Cutaneous Fibrosis Induced by Docetaxel

A Case Report

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BACKGROUND. Docetaxel is a taxoid antineoplastic agent approved for use in the treatment of metastatic breast carcinoma. The current study reports an unusual case of generalized cutaneous fibrosis in a 39-year-old white female after treatment with 18 cycles of docetaxel for metastatic breast carcinoma.

METHODS. Cutaneous fibrosis represents a rare and unique reaction associated with the cyclic use of docetaxel. The reaction is manifested by a distinct sequence of events involving pronounced edema followed by the rapid development of cutaneous fibrosis in dependent areas.

RESULTS. Cessation of therapy results in dramatic reversal of the fibrotic process.

CONCLUSIONS. This case report further substantiates the belief that docetaxel represents one of a very limited number of agents that appear capable of giving rise to scleroderma-like features. ***Cancer* 2000;88:1078–81.**

KEYWORDS: medical oncology, chemotherapy, scleroderma, drug side effects, fibrosis.

Docetaxel (Taxotere; Rhone-Poulenc Rorer, Collegeville, PA) is an antineoplastic agent belonging to the taxoid family. The drug is prepared from a precursor extracted from the needle biomass of yew plants.[1] Docetaxel functions as an antineoplastic agent by disruption of the microtubular network that is essential for normal mitotic processes. The drug binds to free tubulin and promotes the formation of microtubules. This process leads to the stabilization of microtubule bundles and prevents their disassembly during normal phases of the cell cycle. In this manner, mitosis is inhibited.

Cutaneous reactions involving docetaxel are well described and generally give rise to transient erythrodysesthesia wherein erythematous patches or plaques are found with associated sensory changes.[2] These reactions usually are mildly symptomatic and rarely restrict further use of docetaxel. Erythrodysesthesia routinely resolves within days to weeks and full recovery usually is noted prior to the next cycle of therapy. In 5.6% of patients, the erythema and edema can lead to desquamation. Adjustment of the dose is recommended in these cases. The discontinuation rate due to skin toxicity is reported at 1.7%. Neurosensory symptoms occur in 7% of cases whereas fluid retention is noted in 17.4% of cases.

To our knowledge, a single report describing three patients exists that links docetaxel with the development of scleroderma-like features.[3] The case study reported here presents an additional patient in whom a unique cutaneous reaction involving generalized fibrosis was associated with docetaxel use. Features of this syndrome appear to be unique to docetaxel and to our knowledge have not been described

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for other drugs or environmental agents that can give rise to scleroderma-like reactions.

Case Report

A 39-year-old white woman with metastatic breast carcinoma was placed on cyclic docetaxel therapy after failing to respond to a prior chemotherapeutic regimen. She first was diagnosed with infiltrating ductal carcinoma of the left breast 6 years prior to the use of docetaxel. After a lumpectomy, an axillary lymph node dissection revealed positive metastatic involvement in 3 of 12 nodes. She received adjuvant chemotherapy with 5-fluorouracil, leucovorin, and doxorubicin along with radiation therapy to the left chest. Recurrence of the breast carcinoma was noted 4 years later with metastases to the brain and lung. After complete resection of the brain metastasis, the patient underwent readministration of the doxorubicin-based regimen with an initial good response. However, progression of the metastatic disease was noted.

Treatment then was initiated with cyclic docetaxel therapy on an every-4-weeks basis. The docetaxel dose was 125 mg/m^2, with premedication with dexamethasone. In addition, local radiation therapy to the brain was initiated. Anastrazole was started at the same time as docetaxel. The patient's clinical status improved as evidenced by regression of the brain and lung metastases with no further development of new metastasis. She did not experience any skin or sensory changes. The patient tolerated cyclic therapy well for nearly 18 months. During this time, only mild intermittent edema was noted in the left upper extremity, in which the lymphatic drainage had been disrupted by prior lymph node dissection. After the 18th cycle of therapy, the patient was noted to have dependent edema of the legs for which diuretic therapy was instituted (spironolactone and furosemide).

Over a period of 3 months, the patient experienced progressive incoordination and weakness. Simultaneously, a diffuse cutaneous sclerosis was noted, predominantly of the lower extremities, lower trunk, and distal upper extremities. The fibrosis was extensive enough to cause her to have difficulty in rising from a chair or climbing stairs. A formal neurologic examination, which included electromyography studies, revealed normal findings. Her coordination and strength deficits were believed to be in direct proportion to the substantial fibrosis noted on cutaneous examination. She had no history of pleuritic chest pain, Raynaud phenomenon, dysphagia, shortness of breath, or other bowel or urinary symptoms.

Cutaneous examination of the patient revealed a diffuse induration of the skin in dependent areas involving the distal upper extremities, lower extremities, and lower trunk including the buttocks, lower abdomen, and perineum (approximately 50% of her body surface area). Very mild pitting edema was found only on the distal left upper extremity. No erosions, telangiectasias, or pigmentary changes were found. The fibrotic process spared the upper trunk, proximal upper extremities, and head and neck areas. Moderate flexion contractures were present in multiple fingers at the distal and proximal interphalangeal joints. Hip flexion was limited to 90° bilaterally. In addition, tendon rubs were present on the bilateral forearms. Moderate flexion and extension restrictions were found bilaterally in the wrists, hips, and ankles. All joints lacked evidence of effusion or synovitis, and cardiac, pulmonary, and abdominal examinations were otherwise unremarkable.

