Case Reports in Oncology

Case Rep Oncol 2011;4:526–530
DOI: 10.1159/000334233

Published online:
October 26, 2011

ISSN 1662–6575
www.karger.com/cro

Cremophor-Induced Lupus Erythematosus-Like Reaction with Taxol Administration: A Case Report and Review of the Literature

Anthony Q. Pham David Berz Patricia Karwan
Gerald A. Colvin

Rhode Island Hospital, Providence, R.I., USA

Key Words
Cremophor EL · Cutaneous lupus erythematosus · Taxol · Paclitaxel

Abstract
We report the first case of Cremophor EL-induced cutaneous lupus erythematosus-like reaction in a 40-year-old female undergoing treatment for breast cancer. There have been four reported cases of paclitaxel- and four cases of docetaxel-induced cutaneous lupus reactions in the published literature [Dasanu and Alexandrescu: South Med J 2008;101:1161–1162; Adachi and Horikawa: J Dermatol 2007;34:473–476; Lortholary et al: Presse Med 2007;36:1207–1208; Chen et al: J Rheumatol 2004;31:818–820]. Our patient developed findings of a cutaneous lupus-like reaction with administration of paclitaxel which was subsequently discontinued. She was re-challenged with albumin-bound paclitaxel which has no Cremophor EL compound in its formulation. This administration of albumin-bound paclitaxel did not induce further reaction. She did not develop a cutaneous lupus erythematosus-like reaction with three other subsequent administrations of albumin-bound paclitaxel. The diagnosis of lupus-like reaction in our patient was made based on the development of a malar butterfly rash sparing the nasolabial folds, the appearance of this rash in context of recently receiving treatments with paclitaxel, resolution of the rash after discontinuing the paclitaxel, and the presence of autoimmune antibodies in the patient's serum which resolved with discontinuation of the paclitaxel. This is the first case demonstrating that the cause of the cutaneous lupus erythematosus-like reaction is not likely due to the taxane component of paclitaxel but the chemical composition of Cremophor EL. If the chemotherapeutic agent was causing the reaction then the same reaction should be seen by albumin-bound paclitaxel. We propose that previously reported lupus reactions may actually be due to Cremophor EL, which consists of polyoxyethylated castor oil, and not the chemotherapeutic agent itself.

Anthony Q. Pham, MD

Rhode Island Hospital
593 Eddy Street
Providence, RI 02903 (USA)
Tel. +1 401 444 5396, E-Mail apham@lifespan.org

Case Rep Oncol 2011;4:526–530
DOI: 10.1159/000334233

Published online:
October 26, 2011

ISSN 1662–6575
www.karger.com/cro

Introduction

Paclitaxel is a commonly administered chemotherapeutic agent, most often used in the treatment of breast, lung, and ovarian malignancies. It is derived from the bark of the Pacific yew tree and exerts its chemotherapeutic effect by preventing microtubule breakdown causing cell death [5]. The hydrophobic nature of paclitaxel significantly limited its widespread use until the formulation using Cremophor EL was utilized in order to enhance the solubility of the drug [6, 7]. Cremophor EL is composed of polyoxyethylated castor oil in 50% ethanol which enables paclitaxel to be dissolved. The most widely known adverse effects of paclitaxel are anaphylactic reactions. As phase I trials were performed, there were serious considerations to stopping due to the high frequency of hypersensitivity reactions. Interventions such as decreasing the rate of infusion and pretreatment with steroids and histamine blockers allowed progression to phase II and III trials and are the standard of care with administration of paclitaxel today [8, 9]. Other common side effects include peripheral neuropathy, myalgias, allopecia, nausea, vomiting, bone marrow suppression, and rarely cardiac electroconductive pathway abnormalities [9–11]. A rare reaction with the administration of paclitaxel in dissolved Cremophor EL is the development of cutaneous lupus erythematosus reactions. Here we present a patient with breast cancer who developed a lupus-like reaction 24 h after the first administration of paclitaxel. The patient was then administered albumin-bound paclitaxel, which contains no Cremophor EL, with no lupus-like reaction afterwards. This observation poses the question of whether her reaction was due to paclitaxel or Cremophor EL.

