Paclitaxel-Related Lymphedema and Scleroderma-Like Skin Changes

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Abstract
Paclitaxel is an antimicrotubule agent used for the treatment of metastatic breast cancer. The development of scleroderma-like skin changes is an exceptional adverse effect. We report two patients with metastatic breast cancer treated by paclitaxel who presented an unexplained unilateral lymphedema of the upper limb. Medical work-up did not demonstrate any mechanical or tumor obstruction of the lymphatic vessels. Dermatologic examination revealed cutaneous and subcutaneous indurations and hardening of certain areas of the involved arm. The clinical suspicion of scleroderma was confirmed by histology and immunohistology. Treatment was initiated with methotrexate and methylprednisolone, resulting in a clear reduction of the lymphedema and a regression of the scleroderma. These two cases suggest a pathogenic role of paclitaxel-induced scleroderma in the subsequent development of severe localized lymphedema.

Keywords: Paclitaxel; Limited scleroderma; Breast neoplasms; Lymphedema

Introduction
Paclitaxel (Taxol, BMS) is an antimicrotubule chemotherapeutic agent belonging to taxane group; diterpenes derived from the genus Taxus. They stabilize microtubules, preventing their depolymerization, and interfere with the cell cycle leading to apoptosis. Paclitaxel is used in the treatment of metastatic breast cancer, ovarian cancer, non-small cell lung cancer and Kaposi's sarcoma. The most common adverse events are myelosuppression, peripheral neuropathy, fluid retention, myalgia, arthralgia, onychodystrophy and alopecia. Premedication with systemic steroids avoid hypersensitivity and hyperpermeability reactions. Scleroderma-like changes have been exceptionally reported. Up to date, twenty-one cases have been reported with docetaxel [1-6] and thirteen with paclitaxel [5,7-16]. Two cases suggest an, at least partial, pathogenic role of paclitaxel-induced scleroderma in the subsequent development of severe lymphedema without mechanical or tumor obstruction of the lymph vessels.

Case Reports
Patient 1
A 55-year-old white woman was diagnosed in March 2012 with right breast cancer thanks to self-examination. The micro biopsy confirmed an infiltrating ductal carcinoma of the right breast (stage T2N3cM1). The tumor overexpressed HER2 but no hormone receptor. A mastectomy was performed without axillary lymph node dissection. The patient was treated with paclitaxel (once a week), an investigational anti-angiogenic drug. After the second course of paclitaxel, she developed a non-painful enlargement and indurations of her right arm, forearm and dorsal aspect of the hand, severely affecting the mobility of her hand and fingers. After three paclitaxel cycles, the indurations accentuated progressively (Figure 1a) with a right hemifacial edema. The tumor response to treatment was excellent. After the fourth cycle, the edema extended to the lower limbs, especially the left leg. Cardiac function was normal. The discontinuation of paclitaxel was decided after 6 cycles because of grade 2 to 3 nail toxicity. Despite lymphatic drainage, the edemas still progressed, and particularly in the left leg. Deep vein thrombosis was excluded by Doppler ultrasound. Suspecting the role of AMG as origin of the edemas, this treatment was interrupted after seven cycles. These treatment adjustments led to the resolution of the edemas except that of the right arm. Three months later, the patient continued to complain of burning sensations and redness of her right arm. She had no fever and no lymph adenopathies were evidenced. Erysipelas was suggested but the antibiotic therapy did not improve the stiff skin changes of the right hand, forearm and arm. Scleroderma-like changes were evidenced on a skin biopsy of her forearm on haematoxylin/eosin (Figures 2a and 2b) and trichrome (Figure 2c) stainings. FXIIIa (Figure 2d) and CD34 immunostaining further supported the diagnosis of scleroderma. Immunological tests were negative. The patient did not present other clinical features related to systemic sclerosis. Capillaroscopy was not contributory. Four weeks after a treatment with methylprednisolone (4 mg per day) and methotrexate (125 mg per week), the skin stiffness had softened considerably and the edema slowly regressed (Figure 1b). This treatment was maintained for 6 months with an almost complete regression of the scleroderma lesions and a significant reduction of the

Figure 1a: Patient 2: Illustration of the paclitaxel-induced scleroderma and subsequent lymphedema of the dorsal aspect of the left hand.