Skin biopsy from the left thigh, extending into the subcutaneous fat, revealed mild to moderate fibrosis with mild vascular dilatation. Perivascular inflammatory infiltrates were noted in the superficial dermis with delicate fibrosis at the interface between the adipose tissue and dermis. In addition, there was evidence of adnexal structure entrapment and atrophy, as shown in Figure 1. Laboratory studies included the following normal findings: complete blood count, chemistry profile, sedimentation rate, serum protein electrophoresis, antinuclear antibody, extractable nuclear antigen, SCL-70 antibody, RNP/SM antibody, creatinine phosphokinase, vitamin B-12, thyroid-stimulating hormone, and antineutrophilic cytoplasmic antibody.

The constellation of unusual physical findings led to a literature review to determine whether other reports of similar cutaneous fibrosis had been described in patients undergoing cyclic therapy with docetaxel. To our knowledge a single report exists describing three patients with similar cutaneous findings restricted to the distal lower extremities.[3] Therapy with docetaxel was discontinued and the patient was observed over several weeks for changes in the fibrotic process. Within 3 weeks the cutaneous tissues began to soften with near-complete resolution after 6 weeks of observation. No residual functional impairment was noted 6 weeks after cessation of the docetaxel. At last follow-up the patient had received no further chemotherapeutic intervention. Full informed consent was obtained from the patient for publication of this case.

DISCUSSION

To our knowledge the current case study represents the second report and fourth patient described to have cutaneous fibrosis after cyclic therapy with docetaxel. In our patient, approximately 50% of her body surface

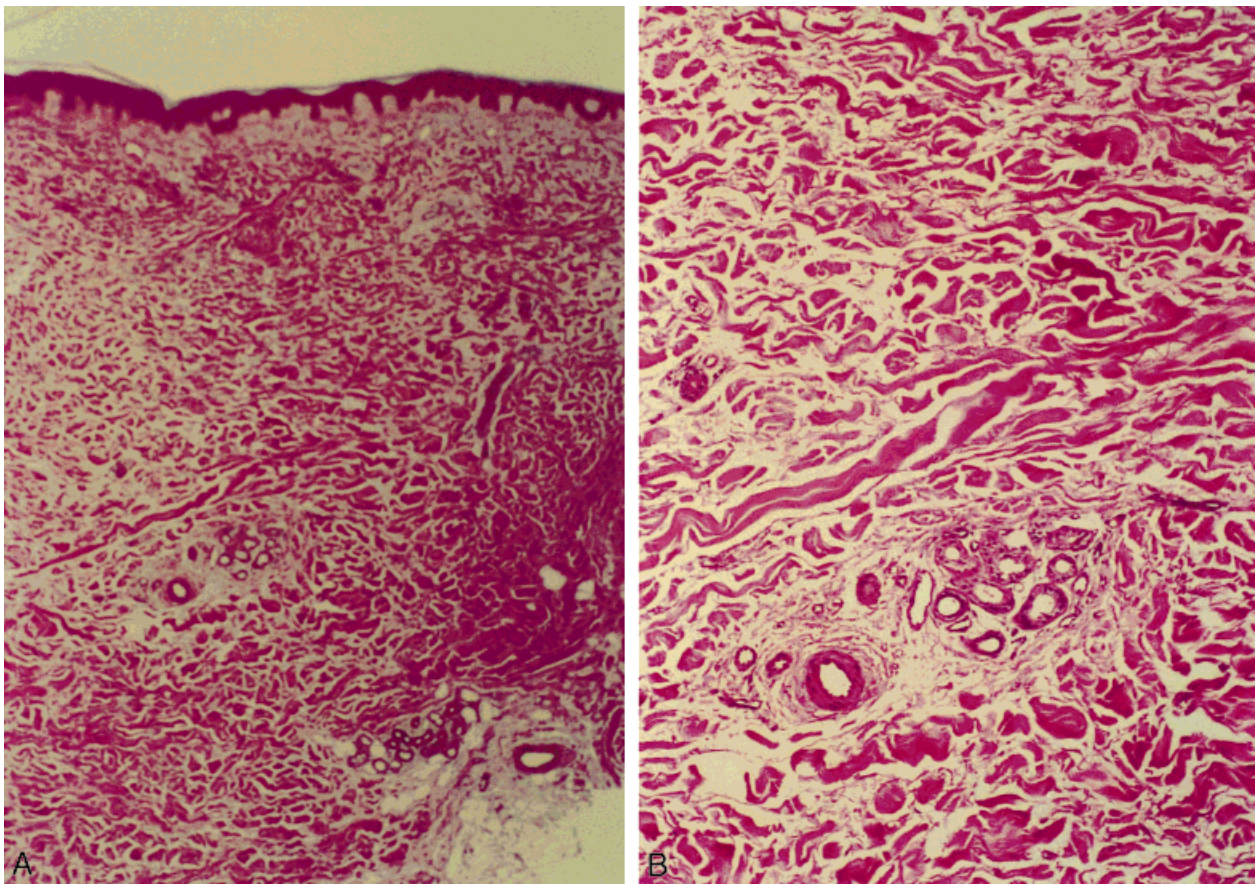

FIGURE 1. (a and b) Skin biopsy from the right thigh showing fibrosis and adnexal structure atrophy.

