Photodermatitis in a woman with infiltrating intraductal breast carcinoma: An uncommon adverse cutaneous drug reaction of paclitaxel revisited

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Abstract:
Paclitaxel-induced photodermatitis is extremely rare despite the frequent use of paclitaxel-trastuzumab combination chemotherapy. A 70-year-old woman with infiltrating intraductal breast cancer developed photodermatitis after ten treatment courses of weekly paclitaxel-trastuzumab combination chemotherapy. Withdrawal of paclitaxel and sun avoidance led to its resolution. A combined effect of solar radiation and enhanced porphyrin synthesis is speculated for photodermatitis in paclitaxel. However, the issue of aberrant porphyrin biosynthesis being causal or an epiphenomenon remains unsettled as elevated porphyrins synthesis does not necessarily cause photosensitivity in all treated cases. The relevant literature on paclitaxel-induced photodermatitis and pathomechanism involved is reviewed.

Keywords: Actinic dermatitis, adverse cutaneous drug reactions, breast cancer, docetaxel, nab-paclitaxel, photosensitivity, taxanes

Introduction
Drug-induced photosensitivity is the third-most common adverse cutaneous reaction and accounts for approximately 2%–15% of patients in tertiary referral. They usually follow the administration of a drug with photosensitizing potential and exposure to ultraviolet (UV) or visible light for a sufficient period. In most instances, UV-A having long-wavelength with the ability to penetrate into the dermis is implicated, whereas UV-B and visible light might elicit such reactions infrequently. Tetracyclines, fluoroquinolones (sparfloxacin, pefloxacin, and ofloxacin), non-steroidal anti-inflammatory drugs (naproxen and ketoprofen), diuretics (furosemide and thiazides), antifungals (griseofulvin and voriconazole), phenothiazines (chlorpromazine, trifluoperazine, and prochlorperazine), amiodarone, sulfonylureas, and dapsone are common photosensitizing drugs. An uncommon case of paclitaxel-induced photodermatitis is presented here and relevant literature is also reviewed.

Case Report
A 70-year-old woman presented with acrofacial erythematous lesions. Historically, she had a radical mastectomy 6 months back for intraductal carcinoma (grade 2) of the right breast infiltrating overlying skin, nipple, and axillary lymph nodes (pT2N3aM0). Immunohistochemistry was
negative for estrogen/progesterone receptor (ER/PR) and cytogenetic studies showed positive human epidermal growth factor receptor 2/HER2 gene amplification. She had received 12 chemotherapy courses each comprising paclitaxel (130 mg/week) and trastuzumab (270 mg/week for three courses followed by 135 mg/week). Ten weeks (ten treatment courses) after initiating chemotherapy, she developed pruritus, burning, diffuse dusky erythema, and minimal edema in a photo distribution pattern involving the face, front of the neck, distal forearms, dorsa of the hands and feet [Figure 1]. However, the chemotherapy was continued for another 2 weeks while her symptoms persisted with daily exacerbations on sun exposure while oral cetirizine 10 mg/d provided temporary relief in itching. She also had diffuse thinning of scalp hair. Other systemic examination and review of recent laboratory reports (hemogram and serum biochemistry) showed no abnormality. She did not consent for skin biopsy, photopatch testing, and assessment for urinary porphyrins despite counseling. Suspecting paclitaxel-induced photodermatitis, its immediate withdrawal was advised. She was prescribed twice daily application of betamethasone dipropionate (0.05%) cream, physical sunscreen containing 7.5% micronized zinc oxide (Sunstop-19®, Ajanta Pharma, India), and desloratadine 5 mg/d per oral. A follow-up 3 weeks later showed complete clearance of photodermatitis. The patient was still receiving maintenance trastuzumab (135 mg/week) and oncologists did not support paclitaxel re-challenge in view of chemotherapy completion.

**Discussion**

Trastuzumab is a recombinant DNA-derived humanized anti-p185-HER2 monoclonal antibody that binds to the extracellular domain of the HER2 receptor. For its antiproliferative action on tumor cells and is used for chemotherapy-resistant metastatic breast cancer with HER2 protein overexpression. It is considered safe except for occasional reports of urticaria, angioedema, and fatal anaphylaxis following intravenous administration. As it enhances the antitumor effect of paclitaxel/docetaxel, both are usually combined for the treatment of chemotherapy-resistant metastatic breast carcinoma wherein severe onychopathy/nail dystrophy or hand and foot syndrome have been reported in such a scenario.[1] Paclitaxel and docetaxel (taxanes), originally extracted from yew tree (Taxus brevifolia/T. bactata) bark, are potent chemotherapeutic agents for treating the metastatic ovarian, breast, head and neck, gastrointestinal, and lung cancers.[2] Nab-paclitaxel is a solvent-free, albumin-bound nanoparticle paclitaxel without associated issues of poor solubility and hypersensitivity. They inhibit mitosis and cell division by binding to β-tubulin of the mitotic spindle that arrest cell cycle in G2-M phase junction, and cause direct apoptosis by bcl-2 phosphorylation.[2] Paclitaxel-induced adverse cutaneous drug reactions are uncommon and include injection site reactions (erythema, tenderness, discoloration and swelling) among others [Table 1]. Although paclitaxel reportedly can trigger photosensitive dermatoses such as photodistributed erythema multiforme, photo-recall phenomenon, photooxygenolysis, lupus erythematosus (LE), or subacute cutaneous LE, photodermatitis per se appears rare in reviewed reports which may develop after any time or any number of treatment courses [Table 2].[2-4] Cohen et al.[3] reported a case of breast cancer with metastasis to lungs having paclitaxel-induced photodermatitis after 4 weeks of weekly paclitaxel and trastuzumab. The photodermatitis resolved after discontinuation of paclitaxel while trastuzumab was continued. Our patient developed characteristic photodermatitis after 10 weeks of combination chemotherapy that resolved following paclitaxel withdrawal in a similar manner. Although we could not perform drug rechallenge, paclitaxel could be implicated for the onset of photodermatitis following its administration (temporal correlation) and resolution of rash and no more recurrence after its discontinuation (de-challenge) as per the World Health Organization Uppsala Monitoring Center causality scale.

