

Onycholysis Associated With Paclitaxel

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Chemotherapeutic agents are known to cause a myriad of cutaneous side effects that the dermatologist is often called upon to identify and treat. The taxoid drug paclitaxel is commonly used in oncology. To date, there have been few adverse dermatologic effects reported secondary to paclitaxel use. This is in contrast to the related drug docetaxel. We report a case in which paclitaxel caused onycholysis and nail loss in a patient being treated for lung cancer. To our knowledge, this finding has not previously been reported in the American dermatologic literature, though it has been reported in association with docetaxel use. It is important for clinicians to recognize that onycholysis can be associated with paclitaxel. Prompt recognition may prevent the unnecessary use of antibiotics or antifungal medications. Discontinuation of paclitaxel chemotherapy generally is not required, and regrowth of nails can be expected following completion of therapy.

The taxoid chemotherapeutic agents paclitaxel and docetaxel are increasingly used in the treatment of a variety of cancers, including breast, ovarian, non-small cell lung, bladder, prostate, head and neck, and esophageal. Onycholysis associated with docetaxel has been reported previously.¹ We report a case of onycholysis associated with weekly administration of paclitaxel. In contrast to previous reports, UV light exposure was not a significant factor in the development of onycholysis in this patient because protected areas of his body also were affected.

Case Report

In July 2000, a 70-year-old white man with a history of lung adenocarcinoma presented with 3 to 4 weeks' loss of sensation in the fingertips and onycholysis of multiple nails. He had been undergoing low-dose weekly chemotherapy with paclitaxel and carboplatin for 19 weeks. During this time, dexamethasone, diphenhydramine, and ranitidine were also administered as premedications. He also had received radiation therapy to the lung 6 months prior to presentation. His medical regimen included losartan, atorvastatin, aspirin, erythropoietin, and diltiazem, as well as latanoprost eyedrops for glaucoma. None of these medications were new to the patient. His medical history was significant for renal cell carcinoma 7 years previously that was treated successfully with left nephrectomy. Although onset of onycholysis was in the summer, the patient categorically denied wearing open-toed shoes and felt confident he had had no sun exposure to the feet.

On physical examination, the patient had onycholysis of all 10 fingernails and pustular discharge of both index fingernails and the right fourth fingernail (Figure 1). Onycholysis of the left great toenail also was present.

The result of a potassium hydroxide examination of nail scrapings was negative. The result of a Gram stain was significant for gram-positive cocci. Our impression was onycholysis of multiple nails secondary to paclitaxel therapy, complicated by superimposed bacterial infection. The patient was treated with mupirocin ointment and amoxicillin/clavulanic acid. Bacterial culture subsequently grew *Staphylococcus aureus*, group B β -hemolytic streptococcus, and *Escherichia coli*.

Two weeks later, the infection resolved, leaving only residual onycholysis. The left index fingernail had shed (Figure 2), and both thumbnails and both great toenails were eventually shed as well. Periodic acid-Schiff stain of the left index fingernail was significant for fungal spores on the underside consistent with *Candida*. A fungal culture ultimately grew *Candida albicans*. Treatment with ciclopirox lotion was initiated.

The patient completed the full course of paclitaxel chemotherapy, receiving an additional 7 weeks

Accepted for publication October 2, 2002.

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Figure 1. Onycholysis of multiple nails on the right hand with pustular material beneath the nail plates of the index and ring fingers.

of treatment. His regimen was not interrupted. Nail changes remained stable for the duration of paclitaxel use. His fingernails completely regrew 6 months after completion of chemotherapy. The affected toenails were slower to recover, but after one year, they were almost completely normal. Throughout treatment with paclitaxel, the patient's absolute neutrophil count remained within normal limits.

Comment

Paclitaxel is a diterpenoid compound containing a complex taxane ring at its nucleus. Originally purified from the bark of the Pacific yew, it is now available by semisynthesis from a precursor found in yew leaves. Paclitaxel promotes microtubule polymerization by binding to the β -tubulin subunit of microtubules and antagonizes the disassembly of this cytoskeletal protein, resulting in bundles of microtubules and aberrant structures and arrest of mitosis.

Administered as either a 3- or 24-hour infusion, paclitaxel has shown activity in breast, ovarian, non-small cell lung, bladder, prostate, head and neck, and esophageal cancers. Toxic effects include neutropenia and peripheral neuropathy, myalgia, hypersensitivity reactions, mucositis, bradycardia, and occasional episodes of ventricular tachycardia.

Docetaxel is a related taxoid antineoplastic drug used for the same cancers as paclitaxel. Adverse skin and nail reactions have been reported

including brown pigmentation, Beau's lines, subungual hemorrhage, orange discoloration, acute painful paronychia, onycholysis, subungual hyperkeratosis, and transverse loss of the nail plate.¹⁻⁵ Interestingly, docetaxel has fewer systemic side effects than paclitaxel.