Case Report

The patient is a 40-year-old female with a significant past medical history that includes hypertension, hypothyroidism, and GERD who was found to have had a left 3.3-cm breast mass in November 2007 with subsequent biopsy showing a stage IIB infiltrating ductal carcinoma with a satellite lesion measuring 1.2 cm. Pathology reports showed that the tumor was ER/PR positive, HER-2 negative. It was decided at the time to perform neoadjuvant therapy with four cycles of Adriamycin and Cytoxan, followed by four cycles of Taxol, and subsequently surgical resection. The patient tolerated her initial treatment with Adriamycin and Cytoxan well, resulting in the reduction of her primary tumor down to approximately 1 cm. She then underwent treatment with Taxol on March 21, 2008. Twenty-four hours after her first dose of paclitaxel, the patient developed left neck and jaw pain, fevers and chills. Her nose began to swell with well-demarcated edema and erythema spreading bilaterally to involve both cheeks in a malar distribution. Pustule formation over the erythematous areas was also appreciated at that time (**fig. 1**). She had no personal or family history of lupus or other collagen vascular diseases; her only medication was levothyroxine, and she was not recently started on any new medications.

The patient was admitted to Rhode Island Hospital and was empirically started on vancomycin for a question of possible cellulitis. The patient was seen in consultation with Dermatology who believed that this was a drug-induced rash secondary to Taxol therapy. No biopsy was obtained given the distribution of the rash on the patient's face. Antinuclear antibodies and anti-histone antibodies were sent which showed a positive ANA titer of 1:40 in a nucleolar pattern with a negative anti-histone antibody. Blood cultures and cultures of the rash were negative for any organisms. Per Dermatology recommendations, the patient was started on both topical and systemic steroids with significant improvement of her rash.

The patient then went on to receive Abraxane, an albumin-bound version of paclitaxel, in April 2008. She had no further reaction with three doses, but continued to have dermatologic sequelae associated with her initial reaction which resolved slowly over a three month period. She subsequently had a left mastectomy in October 2008. Repeat antibody titers revealed nonreactive ANA titers along

Case Rep Oncol 2011;4:526–530
DOI: 10.1159/000334233
Published online: October 26, 2011

ISSN 1662–6575
www.karger.com/cro

with negative cANCA, pANCA, anti-SSA/Ro, anti-SSB/La, anti-histone, and rheumatoid factor antibodies.

Discussion

Cutaneous lupus erythematosus is a distinct disease process separate from systemic lupus erythematosus; however, very commonly patients who have cutaneous lupus erythematosus have manifestations found in the systemic disease. It is thought that this represents an intermediary between an acute dermatological manifestation of the malar rash and chronic manifestation of discoid or lupus profundus. It can present as a small, erythematous, and scaly papule that subsequently progresses to a papulosquamous or annular rash particularly presenting in sun-exposed regions such as the face, neck, shoulders, back, and arms [12]. There appears to be an association between cutaneous lupus erythematosus and anti-Ro/SSA antibodies; however, the incidence of a positive anti-Ro/SSA antibody in patients with cutaneous lupus erythematosus varies between studies [12, 13].

Paclitaxel-induced lupus erythematosus reactions are a particularly rare reaction. In the known literature there appears to have been only four reported cases of systemic lupus erythematosus or cutaneous lupus erythematosus induced by paclitaxel. Adachi and Horikawa [2] first reported two patients with a past medical history of Sjrogen's syndrome who were also diagnosed with breast cancer. These two patients underwent treatment with paclitaxel and subsequently developed annular rashes over their forearms and head. Biopsy was consistent with the diagnosis of cutaneous lupus erythematosus. The two patients both had positive anti-Ro/SSA and negative anti-DS DNA. It was noted that the patients' rash disappeared within six months of discontinuing the paclitaxel. Another reported case of possible paclitaxel-induced lupus was also reported by a French group who diagnosed a patient who developed lupus-like skin reactions initially and upon rechallenge. They made a diagnosis based on a skin biopsy and a high ANA titer [3]. Dasanu and Alexandrescu [1] also reported a case which they believed was a true development of systemic lupus erythematosus secondary to administration of paclitaxel. Their patient was a female with a diagnosis of papillary serous cystadenocarcinoma who developed diffuse myalgias, a malar butterfly rash, arthritis, and right-sided pleural effusion four weeks after starting adjuvant chemotherapy treatment with paclitaxel and carboplatin. This patient's serologies were positive for an ANA titer of 1:320, positive anti-double stranded DNA, and anti-histone antibodies. Anti-Ro/SSA and anti-La/SSB were negative. The patient's symptoms appeared to improve with subsequent discontinuation of paclitaxel and administration of oral prednisone. Despite these cases, a group lead by Pan et al. [14] has noted that there appears to be potential improvement dsDNA antibody titers for lupus in murine models for systemic lupus erythematosus. This appears to raise questions about whether paclitaxel induces or represses the development of systemic lupus erythematosus specifically.