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diameter of the lymphedema. Paclitaxel was interrupted 16 months ago. Concerning her breast cancer, she is currently still treated with trastuzumab every three weeks. She presents a complete response according to the RECIST 1.1 criteria.

**Patient 2**

A 42-year-old white woman was diagnosed with metastatic breast cancer in 2012 after the discovery of a parietal bone pain. Histology revealed an infiltrating ductal carcinoma of the left breast, expressing HER 2 but no hormone receptors. The tumor staging was T2N3cM1. After left mastectomy and axillary node dissection, the patient received the same treatment as patient 1 (paclitaxel, trastuzumab and AMG 386). After three cycles, she developed persistent edema of the left arm despite lymphatic drainage. The dose of paclitaxel was decreased after seven cycles because of nail toxicity and this treatment was stopped after 10 cycles because of peripheral neuropathy. The patient had then lost 6 kg and had a better general condition. Three months after treatment discontinuation, the patient was referred to the dermatology department for persistent edema of left upper limb and pruritus. Physical examination revealed a sclerodermiform aspect of the skin of the left arm. Histology and immunohistology confirmed the diagnosis of scleroderma. She complained about dysphagia and presented Raynaud’s phenomenon when wearing a compression sleeve for her lymphedema. Immunological tests and capillaroscopy were normal. The same treatment as in patient 1 resulted in a significant reduction of the diameter of her arm and an improvement of the scleroderma. Unfortunately, six months ago, and the patient was diagnosed with cerebral carcinomatosis. Methotrexate was replaced by lymphatic drainage. Lymphedema of the left arm and leg recurred with severe pruritus. The patient underwent radiotherapy of brain and bone marrow. She was further treated with lapatinib and capecitabine for four months. As she suffered from severe neurological deficiency consequent to radiotherapy, she requested euthanasia.

**Discussion**

Scleroderma-like skin changes were first reported in patients treated by docetaxel who developed a lower limbs or a generalized edema followed by a thickening of the skin [1]. Histology evidenced scleroderma-like changes but no biological features of systemic scleroderma were observed. Resolution of both the edema and the cutaneous alterations was observed after the discontinuation of docetaxel [1].
Scleroderma-like cutaneous changes have already been reported after exposure to various organic solvents (polyvinyl chloride, benzene, toluene), drugs (bleomycin, carbodopa, pentazocine, isoniazid, valproic acid, bromocriptine, nitrofurantoin, penicillamine, diltiazem, fosinopril, cocaine) and miscellaneous substances (rapunzel oil/aniline, silicon dioxide, L-tryptophan, taxanes, topotecan) [17].

Although most of scleroderma-like skin changes have been attributed solely to the taxanes, some studies suggested that this phenomenon was consecutive to combination chemotherapy, most commonly containing doxorubicin and cyclophosphamide [18]. However, the retreat of taxanes resulted in a clinical improvement that was not observed after the withdrawal of doxorubicin and cyclophosphamide.

Taxane-induced edema starts with an initial enhancement of fluid filtration followed by a capillary protein leakage that leads to edema formation [19]. Taxanes interfere with the cytoskeleton reducing the interstitial fluid pressure and enhance albumin extravasation [20].

However the unilateral character of edema in some cases remains still unclear.

Though edema occurs frequently during taxane therapy, the association with lymphedema is rather uncommon. In all the taxane-induced scleroderma cases, medical work up never demonstrated any mechanical or tumor obstruction of the lymph pathways. Consequently, the role played by node dissection seems to be only accessory albeit probably a confusing factor and responsible of the under-diagnosing of taxane-induced scleroderma.

Morphea, a limited cutaneous form of scleroderma, can be associated with lymphedema [21-23]. The mechanical compression by scleroderma involving the dermis, deep dermis and hypodermis could hinder the lymphatic flow.