To date, paclitaxel has been associated with few skin and nail changes. Reported nail changes include pigmentation or discoloration of the nail bed, occurring in less than 2% of patients.⁶ Localized skin reactions and tissue necrosis have been reported. In addition, 2 articles in the pharmacology literature describe onycholysis associated with paclitaxel use.^{6,7} Flory and colleagues⁶ reported 4 cases of onycholysis associated with weekly administration of paclitaxel in women being treated for ovarian cancer. Purpura or bruising of the nail bed followed by pus formation and onycholysis developed between 10 to 13 weeks of treatment in 3 patients and shortly after beginning therapy in a fourth patient. Patients were being treated with low-dose weekly administration of paclitaxel. Two patients had previously received higher doses on an every-third-week schedule and had not developed onycholysis. Reactions did not require discontinuation of therapy. Paclitaxel use was discontinued in one patient secondary to progression of disease. Nails subsequently regrew normally without further complications. The authors postulated a direct toxicity to the nail bed or inhibition of angio-



Figure 2. Nail plate of the left index finger after spontaneous shedding.

genesis as possible mechanisms. Link et al⁷ reported cutaneous manifestations due to paclitaxel treatment noted during trials of dose-intense paclitaxel with granulocyte colony-stimulating factor in patients with platinum-refractory ovarian cancer. Two patients developed extensive onycholysis of fingernails and toenails after 4 to 6 cycles of the drug. One of these patients complained of moderate nail bed discomfort. Two additional patients developed minor nail changes, including transverse white lines and thickened pitted nails without onycholysis. Nail changes persisted throughout chemotherapy and returned to normal after its discontinuation.

In Europe, Almagro and colleagues⁸ reported 2 cases of onycholysis caused by paclitaxel use. Both patients had ductal carcinoma of the breast. Onset of onycholysis accompanied by red-brown discoloration of the nail occurred 3 months after beginning chemotherapy in the first patient. Painless onycholysis accompanied by subungual hyperkeratosis occurred 5 months after beginning therapy in the second patient. Both patients were able to complete their treatment. In the second case, nails returned to normal after several months.

Hussain et al⁹ reviewed the cases of 91 patients who had received paclitaxel therapy. They found that 5 patients had developed onycholysis while receiving treatment. All 5 patients had received

more than 6 courses of the drug. The authors further noted that onset of onycholysis occurred during the summer months in all cases. They postulated that exposure to sunlight may be a necessary precipitant for onycholysis secondary to paclitaxel use.⁹ Onset of onycholysis in our patient occurred in the summer. However, if UV light is responsible for rupturing the bond between the nail plate and the hyponychium as suggested by Hussain and colleagues, our patient should have developed onycholysis limited to the fingernails. His toes were well protected from UV exposure, yet he developed onycholysis of the great toenails.

To our knowledge, this is the first report of onycholysis associated with paclitaxel chemotherapy in the American dermatologic literature. We believe that the onycholysis seen in our patient was due to paclitaxel use and not to the secondary infection. All 10 fingernails had significant onycholysis, whereas only 3 nails had evidence of infection (probably facilitated by the onycholysis). In addition, it is unusual to have shedding of the entire nail in cases of routine paronychia. Further, paronychia and candidal infection are rare during routine chemotherapy. In general, cases of candidiasis in patients receiving chemotherapy involve the oropharynx and/or esophagus or present as systemic fungemia. In addition, such patients are usually receiving continuous sys-

temic steroids or are neutropenic. Neither of these risk factors was present in our patient.

Onycholysis also has been reported with the administration of bleomycin and vincristine in combination, as well as with cyclophosphamide, etoposide, fluorouracil, hydroxyurea, and methotrexate.¹ We believe weekly paclitaxel should be included in the category of chemotherapeutic agents that cause onycholysis. We do not believe that discontinuation of paclitaxel chemotherapy is required because regrowth of nails can generally be expected following completion of therapy.

REFERENCES

1. Correia O, Azevedo C, Pinto Ferreira E, et al. Nail changes secondary to docetaxel (Taxotere). *Dermatology*. 1999;198:288-290.
2. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol*. 1999;40:367-398.
3. Obermair A, Binder M, Barrada M, et al. Onycholysis in patients treated with docetaxel [letter]. *Ann Oncol*. 1998;9:230-231.
4. Llombart-Cussac A, Pivot X, Spielmann M. Docetaxel therapy induces transverse superficial loss of the nail plate [letter]. *Arch Dermatol*. 1997;133:1466-1467.
5. Slee PH. Images in clinical medicine. nail changes after chemotherapy. *N Engl J Med*. 1997;337:168.
6. Flory SM, Solimando DA Jr, Webster Gf, et al. Onycholysis associated with weekly administration of paclitaxel. *Ann Pharmacother*. 1999;33:584-586.
7. Link CJ Jr, Sarosy GA, Kohn EC, et al. Cutaneous manifestations of Taxol therapy. *Invest New Drugs*. 1995;13:261-263.
8. Almagro M, Del Pozo J, Garcia-Silva J, et al. Nail alterations secondary to paclitaxel therapy. *Eur J Dermatol*. 2000;10:146-147.
9. Hussain S, Anderson D, Salvatti ME, et al. Onycholysis as a complication of systemic chemotherapy: report of five cases associated with prolonged weekly paclitaxel therapy and review of the literature. *Cancer*. 2000;88:2367-2371.