Taxane-induced morphea in a patient with CREST syndrome

Susan M. Bouchard, Melinda R. Mohr, Robert J. Pariser

Department of Dermatology, Eastern Virginia Medical School, Norfolk, VA, USA

Abstract

The taxanes, docetaxel and paclitaxel, are microtubule stabilizing chemotherapeutic agents that have demonstrated antineoplastic effects in a variety of solid tumors. They have been linked to the development of localized cutaneous sclerosis in some patients. We present a case of docetaxel-induced cutaneous sclerosis of the lower extremities in a patient with pre-existing CREST syndrome. We propose that patients with a history of limited or diffuse systemic sclerosis should be given taxane chemotherapy with caution, as these patients may have an immunological predisposition for the development of drug-induced morphea.

Case Report

A 73-year old Caucasian woman received docetaxel and cyclophosphamide chemotherapy for treatment of poorly differentiated infiltrating ductal carcinoma of the breast. Past medical history was significant for osteoporosis, hypothyroidism, and CREST syndrome for 20 to 30 years. Medications included esomeprazole, zoledronate, calcium with vitamin D, levothyroxine, fish oil, aspirin, and a multivitamin. Prior to initiation of docetaxel, she exhibited physical changes consistent with longstanding CREST syndrome, including sclerodactyly, firm subcutaneous nodules consistent with calcinosis cutis, teleangiectasias, and gastroesophageal reflux without overt esophageal dysmotility. On review of systems, she cited a history of infrequent dyspneic episodes. During therapy with docetaxel, she noticed significant swelling of her legs. Three months after completion of her chemotherapy regimen, she presented with firm, erythematous, burning plaques of her lower legs (Figure 1). Additionally, she noticed worsening of her gastroesophageal reflux symptoms. Fluticasone propionate lotion was applied to the legs twice daily for 18 days without benefit. Six months after completion of her chemotherapy, she noticed a slight decrease in pain and stiffness of her legs without any other specific treatment.

Discussion

Scleroderma is a disease characterized by cutaneous and sometimes visceral sclerosis, vasculopathy, and the presence of autoantibodies. Localized cutaneous sclerosis is commonly termed morphea.[1] Systemic sclerosis (SSc) may be categorized into diffuse cutaneous systemic sclerosis (dSSc) and limited cutaneous systemic sclerosis (lSSc). Diffuse cutaneous SSc is characterized by truncal and acral skin involvement, early visceral disease, and a poorer prognosis. Alternatively, limited cutaneous SSc is limited to acral cutaneous involvement of the hands, face, feet, and forearms with occasional late visceral (predominately pulmonary) involvement.[1] CREST syndrome represents a form of lSSc and is manifested by calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias.[2]

The development of cutaneous sclerosis is typically preceded by tissue inflammation, endothelial cell activation, and edema.[3] Histopathological changes include dermal thickening with immense collagen accumulation and resulting epidermal atrophy, flattening of rete pegs, and obliteration of hair follicles and sebaceous and sweat glands.[2] Inflammatory cells commonly aggregate at the dermal-adipose junction, particularly in early lesions.[4] Cytokines produced by these inflammatory cells (transforming growth factor-β,[2] tumor necrosis factor-α (TNF-α),[5,6] interferon gamma (IFN-γ),[6] and interleukin-6 (IL-6)[7]) are all present at high levels in the serum of patients with scleroderma, and are thought to play a central role in the pathogenesis of the disease.[8]

Several studies have demonstrated an increased incidence of breast and lung cancers in patients with pre-existing SSc. Because the cases studied have typically shown a close temporal relationship between the onset of SSc and breast cancer, a number of theories have been proposed to illuminate a pathophysiological link between the two. One theory implicates the aforementioned inflammatory cytokines as promoters of breast and lung cancers. Also, increased endothelial cell activation seen in SSc may stimulate tumor development by elevating the levels of various growth factors. Others have investigated SSc as a possible paraneoplastic syndrome in these cases. Perhaps the most widely accepted theory is that SSc is often the result of the cancer treatment itself.[9]

A variety of chemical agents, including rapeseed oil, organic solvents, herbicides, silica, cocaine, bleomycin, penicillamine, L-tryptophan, pentazocine, ethosuximide,[10] and the taxane family of chemotherapeutic medications[11] have been associated with scleroderma or scleroderma-like changes of the skin.

The taxanes, which include docetaxel and paclitaxel, exert their antineoplastic effects by stabilizing microtubules thus halting mitosis and by inhibiting Bcl-2 to allow apoptosis.[12] These medicines are widely used in the treatment of breast, lung, and ovarian carcinomas.[13] Established toxicities include peripheral edema, neutropenia, and neuropathy.[11] In addition to scleroderma-like changes, cutaneous reactions of the taxanes include acral erythema, pustular eruption, bullous fixed drug eruption, erythema multiforme, onycholysis, erythrodyesthesia, and alopecia.[11,14]

There is a well-established association between the taxanes and scleroderma-like skin changes. Edema characteristically precedes the development of generalized morphea by a few months, and the sclerosis develops most prominently on the lower legs, sparing the hands and feet.[11] The taxanes cause an

Correspondence: Susan M. Bouchard, 7741 Dunfield Place, Apt. 4, Norfolk, VA 23505, USA. E-mail: susan.bouchard@gmail.com

Key words: CREST syndrome, scleroderma, morphea, docetaxel, taxane.

