

A Case of Scleroderma-like Cutaneous Lesions Induced by Docetaxel in a Patient with Breast Cancer

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Docetaxel, an anti-microtubule agent, has been reported to show cytotoxic effects in solid tumors. Its toxicities also include neutropenia, alopecia, skin reaction, and fluid retention. In this study, we report on a case of a 57-year-old Korean female who presented with rapidly progressive scleroderma-like cutaneous changes in the upper and lower extremities after administration of docetaxel. Results of the following tests were normal or negative: full blood count, serum urea, creatinine, electrolytes, liver function test, thyroid function test, rheumatoid factor, anti-nuclear

antibody, and anti-topoisomerase antibody. No structural abnormalities were noted on esophagogastroduodenoscopy, chest computed tomography, and Doppler ultrasonography. A biopsy of skin from the left calf showed dermal sclerosis. There was no other explanation for the lesion, except a scleroderma-like cutaneous change induced by docetaxel in this Korean female undergoing treatment for breast cancer.

Key Words. Scleroderma-like cutaneous lesion, Docetaxel, Skin lesion

Introduction

Docetaxel is an antineoplastic agent that disrupts the microtubular network needed for the normal progression of mitosis. It binds to free tubulin and promotes formation of the microtubule structure (1). In this way, the microtubule bundles become stable and their disassembly is interrupted in the normal phase of the cell cycle. This prevents the completion of mitosis, so that docetaxel acts as an antineoplastic agent. Docetaxel is therefore widely used as an antimicrotubule agent to treat solid tumors, especially breast, gastric, and other cancers.

The major dose-related toxicities reported for docetaxel are neutropenia and mucositis (1). Other reported toxicities include neuropathies, fluid retention, and acute cutaneous reactions. The cutaneous reactions are usually asymptomatic or, in rare cases, mildly symptomatic of impaired function and can include urticaria, pruritis, flushing, hypersensitivity, injection site reaction, acral erythema, and erythrodysesthesia. Toxicity in the form of skin thickening of the extremities is

seldom encountered after docetaxel treatment. We report a case of a rapidly progressing scleroderma-like cutaneous change that occurred in both the upper and lower extremities after docetaxel treatment for breast cancer.

Case Report

A 57-year-old Korean woman was diagnosed with breast cancer (infiltrating ductal carcinoma, grade 2) in a hospital. She underwent a left modified radical mastectomy (May 2008). Biopsy showed the tumor to be pathological stage IIIc (pT2N3M0), estrogen receptor (ER) positive, progesterone receptor (PR) positive, and C-erb B2 negative. She received adjuvant chemotherapy with 4 cycles of adriamycin and cyclophosphamide (from June 2008 to August 2008), followed by 4 cycles of paclitaxel (from August 2008 to October 2008). She was stable in the disease with letrozole for 8 months (until June 2009). Her follow-up image showed metastatic lesions in the first sacral bone, the posterior aspect of left iliac

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spine, and the right ischium. She visited our hospital and received radiotherapy to the sacral bone and both proximal femurs (September 2009) and then chemotherapy for a total of 9 cycles with docetaxel (75 mg/m^2) for 7 months (from September 2009 to April 2010). During that chemotherapy, her breast cancer was stable without aggravation. During the 7th to 9th cycle of docetaxel (from February 2010 to April 2010), she experienced the following symptoms for about 2 months: mild to generalized edema on both hands and feet, a 13-kg weight gain, and thickened and hardened skin on the both upper and lower extremities, especially on the dorsum of both hands and feet (Figure 1).

She was a housewife. There was no family history or cardiopulmonary, gastrointestinal, or genitourinary symptoms. The following tests were negative or normal: full blood count, erythrocyte sedimentation rate (ESR), c-reactive protein

(CRP), brain natriuretic peptide (pro-BNP), serum urea, creatinine, electrolytes, liver and thyroid function test. Chest computed tomography (CT) showed no evidence of cardiomegaly, pulmonary edema, or active lung lesions. Doppler ultrasonography showed no evidence of deep vein thrombosis or structural abnormality. An expert in breast surgery concluded that there was no reason for an association of the skin lesion with lymphedema or surgical complication. The edema was suggestive of general edema rather than lymphedema according to the radiologist.

