

TAXANE-INDUCED SCLERODERMA-LIKE SKIN CHANGES – REVIEW OF THE LITERATURE AND CASE REPORT

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Abstract. *Taxanes (paclitaxel, docetaxel) are antineoplastic agents used in advanced ovarian, breast, lung, head and neck cancer. Diverse cutaneous adverse reactions associated with taxane administration have been reported such as bullous eruption, onycholysis, acral erythema, erythema multiforme, pustular eruption, scleroderma-like skin changes of both upper and lower extremities. Here, we report a case of 48-year-old female patient, who presented for consultation with rheumatologist with complaints of hand and finger oedema and stiffness. Oedema and mild skin thickening of the fingers and hands were evident at physical examination. Inflammatory joint pain, synovitis, Raynaud’s phenomenon and trophic changes were not present. Standard laboratory tests, i.e., complete blood count and biochemistry tests were within normal values. The patient was euthyroid. Immunological tests were negative (antinuclear antibodies; antibodies against extractable nuclear antigens – dsDNA, Sm, RNP, Scl-70; antiphospholipid antibodies – anticardiolipin, anti-beta-2-glycoprotein; anti-CCP antibody and rheumatoid factor). Capillaroscopic examination did not reveal signs of microangiopathy. Skin biopsy was performed in the area of a proximal phalanx and the histological examination revealed dermal oedema and superficial scant perivascular infiltrate containing lymphocytes and histiocytes. The patient had undergone an operation for breast cancer 13 years ago and subsequent second operation because of cancer recurrence 7 years ago. After the second operation chemotherapy was performed that included 1 cycle with paclitaxel and 4 cycles with docetaxel. The analysis of the case led to the conclusion that the scleroderma-like skin changes of the fingers and hands are induced by taxane administration in the past. The patient received corticosteroid treatment for 7 months with gradual resolution of symptoms.*

Key words: *taxanes, scleroderma-like skin changes*

INTRODUCTION

Drug-induced scleroderma-like syndromes include development of skin changes that mimic those in scleroderma. A number of drugs are associated with appearance of scleroderma-like skin changes such as taxanes, bleomycin, L-tryptophan, vinyl chloride, phytonadione (vitamin K1), gemcitabine, gadolinium-based contrast agents, cocaine, interferon- α , levodopa, etc. [1, 2]. Anti-cancer drugs associated with drug-induced scleroderma-like changes were administered most commonly for breast cancer, hematologic malignancy, lung cancer, ovarian carcinoma [2]. Drug-induced scleroderma-like syndromes include two major clinical variants, i.e., symmetrical scleroderma-like changes that most commonly affect the lower extremities and localized cutaneous lesions resembling morphea (morphea-like plaques). Drug induced scleroderma-like changes preferentially develop in the extremities,

more often in the lower extremities, and rarely extend to the trunk. The initial findings include edema, followed by an edematous sclerotic phase. The pathological changes initially involve the deep dermis [1].

Taxanes (paclitaxel, docetaxel) are antineoplastic agents used in advanced ovarian, breast, lung, head and neck cancer. Diverse cutaneous adverse reactions associated with taxane administration have been reported such as bullous eruption, onycholysis, acral erythema, erythema multiforme, pustular eruption, scleroderma-like skin changes most commonly of the lower extremities [3, 4, 5, 6]. Paclitaxel and docetaxel are antimicrotubule agents. They promote tubulin polymerization into highly stable intracellular microtubules that accumulate and lead to disrupting of cell mitosis and cell death [7]. It has been shown that paclitaxel inhibits angiogenesis and induces expression of tumor necrosis factor (TNF)- α , interleukin (IL)-2, 6, interferon- γ , granulocyte-macrophage colony-stimulating factor. The

cytokine – IL-6, is associated with induction of inflammation, promotion of fibrosis, collagen synthesis, and T-helper-2-mediated antibody production. The changes in the cytokine profile may be related to the observed sclerotic skin changes in patients treated with paclitaxel [8]. Taxane-induced scleroderma-like skin changes are usually characterized with skin sclerosis without visceral involvement, absence of Raynaud's phenomenon and negative autoantibodies [8, 9]. They develop weeks or a few months after the onset of treatment with taxanes [5]. Taxane-induced skin lesions may start with initial involvement of lower extremities. In contrast, in systemic sclerosis, skin thickening starts more commonly in the fingers and progresses to the proximal areas. Finger and upper extremity involvement is usually earlier and more severe. Raynaud's phenomenon is a classic initial clinical sign in systemic sclerosis [1].

