Anaphylaxis following administration of extracorporeal photopheresis for cutaneous T cell lymphoma

Jessica Tran[1,2], Lisa Morris[3], Alan Vu[4], Sampreet Reddy[1], Madeleine Duvic[1]

Affiliations: [1]Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]Baylor College of Medicine, Houston, Texas, USA, [3]University of Missouri Columbia School of Medicine, Columbia, Missouri , USA, [4]University of Texas McGovern Medical School, Houston, Texas, USA

Corresponding Author: Madeleine Duvic MD, Department of Dermatology, The University of Texas MD Anderson Cancer Center, Unit 1452, 1515 Holcombe Boulevard, Houston, TX 77030, Tel: 713-792-6800, Email: mduvic@mdanderson.org

Abstract

Extracorporeal photopheresis is a non-invasive therapy used for the treatment of a range of T cell disorders, including cutaneous T cell lymphoma. During extracorporeal photopheresis, peripheral blood is removed from the patient and the white blood cells are separated from whole blood via centrifugation. The white blood cells are exposed to psoralen (a photosensitizing agent) and ultraviolet A radiation, causing cell apoptosis. The apoptotic leukocytes are subsequently re-infused into the patient, resulting in the production of tumor suppressor cells and clinical improvement. Extracorporeal photopheresis is generally regarded as safe with few side effects. We report a dermatology patient who developed anaphylaxis after receiving extracorporeal photopheresis for the treatment of leukemic mycosis fungoides. We suspect that our patient's anaphylaxis resulted from exposure to an agent used in extracorporeal photopheresis.

Keywords: extracorporeal photopheresis, anaphylaxis, cutaneous T cell lymphoma, mycosis fungoides, ethylene oxide, psoralen, heparin

To the Editor:

Extracorporeal photopheresis (ECP) is a non-invasive therapy used for the treatment of a range of T cell-mediated disorders, including erythrodermic cutaneous T cell lymphomas (CTCL), graft-versus-host disease, pemphigus vulgaris, systemic sclerosis, rheumatoid arthritis, and multiple sclerosis [1,2]. Extracorporeal photopheresis involves: (i) removing peripheral blood from a patient, (ii) separating the white blood cells from whole blood by centrifugation, (iii) adding psoralen, a photosensitizing agent, to the white blood cells, (iv) exposing the white blood cells to ultraviolet A (UVA) radiation, and (v) re-infusing the treated white blood cells to the patient [3]. The re-infusion of apoptotic leukocytes triggers an immune response resulting in production of CD8+ tumor suppressor cells in CTCL [3]. Extracorporeal photopheresis is generally regarded as safe with few side effects [3]. We report a dermatology patient who developed anaphylaxis after receiving ECP for the treatment of mycosis fungoides, the most common form of CTCL. To our knowledge, this is the first reported case of anaphylaxis in a patient receiving ECP. Anaphylaxis is a serious, life-threatening condition. Therefore, dermatologists should be aware of the potential risk of anaphylaxis prior to prescribing ECP and should advise patients to seek treatment immediately if symptoms of anaphylaxis occur following treatment. We suspect that our patient's anaphylaxis resulted from exposure to: (i) ethylene oxide used to sterilize the ECP procedure kit, (ii) psoralen added to the buffy coat, and/or (iii) heparin administered during ECP.

A 35-year-old woman presented for management of biopsy-proven stage IB mycosis fungoides in 2015. She first noticed pruritic skin lesions on her trunk and legs during her pregnancy in 2009. The patient was initially diagnosed with atopic dermatitis and was treated with topical steroids without improvement. Owing to the progression of her skin lesions, multiple

skin biopsies were performed in January 2015. Histopathology of these skin biopsies were consistent with mycosis fungoides, and monoclonal T cell receptor gene rearrangement analysis was positive for beta-chain gene rearrangement. Flow cytometry, lymph node biopsy, and CT scan of the chest, abdomen, and pelvis were each negative for evidence of lymphoma. The patient showed no improvement to multiple different therapies, including narrow-band ultraviolet B light therapy, acitretin, methotrexate, topical clobetasol, and intramuscular triamcinolone acetonide.