We considered the possibility of scleroderma, malignancy-associated scleroderma, or a scleroderma-like cutaneous change induced by docetaxel. We observed sclerodactyly but the patient showed no digital pitting scars, Raynaud's phenomenon, calcinosis, telangiectasis, pulmonary lesion, or esophageal lesion identified by esophagogastroduodenoscopy

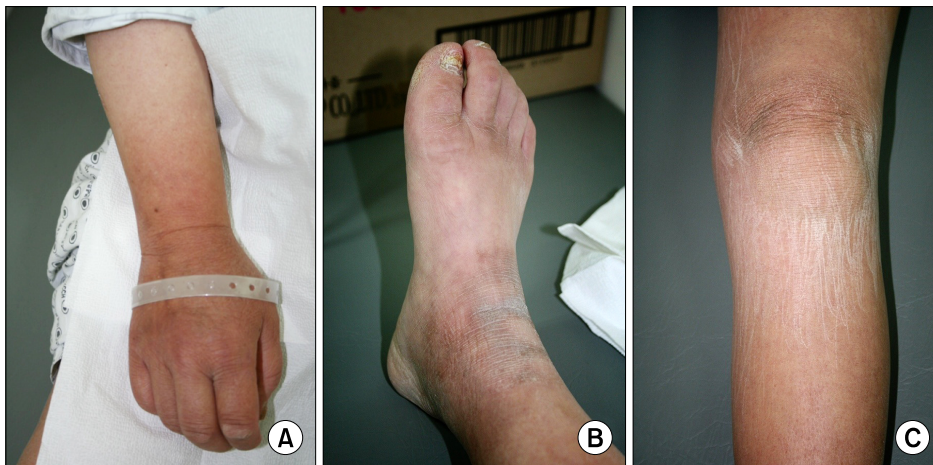


Figure 1. Thickened and hardened skin with edema on both hands (A), feet (B), and the left lower extremity (C).

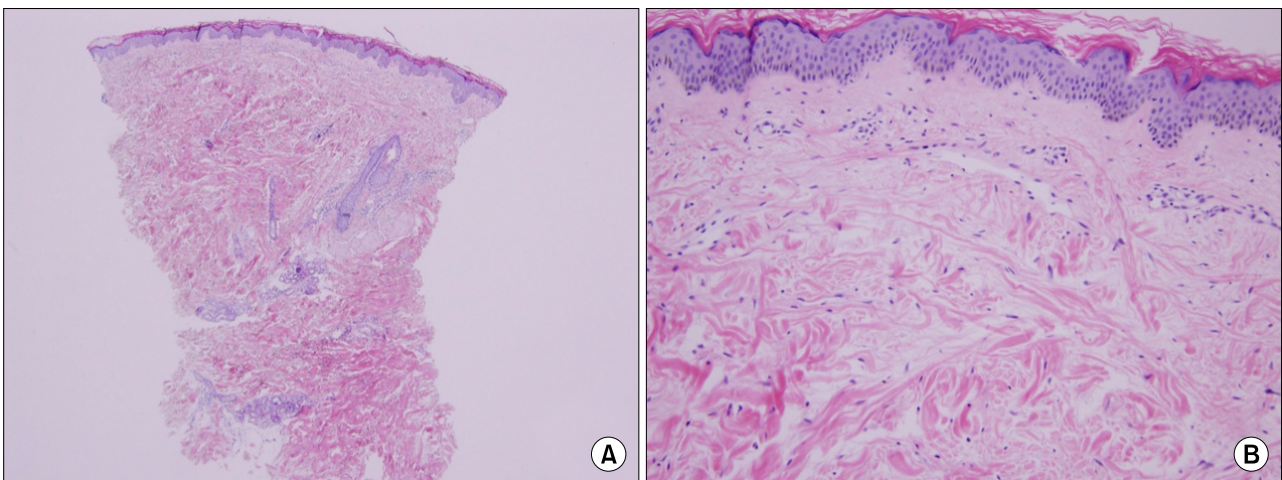


Figure 2. The biopsy was taken from the skin of the left calf. The skin biopsy section shows diffuse dermal sclerosis with discretely thickened collagen bundles in the dermis (hematoxylin-eosin stain; original magnification: (A) $\times 40$ (B) $\times 200$).

