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CASE REPORT

Durable Resolution of Severe Psoriasis in a Patient Treated with Pentostatin for Hairy Cell Leukemia: A Case Report

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ABSTRACT

Introduction: Pentostatin (2′-deoxycoformycin) and cladribine (2-chlorodeoxyadenosine) are adenosine analogues widely used to treat lymphoid malignancies, mainly hairy cell leukemia (HCL). Oral or parenteral adenosine analogues have been also used as immunomodulatory agents in multiple sclerosis and in acute graft-versus-host disease.
Case Report: Here, we report the case of a 43-year-old patient with a history of extensive psoriasis who later developed HCL.
Results: The patient had achieved complete remission of both psoriasis and HCL after receiving intravenous infusions of pentostatin. It is worth noting that cladribine has already been reported to treat plaque psoriasis lesions in two patients with HCL and in a third patient with gastric marginal zone B cell lymphoma [1].
Conclusion: We believe that adenosine analogues constitute a promising therapeutic option for moderate to severe psoriasis, especially for severe and refractory psoriasis, as well as for patients with adjacent lymphoid malignancies.

Keywords: Hairy cell leukemia; Pentostatin; Psoriasis

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INTRODUCTION

Psoriasis is a multifactorial, chronic, inflammatory skin disease, often associated with serious medical comorbidities, which has dire consequences for patients' health and quality of life. Dysregulation of the immune system plays a major role in the pathogenesis of psoriasis [1–3] which involves hyperproliferation of the keratinocytes in the epidermis with an increase in the epidermal cell turnover rate. Common therapeutic options include topical treatments such as corticosteroids or phototherapy, as well as systemic treatments including oral retinoids, methotrexate, and cyclosporine, as well as biotherapies [4]. Response to treatment is unpredictable. In several patients, skin lesions

become resistant to treatment over time and serious side effects can occur. Therefore, the development of alternative therapeutic approaches is essential, especially in the case of severe and refractory psoriasis. Here, we report the case of a patient with a past medical history of severe plaque psoriasis who later developed hairy cell leukemia (HCL). Treatment with the pentostatin (2′-deoxycoformycin) adenosine analogue resulted in complete remission of the leukemia as well as total resolution of his skin lesions.

CASE REPORT

Hereby we discuss a case study of 43-year-old man suffering from extensive chronic plaque psoriasis. This work had been conducted in accordance with the Helsinki Declaration. The patient had given his informed consent to participate in this work and to publish his case and lesions photos.

RESULTS

The patient had been referred to our service for his HCL. He had been heavily treated in the past for psoriasis with multiple different consecutive lines of treatment, including topical corticosteroids and phototherapy, which yielded only a partial response, after using topical steroids for almost 20 years, with ultraviolet B light therapy introduced as a multi-session regimen for nearly a year in total, with no stable clinical benefit. The patient had finally refused any further treatment for his refractory psoriasis, manifested at the moment of treatment cessation as pruritic, thickened, and scaly plaques on his forehead, neck, chest, back, ankles, knees, and thighs.

In December 2008, blood tests ordered by his primary care provider revealed a mild thrombocytopenia (77×10^9/l), 5.2×10^9/l WBC including 30% neutrophils, 37% lymphocytes, 8% monocytes, and 13 g/dl hemoglobin. Peripheral blood smears showed 3% abnormal lymphocytes with prominent hair-like projections on the outer surface, highly suggestive of HCL. Similar cells were found also in the bone marrow aspirate and in the biopsy. These cells showed strong positivity for tartrate-resistant acid phosphatase staining. Flow cytometry analysis of the blood and bone marrow samples indicated that 31% and 60% of the cells, respectively, were positive for the following immunophenotype markers: CD19 (65%), CD20 (62%), CD11c (96%), CD103 (98%), FMC7 (98%). Thus, a diagnosis of HCL was established. Physical examination showed an enlarged asymptomatic splenomegaly, later confirmed on the CT scan, but no lymphadenopathy or hepatomegaly. Large plaques of psoriasis were also present especially on the upper and lower limbs (Fig. 1), on the trunk, and the scalp. Vasculitis and autoimmune disorders were excluded. By March 2009, topical corticosteroids were discontinued for his psoriasis. The patient consented to be intravenously treated by the adenosine analogue for his HCL with pentostatin 4 mg/m^2 every 15 days for up to six cycles. However, complete remission of his HCL was achieved after only four cycles, but treatment was continued as programmed (6 cycles, 24 mg/m^2 of accumulative dose).

In April 2009, after only one cycle of pentostatin, the psoriatic lesions started to improve considerably, and complete regression was achieved by June 2009 when the patient received his sixth and last cycle of pentostatin (Fig. 2). The 100-month follow up confirmed that both HCL and psoriasis were in complete remission.

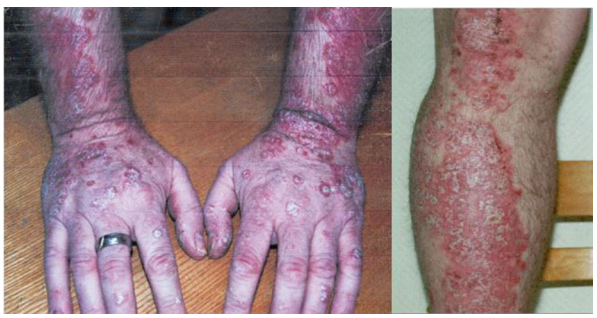

Fig. 1 Patient's upper and lower limbs before Pentostatine treatment. Large plaque psoriasis on upper and lower limbs in March 2009, prior to pentostatin treatment onset