The scleroderma-like skin changes differ from systemic scleroderma by their atypical onset and rapid progression. Additional arguments favoring the involvement of taxanes are the close temporal relationship between onset of the cutaneous changes and the initiation of chemotherapy, the atypical clinical presentation and the disease course as well as the numerous case reports supporting this association.

The scleroderma-like skin changes could be explained as follows: taxanes would induce an increase in the serum levels of IL-2, IL-6, TNFα and GM-CSF, leading to fibroblast proliferation. Adriamycin would stimulate the production of IL-1, IL-2 and TNFα [18]. The Friend leukemia integration 1 (Fli1) protein may also play a part in the fibrotic process. This protein represses the type 1 collagen gene in dermal fibroblasts and regulates angiogenic processes in endothelial cells. Fli1 expression was abundant in control endothelial and fibroblastic cells and in dermal endothelial cells of patient with taxane-induced scleroderma but markedly decreased in dermal fibroblasts [16].

Although prolonged chemotherapy with high-dose paclitaxel is associated with pro-fibrotic and anti-angiogenic changes, low-dose paclitaxel prevents the maintenance/reconstitution of the systemic sclerosis phenotype in SCID mice [24]. This effect may be mediated by stabilizing the MT-Smad complex with suppression of Smad 2 and 3-phosphorylation, and the subsequent inhibition of the TGFβ/Smad signaling pathway. Indeed, TGFβ is one of the cytokines capable of stimulating collagen synthesis associated with systemic sclerosis. It also induces matrix accumulation, promotes endothelial cell apoptosis, inhibits smooth muscle cell apoptosis and regulates T lymphocyte function [24].

In patients who developed systemic sclerosis together with breast cancer, a lack of antinuclear antibodies positivity and the older age at diagnosis of systemic sclerosis was identified in the pre-systemic sclerosis breast cancer patients compared to post-systemic sclerosis patients and control group, suggesting a difference in systemic sclerosis pathogenesis in the pre-systemic sclerosis breast cancer group [25].

A retrospective study reported early lymphedema with scleroderma-like skin changes of the arm after treatment with docetaxel for breast cancer [4]. Among 1693 patients, 24% had been treated by docetaxel as adjuvant treatment. Eleven women (from 44 to 65-years-old at breast cancer diagnosis) presented edema with scleroderma-like skin changes, such as cutaneous in duration, sclerodactyly and inability to wrinkle skin. The mean time between cancer surgery and development of lymphoedema was 7 months and the interval between initiation of docetaxel and scleroderma-like skin changes varied from 3 to 21 months. Only one patient presented positive anti-nuclear antibodies. A long-lasting (about 22 months) persistence of the cutaneous alterations and the lymphedema was revealed despite docetaxel cessation.

Even though a role of taxanes seems now quite undeniable, the involvement of a paraneoplastic phenomenon and/or auto-immune process with an as yet undetected autoantibody or a pseudo-graft versus host disease (related to multiple blood transfusions) remains to be excluded [12].

Apart from discontinuation of the implicated chemotherapy agent, few treatments are partially effective on the scleroderma-like lesions: intense physical therapy and intravenous iloprost [8], prednisone (30 mg daily) and D-penicillamine (125 mg daily) [9] and, in our cases, methyl prednisolone (4 mg daily) and methotrexate (125 mg once a week). This regimen was based on the treatment of extensive cutaneous scleroderma [26]. Diuretics, lymph drainage, corticosteroids with PUA, dermocorticoids, corticoids alone and reduction of dosage of taxanes seem to be of limited effectiveness.

It is currently unclear whether treatment should be maintained for several consecutive years as recommended for extensive cutaneous scleroderma [26].

In our two patients, both lymphedema and the scleroderma-like skin changes developed on the same side as the primary breast cancer. Whether there is a link between this phenomenon and the previous axillary node dissection or the neoplastic process, remains to be determined.

Conclusion

These two cases suggest a pathogenic role of paclitaxel-induced scleroderma in the subsequent development of severe localized lymphedema. This type of edema differs from lymphedema consecutive to node dissection. Whether the taxanes act as initiator or as potentiator of the fibrotic process remains to be elucidated.

References