(EGD) and she had no past history or family history of connective tissue or rheumatologic disease. Serum anti-topoisomerase antibody, anti-centromere antibody rheumatoid factor (RF), fluorescent antinuclear antibody (FANA), and anti-neutrophil cytoplasm antibody (ANCA) were all negative or within normal limits. Unfortunately, a nailfold capillary test and lymphangiography could not be performed because the equipment was not available. A skin biopsy of the left calf showed diffuse dermal sclerosis with thickened collagen bundles in the dermis (Figure 2).

The administration of docetaxel was discontinued because of the hardening and thickening of the skin on both upper and lower extremities, poor performance, and gait disturbance associated with generalized edema. The lesions were initially managed by furosemide 20 mg intravenously once a day and prednisolone 30 mg orally once a day. After 3 months of this treatment, the edema, the hardening and thickening of the skin on both upper and lower extremities, and the weight gain were almost resolved and the gait disturbance was improved. Because the patient showed severe dysfunctions, like the gait disturbance, and poor performance in her daily life after the administration of docetaxel, and also because she had already been treated with the anthracyclines and taxanes that are effective and widely used in breast cancer, our remaining option was to change to the third chemotherapy, gemcitabine and vinorelbine, for 4 cycles (from June 2010 to August 2010). However, this treatment for breast cancer was stopped in a short course as she showed poor performance in daily activities and aggravated breast cancer. The skin lesions were not seen again. She was managed with supportive care for breast cancer. Eventually, she died of extensive pneumonia and breast cancer (May 2011).

Discussion

We report a case of a Korean female with progressive scleroderma-like cutaneous lesions on the upper and lower extremities after docetaxel chemotherapy for breast cancer. Systemic sclerosis (scleroderma) is a connective tissue disorder of unknown cause that shows heterogeneous clinical symptoms and a chronic and often progressive course (2). Scleroderma is characterized by thickening of the skin and/or involvement of multiple internal organs, with the presence of immunologic antibodies.

We took the patient's history again to evaluate her for known rheumatic symptoms. This case had no symptoms associated with any rheumatic condition prior to docetaxel. The proximal (truncal) parts of the skin and other visceral organs were not involved. The histological features of the skin biopsy speci-

men from the left calf showed marked dermal sclerosis with thickened collagen bundles in the dermis. The scleroderma progressed relatively rapidly, as the edematous lesion turned into thickened skin over a two month time span. The diagnosis of scleroderma-like cutaneous lesions induced by docetaxel, rather than scleroderma, was suggested because the patient showed no proximal skin thickening, no digital pitting scars, no bibasilar pulmonary fibrosis, no Raynaud's phenomenon, and her autoantibody tests were negative except for sclerodactyly (3). In addition, the skin lesions improved after discontinuance of the docetaxel and the skin lesions did not reappear after the interruption of the drug.

In this case, the duration of the scleroderma-like cutaneous lesions after the initiation of docetaxel was over a year and a month. In several case studies, paclitaxel or docetaxel-induced scleroderma mostly presented within 1 year (4). In a post-marketing study based on 63 reports from FDA (The U.S. Food and Drug Administration) and user community by eHealthMe, 14,867 people (September 2012) reported side effects when taking paclitaxel. Among these, 63 people (0.42%) had scleroderma. The most common interval from the time of initiating the drugs to the time of scleroderma development was 6~12 months in 80.00% of the patients.