area was involved by the fibrotic process, whereas the cases reported by Battafarano et al. primarily involved the distal lower extremities.[3] All four reported cases describe a very similar syndrome in which scleroderma-like changes are noted in dependent areas after pronounced edema, usually of the lower extremities. Apparently, the fibrosis appears only after multiple cycles of docetaxel. The fibrosis was noted after 18 cycles in our patient and after 7–13 cycles in the cases reported by Battafarano et al.[3] In all the reported cases, profound restrictions in flexion and extension were found in the affected joint areas without evidence of synovitis. Skin biopsies were consistent with moderate fibrosis and other laboratory studies were unremarkable. It is interesting to note that, the cutaneous sclerosis and associated functional deficits improved substantially when the docetaxel therapy was discontinued, even in the extensive case reported here.

Our patient differed from those in the study by Battafarano et al.[3] in that our patient demonstrated more extensive involvement. In addition, specific tendon rubs were present in our patient, possibly indicating involvement of deeper fascial planes. This type of drug-induced cutaneous reaction appears to be unique among drugs reported to cause fibrosis with regard to the rapid development of fibrosis over a few months' time followed by rapid reversal after discontinuation of the medication.

Docetaxel has been associated with an acute cutaneous reaction, namely erythrodysesthesia, which is characterized by discreet erythematous patches or edematous plaques that begin acrally and may be asymptomatic, pruritic, or painful.[2,4] These reactions usually resolve with possible mild desquamation over 3–5 weeks. Acute involvement can result in tingling and decreased sensation. Erythrodysesthesia has been associated with other chemotherapy agents including 5-fluorouracil and cytarabine.[5–7] To minimize these symptoms of erythrodysesthesia, a pretreatment regimen involving systemic corticosteroids is advised. Edema also appears to be a relatively common side effect of multiple courses of docetaxel, involving up to 47% of individuals.[2] The fluid retention may range from mild to severe, with 9% of patients requiring discontinuation of the therapy secondary to the fluid retention.[1] It is interesting to note that, another taxane

chemotherapeutic agent, paclitaxel, also can give rise to edema in 21% of patients.[8] However, to our knowledge paclitaxel has not been reported to be associated with fibrosis.

This report further substantiates that docetaxel is one of a very limited number of medications that can be associated with the development of fibrosis. Medications that may lead to fibrotic syndromes include bleomycin and L-tryptophan (associated with eosinophilia-myalgia syndrome). The majority of cases of fibrosis associated with the use of contaminated lots of L-tryptophan were manifested by histology resembling eosinophilic fasciitis with peripheral eosinophilia and generalized myalgias.[9] Conversely, bleomycin gives rise to more typical scleroderma-like changes.[10] Bleomycin also has been associated with fibrosis in areas of skin treated by localized radiotherapy.[11] Other medications rarely associated with scleroderma-like changes include pentazocine, isoniazid, valproic acid, carbidopa, bromocriptine, nitrofurantoin, and, most recently, fosinopril.[12,13]

Multiple mechanisms have been proposed to explain drug-induced or idiopathic cutaneous fibrosis.[14] The exact mechanism whereby docetaxel produces sclerosis largely is unknown. In prior studies involving individuals with systemic sclerosis, fibroblast activation occurs, which leads to increased amounts of collagen deposition.[15] Multiple cytokines and growth factors are able to modulate extracellular matrix production by fibroblasts.[16] Positive regulators would include transforming growth factor-β, extracellular tissue factor, interleukin-4, and interleukin-6. Other proposed mechanisms include changes in the vascularity of scleroderma-affected skin.[17]

Microvascular injury appears to be an early event in the development of scleroderma as evidenced by a reduction in the number of capillaries, endothelial swelling, basement membrane thickening, intimal hyperplasia, and a perivascular inflammatory cell infiltrate.

We believe the current study further substantiates the finding of Battafarano et al. that cyclic therapy with docetaxel rarely can give rise to remarkable scleroderma-like changes of the skin.[3] This reaction appears to be characterized by a preceding edematous phase with the subsequent development of fibrosis in the affected tissues. Our case further implies that the reaction can be quite extensive, involving up to 50% of the body surface area. To our knowledge, in all reported cases to date, therapy was discontinued due to the potential progressive nature of the fibrotic process, which then led to considerable reversal of the associated fibrosis over time. Features of this cutaneous fibrosis are important to recognize in future patients who may develop similar reactions to docetaxel.

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