Dermatology 2008;216:277–278
DOI: 10.1159/000113152

How to Manage Melanoma in a Psoriatic Patient

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Key Words

Psoriasis · Malignant melanoma · Interferon- α · Interferon- γ

Psoriasis concurrence with malignant melanoma (MM) may cause difficulties in disease management as most modalities, especially photochemotherapy, cyclosporin A (Cy-A) and anti-TNF- α agents, are contraindicated and the use of retinoids and methotrexate (MTX) may not always apply to the biochemistry or blood profile of the patients, respectively [1]. Additionally, the therapeutic use of interferon-alpha (IFN- α) for MM can exacerbate autoimmune disorders such as psoriasis or trigger off its onset [2–8]. Recent reports suggest a mechanism through which IFN- α derived from plasmacytoid predendritic cells (PDCs) has a role in this autoimmune downstream. In this article, we report a case of exacerbation of psoriasis due to IFN- α administration and review the current literature.

A 64-year-old man with a recently excised MM from his right sole, presented with exacerbation of his psoriasis after discontinuation of cyclosporin A. The patient became almost erythrodermic after the initiation of IFN- α treatment for his MM. The patient underwent surgical excision of the plantar MM and of regional inguinal lymph nodes. Histopathology showed a stage Clark IV and Breslow 7.4 mm MM, and metastasis was observed in one lymph node.

His medical history included hypertension, hyperlipidemia and chronic plaque psoriasis. His psoriasis dated back over 15 years and involved his scalp, elbows and knees. He was treated with topical treatment and short-term courses of Cy-A 200 mg/day (2.5 mg/kg/day) for the last 3 years which was discontinued immediately after the diagnosis of the fast growing plantar MM. He presented to the Dermatology Department with aggravation of his plaque psoriasis which was initially treated with topical mild steroids and emollients. Psoriasis was stable with mild improvement until IFN- α treatment was started for his MM which exacerbated his psoriasis to almost erythrodermic. The patient

received adjuvant chemotherapy with IFN- α (INTRON-A) 15×10^6 U/m² i.v. $\times$ 5/7 days every week for 4 weeks followed by consolidation for 6 months with a flat dose of IFN- α 10×10^6 s.c. three times weekly. By the 2nd week of i.v. therapy, his psoriasis further exacerbated with additional plaques and finally progressed to erythroderma. Despite psoriasis exacerbation, the patient continued consolidation with IFN- α at a reduced dose of 6×10^6 U s.c. three times weekly, as required. He was started on MTX 7.5 mg/weekly but developed leucopenia, grade 2, during the 3rd week of MTX administration and MTX was discontinued. His treatment was changed to acitretin, initially at a dose of 25 mg/day which subsequently increased to 35 mg/day. After 2 weeks, his psoriasis significantly improved. His cholesterol and triglycerides further increased but were effectively controlled with statins.

A variety of endogenous and exogenous factors may induce or aggravate psoriasis, including drugs. In 1986, Quesada and Guterman [2] reported two cases of exacerbation and new-onset psoriasis during IFN- α treatment for disseminated malignant disease (renal cancer carcinoma) and suggested that interferons may participate in the pathophysiology of psoriasis. Since then, more than 20 cases have been reported with either exacerbation of pre-existing psoriasis or induction of de novo psoriasis as well as psoriatic arthritis after the therapeutic use of IFN- α for different underlying diseases [2–8]. Review of the literature demonstrated that after the first administration of IFN- α , aggravation of psoriasis occurred within the 1st month in patients with preexisting psoriasis and induction of psoriasis was more delayed in patients with no medical history of psoriasis (up to 17 months) [2–8]. Experience from the management of these patients showed that psoriasis improves in cases where IFN- α administration can be discontinued. Additionally, an antipsoriatic treatment is essential in cases where IFN- α cannot be stopped causing several problems in the management of the patients.

IFN- α therapy is also associated with the risk of autoimmune phenomena such as autoimmune thyroiditis, rheumatoid arthritis and Raynaud's and Sjögren's syndromes [9–10]. Whether interferon is causing the autoimmune disorder or unmasking a pre-existing disorder is unclear. Interestingly, it has been recently shown that the appearance of autoantibodies or clinical manifestations of autoimmunity during treatment with IFN- α -2b is associated with statistically significant improvements in relapse-free survival and overall survival in patients with melanoma [11]. Given that psoriasis is now considered an autoimmune disease, it would be interesting to investigate whether exacerbation of psoriasis during IFN- α treatment may be associated with an improved survival.

Psoriasis is a Th1 cell-mediated inflammatory disease affecting the skin of genetically predisposed individuals. Recently, rapid progress has been made towards dissecting cellular and molecular pathways of inflammation that contribute to disease

pathogenesis. The genomic analysis has identified increased expression of many immune-regulating and proinflammatory gene products. Many of these inflammatory genes can be explained by activation of a type 1 pathway in which T helper 1/T cytotoxic 1 cells release IFN- γ upon activation. Secreted IFN- γ subsequently activates signal transducer and activator of transcription 1 which then increases transcription of a large group of immune-related genes. Chronic exposure of cells to IFN- α will also activate most of these inflammation genes expressed in psoriatic plaques [12]. Recently, it has been shown that IFN- α has a major role at the beginning of psoriasis immune pathway through pDC activation [13]. pDCs are present in the inflamed tissue of patients with autoimmune diseases and have a unique ability to secrete large amounts of IFN- α on viral stimulation (through toll-like receptor-7 and toll-like receptor-9) and/or induce an IFN- α -dependent maturation of bystander myeloid DCs with the ability to drive Th1 responses. An accumulation of pDCs has also been shown in psoriatic skin [13].

Exacerbation of psoriasis in genetically predisposed individuals exposed to IFN- α may be explained by the initiation of a Th1 response through an array of inflammation genes similar to those regulated by IFN- γ . On the other hand, taking into consideration the critical role of pDCs and pDC-derived IFN- α in the immune downstream of psoriasis, various new pathways for targeted anti-psoriatic therapies may be developed in the near future. Finally, individual gene characteristics of patients with psoriasis improve the possibilities of pharmacotherapy using pharmacogenomic approaches which could be further stratified in the future according to the subtypes of psoriasis [14].

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