Scleroderma-Like Condition in Association with the Use of Docetaxel

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The taxanes, paclitaxel (Taxol®) and docetaxel (Taxotere®), are a new class of anti-microtubule agents which have shown cytotoxic activities in numerous solid tumors. Reported toxicities of docetaxel include dose limiting neutropenia, alopecia, skin reactions and fluid retention. Here we report a case of rapid onset, diffuse scleroderma-like condition, which occurred in a 55-year-old male receiving treatment with docetaxel and 5-fluorouracil (5-FU) for advanced gastric cancer. The temporal relationship between the onset of the skin involvement and administration of the drug may indicate an effect of docetaxel.
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Key Words: Scleroderma, Docetaxel

INTRODUCTION

Docetaxel (Taxotere®) is a new class of anti-microtubule agent that is used for the treatment of solid tumors. 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[1]. This process leads to the stabilization of microtubule bundles and prevents their disassembly during normal phase of the cell cycle. In this manner, mitosis is inhibited. The major dose limiting toxicity of docetaxel is neutropenia and mucositis. Other toxicities include neuropathies, fluid retention, generalized alopecia and acute cutaneous reactions. Acute cutaneous reactions are reported to be asymptomatic or mildly symptomatic which rarely impair function. They include urticaria, pruritis, flushing, hypersensitivity, injection site reaction, acral erythema and erythrodysesthesia which are characterized by discrete erythematous patches or edematous plaques that begin acrally. We report here a case of diffuse scleroderma-like change that occurred in both lower extremities during the treatment of advanced gastric cancer.

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CASE REPORT

A 55-year-old Korean male diagnosed with advanced gastric cancer visited our clinic with hidebound skin and generalized alopecia on both distal lower extremities (Fig. 1). The skin lesion started after the initiation of chemotherapy with 5-fluorouracil (5-FU) and docetaxel, which have been administered for a total of 10 courses. The patient experienced several other side effects, which did not require a change in the dose of 5-FU and docetaxel including chemotherapy induced acral erythema, mucositis, neutropenia, nail changes, arthralgias, myalgias, and severe fatigue. Edema of the distal lower extremities started immediately after the onset of chemotherapy with 5-FU and docetaxel that had been administered for a total of 10 courses. The edematous phase rapidly progressed into sclerosing

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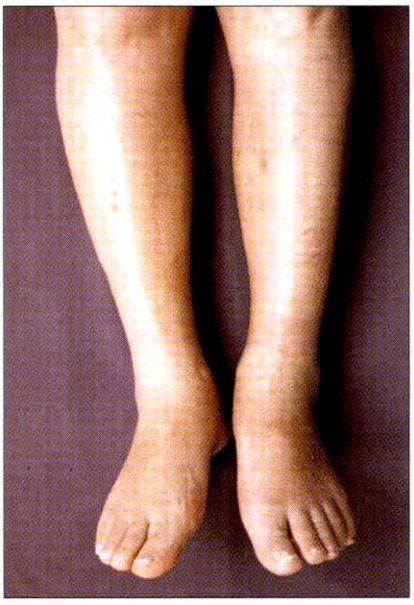

Fig. 1. Sclerotic and shiny skin with alopecia on the both lower extremities.

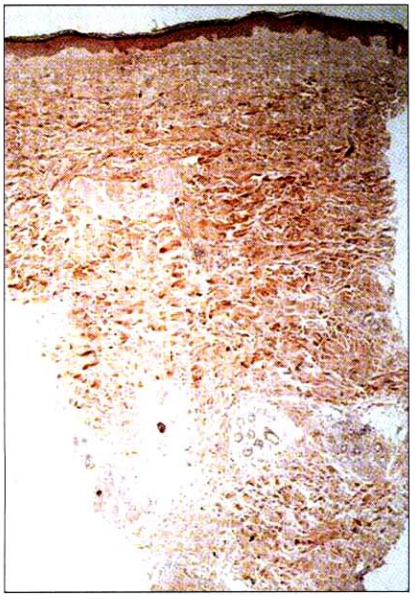

Fig. 2. Skin biopsy from the left leg showing increased thickness of dermis and replacement of fat into collagen around the skin appendages (Hematoxylin-eosin stain; original magnification×40).

phase within 2 months. Doppler sonography performed on both lower extremities showed no evidence of deep vein thrombosis.

A punch biopsy of the left lower leg was performed, revealing increased thickness and sclerotic collagen bands in the dermis that extended down to the subcutis (Fig. 2). Collagen replaced the fat around the eccrine gland, which appeared atrophic. A very mild perivascular chronic inflammatory infiltrate was noted. The histopathological appearance was consistent with scleroderma. Serology results were negative for antinuclear and anti-Scl 70 antibodies. The 11th course of chemotherapy was cancelled due to poor general condition and gradually evolving diffuse tightening of both extremities. Prednisolone (40 mg/day) was recommended and after 3 months of treatment, the diffuse tightening of both lower extremities was gradually resolved. Chemotherapy with 5-fluorouracil (5-FU) and docetaxel was changed to capecitabine. The patient's skin lesion did not recur afterwards.

