Case Report

An Unusual Dermatological Side Effect of Treatment with Non-Pegylated Alpha-Interferon, Acitretin and Puva Therapy: Pigmented Macules on the Fingers in a Patient with Sézary Syndrome

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Abstract

Sézary syndrome is a cutaneous T-cell lymphoma characterized by the triad of erythroderma, generalized lymphadenopathy, and the presence of Sézary cells in skin, lymph nodes and peripheral blood. A 59-year-old Chinese female presented with erythroderma, palmoplantar keratoderma and enlarged right axillary and epitrochlear lymph nodes. Staging investigations showed extensive involvement of peripheral blood, bone marrow and dermatopathic lymphadenopathy. Our patient was diagnosed with Stage IVA Sézary syndrome. Darkly pigmented macules developed on her fingers after three months of interferon treatment, given in combination with acitretin and PUVA (rePUVA). Biopsy of the pigmented macule showed prominent pigmentary incontinence with numerous melanophages.

Our patient responded partially to combination treatment with non-pegylated interferon, acitretin and PUVA but developed acral pigmentation. This is the first report of acral pigmentation complicating non-pegylated alpha-interferon treatment for Sézary syndrome. The putative mechanism is an increased level of alpha-melanocyte-stimulating hormone (MSH) and MSH receptor.

INTRODUCTION

Sézary syndrome is a cutaneous T-cell lymphoma, characterized by a triad of erythema, generalized lymphadenopathy and presence of Sézary cells in skin, lymph nodes and peripheral blood [1]. This case report serves to raise awareness of an unusual complication of cutaneous acral pigmentation secondary to combination therapy with non-pegylated alpha-interferon, acitretin and photochemotherapy with psoralen and ultraviolet A therapy (PUVA).

CASE PRESENTATION

A 59-year-old Chinese female presented to our centre with erythroderma, palmar and plantar keratoderma, as well as enlarged right axillary and epitrochlear lymph nodes. She had been treated during the preceding six years for presumptive eczema.

Haematological investigations revealed a total white count of 13,000/L with 69.6% lymphocytes. Peripheral blood film showed the presence of 67% of Sézary cells. Flow cytometry revealed CD4/CD8 of 24/1, LDH levels were 687 U/L. Skin biopsies from 2 sites revealed epidermotropism, consistent with the diagnosis of mycosis fungoides. Lymphocytes were present within the epidermis at various levels, and lining the basal layer. The lymphocytes exhibited irregular nuclear outlines, clear perinuclear space and clustering of cells to form Pautrier’s microabscesses (Figure 1). Bone Marrow (BM) aspirate reported increase in CD45+ / CD3+ T cells with aberrant immunophenotype consisting of CD3dim/4dim/7dimorphic/38-/TCRab-dim expression. Blood and BM T cell receptor gamma gene analysis showed a matching clonal T cell population. Computed tomography imaging was done of the thorax, abdomen and pelvis, showing an enlarged left infracavicular lymph node and axillary lymph nodes, with prominent superficial inguinal and external iliac lymph nodes. Lymph node biopsy showed features of...
Central dermatopathic lymphadenopathy, including scattered lymphoid follicles adjacent to the capsule and a massive expansion of the paracortex with focal nodular areas composed of reactive Langerhans cells with associated histiocytes and plasma cells.

Based on the updated International Society of Cutaneous Lymphoma (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) staging and classification [2], our patient has Stage IVA Sézary syndrome with tumor-node-metastasis (TNM) and blood (B) classification of T4, N1, M0, B2 with the presence of reactive lymphadenopathy.

Extracorporeal Photochemotherapy (ECP) was offered to our patient as first-line treatment choice and later, chemotherapy as well as chlorambucil [3]. However, she declined both treatment modalities due to cost and risks involved. She was started on palliative treatment with non-pegylated alpha-interferon injections, oral acitretin (0.3mg/kg/day) and phototherapy with psoralen and ultraviolet A therapy (PUVA) as well as prednisolone (0.3mg/kg/day). Non-pegylated alpha-interferon injections were initially given at 3 MU, initially three times a week, and then increased to five times a week after one month of therapy.