Although pathomechanism of paclitaxel-induced photodermatitis is poorly understood for its rarity, nab-paclitaxel, and more frequently, docetaxel as monotherapy or in combination with trastuzumab have caused photodermatitis after 2–4 weekly treatments.[3-9] It has been usually imputed to nonspecific increased porphyrin synthesis as evidenced from increased urinary porphyrins, erythrocyte porphyrins or their precursors (aminolevulinic acid and porphobilinogen), and porphobilinogen deaminase activity among paclitaxel and trastuzumab treated patients.[1] Further, phototesting showed sensitivity to UVB and not to UVA or visible light in a patient on treatment with docetaxel alone for
Table 1: Reported adverse effects of paclitaxel and trastuzumab

| Type of adverse effects          | Paclitaxel                                                                 | Trastuzumab                                                                 |
|---------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Hypersensitivity reactions      | Angioedema                                                                | Angioedema                                                                |
|                                 | Urticaria                                                                 | Urticaria                                                                |
|                                 | Anaphylaxis                                                               | Anaphylaxis                                                               |
|                                 | Flushing/pruritus                                                         | Morbilliform rash                                                         |
|                                 | Morbilliform rash                                                         |                                                                            |
| Cutaneous adverse effects       | Hand and foot syndrome                                                    | Hand and foot syndrome (in combination with paclitaxel)                   |
|                                 | PATEO syndrome                                                            |                                                                            |
|                                 | Intertriginous drug rash                                                 |                                                                            |
|                                 | Maculopapular drug rash                                                  |                                                                            |
|                                 | Photodistributed EM                                                      |                                                                            |
|                                 | Photodermatitis                                                           |                                                                            |
|                                 | AGEP                                                                      |                                                                            |
|                                 | Flagellate and reticulate pigmentation                                   |                                                                            |
|                                 | Drug-induced LE/SCLE                                                     |                                                                            |
|                                 | Sclerodermatus skin changes                                              |                                                                            |
|                                 | Recall (radiation/UV) dermatitis                                          |                                                                            |
|                                 | Inflammation of actinic keratoses                                        |                                                                            |
|                                 | SJS/TEN                                                                   |                                                                            |
| Adverse effects affecting hair and nails | Alopecia - reversible/persistent                                       | Onychotrophy/onychopathy (in combination with docetaxel)                     |
|                                 | Onycholysis/photo onycholysis                                             |                                                                            |
|                                 | Onychopathy                                                               |                                                                            |
|                                 | Onychomadesis, Beau’s lines                                              |                                                                            |
|                                 | Melanonychia/leukonychia                                                 |                                                                            |
|                                 | Paronychia                                                                |                                                                            |
|                                 | Onychorrhexis                                                            |                                                                            |
|                                 | Onychotrophy/onychopathy                                                 |                                                                            |
|                                 | (in combination with docetaxel)                                          |                                                                            |
| Adverse effects affecting mucosal surfaces | Mucositis                                                                | -                                                                         |
|                                 | Dysgeusia                                                                |                                                                            |
|                                 | Tongue pigmentation                                                      |                                                                            |
| Miscellaneous                   | Fixed drug eruptions                                                     | -                                                                         |
|                                 | Inflammation in actinic keratoses                                        |                                                                            |
|                                 | Xerosis                                                                   |                                                                            |

Most of these adverse effects are documented in literature as case reports, small case series, or in postmarketing surveys. AGEP=Acute generalized exanthematous pustulosis, PATEO=Periarticular thenar erythema with onycholysis, EM=Erythema multiforme, LE=Lupus erythematosus, SJS=Stevens-Johnson syndrome, TEN=Toxic epidermal necrolysis, SCLE=Subacute cutaneous lupus erythematosus, UV=Ultraviolet.

