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Rituximab therapy for Severe and Persistent Lichenoid drug-reaction

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ABSTRACT

We report on a patient with severe and fixed lichenoid drug-reaction. She did not respond to 2 months treatment with high-dose corticosteroids. Hence, Rituximab was given. One month later, her lesions improved and remained stable for 14 months of follow up.

Keywords: fixed drug reaction, Prednisone, Rituximab.

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INTRODUCTION

A number of uncommon, clinically diverse and poorly understood inflammatory skin diseases are linked by the presence of a set of histopathological elements that have traditionally been referred to as the "lichenoid tissue reaction/interface dermatitis" (LTR/IFD) [1]. The prototypic skin disease in this category is lichen planus. However, the LTR/IFD can also be seen in skin disorders associated with systemic illnesses (lupus erythematosus, HIV, dermatomyositis), and the skin changes of potentially fatal disorders such as graft-versus-host disease, Stevens-Johnson syndrome, and toxic epidermal necrolysis [2]. In 1998, LTR/IFD has been described following drug exposure and has been labeled as lichenoid drug-reaction (LDR) [3]. Fortunately, most LDR disappear after drug withdrawal or following a short course of Corticosteroids [4]. However, our patient had developed severe form of LDR that persisted for months following drug discontinuation and did not improve with Corticosteroids. Based on its mode of action; Rituximab was used and cured our patient.

THE CASE

The patient is a 73-year-old Kuwaiti woman. She had diabetes mellitus and hypertension. She had received a 5-days course of Ciprofloxacin for treatment of urinary tract infection. Few days later; she presented with several erythematous well limited, patches, of varying size, associated to multiples keratotic erythematous papules with erosions covered by hemorrhagic crusts, dispersed to the trunk and limbs with adherent whitish scales. Despite discontinuation of the drug and a 2 weeks course of Prednisone 1 mg/kg/day; she did not improve. On her initial examination; she was conscious and oriented X3. She was afebrile and systemic examination did not show abnormality. All her body was covered with multiple, well-circumscribed hyperkeratotic erythemtous skin lesions covered by hemorrhagic crusts with adherent whitish scales (Fig. 1A). Laboratory investigations; showed normal complete blood counts, urine routine and microscopy, renal and liver profiles as well as serum complements (C3 & C4), IgA level and protein electrophoresis. ANA, anti-ds DNA, ANCA, anti-GBM-antibodies, RA, hepatitis B surface antigen and anti-HCV antibodies were negative.

Chest x-ray, abdominal and pelvic ultrasounds were normal. She was treated with Rituximab 1 g followed by 1 g 2 weeks later. Over the next month; all her keratotic skin lesions had disappeared and she was left only with areas of hyperpigmentation (Fig .1B).

