

Medical Center, Jerusalem, Israel (Molho-Pessach, Zlotogorski); Faculty of Medicine, Hebrew University, Jerusalem, Israel (Gordon); Jenin Health Directorate, Palestinian Ministry of Health, Palestinian Authority, West Bank (Jaradat).

**Corresponding Author:** Abraham Zlotogorski, MD, Department of Dermatology, Hadassah-Hebrew University Medical Center, Kiryat Hadassah, POB 12000, Jerusalem, 9112001, Israel (zloto@cc.huji.ac.il).

**Published Online:** February 22, 2017. doi:10.1001/jamadermatol.2016.5705

**Conflict of Interest Disclosures:** None reported.

1. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620-628.
2. Imafuku S, Honma M, Okubo Y, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from phase III open-label multicenter Japanese study. *J Dermatol*. 2016;43(9):1011-1017.
3. Rossi-Semerano L, Piram M, Chiaverini C, De Ricaud D, Smahi A, Koné-Paut I. First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. *Pediatrics*. 2013;132(4):e1043-e1047.
4. Arakawa A, Ruzicka T, Prinz JC. Therapeutic Efficacy of Interleukin 12/Interleukin 23 Blockade in Generalized Pustular Psoriasis Regardless of IL36RN Mutation Status. *JAMA Dermatol*. 2016;152(7):825-828.
5. Yilmaz SB, Cicek N, Coskun M, Yegin O, Alpsoy E. Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. *Arch Dermatol Res*. 2012;304(6):465-469.
6. Carrier Y, Ma HL, Ramon HE, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. *J Invest Dermatol*. 2011;131(12):2428-2437.

### Focal Pegylated Liposomal Doxorubicin-Induced Urticarialike Reaction at Cutaneous Transformed Sézary Lesions

Pegylated liposomal doxorubicin (PLD) is a commonly used treatment for advanced stages of cutaneous T-cell lymphoma (CTCL). We report a case of transient focal PLD-induced urticarial lesions in a patient with Sézary syndrome (SS) located exclusively on transformed Sézary lesions. To our knowledge, this is the first report of focal PLD-related urticarial reaction overlying CTCL.

**Case Report** | A 35-year-old woman was seen for a worsening pruritic eczematous eruption that had recently become erythrodermic. Punch biopsies showed lymphocytes with hyperconvoluted nuclei along the basal layer and in the upper dermis. Further studies revealed circulating Sézary cells (1080/mm<sup>3</sup>), a high CD4/CD8 ratio (23.6), and identical T-cell clones in blood and skin. The diagnosis of SS was confirmed, and the patient was started on treatment with interferon alfa, then with bexarotene, both concomitantly with extracorporeal photopheresis, with minimal improvement.

Treatment with mogamulizumab was then begun, and after initial clinical and hematological improvement, thick infiltrated plaques appeared on the face and scalp with more than 30% large lymphocytes found on histologic analysis, which was compatible with a cutaneous localization of a transformed SS lesion. Treatment was then started with intravenous PLD (Caelyx; Janssen Inc), a 2-hour infusion at 1 mg/min, 40 mg/m<sup>2</sup>, every 2 weeks, and the first infusion was completed without incident. However, 10 minutes after the start of the second infusion, the patient experienced edematous urticarial lesions limited to sites overlying the preexisting SS plaques (Figure 1), with no systemic

**Figure 1. Focal Urticarialike Lesions Overlying Lesions of Transformed Sézary Syndrome on the Face**



Edematous urticarial lesions are limited to sites overlying the transformed Sézary syndrome plaques; they appeared 10 minutes after the second infusion of pegylated liposomal doxorubicin.

manifestation. The infusion was immediately stopped, and the patient was treated with oral antihistamine, leading to complete disappearance of the edematous reaction within 30 minutes. Treatment with PLD was resumed the same day but at a slower infusion rate and with no complications. Neither edema nor any other adverse effect was observed during the following infusions that were also all performed at a reduced perfusion rate. Treatment with PLD resulted in clinical improvement of the SS plaques (Figure 2).

**Discussion** | Pegylated liposomal doxorubicin is an effective treatment for refractory, advanced, or transformed CTCL and has a better toxic effect profile than free doxorubicin.<sup>1,2</sup> We describe here the first case to our knowledge of focal PLD-induced urticarial reaction overlying CTCL. Pegylated liposomal doxorubicin is a formulation of doxorubicin encapsulated in liposomes that acts by (1) intercalation into DNA and (2) generation of free radicals, thus triggering apoptotic pathways through ubiquitin-proteasomal degradation and Bcl-2 down-regulation.<sup>3</sup> Even though acute hypersensitivity infusion reactions have been reported in up to 9% of patients receiving PLD,<sup>1</sup> immediate urticarial reactions to PLD developing over tumor lesions have never been described before to our knowledge.