The patient was subsequently referred to MD Anderson Cancer Center for further workup and management. On presentation, physical examination demonstrated diffuse erythema and scaling involving 74.75% body surface area (BSA) with areas of sparing on the abdomen, chest, thighs, hands, and lower legs. She had palpable bilateral axillary and inguinal lymphadenopathy. Flow cytometry demonstrated evidence of blood involvement (<1,000 Sézary cells/mm^3) and fine needle aspiration of the right inguinal lymph node demonstrated lymph node involvement. The patient was re-staged to IVA2. For religious reasons, she declined a stem cell transplant. Extracorporeal photopheresis was prescribed for the patient.

Extracorporeal photopheresis was performed on the patient with the THERAKOS® CELLEX® Photopheresis System utilizing psoralen, heparin, and an ethylene oxide-sterilized THERAKOS® CELLEX® procedural kit. Within 30 minutes of her first ECP session, the patient developed a pruritic, erythematous rash and swelling of her throat. Approximately one hour following treatment, she began to experience nausea and swelling of the eyelids, lips, and uvula. A diffuse urticarial eruption was present by the next day (**Figure 1**), when she presented for her second ECP session. She denied any changes in medications or diet that may have caused the reaction. Intravenous (IV) diphenhydramine and two doses of IV hydrocortisone were immediately administered. In the setting of persistent throat swelling and urticaria, she also received oral prednisone and was prescribed oral methylprednisolone. The patient was advised to present to the emergency department if she developed trouble breathing or further progression of the urticaria. Three days later, the patient present to the emergency department for persistent urticaria and intense pruritus. In the emergency department, she was given an additional dose of IV diphenhydramine as well as lorazepam for anxiety. She was discharged with oral hydroxyzine. Given the patient's anaphylactic reaction, ECP was discontinued indefinitely.

Thereafter, the patient received total skin electron beam therapy (20Gy over three weeks) which resulted in near complete remission. Within two months of beginning total skin electron beam therapy, she had 0% BSA involvement and no pruritus.

To our knowledge, this is the first report of a patient experiencing anaphylaxis secondary to ECP. Although the definitive cause of our patient's anaphylactic reaction remains unknown, there have been reports of allergic reactions to agents used in ECP such as ethylene oxide [4,5], psoralen [6], and heparin [7]. Although allergen sensitization typically occurs before an episode of anaphylaxis, the reaction can occur on first known exposure to an allergen.

Ethylene oxide is a surface disinfectant commonly used to sterilize heat-sensitive medical equipment, such as the procedural kits used in ECP [4]. Acute hypersensitivity reactions have been observed in patients undergoing hemodialysis using ethylene

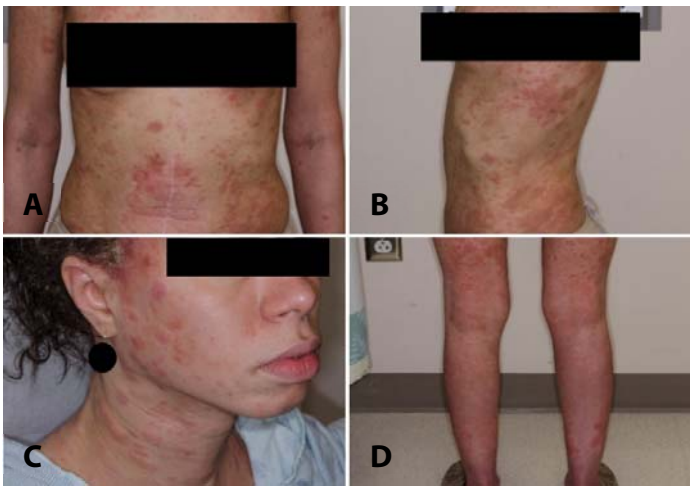

Figure 1. *Clinical images of patient's diffuse urticarial reaction on the **A)** anterior trunk, **B)** left flank, **C)** face, and **D)** posterior thighs and lower legs.*

oxide-sterilized equipment [5,8,9]. In one clinical study, the replacement of ethylene oxide-sterilized material with gamma-irradiated material resulted in clinical improvement of symptoms within three months and reduced levels of IgE antibodies to ethylene oxide [9]. Moreover, there has been a reported case of a patient who developed generalized, severe pruritus while undergoing ECP for CTCL [4]. The adverse reaction began approximately 20 minutes after the initiation of ECP and persisted for three days [4]. This pruritic eruption occurred following each of the patient's 19 ECP sessions [4]. Blood samples from the patient revealed IgE antibodies to ethylene oxide, leading to the belief that the cause of the reaction was an IgE-mediated type 1 allergic reaction to ethylene oxide [4]. In our patient, ECP was administered using a photopheresis procedure kit sterilized with ethylene oxide.

