

## Paclitaxel-Associated Melanonychia

To the Editor:

Taxane-based chemotherapy including paclitaxel and docetaxel is commonly used to treat solid tumor malignancies including lung, breast, ovarian, and bladder cancers.<sup>1</sup> Taxanes work by interrupting normal microtubule function by inducing tubulin polymerization and inhibiting microtubule depolymerization, thereby leading to cell cycle arrest at the gap 2 (premitotic) and mitotic phase and the blockade of cell division.<sup>2</sup>

Cutaneous side effects have been reported with taxane-based therapies, including alopecia, skin rash and erythema, and desquamation of the hands and feet (hand-foot syndrome).<sup>3</sup> Nail changes also have been reported to occur in 0% to 44% of treated patients,<sup>4</sup> with one study reporting an incidence as high as 50.5%.<sup>5</sup> Nail abnormalities that have been described primarily include onycholysis, and less frequently Beau lines, subungual hemorrhagic bullae, subungual hyperkeratosis, splinter hemorrhages, acute paronychia, and pigmentary changes such as nail bed dyschromia. Among the taxanes, nail abnormalities are more commonly seen with docetaxel; few reports address paclitaxel-induced nail changes.<sup>4</sup> Onycholysis, diffuse fingernail orange discoloration, Beau lines, subungual distal hyperkeratosis, and brown discoloration of 3 fingernail beds sparing the lunula have been reported with paclitaxel.<sup>6-9</sup> We report a unique case of paclitaxel-associated melanonychia.

A 54-year-old black woman with a history of multiple myeloma and breast cancer who was being treated with paclitaxel for breast cancer presented with nail changes including nail darkening since initiating paclitaxel. She was diagnosed with multiple myeloma in 2010 and received bortezomib,

dexamethasone, and an autologous stem cell transplant in August 2011. She never achieved complete remission but had been on lenalidomide with stable disease. She underwent a lumpectomy in December 2012, which revealed intraductal carcinoma with ductal carcinoma in situ that was estrogen receptor and progesterone receptor negative and *ERBB2* (formerly *HER2*) positive. She was started on weekly paclitaxel (80 mg/m<sup>2</sup>) to complete 12 cycles and trastuzumab (6 mg/kg) every 3 weeks. While on paclitaxel, she developed grade 2 neuropathy of the hands, leading to subsequent dose reduction at week 9. She denied any other changes to her medications. On clinical examination she had diffuse and well-demarcated, brown-black, longitudinal and transverse bands beginning at the proximal nail plate and progressing distally, with onycholysis involving all 20 nails (Figure, A and B). A nail clipping of the right hallux nail was sent for analysis. Pathology results showed evidence of scattered clusters of brown melanin pigment in the nail plate. Periodic acid-Schiff staining revealed numerous yeasts at the nail base but no infiltrating hyphae. Iron stain was negative for hemosiderin. The right index finger was injected with triamcinolone acetonide to treat the onycholysis. Four months after completing the paclitaxel, she began to notice lightening of the nails and improvement of the onycholysis in all nails (Figure, C and D).

The highly proliferating cells that comprise the nail matrix epithelium mature, differentiate, and keratinize to form the nail plate and are susceptible to the antimetabolic effects of systemic chemotherapy. As a result, systemic chemotherapies may lead to abnormal nail plate production and keratinization of the nail plate, causing the clinical manifestations of Beau lines, onychomadesis, and leukonychia.<sup>10</sup>

Melanonychia is the development of melanin pigmentation of the nail plate and is typically caused by matrix melanin deposition through the activation of nail matrix melanocytes. There are 3 patterns of melanonychia: longitudinal, transverse, and diffuse. A single nail plate can involve more than one pattern of melanonychia and several nails may be affected. Longitudinal melanonychia typically develops from the activation of a group of melanocytes in the nail matrix, while diffuse pigmentation arises from diffuse melanocyte activation.<sup>11</sup> Longitudinal melanonychia

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Initial appearance of diffuse, well-demarcated, brown-black, longitudinal and transverse bands beginning at the proximal nail plate and progressing distally, with onycholysis in the nails on the right hand (A) and left hand (B). Four months after completing paclitaxel, the patient began to notice lightening of the nails and improvement of the onycholysis in the nails on the right hand (C) and left hand (D).

is common in darker-pigmented individuals<sup>12</sup> and can be associated with systemic diseases.<sup>10</sup> Transverse melanonychia has been reported in association with medications including many chemotherapy agents, and each band of transverse melanonychia may correspond to a cycle of therapy.<sup>11</sup> Drug-induced melanonychia can affect several nails and tends to resolve after completion of therapy. Melanonychia has previously been described with vincristine, doxorubicin, hydroxyurea, cyclophosphamide, 5-fluorouracil, bleomycin, dacarbazine, methotrexate, and electron beam therapy.<sup>11</sup> Nail pigmentation changes have been reported with docetaxel; a patient developed blue discoloration on the right and left thumb lunulae that improved 3 months after discontinuation of docetaxel therapy.<sup>13</sup> While on docetaxel, another patient developed acral erythema, onycholysis, and longitudinal melanonychia in photoexposed areas, which was thought to be secondary to possible photosensitization.<sup>14</sup> Possible explanations for paclitaxel-induced melanonychia include a direct toxic effect on the nail bed or nail matrix,

or melanocytes, or photosensitization. Drug-induced melanonychia commonly appears 3 to 8 weeks after drug intake and typically resolves 6 to 8 weeks after drug discontinuation.<sup>15</sup>

Predictors of taxane-related nail changes have been studied.<sup>5</sup> Taxane-induced nail toxicity was more prevalent in patients who were female, had a history of diabetes mellitus, had received capecitabine with docetaxel, and had a diagnosis of breast or gynecological cancer. The nail changes increased with greater number of taxane cycles administered, body mass index, and severity of treatment-related neuropathy.<sup>5</sup> Although nail changes often are temporary and typically resolve with drug withdrawal, they may persist in some patients.<sup>16</sup> Possible measures have been proposed to prevent taxane-induced nail toxicity including frozen gloves,<sup>17</sup> nail cutting, and avoiding potential fingernail irritants.<sup>18</sup>

It is possible that the nails of our darker-skinned patient may have been affected by some degree of melanonychia prior to starting the therapy, which cannot be ruled out. However, according to the

patient, she only noticed the change after starting paclitaxel, raising the possibility of either new, worsening, or more diffuse involvement following initiation of paclitaxel therapy. Additionally, she was receiving weekly administration of paclitaxel and experienced severe neuropathy, both predictors of nail toxicity.<sup>5</sup> No reports of melanonychia from lenalidomide have been reported in the literature indexed for MEDLINE. Although these nail changes are not life threatening, clinicians should be aware of these side effects, as they are cosmetically distressing to many patients and can impact quality of life.<sup>19</sup>

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