

Correspondence

Acid citrate dextrose extracorporeal photopheresis is an alternative treatment option for patients with heparin allergy

Extracorporeal photopheresis (ECP) is used as an immunomodulating therapy for treatment of patients with Sézary syndrome, a leukemic variant of cutaneous T-cell lymphoma. ECP is a leukapheresis-based therapy where patients' mononuclear cells are treated with 8-methoxypsoralen (8-MOP) *ex vivo* and are then irradiated with ultraviolet A before reinfusion.¹

Here, we report on a 58-year-old female patient who was successfully treated with ECP due to a Sézary syndrome, stage IVA2, since June 2009. After the 65th cycle of ECP treatment (every 2–4 weeks) with a THERAKOS™ UVAR XTS® Photopheresis System Instrument (Therakos, West Chester, PA, USA), the patient complained for the next four cycles of an urticarial as well as maculopapular exanthema on the integument, which was associated with itching especially after ECP treatment (see Fig. 1). To exclude a disease progress or a drug-related skin reaction, a biopsy was taken. Histological findings of perivascular and interstitial infiltration predominated by lymphocytes with eosinophils in the superficial dermis indicated a drug-mediated skin eruption. As the patient did not take any medication that could be an obvious trigger, we postulated a compound used during the ECP treatment of triggering an allergic reaction. To determine the cause of the allergic reaction, we performed prick, scratch, intracutaneous, and epicutaneous provocations seven weeks after the exanthema was diagnosed. We utilized the original compound formulations used during the ECP treatment (heparin and 8-MOP). A positive reaction of nadroparin-sodium, heparin-sodium, and danaparoid-sodium was seen after 15 minutes in the intracutaneous provocation. Negative results were obtained for methoxypsoralen 0.001%. No eczematous reactions could be seen after 24 hours to 8 days after test exposure. Owing to the positive test result, the diagnosis of a hypersensitivity induced by heparin during ECP was made.

Heparin belongs to the class of glycosaminoglycans, which are polysaccharides widespread in vertebrates, including humans. Polyvalent anions such as heparin-binding protein are able to lead to sensitization. Most cutaneous hypersensitivity reactions to heparin are noticed one week after initiation of anticoagulant treatment, but most of them are caused by a subcutaneous heparin administration. Delayed hypersensitivity reactions induced

by heparins occur in 7.5% of the treated patients,² and potential cross-reactivity between the different heparins can be seen.³ Risk factors such as female sex, older age, pregnancy, or prolonged exposure have been documented.^{4–6} Several reports in the past have shown that intravenous heparin treatment is tolerable despite patients with type IV hypersensitivity responses towards subcutaneous injected heparin.^{5,7} Hirudins (lepirudin or desirudin), low molecular weight heparins, or fondaparinux might also be good alternatives in case of heparin allergy.^{2–6}

For treatment with ECP, we had to find an alternative anticoagulation protocol. Acid citrate dextrose solution A (ACD-A) is a commonly used anticoagulant in many apheresis procedures, such as plasma exchange, but has been less commonly used in ECP as the manufacturer of the equipment widely used to perform these procedures has not received clearance from the US Food and Drug Administration for the use of citrate with the device.^{8,9} The most reported side effect of ACD-A is an acute hypocalcemia. Symptoms of hypocalcemia can be controlled by a decrease of infusion rate and by calcium supplementation.

Nedelcu *et al.* performed 94 ECP procedures on five patients using ACD-A as the anticoagulant and reported no significant complications.⁹ Our patient successfully received eight ECP treatment cycles (every 3–4 weeks) with ACD-A and tolerated the procedure without any complications. To our knowledge, there are no studies comparing response rates to therapy in patients treated with ECP utilizing heparin versus those utilizing ACD-A. In addition, there are no published comparisons of



Figure 1 Urticarial, maculopapular exanthema on the integument after extracorporeal photopheresis

heparin versus ACD-A with regard to the content of the collections nor the effects of the 8-MOP/photoactivation. Because of the lack of understanding of the mechanism of treatment, it is impossible to say whether the use of citrate may adversely affect efficacy.

In conclusion, our case of a hypersensitivity induced by heparin during ECP treatment shows that an alternative protocol with ACD-A as anticoagulant is a workable alternative.

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Recurrent extramammary Paget's disease with an unusual histopathological finding

Extramammary Paget's disease (EMPD) is a malignant neoplasm with a predilection for the apocrine-rich skin; due to this, the apocrine gland has been proposed as its origin.¹ EMPD of the axilla is infrequent, and it has been reported only in few clinical cases.²

A 77-year-old woman, who presented with PD on her left axilla two years before, which was treated with complete excision, arrived at our consult with a 4 mm diameter erythematous plaque around a previous surgical scar (Fig. 1). A mammography showed no abnormal findings. An incisional biopsy showed an intraepidermal neoplasm composed of nests and individual cells in an irregular epidermis accompanied by hyperkeratosis. The cells were round with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. There was pagetoid

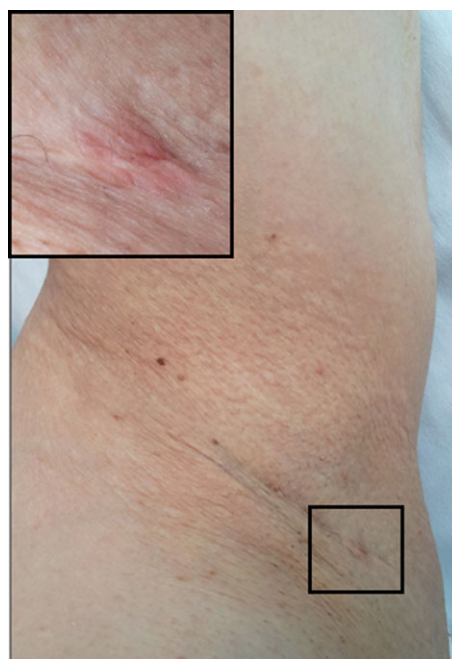


Figure 1 Erythematous plaque on left axilla