Similarly docetaxel, which was the second taxane approved by the FDA for treatment of several malignancies, has been suspected to cause cutaneous lupus erythematosus. Chen et al. [4] reported four cases of patients treated for breast and lung cancer who subsequently were treated with docetaxel. These patients then developed typical cutaneous lupus erythematosus rashes with initial onset beginning as early as after the first treatment to several months afterwards. The patients' rashes appeared to improve

Case Rep Oncol 2011;4:526–530
DOI: 10.1159/000334233
Published online: October 26, 2011

ISSN 1662–6575
www.karger.com/cro

with discontinuation of docetaxel; some received treatments subsequently with oral prednisone, triamcinolone cream, or with simple removal of the chemotherapeutic agent itself. Three of the four cases had verification of cutaneous lupus erythematosus with direct immunofluorescence of epidermal keratinocytes positive for IgG deposition and all of the cases had findings of C5b-9.

Our patient developed a lupus-like reaction after it was noted that she developed a rash over a malar distribution two days after receiving paclitaxel. Biopsy was not performed due the area of distribution on the patient's face. The patient was tested for antibody titers, which revealed a finding of an ANA titer of 1:40 which subsequently resolved after withdrawal of paclitaxel and treatment with topical and systemic steroids. The inciting cause was thought to be secondary to the paclitaxel, given the acute onset after administration and significant improvement after stopping the medication; the timing is consistent with previous noted reactions as discussed in the literature.

Both paclitaxel and docetaxel have been known to cause adverse side effects such as hypersensitivity reactions; and, as suggested by the reports, both of these medications and their formulations have been known to cause lupus-like reactions. Docetaxel was initially presented as an alternative to paclitaxel due to the significant rate of hypersensitivity reactions; since the incorporation of docetaxel into treatment of breast, lung, and ovarian cancer, there have been observations that there was a significant decrease in the amount of hypersensitivity reactions. This observation has led people to believe that the hypersensitivity reaction might be caused by the diluent, Cremophor EL, as opposed to the chemotherapeutic agent itself [9, 11, 15]. If the reactions were caused by the taxane ring, which is the chemically reactive component of the chemotherapeutic agents, then the hypersensitivity reaction should be relatively equal with both paclitaxel and docetaxel. It is possible that instead the fatty acid esters or the glycol components of both Cremophor EL, the emollient used in paclitaxel, and polysorbate 80, the emollient used in docetaxel, could induce both the hypersensitivity reactions and the lupus-like reactions. There are various other medications that use Cremophor EL as an emollient which do not have evidence of lupus-like reactions; however, the amount of Cremophor EL mixed with paclitaxel is significantly higher than in other medications [16]. Furthermore, this solution is administered intravenously as opposed to some of the other medications using Cremophor EL. The larger amount of exposure to Cremophor EL is likely to induce these reactions.

Paclitaxel was stopped in our patient due to the possibility of recurrent lupus-like reaction with re-administration. Instead, the patient was subsequently treated with Abraxane, an albumin-bound paclitaxel, which does not contain Cremophor EL. Albumin-bound paclitaxel does not appear to have a significant occurrence of hypersensitivity reactions due to the elimination of Cremophor EL [17, 18]. Our patient did not develop any further lupus-like reactions with three administrations of the drug. If the paclitaxel was the chemical compound that induced the development of the patient's lupus-like reaction, then we would expect the patient to have further flares of her disease; however, given that she tolerated the albumin-bound paclitaxel without issues, this would imply that the implicating substance is the Cremophor EL instead. To our knowledge, this is the first published attempt of treating a patient with albumin-bound paclitaxel after that patient developed a lupus-like reaction to the current formulation of paclitaxel. We suggest that this is the first case of a Cremophor EL induced lupus-like reaction.

