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Understanding the enigmatic association between mycosis fungoides and psoriasis: Report of two cases and review of the literature

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ABSTRACT

Psoriatic patients present an increased risk for developing lymphoma, particularly cutaneous T-cell lymphoma (CTCL). To what degree psoriasis itself through chronic immune stimulation, or the immunosuppressive medications used for its treatment or comorbidities (obesity, diabetes mellitus, etc), or lifestyle (smoking, alcohol, diet, etc) may play a role in the onset of MF is not yet clear. Psoriasis and Mycosis Fungoides (MF), the most common variant of CTCL, represent two distinct entities sharing common pathogenetic mechanisms and a wide spectrum of common clinical features associated with the abnormal activation of T-cells. The aim of this study is to explore the relationship between MF and psoriasis by presenting two cases with clinical and histopathologic features of both psoriasis and MF with a particular emphasis on the time of presentation of both disorders, the use of previous immunosuppressive drugs as well as the therapeutic management of patients. Biopsy of the cutaneous lesions before the introduction of biologics should be incorporated in clinical practice. Biopsy of the cutaneous lesion should also be performed in the case of appearance of psoriasiform lesions during biologic treatment for autoimmune disorders because this may represent an indolent form of MF. Psoriatic patients with poor or no-response to treatment should be examined thoroughly for MF using immunochemistry and, if necessary, molecular biology techniques. In concomitant MF and psoriasis, combination treatment may be beneficial for both entities. Finally, a large multicentric registry of MF patients who were treated for benign dermatoses (i.e. eczema, psoriasis) with classic immunosuppressive drugs and/or biologics is needed to collect data and further clarify the enigmatic relationship between psoriasis, MF and immunosuppressive treatment.

1. Introduction

Early stage mycosis fungoides (MF), the most common type of Cutaneous T-Cell Lymphoma (CTCL), can mimic frequent and benign dermatoses such as eczema or psoriasis, delaying the diagnosis by several years [1]. MF has been characterized as a "dermatological masquerader" due to its multiple clinical variants, such as folliculotropic, poikilodermatous, hypopigmented, capillaritis-like, verrucous/hyperkeratotic, psoriasiform, ichthyosiform and bullous. In its erythrodermic form, the differential diagnosis between eczema or psoriasis and MF is virtually impossible based on clinical appearance [1,2].

Psoriasis is one of the commonest chronic dermatoses, with approximately 2–3% of subjects affected worldwide, presenting with erythematous scaly plaques that can be clinically indistinguishable from psoriasiform MF [2–12]. Psoriasis, a chronic immune-mediated inflammatory disorder, has been linked to a moderately higher risk of certain malignancies, particularly keratinocyte, lung, urinary/bladder, oropharynx/larynx, hepatic and colorectal cancers as well as lymphomas [2,13,14].

During the last century, the occurrence of lymphoma in autoimmune disorders including psoriasis has been extensively investigated. More specifically, in rheumatoid arthritis (RA), the overall incidence of lymphoma is approximately twice than that in the general population [15–21]. A very recent collaborative analysis of 12 European registries

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has shown that although the subtype of lymphoma distribution differed between RA and the general population, there were no differences in the distribution of lymphoma subtypes in patients with RA treated with Tumor Necrosis factor-alpha (TNF-α) inhibitors compared with bio--naïve patients [22]. The association between psoriasis and lymphoma has also been discussed [2,14,23,24]. Two large population-based studies have shown that the incidence rates for Hodgkin lymphoma, non-Hodgkin lymphoma and CTCL were higher among patients with psoriasis compared with the general population [23,24]. A recent meta-analysis has shown that, compared to controls, patients with moderate-to-severe psoriasis presented a slightly elevated risk for developing lymphohematopoietic cancer (LHC), ranging from 1.7-fold for Hodgkin lymphoma, 1.3-fold for Non-Hodgkin lymphoma (NHL), multiple myeloma and leukemia to 6-fold for CTLC/MF [14].

On the other hand, based on case series and case reports [25,26], there have been cases of MF misdiagnosed as psoriasis. In these cases, it is very difficult to clarify: 1) whether patients also presented psoriasis that evolved to MF, and 2) what could be the potential link between MF and the use of immunosuppressive drugs, such as TNF-α inhibitors in psoriasis. However, it is worth noting that: 1) diagnosis of psoriasis is not supported by pathology most of the time and 2) histologic findings of lesions in early MF may be misinterpreted as psoriasis. Another intriguing point is the chronic sequence of the MF and psoriasis coexistence, and its connection with the use of biologics such as TNF-inhibitors in psoriasis. More specifically, regarding the time of MF appearance, it seems that MF appears frequently later in the course of an autoimmune or inflammatory disorder such as psoriasis and after the use of immunosuppressive drugs or biologics [25–28]. However, in a cohort of 177 patients with MF, MF preceded psoriasis diagnosis in 58.1% of cases, while 25.6% of psoriasis diagnoses were supported by pathology suggesting that the purported association between those two disorders is less likely due to misclassification bias [27].

The aim of this study is to explore the relationship of MF and psoriasis by presenting two cases with clinical and histopathologic features of both psoriasis and MF with a particular emphasis on the time of presentation of both disorders, the use of previous drugs as well as the therapeutic management of patients.

2. Case reports

2.1. First case

A 65-year-old Caucasian male patient with a history of refractory psoriasis to many previous systemic treatments, including several biologics had been hospitalized in our Dermatology Department, being erythrodermic upon admission (Body Surface Area/BSA: 100%) with a longstanding exfoliative dermatitis (Fig. 1A and B). At the age of 43, he presented with xeroderma of the shins and 7 years later with moderate generalized xerosis of his body without erythema. The skin biopsy revealed ichthyosis. After 4 years, he reported a progressive loss of scalp hair leading to alopecia totalis, and 8 years later a rapidly spreading macular erythroderma with scattered thicker plaques and intense pruritus. Histology of the latter revealed psoriasis. Since then, the patient has undergone a series of unsuccessful treatments depicted in Table 1.

