

Nab-paclitaxel-associated photosensitivity: report in a woman with non-small cell lung cancer and review of taxane-related photodermatoses

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ABSTRACT **Background:** Taxanes [paclitaxel, nab-paclitaxel (Abraxane, Celgene Corp, USA), and docetaxel]—used in the treatment of lung, breast, and head and neck cancers—have been associated with cutaneous adverse effects, including photodermatoses.

Purpose: We describe a woman with non-small cell lung cancer who developed a photodistributed dermatitis associated with her nab-paclitaxel therapy and review photodermatoses in patients receiving taxanes.

Materials and methods: The features of a woman with a nab-paclitaxel-associated photodistributed dermatitis are presented and the literature on nab-paclitaxel-associated photosensitivity is reviewed.

Results: Our patient developed nab-paclitaxel-associated photodistributed dermatitis on the sun-exposed surfaces of her upper extremities, which was exacerbated with each course of nab-paclitaxel. Biopsies revealed an interface dermatitis and laboratory studies were negative for lupus erythematosus and dermatomyositis. Her condition improved following topical corticosteroid cream application and strict avoidance of sunlight.

Conclusion: Chemotherapy can be associated with adverse mucocutaneous events, including dermatoses on sun-exposed areas of the skin. Paclitaxel and nab-paclitaxel have both been associated with photodermatoses, including dermatitis, erythema multiforme, onycholysis, and subacute cutaneous lupus erythematosus. Strict avoidance of sun exposure, topical or oral corticosteroids, and/or discontinuation of the drug results in improvement with progressive resolution of symptoms and skin lesions. Development of photodermatoses is not an absolute contraindication to continuing chemotherapy, provided that the cutaneous condition resolves with dermatosis-directed treatment and the patient avoids sun exposure.



Figure 1. Erythematous plaques on the sun-exposed extensor surfaces of the patient's arms with focal sparing of the dermatosis on her left extensor arm corresponding to the area of her skin that had been covered by a wrist watch; there is also hyperpigmentation on her posterior neck. [Copyright: ©2015 Beutler et al.]

Introduction

Taxane-associated cutaneous adverse reactions include photodermatoses [1-3]. We describe a woman with non-small cell lung cancer who developed a dermatitis on sun-exposed areas that progressively worsened with each dose of nab-paclitaxel. We also review other photodermatoses in patients receiving paclitaxel or nab-paclitaxel and address the treatment options for individuals affected by these drug-associated conditions.

Case report

A 69-year-old woman presented for evaluation with a photodistributed rash on the extensor surfaces of her upper extremities. Her past medical history was significant for stage IV non-small cell lung cancer. She had progressive disease after sequentially receiving prior antineoplastic therapies,

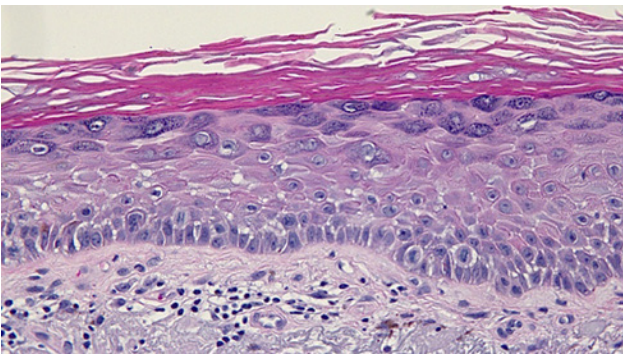


Figure 3. Hematoxylin and eosin stained sections of nab-paclitaxel-associated photodermatitis show hyperkeratosis, mild acanthosis, and spongiosis with effacement of the rete ridges. There is a sparse interface dermatitis with subtle alteration of the epidermal basal layer and incontinence of pigment in the papillary dermis (hematoxylin and eosin; x40). [Copyright: ©2015 Beutler et al.]

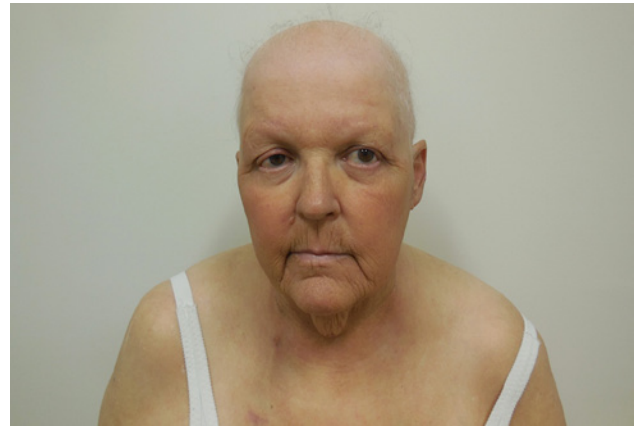


Figure 2. Hyperpigmentation of sun-exposed locations: the face, anterior neck, and "V" area of the upper chest. [Copyright: ©2015 Beutler et al.]

including: carboplatin and pemetrexed, gemcitabine, and vinorelbine. Treatment with nab-paclitaxel [185 milligrams (100 mg/m²) each week] had been initiated two months prior to the development of the rash.