Besides, porphyrinogenic effect of paclitaxel has been demonstrated experimentally in primary neural tissue cell cultures. On the other hand, trastuzumab, although, known to increase sensitization of cancer cells for ionizing radiation therapy usually involving 4–6 MV X-ray photons or other electromagnetic rays, it is not implicated for photodermatitis despite combined administration of both drugs is known to elevate serum concentrations of trastuzumab by nearly 1.5 times. It seems plausible as electromagnetic rays used for radiation therapy lie beyond the UVA (320–400 nm), UVB (290–320 nm) or visible light (400–760 nm) spectrum responsible for most photobiologic reactions whereas UVC (200–290 nm) is absorbed in the atmosphere before reaching the earth.

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In view of the foregoing, it is possible that solar radiation combined with enhanced porphyrin synthesis from paclitaxel caused an interaction that is perhaps responsible, may be partially, for the increased likelihood of photodermatitis in our patient as well. However, whether this aberrant porphyrin biosynthesis in these patients is causal or just an epiphenomenon remains unclear currently since elevated porphyrins synthesis does not necessarily cause photosensitivity in all treated cases. In addition, paclitaxel-induced photosensitivity is reportedly not an absolute contraindication for its further use since many patients tolerated subsequent additional therapy with concurrent use of photoprotection. Nevertheless, dermatologists need to be aware of the possibility of paclitaxel-induced photodermatitis as additional cases may be seen in future, especially due to the potential usefulness of paclitaxel in psoriasis management.

Statement of ethics

Informed consent was obtained from the patient wherein she has given her consent for her images and other clinical information to be reported in scientific journal without disclosing her identity, name, initials, or personal information knowing fully that anonymity...
| Reference number | Case number | Age in years/ gender | Primary diagnosis | Chemotherapy schedule | Number of chemotherapy courses (duration) before the onset of rash | Remarks |
|------------------|-------------|----------------------|-------------------|-----------------------|---------------------------------------------------------------|---------|
| Cohen et al. 2009[1] | 1           | 40/female            | Breast cancer with metastasis to lungs | Paclitaxel (160 mg/week) + Trastuzumab 225 mg/week followed by 110 mg/week for 3 m | 4 treatment courses (4 weeks) | Had earlier received docetaxel without response Lesional biopsy showed vacuolar degeneration of basal cells, sparse necrotic keratinocytes, papillary dermal edema, perivascular mononuclear cell infiltrate Increased urinary porphyrins (ALA, PBG, PBGD) |
| Ferreira et al. 2010[2] | 2           | 60/male              | Nonsmall cell lung cancer with bone metastasis | Docetaxel + local radiotherapy | 2 treatment courses (2 weeks) | Treated earlier with left pneumonectomy + carboplatin and vinorelbine Dose and schedule of docetaxel administration not mentioned Onycholysis was present |
| Beutler et al. 2015[3] | 3           | 69/female            | Nonsmall cell lung cancer (stage-IV) with bone metastasis | Nab-paclitaxel 100 mg/m² (185 mg/week) | 4 treatment courses (4 weeks) | Lesional biopsy showed hyperkeratosis, mild spongiosis, scattered dyskeratotic cells, sparse interface dermatitis, mild melanin incontinence, and increased mucin Normal CK, aldolase, LDH, AST, and ALT. ANA + Negative autoantibodies for dsDNA, RO, LA, Smith, RNP, SCl-70, Jo-1, and histone |
| Akay et al. 2010[4] | 4           | 63/female            | Metastatic breast carcinoma | Docetaxel 75 mg/m² + Trastuzumab 8 mg/kg followed by 6 mg/kg, at every 3 weeks | Two treatment courses (2 weeks) | Lesional biopsy showed lymphocytic cell infiltrate Increased total urinary porphyrins, UP, PCP, CP Normal ALA, PBG Normal C3/C4, and liver enzymes. Negative HBsAg, Hepatitis C, and autoantibodies (ANA, anti ds DNA, anti-Ro, anti-SS-A/SS-B, anti-histone, anti-Smith) |
| Tokunaga et al. 2013[5] | 5           | Male (age not stated) | Scalp angiosarcoma | Docetaxel (dosing schedule not provided) | 3 m after initiating docetaxel | Reviewed other five patients with photosensitivity from 2 to 22 courses of docetaxel/paclitaxel treatment courses All showed increased erythrocyte protoporphyrin All shoed sensitivity to UV-B light on photo testing Rash resolved with topical steroid ointment |
| Present case | 6           | 70/female            | Intraductal breast carcinoma with metastasis to lymph nodes | Paclitaxel (130 mg/week) + Trastuzumab (270 mg/week followed by 135 mg/week) | 10 treatment courses (10 weeks) | Radical mastectomy performed prior to chemotherapy Skin biopsy or estimation of urinary porphyrins not performed for want of consent/in house facility Blood biochemistry, hemogram was normal Photo dermatitis resolved after withdrawal of paclitaxel |

ANA=Antinuclear antibody, ALA=Aminolevulinic acid, CK=Creatine kinase, PBG=Porphobilinogen, PBGD=Porphobilinogen deaminase, UP=Uroporphyrin, PCP=Pentacarboxyporphyrin, CP=Coproporphyrin-I and III, LDH=Lactate dehydrogenase, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, HBsAg=Hepatitis B virus surface antigen, UVB=Ultraviolet-B
may not be guaranteed despite all efforts made. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. The patient was provided standard medical treatment and counseling.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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