A new skin biopsy during his hospitalization in our clinic was diagnostic of folliculotropic MF (Fig. 1C). CT scans of neck, chest, upper and

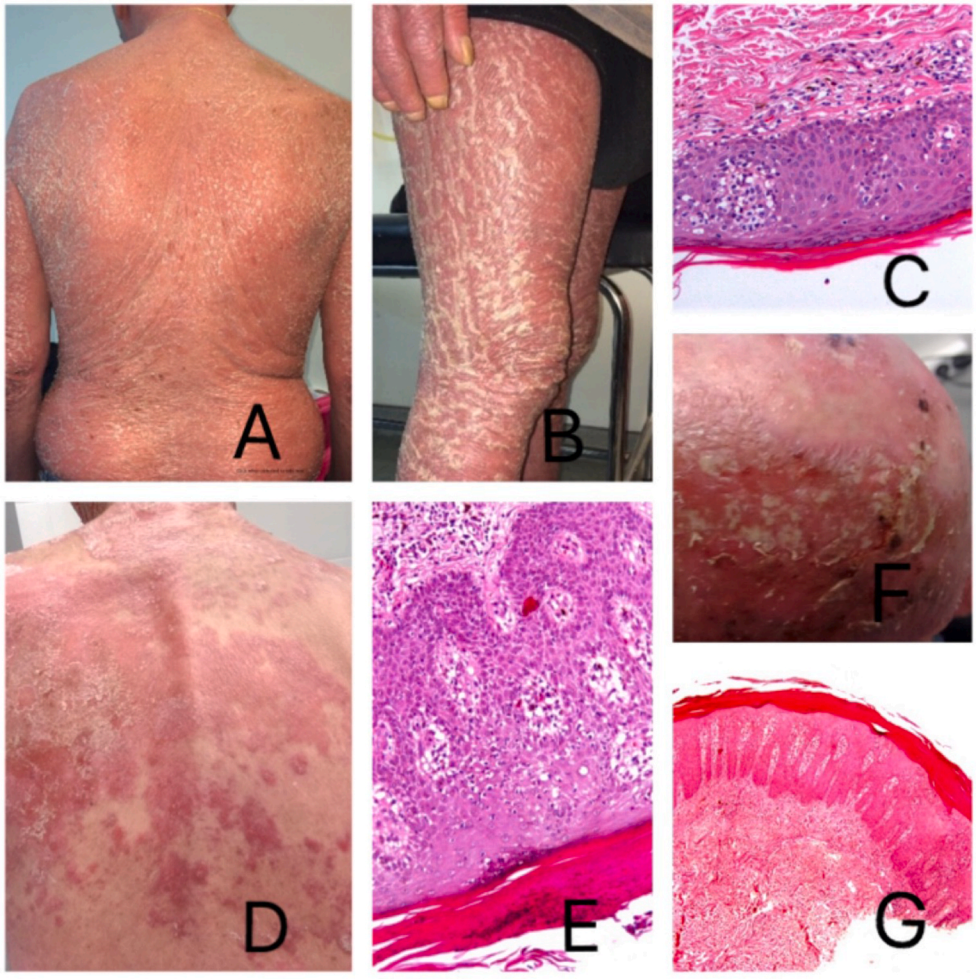

Fig. 1. A & B. The patient presented with longstanding exfoliative dermatitis. No nail psoriasis or psoriatic arthritis were observed. C. H&Ex40. Clear epidermotropism of atypical lymphocytes and one Pautrier's microabscess are observed. D. Psoriasiform appearance of the patient's lesions, one month after initiation of interferon-alpha-2b. E. H&E x40. Biopsy of a lesion of the shoulder revealed both epidermotropism of atypical lymphocytes, as well as Munro's microabscesses, acanthosis, hyper- and parakeratosis and effacement of the granular layer, elements of both MF and psoriasis within the same lesion. F. Pustular eruption on the patient's scalp after 1.5 month of treatment with interferon-alpha-2b.
G. Pustular lesion of the scalp revealed regular acanthosis, effacement of the granular layer, intense neutrophilic infiltrate and presence of Munro's microabscesses. No features of MF were observed.

Table 1
Treatment modalities received by the first patient for psoriasis and mycosis fungoides.

SERIES OF TREATMENT	MEDICATION	TREATMENT DURATION	INITIAL BSA (%)	BEST RESPONSE (% BSA)	%BSA AT THE END OF TREATMENT
PATIENT'S TREATMENT FOR PSORIASIS					
1	Acitretin 35 mg qd	3 months	100	50	100
2	Adalimumab 40 mg q2w + MTX 7.5 mg qw	4 months	100	0	100
3	Acitretin 25 mg qd	7 months	100	60	100
4	Secukinumab 300 mg q4w	8 months	100	70	80
5	Adalimumab 40 mg q2w	3 months	80	70	80
6	Ustekinumab 90 mg	Once	80	80	100
PATIENT'S TREATMENT FOR MF					
7	Bexarotene 300 mg qd	6 months	100	42	97
8	Interferon a-2b 3MIU tiw	6 weeks	97	35	85
9	Interferon a-2b 3MIU tiw + MTX 10 mg qw	2 weeks	85	75	75
PATIENT'S TREATMENT FOR MF AND PSORIASIS					
10	MTX 20 mg qw	6 weeks	75	68	73
11	Acitretin 30 mg qd	3 weeks	73	70	70
12	Bexarotene 300 mg qd + acitretin 25 mg qd	2 months	70	35	35

Abbreviations: BSA: Body Surface Area; MF: mycosis fungoides; MTX: methotrexate.

lower abdomen were negative for enlarged lymph nodes and visceral involvement. The stage of MF was T4N0M0B0 (IIIA). Treatment for MF was initiated (Table 1). After 1 month of treatment with interferon monotherapy, lesions gave the clinical impression of psoriasis and histology from his posterior trunk and his right shoulder confirmed a limited infiltration by atypical cells diagnostic of MF, but the specimen from the shoulder demonstrated elements of both MF and psoriasis (Fig. 1D and E).