The mechanism of the urticarialike reaction observed in the present case does not seem to be allergic because it was

**Figure 2. Clinical Improvement After Treatment With Liposomal Doxorubicin at a Reduced Perfusion Rate**



After 2 months of treatment with pegylated liposomal doxorubicin, the lesions at the transformed Sézary syndrome sites have disappeared.

observed solely during a single PLD infusion. In fact, PLD-induced skin toxic effects have been shown to be caused by apoptosis of human keratinocytes through the mitochondrial death pathway.<sup>4</sup> Pegylated liposomal doxorubicin might also activate macrophages, release proinflammatory cytokines, and increase blood vessel permeability exclusively in tumor lesions. Both reactive oxygen species generation and cytokine release might explain the focal urticarialike reaction observed in the present case.

During initial phase 1 studies of PLD, microvessel density and smaller tumor size were found to correlate with the degree of liposomal accumulation<sup>3,5</sup>; hence, the rapid onset of the urticarial reaction in our case might be due to the preexisting small tumor size and to its high vascularization. Similar urticarial reactions to rituximab developing over tumor lesions of primary cutaneous B-cell lymphoma have been similarly described. The efficacy of rituximab in these reported cases and the clinical and hematological improvement in our case suggest that this local reaction could forecast a positive response to both drugs.<sup>6</sup>

In conclusion, the exact mechanism of this reaction is still not fully understood, but we believe it could be probably due

to an antitumor effect at the sites of CTCL rather than the occurrence of a hypersensitivity reaction. This reaction is not severe and should not lead to an interruption of PLD; treatment can be performed safely at slower infusion rates. Further cases of PLD-treated patients are needed to better understand the underlying mechanisms and the prognostic value of these urticarial reactions.

Roger Haber, MD  
Caroline Ram-Wolff, MD  
Pauline Laly, MD  
Martine Bagot, PhD

**Author Affiliations:** Department of Dermatology and Venereology, Université Paris 13, Bobigny, Saint Louis Hospital, Paris, France.

**Corresponding author:** Roger Haber, MD, Department of Dermatology, Saint Louis Hospital, One Ave Claude Vellefaux, Paris 75010, France (roger.haber@net.usj.edu.lb).

**Published Online:** March 29, 2017. doi:10.1001/jamadermatol.2017.0038

**Conflict of Interest Disclosures:** None reported.

**Additional Contributions:** We thank the patient for granting permission to publish this information.

1. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sézary syndrome. *Arch Dermatol*. 2008;144(6):727-733.
2. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. *J Clin Oncol*. 2012;30(33):4091-4097.
3. Solomon R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal doxorubicin. *Clin Lymphoma Myeloma*. 2008;8(1):21-32.
4. Luanpitpong S, Chanvorachote P, Nimmannit U, et al. Mitochondrial superoxide mediates doxorubicin-induced keratinocyte apoptosis through oxidative modification of ERK and Bcl-2 ubiquitination. *Biochem Pharmacol*. 2012;83(12):1643-1654.
5. Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. *Clin Pharmacokinet*. 2003;42(5):419-436.
6. Rey J, Wickenhauser S, Ivanov V, Coso D, Gastaut JA, Bouabdallah R. A case of rituximab-related urticarial reaction in cutaneous B-cell lymphoma. *J Eur Acad Dermatol Venereol*. 2009;23(2):210.

### Lamellar Ichthyosis in Sub-Saharan Africa: Social Stigmatization and Therapeutic Difficulties

Ichthyoses are a heterogeneous group of monogenic diseases of keratinization characterized clinically by the presence of scales on the surface of the skin.<sup>1</sup> The clinical manifestations of lamellar ichthyosis may complicate the medical and psychosocial care of the patient.<sup>2</sup> In sub-Saharan Africa, this chronic condition occurring in children causes concern about their social inclusion because of beliefs related to the clinical appearance. These children are often called “snake children.” We report 3 cases of pediatric lamellar ichthyosis in sub-Saharan Africa involving difficulties in school and social integration.

**Cases 1 and 2 |** A pair of twins aged 11 months were hospitalized in a state of malnutrition. The twins had been born as collodion babies, and the appearance of the skin had gradually changed into a scaly condition. The parents were cous-