An allergy to psoralen may have also been a trigger for anaphylaxis in our patient. Anaphylaxis has been reported in patients undergoing UVA treatment with psoralen derivatives such as 5-MOP or 8-MOP [6]. Extracorporeal photopheresis utilizes psoralen and UVA irradiation to photoactivate and damage leukocytes [2].

Lastly, ECP requires the administration of an anticoagulant. Heparin is classically used as the anticoagulant of choice for ECP [10]. Allergic reactions to anticoagulants such as heparin, although uncommon, have been reported [7]. Although allergic reactions to heparin typically manifest as erythematous eruptions and maculopapular rashes, there have been reported instances of anaphylactic reactions [7].

Given the prior reports of allergic reactions to each of ethylene oxide, psoralen, and heparin, we believe that these agents may have individually or together contributed to our patient's anaphylactic reaction. Because of the previously observed acute hypersensitivity reactions to ethylene oxide with other procedures, we believe that the ethylene oxide used to sterilize the ECP procedural kit was the most likely cause of our patient's anaphylactic reaction.

To our knowledge, there have been no previous reports of patients experiencing anaphylactic reactions from ECP. Although the definitive cause of anaphylaxis in our patient remains unknown, the temporal relationship between administration of ECP and the development of anaphylaxis in our patient leads us to believe that one or more of the components of ECP likely contributed to this reaction. Anaphylaxis is a serious, life-threatening condition. Therefore, dermatologists should be aware of the potential risk of anaphylaxis prior to performing ECP and should advise patients to immediately seek treatment if symptoms of anaphylaxis occur during or following ECP. Additional research is required to further characterize the association between ECP and the development of anaphylaxis.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Arora S, Setia R. Extracorporeal photopheresis: Review of technical aspects. *Asian J Transfus Sci.* 2017;11:81–6. [PMID: 28970672].
2. Heald PW, Edelson RL. Photopheresis for T cell mediated diseases. *Adv Dermatol.* 1988;3:25–40. [PMID: 3152822].
3. Knobler R, Berlin G, Calzavara-Pinton P, et al. Guidelines on the use of extracorporeal photopheresis. *J Eur Acad Dermatol Venereol.* 2014;28 Suppl 1:1–37. [PMID: 24354653].
4. Georgieva J, Steinhoff M, Orfanos CE, Treudler R. Ethylene-oxide-induced pruritus associated with extracorporeal photochemotherapy. *Transfusion.* 2004;44:1532–3. [PMID: 15383029].
5. Lemke HD, Heidland A, Schaefer RM. Hypersensitivity reactions during haemodialysis: role of complement fragments and ethylene oxide antibodies. *Nephrol Dial Transplant.* 1990;5:264–9. [PMID: 2113222].
6. Legat FJ, Wolf P, Kränke B. Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol.* 2001;145:821–2. [PMID: 11736909].
7. Leguísamo S, Castaño MP, Saavedra MP, Cimbollek S. Recurrent Anaphylaxis Due to Enoxaparin. *J Investig Allergol Clin Immunol.* 2015;25:297–9. [PMID: 26310046].
8. D'Ambrosio FP, Savica V, Gangemi S, et al. Ethylene oxide allergy in dialysis patients. *Nephrol Dial Transplant.* 1997;12:1461-3. [PMID: 9249786].
9. Cavaillon JM, Poignet JL, Fitting C, Delons S, David B. Reduction of allergic reactions in patients undergoing long-term hemodialysis.

J Allergy Clin Immunol. 1993;92:355–7. [PMID: 8349945].

10. Nedelcu E, Ziman A, Fernando LP, et al. Exclusive use of acid citrate dextrose for anticoagulation during extracorporeal photopheresis in patients with contraindications to heparin: an effective protocol. *J Clin Apher*. 2008;23:66–73. [PMID: 18286495].