Low dose methotrexate (10 mg q.w. per os) was added to interferon. Two weeks later, the patient initially showed slight improvement of his erythroderma (from 85% BSA to 75% BSA), but in a follow-up visit, he presented with pustular psoriasis of the scalp. New skin biopsies, one from the back and one from a pustule of the scalp (Fig. 1F and G), were diagnostic of MF and psoriasis respectively. The patient was

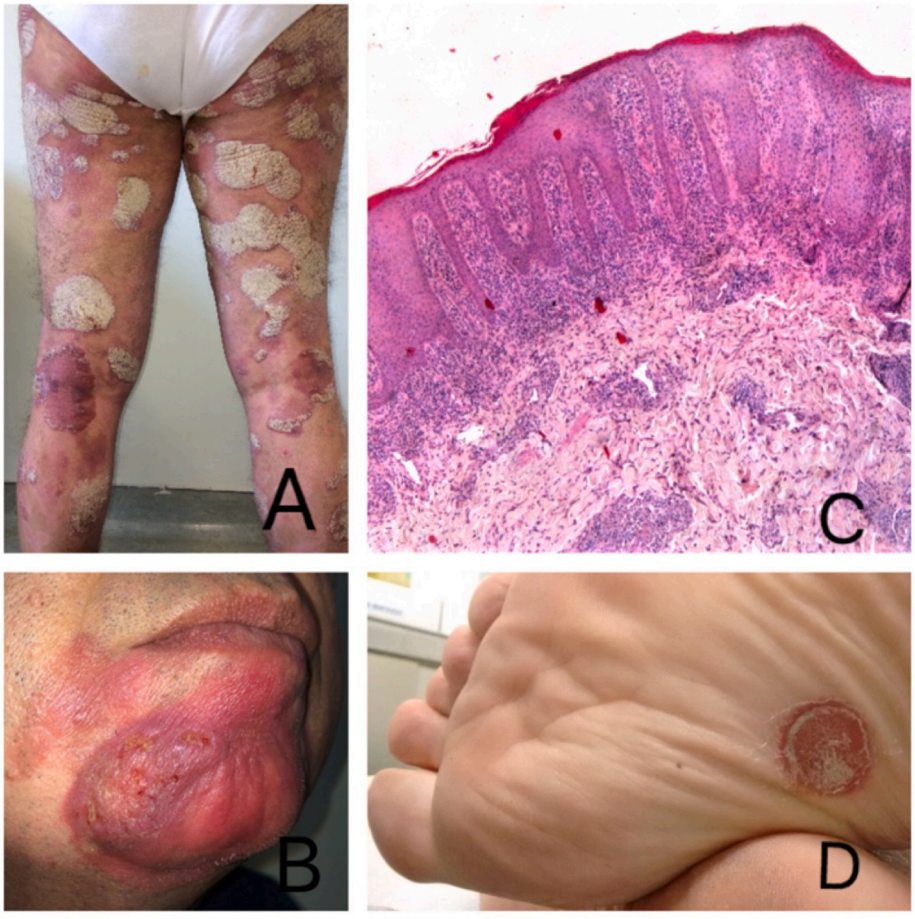

Fig. 2. A & B. Psoriasiform lesions on the lower limbs with thick white scale and a tumor with erosions on the right chin, appearing 2 months after cyclosporine therapy. C. Histopathology of a psoriasiform plaque of the back revealed epidermotropism of atypical lymphocytes, along with psoriasis features: regular acanthosis, elongation of the rete ridges, effacement of the granular layer, hyperkeratosis and parakeratosis. D. Psoriasiform plaque on the left sole of the patient, appearing 18 months after TSEB therapy, confirmed as MF histologically.

consequently treated with a combination treatment targeting both MF and psoriasis (Table 1), and till today he has remained in partial remission.

2.2. Second case

A 55-year-old male Caucasian patient with a 4-year history of psoriasis presented with erythematous scaly plaques and recent diagnosis of bullous pemphigoid (BP) under remission, was hospitalized in the Dermatology Department with a newly appearing tumor on the right side of his chin. The latter appeared after 2 months of immunosuppressive treatment with cyclosporine for BP (Fig. 2A and B).

Histology from the tumor of the chin and two specimens from psoriasiform plaques from his back and thigh respectively revealed MF and MF plaques with psoriasiform characteristics. (Fig. 2C). CT imaging, peripheral blood smear examination and immunophenotyping by flow cytometry were unremarkable. The MF stage was T3N0M0B0 (stage IIb).

The patient underwent low dose Total Skin Electron Beam (TSEB) therapy (12 Gy) with complete response and remained completely clear for 18 months, after which he presented with a 1.5 cm psoriasiform plaque on his left sole (Fig. 2D), which was treated with electron beam therapy.

3. Discussion

Psoriasis and MF share common pathogenetic features associated with the abnormal function of T-cells although the precise mechanism of abnormal T-cell stimulation and migration is still under investigation. Both psoriasis and early MF exhibit a Th1 phenotype while recent data support a prevailing role of Th17 immune response in psoriasis and IL17 expression in CTCL lesions induced by the JAK3/STAT3 signaling intracellular pathway [26,28]. Based on our cases, we underscore the following key points: 1) the coexistence of MF and psoriasis; 2) the clinical resemblance of psoriasiform MF to plaque psoriasis leading to difficulties in the differential diagnosis; and 3) the potential evolution from a cutaneous inflammatory disorder such as psoriasis to a malignant neoplastic disease such as MF after immunosuppressive treatment or due to the chronic immune stimulation [14,29,30] induced by psoriasis.