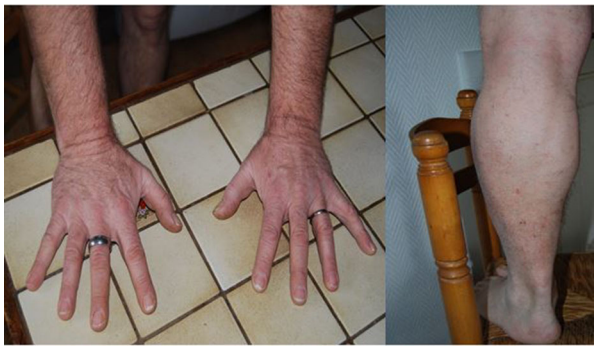

Fig. 2 Patient's upper and lower limbs after pentostatin treatment. Resolution of psoriasis on upper and lower limbs after pentostatin treatment as of September 2009

DISCUSSION

Psoriasis is a chronic inflammatory disease of the skin, for which the pathophysiology is still poorly understood despite many evidences suggesting the implication of genetic and environmental factors [1, 3]. Dysregulation of the immune system is now recognized as a critical event in psoriasis [2]. Complex infiltrates of leukocytes involved in both innate and adaptive immunity have been described in plaque psoriasis in association with the overexpression of a large number of pro-inflammatory cytokines, including TNF-α, IL-1beta, IL-6, IL12/IL23, and IL17. In spite of a large range of therapeutic options, effective treatment for psoriasis can be challenging, in particular for the severe forms. The deeper understanding of the pathophysiology of psoriasis led to the development of new therapeutic agents, targeting TNF-α, the p40 subunit of IL2/IL23R, IL17, and IL17 receptors. Inhibitors of signaling molecules involved in the signaling pathways of number of these cytokine receptors such as JAK are currently under evaluation [4–6]. Yet, these biotherapies may not always be well tolerated and patients respond unequally to these treatments, probably because of genetic variability. Further development of therapeutic agents is needed for refractory and severe psoriasis.

Hairy cell leukemia is a rare B lymphocyte malignancy which is very frequently associated with the BRAFV600E mutation. Vasculitis and autoimmune disorders are frequently observed in HCL patients [7, 8]; however, the association with psoriasis has rarely been reported. The clinical course of HCL has been dramatically improved by the adenosine analogues such as cladribine (2-chlorodeoxyadenosine) and pentostatin. Although the mechanisms of action of these molecules have not been entirely uncovered yet, a number of mechanisms have been postulated [9].

In the case hereby reported, pentostatin acts as a potent inhibitor of adenosine deaminase (ADA) leading to the plasmatic accumulation of deoxyadenosine (dAdo) and adenosine (Ado). In lymphocytes, dAdo is phosphorylated to deoxyadenosine monophosphate (dAMP) and is subsequently converted to deoxyadenosine triphosphate (dATP). Cladribine, the chlorinated derivative of deoxyadenosine is resistant to degradation by ADA and accumulates in lymphocytes as CdATP. Both dATP and CdATP interfere with DNA synthesis and lead to accumulation of DNA strand breaks in lymphocytes, p53 activation, cytochrome c release from mitochondria, and ultimately to cell apoptosis [9]. These mechanisms may explain the sustained severe reduction in circulating lymphocytes in patients treated with purine analogues that may lead to long remission of some lymphocyte-dependent autoimmune diseases and the increased risk of serious infections, including opportunistic infections.

There is increasing evidence that adenosine analogues can be also used as immunomodulatory agents. For instance, cladribine has been shown to inhibit cytokine secretion by T cells [10]. In addition, pentostatin has also been shown to prevent murine marrow allograft rejection [11], and recent studies support the relevant role of oral cladribine in multiple sclerosis treatment by reducing the levels of pro-inflammatory cytokines and of serum and cerebrospinal fluid chemokines. Cladribine has also been reported to reduce adhesion molecule expression and mononuclear cell migration [12]. In our patient, infusions of pentostatin for HCL yielded a rapid and complete resolution of the patient's extensive psoriasis which was later confirmed at the 100-month follow-up. Additionally, no significant side effects occurred. Pentostatin can act through significant

depletion of lymphocytes, in particular the TH1 and TH17 T lymphocyte subsets which have been previously shown to play an important role in psoriasis pathophysiology. However, more specific mechanisms may be implicated in the effectiveness of pentostatin in our patient, such as inhibition of leukocyte migration to skin and inhibition of the secretion of the main cytokines implicated in psoriasis pathophysiology; pentostatin also impairs T effector cell expansion while preserving regulatory T cell populations and function [13]. Efficacy may be also explained by the fact that the $CD8^+$ T cells respond to specific antigen(s) in the psoriatic lesion, helped by $CD4^+$ T cells that are probably also antigen specific, while cladribine, or in our case pentostatin, eliminates them [14–17].

A similar response has been previously reported in two patients with psoriasis who were treated with cladribine for HCL [14–16] and in some patients with psoriatic arthritis [17].

Efficacy and safety of adenosine analogues to treat severe and refractory psoriasis need to be assessed in a larger series of patients, since pentostatin, like many other agents including those used for psoriasis treatment, is known for different toxicities and side effects [18, 19], including hematologic and renal insufficiency, opportunistic infections, nausea, and conjunctivitis. Pentostatin has also been associated with angina and myocardial infarction, heart failure, and acute arrhythmias in patients with predisposing conditions and comorbidities [18–20]. These molecules might also be of interest for the treatment of psoriatic arthritis. Lower doses of pentostatin or cladribine than those prescribed in malignant disorders and use of oral dosage forms of these molecules might been investigated to help decrease the risk of side effects, in particular infections [18–21].

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Compliance with Ethics Guidelines. The patient had given his informed consent to participate in this work and to publish his case and photos of his lesions.

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