The approach to drug-induced scleroderma-like syndromes is individual and depends on the severity of the manifestations that varies in different clinical cases. The suspected drug should be discontinued. The data about the time for improvement are variable [1]. Systemic corticosteroids, D-penicillamine, methotrexate have been used for the treatment of taxane-induced scleroderma-like skin changes [8, 10].

Drug-induced scleroderma-like syndromes are rare. Thus, their incidence, clinical characteristics, severity and prognosis have not been fully clarified [1]. Here, we report a case of taxane-induced scleroderma-like skin changes which developed late after the cytotoxic therapy.

CASE REPORT

A 48-year-old female patient presented for consultation with rheumatologist due to complaints of hand and finger oedema and stiffness that the patient had noticed for a period longer than 6 months. Oedema and mild skin thickening of the fingers and hands were evident at physical examination (Fig. 1). Inflammatory joint pain, synovitis, Raynaud's phenomenon and trophic changes were not present. Standard laboratory tests, i.e., complete blood count and biochemistry tests were within normal values. The patient was euthyroid. Immunological tests were negative (antinuclear antibodies; antibodies against extractable nuclear antigens – dsDNA, Sm, RNP, Scl-70; antiphospholipid antibodies – anti-cardiolipin, anti-beta-2-glycoprotein; anti-CCP antibody and rheumatoid factor). Capillaroscopic examination did not reveal signs of microangiopathy (Fig. 2). Skin biopsy was performed in the area of a proximal phalanx and the histological examination revealed dermal oedema and superficial scant perivascu-

lar infiltrate containing lymphocytes and histiocytes (Fig. 3). The patient had undergone an operation for breast cancer 13 years ago and subsequent second operation because of cancer recurrence 7 years ago. After the second operation chemotherapy that included 1 cycle with paclitaxel and 4 cycles with docetaxel administered in combination with dexamethasone was performed. Other cytotoxic drugs were not used. The analysis of the case led to the conclusion that the scleroderma-like skin changes of the fingers and hands are induced by taxane administration in the past. The gradual onset of the complaints may lead to misperception of the exact time of onset. However, it could be defined as a late drug-induced syndrome as the patient did not have complaints during treatment with taxanes and in the first years after it. The degree of oedema and skin thickening were mild and did not impair significantly the patient functional capacity. The patient received corticosteroid treatment (intermittent intramuscular injections of depot-corticosteroid) for 7 months with gradual resolution of symptoms. The improvement is durable during a 4-year follow-up.



Fig. 1. Oedema and mild skin thickening of the fingers and dorsal surface of the hand

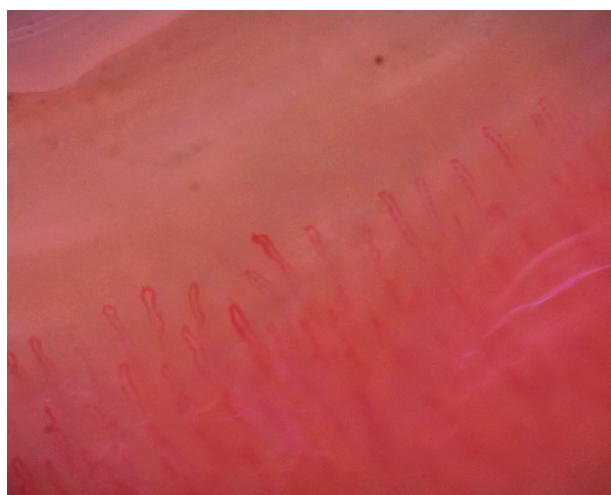


Fig. 2. Normal capillaroscopic picture (magnification 200x)