MF and psoriasis are two distinct skin disorders that, in the vast majority of cases, present as separate entities, whereas in some cases they may coexist, or MF may present after psoriasis treatment, or MF may resemble psoriasis. Interestingly, there have been reports of CTCL presenting in patients with severe atopic eczema [31]; however, this association has not been confirmed in a case-control study [32]. Despite differences in their etiology, psoriasis and MF may share some common clinical, immunologic and histopathologic characteristics that render their distinction difficult as observed in the presented case reports. In the vast majority of cases with concomitant MF and psoriasis, the onset of psoriasis precedes the onset of MF [26].

In case #1, it is evident that the patient has suffered from MF since the alopecia appearance, with a psoriatic component. To what degree anti-TNF agents and other biologics contributed to the etiopathogenesis of MF is a matter of debate. There has been a delay in the diagnosis of MF (approximately 20 years). Intriguingly, the non-response of psoriasis to practically all biologics that he had received raised the suspicion of MF, which turned out to have histologic features of psoriasis. Case #2 was a typical case of psoriasis. The patient had erythematous, sharply defined scaly plaques, on both non-sun and sun-exposed areas of his skin. A common feature of both cases is the appearance of histologically confirmed MF lesions after receiving immunosuppressive therapy. In case #2, while the BP subsided rapidly (within 4 weeks), it seems that cyclosporine may have played a certain role in the progression of plaque stage to tumor stage MF.

Psoriasiform MF is not a common variant of MF; nevertheless, it has been demonstrated in case reports [33–37]. It can mimic psoriasis both clinically and histologically. MF can even present as pustulosis of the palms and soles [24,38]. Apart from the characteristic features of MF, histologic features of psoriasis, such as elongation of the rete ridges with regular acanthosis, hyperkeratosis with parakeratosis, thinning, or total effacement of the granular layer and Munro microabscesses are present. Overall, it appears reasonable that misclassification between the two disease entities, psoriasis and MF, could explain the strong associations between psoriasis and CTLC observed in the literature [2].

The relationship between psoriasis and LHC has been controversial due to the limitations of the epidemiologic studies conducted in the USA and Europe, including among others their retrospective design, the modest sample size, the diagnosis misclassification bias and the evaluation of psoriasis severity [2]. The relative risks associating psoriasis with LHC may also reflect the co-risk parameters of metabolic associated disorders, such as obesity and diabetes mellitus (DM), smoking and alcohol consumption [2,5,6,8,10,39,40]. We cannot exclude that the increased likelihood of LHC in psoriasis patients may be explained by genetic factors, unhealthy lifestyle (smoking, alcohol, diet, etc), comorbidities such as obesity and DM, chronic use of immunosuppressant drugs and the chronic immune/inflammatory state with persistent stimulation of lymphocytes that characterizes chronic psoriasis [2,6]. Indeed, chronic psoriatic skin inflammation is related with sustained skin T-cell activation, elevating the risk of accumulating genetic mutations and ultimately lymphomagenesis [14]. As T cells are the overactivated lymphocytes in psoriasis, a higher occurrence of T lymphoma, such as CTCL, is expected in psoriasis. Besides, psoriasis and CTLC may share common genetic background that enhance tumor cell proliferation and survival [14]. Moreover, obesity, which represents the most common comorbidity in psoriasis, is characterized by the overgrowth and dysfunctionality of the adipose tissue resulting in substantial alterations in its cellular composition as well as in the dysregulation of proinflammatory adipocytokines that synergically promote chronic subclinical inflammation, insulin resistance, microenvironmental and cellular perturbations and tumor transformation in pre-existing clones [41–57].

Whether the chronic use of selected immunomodulatory drugs may influence the risk of LHC/CTCL is a matter of debate. Immunosuppressive agents may elicit a lack of immune surveillance facilitating thereby the development of CTCL. Immunosuppression elicited by cyclosporine, methotrexate with photochemotherapy (PUVA), and TNF-inhibitors or other biologics could speed up the onset and evolution of MF in psoriatic patients [2]. The chronic use of high dose of cyclosporine has been linked to an elevated risk of lymphoma in patients with psoriasis [58]. Whilst acitretin may be protective against LHC, the use of methotrexate has shown mixed results [14,59,60]. The mechanisms by which anti-TNFα agents either trigger or promote progression of cutaneous lymphoma have not yet been elucidated. Anti-TNFα agents may negatively affect the stimulation and function of NK cells by impairing the immunosurveillance against B-cell lymphoma [61]. In a recent meta-analysis, patients with inflammatory bowel disease treated with anti-TNFα agents presented a moderate increased risk of lymphoma while in the setting of psoriasis patients, their chronic use presented comparable malignancy risk with that of surveillance and epidemiologic registries [14,62–65]. However, a recent multicenter retrospective study of 22 patients (20 patients with CTCL and 2 with Cutaneous B-Cell Lymphoma) provided extensive data highlighting the potential connection between anti-TNFα agents and cutaneous lymphoma [66]. In most patients, a primary skin disorder was the indication for the use of anti-TNFα agents. The majority of them had been clinically diagnosed with psoriasis, psoriasiform dermatitis, or idiopathic erythroderma prior to the use of anti-TNFα therapy. A baseline biopsy was performed in 83.3% of patients with cutaneous disorder. None of the performed biopsies has shown any features of cutaneous lymphoma, and the most frequent histologic diagnosis was “psoriasis” or “psoriasiform dermatitis”. The median time from anti-TNFα initiation to a histologically confirmed cutaneous lymphoma diagnosis was 6 months (range: 1–24 months). So far, a total of 31 cases have been reported in the literature with presentation of cutaneous lymphoma after treatment with anti-TNFα agents [24–26].

