66: 1472-1481, 2014.
24. Lupu M, Caruntu A, Caruntu C, Papageorghe CML, Ilie MA, Voiculescu B, Boda D, Constantin C, Tanase C, Sifaki M, et al: Neuroendocrine factors: The missing link in non melanoma skin cancer (Review). Oncol Rep 38: 1327-1340, 2017.
25. Polacheck A, Muntanyana A, Lee KA, Ye JY, Chandran V, Cook RJ and Gladman DD: Malignancy in psoriatic disease: Results from prospective longitudinal cohorts. Semin Arthritis Rheum 51: 144-149, 2021.
26. Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A and Gelfand JM: The risk of cancer in patients with psoriasis: A population-based cohort study in the health improvement network. JAMA Dermatol 152: 282-290, 2016.

27. Nwabudike LC and Tata AL: Reply to Gambichler T, et al: Altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery. J Eur Acad Dermatol Venereol 33: e3-e4, 2019.

28. Rebega L, Furescu D, Baciu G and Ciubara A: Psycho-oncology support. BRAIN Broad Res Artif Intell Neurosci 10: 77-88, 2019.

29. Beyaert R, Beaugerie L, Van Assche G, Brochez L, Renaud JC, Viguier M, Coquyti V, Jerusalem G, Machiels JP, Prenen H, et al: Cancer risk in immune mediated inflammatory diseases (IMID). Mol Cancer 12: 98, 2013.

30. Pérez Ramírez S, Parra V, Avilés Izquierdo JA, Vicario JL, Martín M and Márquez-Rodas I: Metastatic melanoma with spontaneous regression, psoriasis and HLA-Cw6: Case report and a hypothesis to explore. Tumori 100: 144e-147e, 2014.

31. Niculet E, Bobeica C and Tata AL: Glucocorticoid-induced skin atrophy: The old and the new. Clin Cosmet Investig Dermatol 13: 1041-1050, 2020.

32. Sezer E, Ozturk Durmaz E, Çetin E and Şahin S: Meyerson phenomenon as a component of melanoma in situ. Acta Dermatovenerol Croat 24: 81-82, 2016.

33. Kluger N, Estève E, Fouére S, Dupuis-Fourdan F, Jegou MH and Lévy-Rameau C: Tattooing and psoriasis: A case series and review of the literature. Int J Dermatol 56: 822-827, 2017.

34. Chapman BP and Mounihan J: The brain-skin connection: Role of psychosocial factors and neuropeptides in psoriasis. Expert Rev Clin Immunol 5: 623-627, 2009.

35. Kamata M and Tada Y: Safety of biologics in psoriasis. J Dermatol 45: 279-286, 2018.

36. Cohen BL and Sachar DB: Update on anti-tumor necrosis factor agents and other new drugs for inflammatory bowel disease. BMJ 357: j2505, 2017.

37. Crusz SM and Balkwill FR: Inflammation and cancer: Advances and new agents. Nat Rev Clin Oncol 12: 584-596, 2015.

38. Neagu M, Constantin C, Tanase C and Boda D: Patentied biomarker panels in early detection of cancer. Recent Pat Biomark 1: 10-14, 2011.

39. Geller S, Xu H, Libwohl M, Nardone B, Lacouture ME and Xu H: Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). J Drugs Dermatol 14: 706-714, 2015.

40. Karram S, Novy M, Saroufim M, Loya A, Taraif S, Houreih MA, Khaterpal M: Malignancy risk and recurrence with psoriasis: A population-based prospective case-control study. J Am Acad Dermatol 73: 623-629, 2015.

41. Koseoglu G, Akay BN, Kucukaslan O, Ayala F: Psoriasis and melanocytic naevi: Does the first confer a protective role against melanocyte progression to naevi? Br J Dermatol 164: 1262-1270, 2011.

42. Katoulis AC, Kanelles A, Zambacos G, Panayiotides I and Stavrianes NG: Development of two primary malignant melanomas after treatment with adalimumab: A case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation. Dermatology 221: 9-12, 2010.

43. Queirós CS, Laureano-Oliveira A, Lopéz-Presa D and Filipe P: Spitz nevus and infiltrixim: Association or coincidence? An Bras Dermatol 95: 615-618, 2020.

44. Manganoni AM, Zane C, Pavoni L, Farìsoglio C, Sereni E and Calzavara-Pinton P: Cutaneous melanoma in patients in treatment with biological therapy: Review of the literature and case report. Dermatol Online J 17: 12, 2011.

45. Zurac S, Neagu M, Constantin C, Cioplea M, Nedelcu R, Bastian A, Popp C, Nichita L, Andrei R, Tebeica T, et al: Variations in the expression of TIMP1, TIMP2 and TIMP3 in cutaneous melanoma with regression and their possible function as prognostic predictors. Onco Lett 11: 3354-3360, 2016.

46. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, Guminski A, Puzanov I, Lawrence DP, Buchbinder EI, et al: Epithiubum therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2: 234-240, 2016.

47. Nadesalingam K, Goodfield M and Emery P: Halo naevi, vitiligo and diffuse alopecia areata associated with tocilizumab therapy. J Exp Ther Med 21: 263, 2021.

48. Niculet E, Chiocci V, Elisei AM, Miulescu M, Buzia OD, Nwabudike LC, Craescu M, Draganescu M, Bujoreanu F, Marinescu E, Marinescu E, et al: Multifatorial expression of IL-6 with update on COVID-19 and the therapeutic strategies of its blockade (review). Exp Ther Med 21: 623, 2021.

49. Koseoglu G, Akay BN, Kucukaslan O and Erdem C: Dermoscopic changes in melanocytic nevi in patients receiving immunosuppressive and biologic treatments: Results of a prospective case-control study. J Am Acad Dermatol 73: 623-629, 2015.

50. Giurcaneanu C, Nitipir C, Popa LG, Forsea AM, Popescu I and Calzavara-Pinton P: Cutaneous melanoma in patients in treatment with biological therapy: Review of the literature and case report. Dermatol Online J 17: 12, 2011.

51. Bastian BC: The molecular pathology of melanoma: An integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 9: 239-271, 2014.

52. Stefan O, Tudor G, Constantinescu C, Luca C, Boda D, Caruntu C, Cioplea M, Nichita L and Zurac SA: E-cadherin and N-cadherin expression pattern in common melanocytic nevi. Virchows Arch 475: S28, 2019.

53. Cengiz FP, Emiroglu N, Bahali AG, Ozkaya DB, Su O and Onsun N: The relationship of psoriasis and melanocytic nevi. Indian J Dermatol 66: 664-667, 2016.

54. Balato N, Di Costanzo L, Balato A, Patruno C, Scalenzi M and Ayala F: Psoriasis and melanocytic naevi: Does the first confer a protective role against melanocyte progression to naevi? Br J Dermatol 164: 1262-1270, 2011.

55. Tomaselli MS, Bousetta M, Zeidan S, Cattaneo S, Benamara L, Lachkar H, Bouadjenek A, Boussay M, El Amrani N, et al: Evolution of melanocytic nevi under vemurafenib, followed by combination therapy with dabrafenib and trametinib for metastatic melanoma. Acta Dermato-Venereol 23: 114-121, 2015.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.