DISCUSSION

We report here a case of a diffuse scleroderma-like condition in a male patient with advanced gastric cancer receiving docetaxel and 5-FU. Prior to the commencement of the medications, the patient showed no suggestive symptoms of an underlying connective tissue disease. The serologic results were negative for antinuclear and anti-Scl 70 antibodies. There was no family or occupational histories that may have placed him at a risk for the development of scleroderma. Although there have been one report of scleroderma-like reaction induced by uracil-tegafur (UTF)[2], it is not as well known as docetaxel yet. The patient described in the current paper demonstrated similar phases of dermal involvement seen in systemic sclerosis[3]. However, unlike systemic sclerosis, there was a rapid transition from edematous to sclerosing phase within 2 months and there was only slight evidence of endothelial injury on biopsy specimens. Clinical variants of systemic sclerosis have been described in patients after exposure to certain organic solvents (i.e., vinyl chloride, benzene, toluene), drugs (i.e., bleomycin, carbiodopa, pentazocine, cocain), and miscellaneous substances (i.e., rapeseed oil/aniline, silicone implants, L-trytophan)[4,5]. Clinically, diffuse variety of scleroderma-like condition must be distinguished from myxedema, scleredema, and scleromyxedema in which the parts are softer, more edematous, and not atrophic.

Multiple mechanisms have been proposed to explain drug-induced or idiopathic cutaneous fibrosis[6]. The exact mechanism whereby docetaxel produces sclerosis is unknown. In prior studies involving individuals with systemic sclerosis, fibroblast activation occurs which leads to an increased amount of collagen deposition[7]. Multiple cytokines and growth factors are able to modulate extracellular matrix production by fibroblasts[8]. Positive regulators 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[9].

Previously, eight cases of scleroderma-like conditions associated with taxanes[10-16] have been reported in the literature. Six of the patients were induced by docetaxel and three were by paclitaxel. To our knowledge, this is the first case report of a scleroderma-like condition induced by docetaxel in Korea. With increasing clinical use of taxanes, we should be aware of their potential to lead to clinical variants of scleroderma.

REFERENCES

1. Gueritte-Voegelian F, et al.: Relationships between the structure of taxol analogues and their antimitotic activity. J Med Chem 1991;34:992-998.
2. Kono T, Ishii M, Negoro N, Taniguchi S: Scleroderma-like reaction induced by uracil-tegafur (UTF), a second-generation anticancer agent. J Am Acad Dermatol 2000;42:519-520.
3. Silver RM: Clinical aspects of systemic sclerosis (scleroderma). Ann Rheum Dis 1991;50:846-853.
4. Perez MI, Kohn SR: Systemic sclerosis. J Am Acad Dermatol 1993;28:525-547.
5. Yoshida S, Gershwin ME: Autoimmunity and selected environmental factors of disease induction. Semin Arthritis Rheum 1993;22:399-419.
6. White B: Immunopathogenesis of systemic sclerosis. Rheum Dis Clin North Am 1996;22:1242.
7. Jimenz SA, Hitraya E, Varga J: Pathogenesis of scleroderma: collagen. Rheum Dis Clin North Am 1996;22:647-674.
8. Piela-Smith TH, Korn JH: Lymphocyte modulation of fibroblast function in systemic sclerosis. Clin Dermatol 1994;12:369-377.
9. Kahaleh MB: The role of vascular endothelium in the pathogenesis of connective tissue disease: endothelial injury activation, participation and response. Clin Exp Rheum 1990;8:595-601.
10. Zimmerman GC, et al.: Acute cutaneous reaction to Doxetaxel, a new chemotherapeutic agent. Arch Dermatol 1995;131:202-206.
11. Cleveland MG, Ajaikumar BS, Reganti R: Cutaneous fibrosis induced by doxetaxel: a case report. Cancer 2000;88:1078-1081.
12. Hassett G, Harnett P, Manolios N: Scleroderma in association with the use of doxetaxel (taxotere) for breast cancer. Clin Exp Rheum 2001;19:197-200.
13. Battafarano DF, Zimmerman GC, Older SA, Keeling JH, Burris HA: Doxetaxel (Taxotere) associated scleroderma-like changes of the lower extremities. Cancer 1995;76:110-115.
14. Kupfer I, Balguerie X, Courville P, Chinet P, Joly P: Scleroderma-like cutaneous lesions induced by paclitaxel: A case study. J Am Acad Dermatol 2003;48:279-281.
15. Lauchli S, Trueb RM, Fehr M, Hafner J: Scleroderma-like drug reaction to paclitaxel (Taxol®). Br J Dermatol 2002;147:619-621.
16. De Angelis R, Bugatti L, Cerioni A, Del Medico P, Filosa G: Diffuse scleroderma occurring after the use of paclitaxel for ovarian cancer. Clin Rheumatol 2003;22:49-52.