Data on the association between CTCL and non-anti-TNFα biologics are scant. There have been no reported cases connecting the onset of MF with the anti-IL12/23 biologic ustekinumab. Interestingly, Yoo et al. have shown the histopathologic confirmation of MF after 12 and 8 weeks of secukinumab (interleukin-17A antagonist) use for psoriasis treatment in two cases [28]. Inhibition of the Th17-mediated immune response may theoretically lead to further immunosuppression and disease progression in CTCL by shifting the Th17/Tregs equilibrium towards Tregs that may play an important role in the pathogenesis of CTLC [28]. However, the major limitation of this study was the non-performance of a baseline skin biopsy before secukinumab initiation, implying that the two patients may have probably suffered from MF instead of psoriasis. Additionally, these patients had failed to respond to other psoriasis treatments before secukinumab, such as apremilast, NB-UVB phototherapy and acitretin. Interestingly, there have also been reported CTCL-like cases triggered by drugs [67]. However, these cases should not be considered true lymphomas, but rather lymphomatoid drug reactions. Their prominent characteristic is that the dermopathy subsides with the withdrawal of the incriminating medication. Therefore, these cases should not be confused with true lymphomas that could be triggered by TNF-α inhibitors [66].

4. Conclusion

Psoriasis and MF are two distinct entities sharing common pathogenetic features associated with the abnormal activation of T-cells. Nonetheless, there is growing evidence that psoriatic patients may develop MF in the course of the disease. Dermatologists should be aware of an elevated risk of CTCL, particularly MF, in patients with psoriasis. To what degree psoriasis itself through chronic immune stimulation, or the medications used for its treatment or comorbidities and lifestyle may play a role in the onset of MF is not yet clear. There is not sufficient evidence to support a causal association between the use of biological therapies and MF in patients with psoriasis. Besides, MF can be an imitator of psoriasis –both clinically and histopathologically– an entity referred to as “psoriasiform MF”. Biopsy of the cutaneous lesions before the introduction of biologics should be incorporated in the clinical practice. Biopsy of the cutaneous lesion should also be performed in the case of appearance of psoriasiform lesions during biologic treatment for autoimmune disorders because this may represent an indolent form of MF. Psoriatic patients with poor or no-response to treatment should be examined thoroughly for MF using immunochemistry and, if necessary, molecular biology techniques. In cases where histologic features of both MF and psoriasis are found, combination treatment should be given addressing both disorders. A large multicentric registry of MF patients who were treated for benign dermatoses (i.e. eczema, psoriasis) with classic immunosuppressive drugs and/or biologics is needed to collect data and further clarify the enigmatic association between psoriasis, MF and immunomodulatory treatment. Finally, larger well-designed prospective studies in patients with histologically confirmed psoriasis are required to elucidate the association between psoriasis, its treatment and MF.

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Declaration of competing interest

No conflict of interest to disclose.

References

[1] Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, Servitje O, Berti E, Ortiz-Romero P, et al. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol 2019;181(2):350–7. https://doi.org/10.1111/bjd.17258.

[2] Biondo G, Cerroni L, Brunasso AMG, Sola S, Cota C, Javor S, Massone C. Risk of mycosis fungoides in psoriatic patients: a critical review. J Eur Acad Dermatol Venereol 2020;34(6):1186–95. https://doi.org/10.1111/jdv.16160.

[3] Papadavid E, Katsimbri P, Kapniari I, Koumaki D, Karamparpa A, Dalamaga M, Tzannis K, Boumpas D, Rigopoulos D. Prevalence of psoriatic arthritis and its correlates among patients with psoriasis in Greece: results from a large retrospective study. J Eur Acad Dermatol Venereol 2016;30(10):1749–52. https://doi.org/10.1111/jdv.1370.

[4] Papadavid E, Dalamaga M, Vlami K, Koumaki D, Gyftopoulos S, Christodoulatos GS, Papiris S, Rigopoulos D. Psoriasis is associated with risk of obstructive sleep apnea independently from metabolic parameters and other comorbidities: a large hospital-based case-control study. Sleep Breath 2017;21(4):949–58. https://doi.org/10.1007/s11325-017-1507-4.

[5] Dalamaga M, Papadavid E. Can we better strategize our choice of pharmacotherapy for patients with co-morbid psoriasis and obesity? Expet Opin Pharmacother 2019;20(11):1303–8. https://doi.org/10.1080/14656566.2019.1603294.

[6] Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. Curr Obes Rep 2020;9(3):165–78. https://doi.org/10.1007/s13679-020-00380-3.

[7] Theodorakopoulou E, Dalamaga M, Katsimbri P, Boumpas DT, Papadavid E. How does the joint dermatology-rheumatology clinic benefit both patients and dermatologists? Dermatol Ther 2020;33(3):e13283. https://doi.org/10.1111/dth.13283.

[8] Korovesi A, Dalamaga M, Kotopouli M, Papadavid E. Adherence to the Mediterranean diet is independently associated with psoriasis risk, severity, and quality of life: a cross-sectional observational study. Int J Dermatol 2019;58(9):e164–5. https://doi.org/10.1111/ijd.14523.

[9] Papadavid E, Ferra D, Koumaki D, Dalamaga M, Stamou C, Theodoropoulos K, Rigopoulos D. Ustekinumab induces fast response and maintenance of very severe refractory scalp psoriasis: results in two Greek patients from the psoriasis hospital-based clinic. Dermatology 2014;228(2):107–11. https://doi.org/10.1159/000357030.