Case Rep Oncol 2011;4:526–530
DOI: 10.1159/000334233
Published online: October 26, 2011

ISSN 1662–6575
www.karger.com/cro

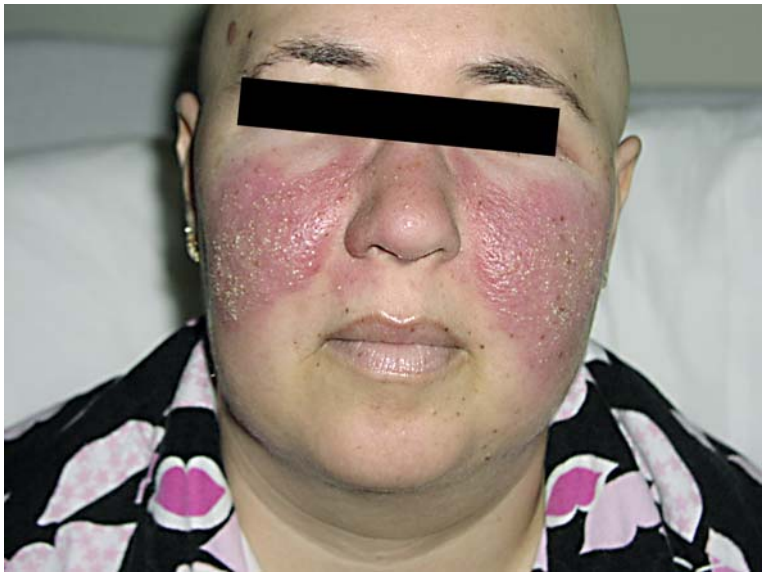

Fig. 1. Patient with development of a rash in malar distribution 24 h after administration of paclitaxel.

References

1 Dasanu CA, Alexandrescu DT: Systemic lupus erythematosus associated with paclitaxel use in the treatment of ovarian cancer. South Med J 2008;101:1161–1162.
2 Adachi A, Horikawa T: Paclitaxel-induced cutaneous lupus erythematosus in patients with serum anti-SSA/Ro antibody. J Dermatol 2007;34:473–476.
3 Lortholary A, et al: [Paclitaxel-induced lupus]. Presse Med 2007;36:1207–1208.
4 Chen M, et al: Docetaxel (taxotere) induced subacute cutaneous lupus erythematosus: report of 4 cases. J Rheumatol 2004;31:818–820.
5 Singh S, Dash AK: Paclitaxel in cancer treatment: perspectives and prospects of its delivery challenges. Crit Rev Ther Drug Carrier Syst 2009;26:333–372.
6 Gelderblom H, et al: Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 2001;37:1590–1598.
7 Kim SC, et al: In vivo evaluation of polymeric micellar paclitaxel formulation: toxicity and efficacy. J Control Release 2001;72:191–202.
8 Price KS, Castells MC: Taxol reactions. Allergy Asthma Proc 2002;23:205–208.
9 Finley RS, Rowinsky EK: Patient care issues: the management of paclitaxel-related toxicities. Ann Pharmacother 1994;28(5 suppl):S27–S30.
10 Rowinsky EK, et al: Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 1993;20(4 suppl 3):1–15.
11 Adams JD, et al: Taxol: a history of pharmaceutical development and current pharmaceutical concerns. J Natl Cancer Inst Monogr 1993:141–147.
12 Stavropoulos PG, et al: Pathogenesis of subacute cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol 2008;22:1281–1289.
13 Black DR, et al: Frequency and severity of systemic disease in patients with subacute cutaneous lupus erythematosus. Arch Dermatol 2002;138:1175–1178.
14 Pan HF, et al: Paclitaxel: friend or foe for systemic lupus erythematosus? South Med J 2009;102:554–555.
15 Lokich J, Anderson N: Paclitaxel hypersensitivity reactions: a role for docetaxel substitution. Ann Oncol 1998;9:573.
16 Dorr RT: Pharmacology and toxicology of Cremophor EL diluent. Ann Pharmacother 1994;28(5 suppl):S11–S14.
17 Pinder MC, Ibrahim NK: Nanoparticle albumin-bound paclitaxel for treatment of metastatic breast cancer. Drugs Today (Barc) 2006;42:599–604.
18 Scripture CD, Figg WD, Sparreboom A: Paclitaxel chemotherapy: from empiricism to a mechanism-based formulation strategy. Ther Clin Risk Manag 2005;1:107–114.