Cutaneous examination revealed individual and confluent, erythematous and scaly, plaques on the sun-exposed areas of her neck and arms (Figure 1). Hyperpigmentation was observed on her face, neck, and upper chest (Figures 1 and 2).

Punch biopsies from the extensor distal left and right arms both show mild spongiosis with hyperkeratosis; scattered dyskeratotic cells are present in the epidermis. There is a sparse interface dermatitis; mild incontinence of pigment is present in the dermis (Figure 3). Colloidal iron stained sections demonstrate a mild increase of mucin (Figure 4).

Laboratory studies revealed a positive ANA at a low titer of 1:160 with a nucleolar pattern. Negative studies included antibody to: dsDNA, Ro, La, Smith, RNP, SCL-70, Jo-1, and histone IgG. Normal studies included: creatine kinase, aldolase, LDH, AST, and ALT.

After correlating the clinical, pathology, and laboratory findings, a diagnosis of nab-paclitaxel-associated photosen-

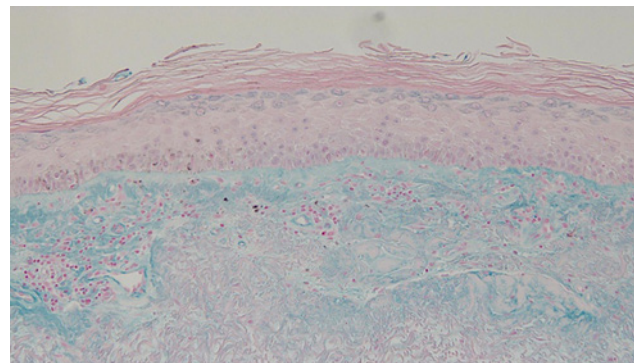


Figure 4. Colloidal iron stained sections of nab-paclitaxel-associated photodermatitis show a mild increase of mucin in the upper dermis. There are scattered dyskeratotic cells in the epidermis and incontinence of pigment in the papillary dermis (colloidal iron; x20). [Copyright: ©2015 Beutler et al.]

sitive dermatitis was established. Clobetasol 0.05% cream was applied twice daily and she avoided exposure to the sun. Most of the erythematous plaques resolved within two weeks. Triamcinolone 0.1% cream was substituted — initially, twice and then once daily — until the dermatitis completely resolved. The patient was able to continue receiving nab-paclitaxel therapy without recurrence of her symptoms.

Discussion

Taxanes are used in the treatment of lung, breast, ovarian, pancreatic, and head and neck cancers. The first taxane, paclitaxel, was isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) by Monroe E. Wall and Mansukh C. Wani in 1967. Its structure was subsequently elucidated in 1971. However, due to the cost and difficulty of the extraction process and the limited supply of the Pacific yew tree, commercial development of paclitaxel did not begin until 1991 [4,5].

Paclitaxel is poorly soluble in water and thus most commercially available preparations once contained the non-ionic solvent Kolliphor EL (BASF, USA, formerly Cremophor EL). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was developed in order to reduce or eliminate the risk of hypersensitivity reactions associated with Kolliphor EL-based paclitaxel. Nab-paclitaxel, marketed under the trade name “Abraxane,” is an injectable formulation of albumin-linked paclitaxel that can be administered without steroid or antihistamine prophylaxis for hypersensitivity reactions [6].

Paclitaxel-induced photodermatoses include erythema multiforme, onycholysis, photo recall phenomenon, and subacute cutaneous lupus erythematosus [1]. It is possible that the photodermatosis in some of these patients was associated with Kolliphor EL rather than paclitaxel. To the best of our knowledge, subacute cutaneous lupus erythematosus is the only photosensitivity disorder that has been linked specifically to nab-paclitaxel therapy [7].

Paclitaxel-induced erythema multiforme on sun-exposed skin has previously been observed. A 40-year-old woman with metastatic breast cancer presented with photodistributed erythema multiforme and onycholysis following treatment with paclitaxel and trastuzumab. Elevated urinary and erythrocyte porphyrins were also observed. The severity of the reaction necessitated withdrawal of paclitaxel therapy. The lesions gradually resolved and the porphyrins normalized following withdrawal of the drug [2].