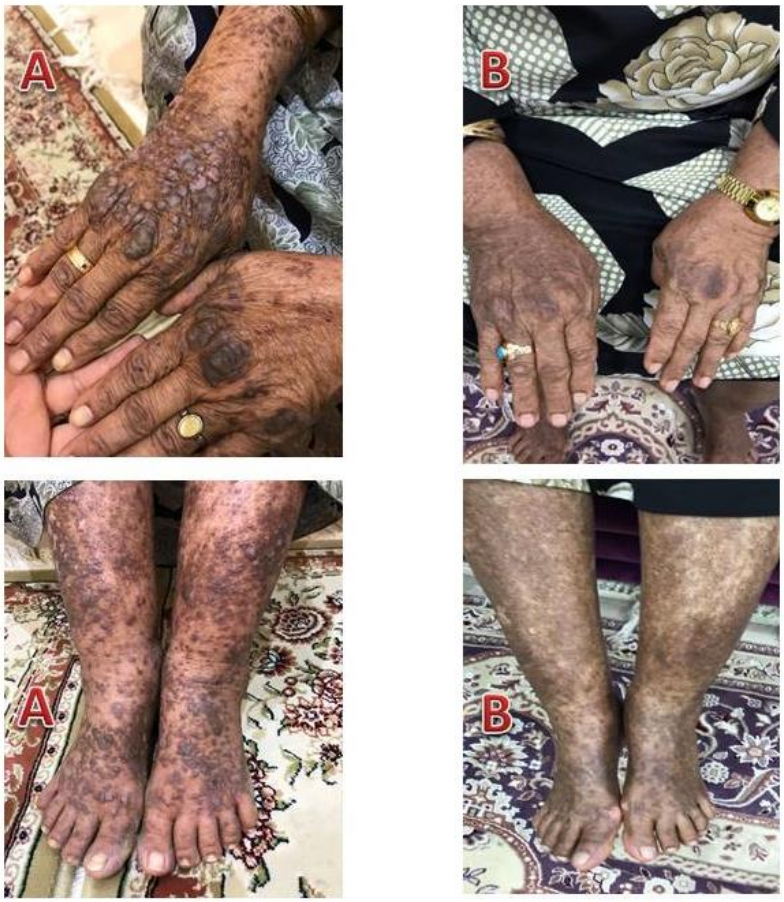

Figure 1 Lichenoid fixed drug reaction before (A) and after (B) treatment with Rituximab

DISCUSSION

Lichenoid drug eruptions have been reported with ACE inhibitors, Beta blockers, Amlodopine, Diliazem, Gold salts, Interferon alpha-2b, Immunoglobulins, Levamisole, Methyldopa, NSAIDs, PPI, Penicillamine, Simvostatins, Carbamazepine, Chloropromazine, Quinine, Tetracycline, Thiazide and anti-tuberculous drugs [2]. Ciprofloxacin is a quinolone antibiotic, which is widely used to treat gram positive and gram negative organisms as well as the anerobes in different parts of the body [5]. Multiple cutaneous reactions to the drug have been reported yet fixed and persistent lichenoid reactions are rare [4]. Clinically, LED is characterized by an extensive symmetric eruption of flat-topped violaceous plaques involving the trunk and extremities. Lesions of LDE are, violaceous papules and plaques, often larger in size, less monomorphic and more prone to be eczematous and associated with desquamation in contrast to that of lichen planus. They often spare the nails, oral and genital mucosae. Also, the absence of Wickham's striae, photodistribution and a temporal association with drug intake help to differentiate the two [6]. Lichenoid drug eruptions usually occur with a latent period of few weeks to several months [4]. Histologically, all the features of lichen planus can be seen in lichenoid drug eruptions, but Clues to the drug-induced etiology include epidermal parakeratosis, absence of wedge-shaped hypergranulosis, transepidermal necrotic keratinocytes, deeper mid-dermal perivascular and peri- adnexal infiltrates, and the presence of eosinophils [7]. Our patient exhibited 5 unique features viz. (a) an acute onset after drug use (b) lichenoid features (c) persistent severe lesions (d) refractoriness even to systemic Corticosteroid-therapy, and (e) long-lasting remission after Rituximab treatment. To our knowledge, the pathogenesis of lichenoid drug eruptions is a cytotoxic T-cell mediated autoimmune damage to basal keratinocytes that are altered by the drug. The drug acts as hapten, binding to keratino/melanocytes producing an antibody-dependent suppressor/cytotoxic T-cell lymphocytes attack of the drug-altered epidermal cells leading to the eruption [8]. At the same time, cutaneous memory T-lymphocytes is recruited and amplify the allergic reaction in future exposure [9]. Moreover, amplification of such pathway involve the actions of plasmacytoid dendritic cell-derived IFN-alpha [8]. Resolution of the rash occurs once these altered keratinocytes are cleared [10]. Those were the basis of the use Rituximab in our patient. The drug is a chimeric human/mouse monoclonal antibody that was approved in USA since 1997 for treatment of non-Hodgkin lymphoma and recently for severe rheumatoid arthritis and glomerulopathy [11]. The drug binds to CD20 antigen expressed on normal differentiated B-lymphocytes and pre-B-cells. Unlike other murine monoclonal antibodies to CD20, R persists in the circulation for long- periods, rarely generates human anti-mouse antibodies and interacts with human effector cells including T-lymphocytes. The latter is though inhibition of antigen-presenting to the T-cells [12, 13]. The benifical effect of R is via suppression of antigen-presentation followed by inhibition of T-cell recruitment, blockage of the amplification pathway of IFN-alpha and finally its long-term effect by suppression B-memory cell expansion [14].

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