[10] Dalamaga M, Papadavid E, Vlami K. Unmasking the Janus face of the association between psoriasis, metabolic syndrome and obstructive sleep apnea. Sleep Breath 2013;17(2):449–50. https://doi.org/10.1007/s11325-012-0749-4.

[11] Kapniari E, Papadimitriou P, Dalamaga M, Makavos G, Piaserico S, Egeberg A, Ikonomidis I, Papadavid E. Investigating the link between psoriasis and cardiovascular disease: current evidence, therapeutic implications and perspectives. Curr Vasc Pharmacol 2020;18(6):592–609. https://doi.org/10.2174/1570161118666200523154318.

[12] Kapniari E, Dalamaga M, Papadavid E. Comorbidities burden and previous exposure to biological agents may predict drug survival of apremilast for psoriasis in a real-world setting. Dermatol Ther 2020;33(6):e14168. https://doi.org/10.1111/dth.14168.

[13] Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. JAMA Dermatol 2020;156(4):421–9. https://doi.org/10.1001/jamadermatol.2020.0024.

[14] Bellinato F, Gisondi P, Girolomoni G. Risk of lymphohematologic malignancies in patients with chronic plaque psoriasis: a systematic review with meta-analysis. J Am Acad Dermatol 2021. S0190-9622(21)02212-X.

[15] Smedby KE, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A, Sundström C, Akerman M, Melbye M, Glimelius B, Adami HO. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst 2006;98(1):51–60. https://doi.org/10.1093/jnci/djj004.

[16] Ekström K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, Askling J. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 2003;48(4):963–70. https://doi.org/10.1002/art.10939.

[17] Mercer LK, Galloway JB, Lunt M, Davies R, Low AL, Dixon WG, Watson KD, BSRBR Control Centre Consortium, Symmons DP, Hyrich KL. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2017;76(3):497–503. https://doi.org/10.1136/annrheumdis-2016-20938.

[18] Hellgren K, Baecklund E, Backlin C, Sundstrom C, Smedby KE, Askling J. Rheumatoid arthritis and risk of malignant lymphoma: is the risk still increased? Arthritis Rheum 2017;69(4):700–8. https://doi.org/10.1002/art.40017.

[19] Dreyer L, Mellemkjær L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, Hansen TH, Jensen DV, Linde L, Lindegaard HM, Loft AG, Nordin H, Omerovic E, Rasmussen C, Schlemmer A, Tarp U, Hetland ML. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis 2013;72(1):7 9–82. https://doi.org/10.1136/annrheumdis-2012-201969.

[20] Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008;10(2):R45. https://doi.org/10.1186/ar2404.

[21] Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer 2000;88(3):497–502. PMID: 11054684.

[22] Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K, et al. Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project. Ann Rheum Dis 2017;76(12):2025–30. https://doi.org/10.1136/annrheumdis-2017-211623.