Contributions: SMB primary author; MRM clinical investigator and first editor; RJP clinical investigator and second editor.

Conflicts of interest: the authors have no conflict of interest to disclose.

Received for publication: 29 June 2010.
Accepted for publication: 1 July 2010.

Dermatology Reports 2010; 2:e9
doi:10.4081/dr.2010.e9

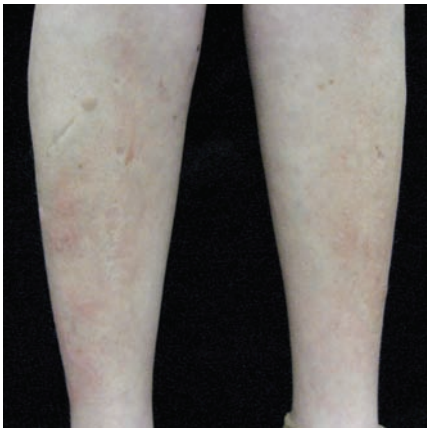

Figure 1. Firm, indurated, slightly erythematous plaques on bilateral lower legs.

increase in the expression of several of the same inflammatory cytokines that are naturally increased in patients with scleroderma, including TNF-α, IL-2, IL-6, and INF-γ.[2,11] This immunological *milieu* likely contributes to both the taxanes' therapeutic efficacy and the development of skin sclerosis.

Several cases of taxane-induced scleroderma have displayed dramatic improvement with simple withdrawal of chemotherapy.[14,15] Alternatively, it may be treated with systemic steroids and/or d-penicillamine.[11,16] Ironically, pencillamine has also been implicated as a cause of cutaneous sclerosis.[10]

We present this case because of our patient's distinguishing feature of pre-existing CREST syndrome. Patients with a history of scleroderma and subsequent or concurrent neoplasia may be immunologically predisposed to the development of drug-induced morphea. We propose that this population should be given taxane chemotherapy with caution in order to decrease the incidence of this rare, but potentially debilitating, side effect.

References

1. LeRoy EC, Krieg T, Black C, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
2. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann Intern Med 2004;140:441-51.
3. Krieg T, Takehara K. Skin disease: a cardinal feature of systemic sclerosis. Rheumatol 2009;48:14-8.
4. Fleischmajer R, Perlish JS, Reeves JRT. Cellular infiltrates in scleroderma skin. Arthritis Rheum 1977;20:975-84.
5. Sharpe RJ, Margolis RJ, Askari M, et al. Induction of dermal and subcutaneous inflammation by recombinant cachectin tumor necrosis factor (TNF-alpha) in the mouse. J Invest Dermatol 1988;91:353-7.
6. Gruschwitz MS, Vieth G. Up-regulation of class II major histocompatibility complex and intercellular adhesion molecule 1 expression on scleroderma fibroblasts and endothelial cells by interferon-gamma and tumor necrosis factor alpha in the early disease stage. Arthritis Rheum 1997;40: 540-50.
7. Hasegawa M, Sato S, Ihn H, et al. Enhanced production of interleukin-6 (IL-6), oncostatin M and soluble IL-6 receptor by cultured peripheral blood mononuclear cells from patients with systemic sclerosis. Rheumatol 1999;38:612-7.
8. Sato S. Abnormalities of adhesion molecules and chemokines in scleroderma. Curr Op Rheumatol 1999;11:503-7.
9. Launay D, Le Berre R, Hatron PY, et al. Association between systemic sclerosis and breast cancer: eight new cases and review of the literature. Clin Rheumatol 2004;23:516-22.
10. Zhai H, Wilhelm K-P, Maibach HI. Dermatotoxicology. Fair Lawn, NJ: Informa HealthCare; 2007.
11. Itoh M, Yanaba K, Kobayashi T, et al. Taxane-induced scleroderma. Br J Dermatol 2007;156:363-7.
12. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by Taxol. Nature 1979;277:665-7.
13. Kingston DGI, Bane S , Snyder JP. The Taxol pharmacophore and the T-Taxol bridging principle. Cell Cycle 2005;4:279-89.
14. Kupfer I, Balguerie X, Courville P, et al. Scleroderma-like cutaneous lesions induced by paclitaxel: A case study. J Am Acad Dermatol 2003;48:279-81.
15. Battafarano DF, Zimmerman GC, Older SA, et al. Docetaxel (Taxotere) associated scleroderma-like changes of the lower-extremities – a report of 3 cases. Cancer 1995;76:110-5.
16. De Angelis R, Bugatti L, Cerioni A, et al. Diffuse scleroderma occurring after the use of paclitaxel for ovarian cancer. Clin Rheumatol 2003;22:49-52.