Fluid retention appears to be related to the cumulative dose of docetaxel, increasing in incidence at cumulative doses of over 400 mg/m² (1). In this case, the scleroderma-like cutaneous lesions appeared 5 months after the initiation of docetaxel. A docetaxel accumulation dose of over 400 mg/m² (525 mg/m²) over 5 months could therefore cause fluid retention and trigger scleroderma-like cutaneous lesion. Docetaxel could promote edema and skin thickening to a greater extent than does paclitaxel.

Systemic chemotherapeutic agents such as docetaxel have known associations with scleroderma-like cutaneous reactions (5). In our case, scleroderma-like cutaneous lesions presented after 1 year and 3 months of cyclophosphamide and adriamycin treatment. It is possible, but probably too long a time had elapsed, for those drugs to have caused a scleroderma-like cutaneous change. In several other studies, cyclophosphamide is still being tested for prevention of disease progression (6). This further suggests a low likelihood that this drug is associated scleroderma-like cutaneous changes. In Koreans, some reports have shown an association between docetaxel and scleroderma-like cutaneous lesions in gastric and ovarian cancer patients (7,8). However, no case study has yet reported scleroderma-like cutaneous lesions after docetaxel treatment for breast cancer.

Several studies have suggested that drug-induced sle-

roderma could be associated with specific mechanisms. For example, transforming growth factor-beta (TGF-beta) expression and fibroblast activation could be important in scleroderma (9) and could be associated with the progressive fibrosis associated with it. Injury to the vascular endothelium and defective apoptosis of fibroblasts in the skin could also be responsible for scleroderma (10). Smad proteins are intracellular signaling effectors of the TGF-beta superfamily. Endogenous Smad-2, 3, and 4 molecules bind to microtubules (MTs), and this binding serves as a negative regulatory mechanism to control TGF-beta activity (11). Disruption of the MT network by chemical agents such as paclitaxel increases TGF-beta-induced Smad activity. Smad3 expression is increased in scleroderma fibroblasts, whereas inhibitory Smad7 is selectively decreased in these fibroblasts (12).

Our patient had undergone previous treatment when her breast cancer was diagnosed, so some possibility exists that the cutaneous lesion could be associated with malignancy. A strong association has been demonstrated between scleroderma and certain cancers, especially lung cancer and breast cancer (1). A relationship between paraneoplastic scleroderma and malignancy of the breast, ovary, uterus, and prostate has been reported in small numbers of patients. However, paraneoplastic scleroderma shows a much more rapid and severe progression than do other forms of scleroderma and is associated with a close temporal relationship between the development of scleroderma and malignancy (13). We cannot find any criteria that would exclude paraneoplastic scleroderma. The skin lesions took over a year to present following the discovery of the patient's malignancy. The edema, the hardening and thickening of the skin on both upper and lower extremities, and the weight gain were almost resolved after the discontinuation of docetaxel. In addition, the cancer was stable at the time of scleroderma diagnosis and the levels of the tumor marker CA 15-3 were normal. A paraneoplastic scleroderma was therefore considered less likely in this case. However, the interpretation of the association between scleroderma and cancer is complicated because some epidemiologic studies have suggested that patients with scleroderma have an increased risk of malignancy (14).

The scleroderma-like skin lesion observed in this patient was similar to myxedema and scleromyxedema. These are softer, more edematous skin changes and show deposits of mucin within the superficial dermis (15). The examination of the thickening and hardening of the skin by a physician and the biopsy result showed no evidence of these diseases in this case.

In conclusion, we describe here the first Korean female case of a scleroderma-like cutaneous lesion after docetaxel chemo-

therapy for breast cancer. Docetaxel is widely used and has been found to have a survival benefit in patients with breast and gastric cancer. The incidence of breast cancer is increasing and the use of docetaxel is expected to increase as well. In cases of edema and skin thickening of upper and lower extremities after docetaxel chemotherapy for breast cancer, a scleroderma-like cutaneous lesion should be considered as a differential diagnosis. Further study will be needed to determine the details regarding the association between docetaxel and scleroderma-like changes.

Summary

We describe here the first Korean female case of a scleroderma-like cutaneous lesion after docetaxel chemotherapy for breast cancer.

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