[23] Kamstrup MR, Skov L, Zachariae C, Thyssen JP, Egeberg A. Psoriasis and risk of malignant lymphoma: a population-based cohort study. Br J Dermatol 2018;178(6):1435–6. https://doi.org/10.1111/bjd.16245.
[24] Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol 2006;126(10):2194–201. https://doi.org/10.1038/sj.jid.5700410.
[25] Nikolaou V, Papadavid E, Economidi A, Marinos L, Moustou E, Karampidou K, Papadaki T, Stratigos A, Antoniou C. Mycosis fungoides in the era of antitumour necrosis factor-α treatments. Br J Dermatol 2015;173(2):590–3. https://doi.org/10.1111/bjd.13705.
[26] Nikolaou V, Marinos L, Moustou E, Papadavid E, Economidi A, Christofidou E, Gerochristou M, Tasidou A, Economaki E, Stratigos A, Antoniou C. Psoriasis in patients with mycosis fungoides: a clinicopathological study of 25 patients. J Eur Acad Dermatol Venereol 2017;31(11):1848–52. https://doi.org/10.1111/jdv.14365.
[27] Donigan JM, Snowden C, Carter JB, Kimball AB. The temporal association between cutaneous T-cell lymphoma and psoriasis: implications for common biologic processes. J Eur Acad Dermatol Venereol 2016;30(10):e31–2. https://doi.org/10.1111/jdv.1328.
[28] Yoo J, Shah F, Velangi S, Stewart G, Scarisbrick JS. Secukinumab for treatment of psoriasis: does secukinumab precipitate or promote the presentation of cutaneous T-cell lymphoma? Clin Exp Dermatol 2019;44(4):414–7. https://doi.org/10.1111/ced.13777.
[29] Dalamaga M, Karmaniolas K, Matekovits A, Migdalis I, Papadavid E. Cutaneous manifestations in relation to immunologic parameters in a cohort of primary myelodysplastic syndrome patients. J Eur Acad Dermatol Venereol 2008;22(5):543–8. https://doi.org/10.1111/j.1468-3083.2007.02520.x.
[30] Papadavid E, Kapsimali V, Psarra A, Antoniou C, Papasteriadi C, Ekonomidou J, Anagnostou D, Nikolaou V, Kounaki D, Dalamaga M, Bamia C, Stratigos A, Stavrianeas N, Katsambas A. TCRVb repertoire abnormalities in patients with cutaneous T-cell lymphoma. Leuk Lymphoma 2009;50(1):130–2. https://doi.org/10.1080/10428190802526956.
[31] Fletcher CL, Orchard GE, Hubbard V, Whittaker SJ, Edelson RL, Russell-Jones R. CD30(+) cutaneous lymphoma in association with atopic eczema. Arch Dermatol 2004;140(4):449–54. https://doi.org/10.1001/archderm.140.4.449.
[32] Morales MM, Olsen J, Johansen P, Kaerlev L, Guénel P, Arveux P, Wingren G, Hardell L, Ahrens W, Stang A, Llopis A, Merletti F, Villanueva MA. Viral infection, atopy and mycosis fungoides: a European multicentre case-control study. Eur J Cancer 2003;39(4):511–6. https://doi.org/10.1016/s0959-8049(02)00773-6.
[33] Yamaguchi Y, Fujita Y, Hirata Y, Nishimura M, Shinkuma S, Natsuga K, Nomura T, Hida T, Kato N, Shimizu H. Psoriasiform mycosis fungoides masquerading as tumourous plaques. Eur J Dermatol 2017;27(3):295–6. https://doi.org/10.1684/ejd.2017.2971.
[34] Azizpour A, Ghanadan A, Nasimi M, Etesami I. Psoriasiform mycosis fungoides: a rare form of the disease with review of the literature. Dermatol Online J 2017;23(9). 13030/qt9mv8r0j7. PMID: 2946972.
[35] Jinno N, Yamana Y, Kawashima M, Tsunemi Y. Mycosis fungoides with psoriasiform lesions. J Dermatol 2015;42(2):227–9. https://doi.org/10.1111/1346-8138.12749.
[36] Zackheim HS, Koo J, LeBoit PE, McCalmont TH, Bowman PH, Kashani-Sabet M, Jones C, Zehnder J. Psoriasiform mycosis fungoides with fatal outcome after treatment with cyclosporine. J Am Acad Dermatol 2002;47(1):155–7. https://doi.org/10.1067/mjd.2002.120571.
[37] Doukaki S, Aricò M, Bongiorno MR. A rare presentation of mycosis fungoides mimicking psoriasis vulgaris. Case Rep Dermatol 2009;1(1):60–5. https://doi.org/10.1159/000249148.
[38] Papadavid E, Gazi S, Dalamaga M, Stavrianeas N, Ntelis V. Palmoplantar and scalp psoriasis occurring during anti-tumour necrosis factor-alpha therapy: a case series of four patients and guidelines for management. J Eur Acad Dermatol Venereol 2008;22(3):380–2. https://doi.org/10.1111/j.1468-3083.2007.02335.x.
[39] Rademaker M, Rubel DM, Agnew K, Andrews M, Armour KS, Baker C, Foley P, Gebauer K, Goh MS, Gupta M, Marshman G, Prince HM, Sullivan J. Psoriasis and cancer. An Australian/New Zealand narrative. Australas J Dermatol 2019;60(1):12–8. https://doi.org/10.1111/ajd.12889.
[40] Perifani V, Dalamaga M, Theodoropoulos K, Theotokoglou S, Syrmali A, Loumou P, Papadavid E. Real world evidence: patients with refractory pemphigus treated with Rituximab. Metabolism Open 2021;12:100142. https://doi.org/10.1016/j.metop.2021.100142.
[41] Kassi E, Dalamaga M, Faviou E, Hroussalas G, Kazanis K, Nounopoulos Ch, Dionyssiou-Asteriou A. Circulating oxidized LDL levels, current smoking and obesity in postmenopausal women. Atherosclerosis 2009;205(1):279–83. https://doi.org/10.1016/j.atherosclerosis.2008.11.006.
[42] Tsigalou C, Vallianou N, Dalamaga M. Autoantibody production in obesity: is there evidence for a link between obesity and autoimmunity? Curr Obes Rep 2020;9(3):245–54. https://doi.org/10.1007/s13679-020-00397-8.
[43] Argyrakopoulou G, Dalamaga M, Spyrou N, Kokkinos A. Gender differences in obesity-related cancers. Curr Obes Rep 2021;10(2):100–15. https://doi.org/10.1007/s13679-021-00426-0.
[44] Christodoulatos GS, Spyrou N, Kadillari J, Psallida S, Dalamaga M. The role of adipokines in breast cancer: current evidence and perspectives. Curr Obes Rep 2019;8(4):413–33. https://doi.org/10.1007/s13679-019-00364-y.
[45] Spyrou N, Avgerinos KI, Mantzoros CS, Dalamaga M. Classic and novel adipocytokines at the intersection of obesity and cancer: diagnostic and therapeutic strategies. Curr Obes Rep 2018;7(4):260–75. https://doi.org/10.1007/s13679-018-0318-7.
[46] Dalamaga M, Christodoulatos GS, Mantzoros CS. The role of extracellular and intracellular Nicotinamide phosphoribosyl-transferase in cancer: diagnostic and therapeutic perspectives and challenges. Metabolism 2018;82:72–87. https://doi.org/10.1016/j.metabol.2018.01.001.