Three months after receiving treatment, the patient developed pigmented macules over acral sites; the left second and third fingers, right second, third, and fifth fingers, and over her lower lip. Longitudinal pigmented bands were also noted over left thumbnail and right third fingernail (Figure 2). Differentials include pigmentation secondary to drugs, melanocytic or vascular lesions. Biopsy from the left second fingertip pigmented macule showed pigmentary incontinence (Figure 3a). Alpha-MSH stain shows diffuse enhanced staining throughout the epidermis (Figure 3b).

We postulate that the pigmentation is most likely due to a combination of factors including non-pegylated alpha-interferon, acitretin, PUVA therapy and skin type. Nevertheless, our patient continued the above combination therapy for treatment of Sézary syndrome with no further progression of pigmentation.

DISCUSSION

Interferons have cytotoxic, antiproliferative and antiviral properties. It has been demonstrated that alpha-interferon is efficacious for all stages of mycosis fungoides and Sézary syndrome [4]. Alpha-interferon in combination with PUVA or retinoids have also been tried in studies with some success [5].

Known side effects of alpha-interferon include flu-like symptoms; leucopenia, anemia, thrombocytopenia and transaminitis [6]. Cutaneous effects include hair loss and discoloration, eczema, itch, dryness, Raynaud’s phenomenon livedo reticularis and vitiligo. Although the adverse events with alpha-interferon are frequent, they usually do not necessitate discontinuation of treatment [7]. To our knowledge, this is the

Hyperpigmentation is a common cutaneous side effect of many drugs, including antibiotics, methyldopa and tricyclic antidepressants. There are less than 40 cases reported worldwide of pigmentation due to pegylated interferon. In a recent review, 21% of patients developed secondary hyperpigmentation during pegylated interferon alfa treatment for chronic hepatitis C virus infection. Pigmentation was seen in the oral mucosal, face and affecting the nails presenting as longitudinal melanonychia [8]. To the best of our knowledge, acral pigmentation due to non-pegylated alpha-interferon used in treatment of Sézary syndrome has not been documented in the literature.

Melanocytes are involved in regulation of constitutive pigmentation and react to various stimuli including alpha-MSH and ultraviolet light. Alpha-MSH binds to MSH receptors, increasing the cytosolic levels of cyclic Adenosine Monophosphate (cAMP) and tyrosinase activity in melanocytes, resulting in transcription of melanogenic genes leading to pigmentation [9].

Interferon is known to modulate and upregulate MSH receptor expression on cells, augmenting melanin pigment production in the presence of MSH [10]. It has been observed that dark skinned patients are at higher risk of pigmented side effects with pegylated-interferon used in treatment of chronic hepatitis C infection. These patients may have higher innate alpha-MSH levels and demonstrate higher serum MSH receptor levels after administration of interferon [11].

We postulate that, in our patient with Fitzpatrick skin type IV, higher endogenous levels of alpha-MSH levels result in increased interferon-induced MSH receptors. Interferon therapy increases the expression of surface MSH receptors and PUVA therapy raises the levels of alpha-MSH levels. This combination of factors resulted in increased production of eumelans and led to acral pigmentation. It is not clear as to why pigmentation with interferon therapy favors certain sites in patients. Nor has it been demonstrated why hyperpigmentation of the face occurred alone while oral mucosal pigmentation was strongly associated with longitudinal melanonychia [8].

The development of acral pigmentation in our patient could have been contributed by the concurrent treatment with PUVA and acitretin. Long term exposure to PUVA has been known to affect the nails presenting as longitudinal melanonychia [8]. The development of perilesional hyperpigmentation over legs and back after acitretin and narrow-band ultraviolet B for psoriasis has been reported [13].

In conclusion, we have described an unusual case of acral pigmentation secondary to a combination of non-pegylated alpha-interferon, acitretin and PUVA therapy and its proposed pathogenetic mechanisms. Benefits of combination therapy outweigh the risks and development of hyperpigmentation should not pose as an indication for discontinuation of treatment.

REFERENCES