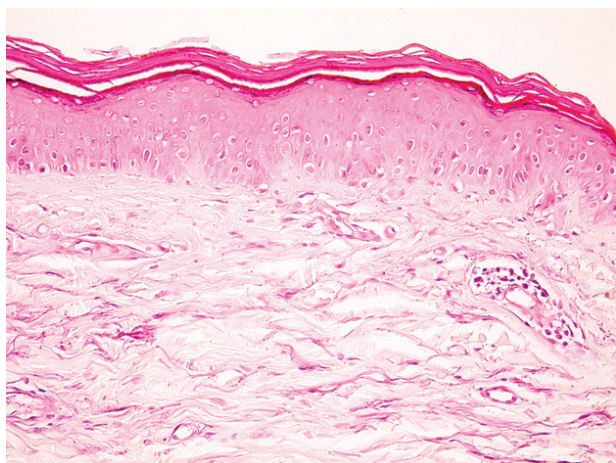


Fig. 3. Dermal oedema and superficial scant perivascular infiltrate containing lymphocytes and histiocytes (H&E staining, magnification 20x)

DISCUSSION

Development of scleroderma-like skin changes is a characteristic complication in patients treated with taxanes. Their atypical appearance require further analysis to improve clinical vigilance of this complication. Itoh et al. (2007) have reported 5 clinical cases with taxane-induced scleroderma. The patients did not display symptoms of Raynaud's phenomenon, pathological nailfold capillaroscopic changes and visceral involvement like pulmonary fibrosis. In systemic sclerosis, skin thickening most commonly starts from the fingers and advances proximally in a symmetrical pattern with more severe involvement of the upper extremities in the majority of the cases. In taxane-induced scleroderma, skin involvement frequently starts from the legs. Asymmetrical involvement of the arms has been also observed. Severe skin sclerosis with joint contracture has been also detected as an adverse event during treatment with taxanes. Systemic steroid administration has induced mild improvement in oedema and skin sclerosis that may be also result of taxane discontinuation [9].

The extent of taxane-induced scleroderma-like changes is variable [11, 10, 12, 13, 14, 15]. It may be significant resembling changes in diffuse scleroderma [10, 14, 15, 16]. Diffuse scleroderma with involvement of skin of the face, hands, forearms, left upper arm, both feet, legs and thighs bilaterally, with a modified Rodnan's skin score of 27/51 has been described by Ketpueak et al. (2022) in a female patient after paclitaxel therapy for ureter cancer. The patient had also Raynaud's phenomenon, gastro-esophageal reflux and possible scleroderma renal crisis [14]. Severe skin sclerosis of both lower (including

the thighs) and upper extremities were reported after treatment with paclitaxel. Dermatogenic contractions of the knees and finger joints were observed. The changes worsened progressively despite discontinuation of paclitaxel. The patient responded poorly to oral corticosteroids (starting initial dosage of 60 mg with gradual tapering) and bath photochemotherapy (PUVA) for 8 weeks. Intense physical therapy and intravenous iloprost led to some improvement. The pathological changes appeared when the patient was tumor-free and the clinical course suggested the diagnosis drug-induced scleroderma rather than a paraneoplastic condition [6].

Antinuclear antibodies and scleroderma-related antibodies are usually negative in cases with taxane-induced scleroderma-like syndromes [3, 9, 11, 16, 17] like in our case. However, positive total antinuclear antibodies have been also reported by some authors [10, 18, 12, 19]. Of note, positivity of scleroderma-related autoantibody, i.e., anti-RNA-polymerase III has been reported in a clinical case after treatment with docetaxel [20]. Positive antinuclear antibodies (1:2560) and pathological capillaroscopic findings have been detected in a clinical case of a female patient with breast cancer who received 6 cycles treatment with docetaxel. Initial skin thickening appeared after the fourth cycle and subsequently the patient developed progressive skin thickening of the arms, face, anterior chest wall, abdomen and upper thighs, with impaired hand function. The presence of antinuclear antibodies, nailfold capillary abnormalities, synovitis, and telangiectasia raised the possibility of development of idiopathic diffuse systemic sclerosis. However, rapid resolution of scleroderma was observed nine months after discontinuation of docetaxel. The patient has received treatment with prednisolone and D-penicillamine. The scleroderma-like changes developed several years after clinically detectable cancer and continued to progress during chemotherapy. Thus, the authors have concluded that the association between breast cancer and scleroderma is unlikely [10].