[47] Dalamaga M, Christodoulatos GS. Adiponectin as a biomarker linking obesity and adiposopathy to hematologic malignancies. Horm Mol Biol Clin Invest 2015;23(1):5–20. https://doi.org/10.1515/hmbci-2015-0016.
[48] Kassi E, Dalamaga M, Hroussalas G, Kazanis K, Merantzi G, Zachari A, Giamarellos-Bourboulis EJ, Dionyssiou-Asteriou A. Adipocyte factors, high-sensitive C-reactive protein levels and lipoxidative stress products in overweight postmenopausal women with normal and impaired OGTT. Maturitas 2010;67(1):72–7. https://doi.org/10.1016/j.maturitas.2010.05.004.
[49] Dalamaga M, Crotty BH, Fargnoli J, Papadavid E, Lekka A, Triantafilli M, Karmaniolas K, Migdalis I, Dionyssiou-Asteriou A, Mantzoros CS. B-cell chronic lymphocytic leukemia risk in association with serum leptin and adiponectin: a case-control study in Greece. Cancer Causes Control 2010;21(9):1451–9. https://doi.org/10.1007/s10552-010-9573-y.
[50] Hroussalas G, Kassi E, Dalamaga M, Delimaris I, Zachari A, Dionyssiou-Asteriou A. Leptin, soluble leptin receptor, adiponectin and resistin in relation to OGTT in overweight/obese postmenopausal women. Maturitas 2008;59(4):339–49. https://doi.org/10.1016/j.maturitas.2008.03.012.
[51] Dalamaga M, Karmaniolas K, Lekka A, Antonakos G, Thrasyvoulides A, Papadavid E, Spanos N, Dionyssiou-Asteriou A. Platelet markers correlate with glycemic indices in diabetic, but not diabetic-myelodysplastic patients with normal platelet count. Dis Markers 2010;29(1):55–61. https://doi.org/10.3233/DMA-2010-0726.
[52] Marouga A, Dalamaga M, Kastania AN, Kroupis C, Lagiou M, Saounatsou K, Dimas K, Vlahakos DV. Circulating resistin is a significant predictor of mortality independently from cardiovascular comorbidities in elderly, non-diabetic subjects with chronic kidney disease. Biomarkers 2016;21(1):73–9. https://doi.org/10.3109/1354750X.2015.1118536.
[53] Dalamaga M, Polyzos SA, Karmaniolas K, Chamberland J, Lekka A, Triantafilli M, Migdalis I, Papadavid E, Mantzoros CS. Fetuin-A levels and free leptin index are reduced in patients with chronic lymphocytic leukemia: a hospital-based case-control study. Leuk Lymphoma 2016;57(3):577–84. https://doi.org/10.3109/10428194.2015.1075523.
[54] Dalamaga M, Karmaniolas K, Chamberland J, Nikolaidou A, Lekka A, Dionyssiou-Asteriou A, Mantzoros CS. Higher fetuin-A, lower adiponectin and free leptin levels mediate effects of excess body weight on insulin resistance and risk for myelodysplastic syndrome. Metabolism 2013;62(12):1830–9. https://doi.org/10.1016/j.metabol.2013.09.007.
[55] Dalamaga M, Polyzos SA, Karmaniolas K, Chamberland J, Lekka A, Migdalis I, Papadavid E, Dionyssiou-Asteriou A, Mantzoros CS. Circulating fetuin-A in patients with pancreatic cancer: a hospital-based case-control study. Biomarkers 2014;19(8):660–6. https://doi.org/10.3109/1354750X.2014.974071.
[56] Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcopenic obesity: epidemiologic evidence, pathophysiology, and therapeutic perspectives. Curr Obes Rep 2019;8(4):458–71. https://doi.org/10.1007/s13679-019-00359-9.
[57] Marouga A, Dalamaga M, Kastania AN, Antonakos G, Thrasyvoulides A, Kontelia G, Dimas C, Vlahakos DV. Correlates of serum resistin in elderly, non-diabetic patients with chronic kidney disease. Clin Lab 2013;59(9–10):1121–8. https://doi.org/10.7754/clin.lab.2012.121112.
[58] Paul CF, Ho VC, McGeown C, Christophers E, Schmidtmann B, Guillaume JC, Lamarque V, Dubertret L. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J Invest Dermatol 2003;120(2):211–6. https://doi.org/10.1046/j.1523-1747.2003.12040.x.
[59] Huen AO, Kim EJ. The role of systemic retinoids in the treatment of cutaneous T-cell lymphoma. Dermatol Clin 2015;33(4):715–29. https://doi.org/10.1016/j.det.2015.05.00.
[60] Fiorentino D, Ho V, Lebwohl MG, Leite L, Hopkins L, Galindo C, Goyal K, Langholff W, Fakharzadeh S, Srivastava B, Langley RG. Risk of malignancy with systemic psoriasis treatment in the psoriasis longitudinal assessment registry. J Am Acad Dermatol 2017;77(5):845–54. https://doi.org/10.1016/j.jaad.2017.07.013.e5.
[61] Nocturne G, Boudaoud S, Ly B, Pascaud J, Paoletti A, Mariette X. Impact of anti-TNF therapy on NK cells function and on immunosurveillance against B-cell lymphomas. J Autoimmun 2017;80:56–64. https://doi.org/10.1016/j.jaut.2017.02.001.
[62] Chupin A, Perduca V, Meyer A, Bellanger C, Carbonnel F, Dong C. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2020;52(8):1289–97. https://doi.org/10.1111/apt.16050.
[63] Papp KA, Poulin Y, Bissonnette R, Bourcier M, Toth D, Rosoph L, Poulin-Costello M, Setterfield M, Syrotuik J. Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J Am Acad Dermatol 2012;66(2):e33–45. https://doi.org/10.1016/j.jaad.2010.07.026.
[64] Gordon K, Papp K, Poulin Y, Gu Y, Rozzo S, Sasso EH. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. J Am Acad Dermatol 2012;66(2):241–51. https://doi.org/10.1016/j.jaad.2010.12.005.
[65] Reich K, Wozel G, Zheng H, van Hoogstraten HJ, Flint L, Barker J. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension

trial (RESTORE2). Br J Dermatol 2013;168(6):1325–34. https://doi.org/10.1111/bjd.12404.

[66] Martinez-Escala ME, Posligua AL, Wickless H, Rutherford A, Sable KA, Rubio-Gonzalez B, Zhou XA, Kaplan JB, Pro B, Choi J, Querfeld C, Rosen ST, Guitart J. Progression of undiagnosed cutaneous lymphoma after anti-tumor necrosis factor-alpha therapy. J Am Acad Dermatol 2018;78(6):1068–76. https://doi.org/10.1016/j.jaad.2017.12.068.

[67] Magro CM, Olson LC, Nguyen GH, de Feraudy SM. CD30 positive lymphomatoid angiocentric drug reactions: characterization of a series of 20 cases. Am J Dermatopathol 2017;39(7):508–17. https://doi.org/10.1097/DAD.0000000000000692.