Another patient—a 56-year-old woman who was receiving adjuvant weekly paclitaxel for the treatment of intraductal breast carcinoma—developed photodistributed erythema multiforme and onycholysis shortly after brief exposure to sunlight. She developed pruritic and erythematous skin lesions that spread only to sites that were exposed to sunlight:

the face, upper central chest, and extensor forearms. The condition was successfully treated with topical corticosteroids and strict photoprotection. The patient was able to continue to receive paclitaxel therapy with no recurrence of erythema multiforme or onycholysis [1].

Photo recall phenomenon [3] and subacute cutaneous lupus erythematosus [8-10] have been associated with paclitaxel therapy in female patients. One woman developed a lupus erythematosus-like reaction one day after her first dose of paclitaxel. She presented with edema and erythema spreading bilaterally from her nose to her cheeks. A positive ANA titer of 1:40 in a nucleolar pattern was observed. Topical and systemic corticosteroids were administered and the lesions began to clear. Interestingly, the patient was subsequently able to tolerate nab-paclitaxel therapy; the authors attributed her eruption to the Kolliphor EL solvent rather than the paclitaxel [10].

However, a recent report has linked subacute cutaneous lupus erythematosus to Kolliphor EL-free nab-paclitaxel. A 62-year-old woman developed erythematous papules and plaques of subacute lupus erythematosus on her sun-exposed arms and chest that appeared after her third infusion with nab-paclitaxel. The lesions completely disappeared after the nab-paclitaxel was withdrawn [7].

Reports of photosensitivity dermatitis in patients receiving paclitaxel or nab-paclitaxel therapy are uncommon. However, it is possible that the incidence of these cases is higher than reflected in the literature. We hypothesize that additional affected individuals may not have been recognized or reported since the treatment duration is limited and the dermatoses resolve spontaneously once the agent has been discontinued.

Drug-induced photosensitivity can be phototoxic or photoallergic. Phototoxic dermatoses are common and typically present as a sunburn that appears immediately after moderate exposure to ultraviolet radiation. Conversely, photoallergic reactions are rare and are often characterized by pruritic or eczematous lesions that appear on sun exposed areas of the skin 24-72 hours after minimal sun exposure (Table 1) [11]. The clinical presentation of our patient’s nab-paclitaxel-induced photodermatosis is most consistent with a photoallergic reaction.

The mechanism of pathogenesis for taxane-associated photosensitivity remains to be determined. In some of the patients treated with paclitaxel, aberrations in the biosynthesis of porphyrins have been demonstrated [10,12]. Whether elevated porphyrins are an essential feature or an epiphenomenon for the development of paclitaxel-related photosensitivity remains to be determined. Our patient declined additional blood and urine studies to evaluate porphyrins after her dermatosis resolved.

TABLE 1. Drug-induced photosensitivity: phototoxicity versus photoallergy

	Phototoxicity	Photoallergy
Incidence	Common	Rare
Appearance	Sunburn-like appearance with erythema and/or edema	Dermatitis
Onset	Immediately after exposure to sunlight	24-72 hours after exposure to sunlight
Required dose of UV radiation	Moderate-high	Low
Required dose of drug	Moderate-high	Low
Areas affected	Sun-exposed areas only	Initially sun-exposed areas and may spread to photoprotected areas
Pathophysiology	Tissue injury	Cell-mediated immune response

Treatment of taxane-induced photodermatoses typically involves topical or systemic corticosteroids and photoprotection. Oral antihistamines may also be helpful for some patients [3,13]. The presence of a photodermatosis is not an absolute contraindication to continuing chemotherapy, especially with strict avoidance of sun exposure. However, withdrawal of the drug may be required if the cutaneous reaction is severe or if the lesions fail to resolve with conservative treatment.

Conclusion

Taxanes are chemotherapeutic agents used in the management of various neoplasms. Paclitaxel and nab-paclitaxel are taxanes that have been associated with photodermatoses, including erythema multiforme, onycholysis, photo recall phenomenon, and subacute cutaneous lupus erythematosus. The incidence of photodermatoses secondary to paclitaxel or nab-paclitaxel may be higher than the published literature reflects.

The development of symptoms and/or skin lesions on sun-exposed areas in patients receiving these agents should prompt the clinician to evaluate the patient for a drug-related photodermatosis. Evaluation could include serologic tests (to evaluate for lupus erythematosus and porphyria) and tissue biopsy for microscopic examination.

Strict adherence to avoiding exposure to sunlight should be initiated. Symptomatic treatments with topical or, if necessary, systemic corticosteroids should also be considered. The development of a taxane-associated photodermatosis is not an absolute contraindication to continuing treatment with the drug. However, limited exposure to ultraviolet radiation is recommended.

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