Although taxane-induced scleroderma lesions are not associated with vascular and visceral pathology in the majority of cases [11], associations with Raynaud's phenomenon [8, 12, 20, 14], gastroesophageal reflux [8, 14], pathological capillaroscopic findings [16], interstitial lung disease [20], diffuse muscular weakness [8], possible scleroderma renal crisis [14], kidney flare with thrombotic microangiopathy [20] have been also reported. In a clinical case, it has been observed an association of scleroderma-like skin changes with Raynaud's phe-

nomenon and digital gangrene in a patient treated with paclitaxel in combination with doxorubicin [21].

Lag-time between taxane administration and appearance of skin lesions. Localization of the skin changes

The median time between the taxane administration and development of scleroderma-like skin changes is 6-7 months [2, 22]. However, some authors have reported longer lag time. In a clinical case of Farrant et al., scleroderma-like skin changes developed 5 years after treatment with paclitaxel, cisplatin, carboplatin and a third drug in a female patient with ovarian carcinoma. The long period between taxane administration and development of scleroderma-like skin changes has led to the suggestion that they might be related to treatment with carboplatin or a third drug that the patient received 11 months prior to the onset of the symptoms. The localization of the skin lesions was upper arm, upper trunk and neck [22]. Early skin reactions have been also reported after taxane administration. A 63-year-old white woman with primitive peritoneal cancer presented with erythema of the head, neck, axillae, and left hand 10 days after intravenous administration of paclitaxel and paraplatin. Edema and infiltrated erythema of the left hand, shoulders and upper back, infiltrated erythematous and purpuric lesions on the scalp, axillae, and groin were also observed one month later. Paclitaxel was changed to cyclophosphamide for two subsequent courses of chemotherapy that resulted in improvement in cutaneous lesions. Subsequently, paclitaxel was reintroduced leading to their recurrence. Paclitaxel was then definitely discontinued. However, cutaneous lesions evolved for a 4-month period to sclerosis of the upper back, shoulders, neck, and left hand with palmar fasciitis and tendinous flexor retraction that was associated with significant functional impairment. Histological skin assessment revealed dermal fibrosis with collagen bundles [3].

PROGNOSIS

Diverse data are reported regarding the prognosis of taxane-induced scleroderma-like changes. Near-complete resolution of skin sclerosis has been reported in a clinical case of 39-year-old female patient with breast carcinoma, who developed skin fibrosis after 18-month treatment with docetaxel. Skin softening has begun within 3 weeks after discontinuation of docetaxel and almost complete recovery was observed in 6 weeks [23].

In a 64-year-old woman with ovarian cancer, skin sclerosis of the face, neck, upper chest, upper extrem-

ities, and feet developed after six cycles of chemotherapy with paclitaxel and carboplatin. Initial changes with swelling of the hands and feet and skin thickening of the fingers were noted between the second and third cycles. The patient also developed Raynaud's phenomenon, gastroesophageal reflux, and diffuse muscular weakness. Oral aperture was restricted to 4.5 cm and modified Rodnan skin score was 17/51. The suggested diagnosis was diffuse cutaneous systemic sclerosis. Total antinuclear antibodies, anti-Scl-70, anti-centromere antibodies were negative. The patient was treated with 20 mg methotrexate weekly and 20 mg prednisone daily. The symptoms progressed after completion of chemotherapy and persisted one year from their onset. Resolution of all physical findings was reported by the patient in 26 months. This shows that the observed changes are not transient drug reaction. The remission of the ovarian cancer excludes paraneoplastic condition. These observations suggest the hypothesis that taxane-induced scleroderma might be more similar to idiopathic systemic sclerosis than initially thought [8].

Paraneoplastic scleroderma-like changes are reported in the literature having a parallel course with the underlying malignancy. These pathological paraneoplastic changes should be differentiated from drug-induced scleroderma-like syndrome as they occur concomitantly with the cancer and the successful cancer treatment leads to their regression. Contrary, drug-induced scleroderma-like changes appear while cancer is not clinically detectable [2, 6, 10].

CONCLUSION

In conclusion, scleroderma-like skin changes could be observed also as a later finding after taxane administration and may have atypical characteristics and variable severity. In the majority of the cases, they are not associated with concomitant microvascular capillaroscopic abnormalities, positive autoantibodies and visceral involvement. In clinical practice, the specialists should be aware of this rare drug-induced manifestations in the differential diagnosis of scleroderma-like syndromes. The approach is individual according to the severity and the degree of functional impairment.

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