

# Taxane-induced scleroderma. Report of two cases

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## ABSTRACT

*Taxanes are a class of chemotherapeutic agents with common associated dermatologic adverse events, such as skin hyperpigmentation, hand-foot skin syndrome, paronychia and onycholysis. Taxane-induced scleroderma is rare. Few cases with skin findings resembling systemic sclerosis, have been reported after the administration of these agents. We report two cases with stage IV breast cancer, aged 66 and 71 years, who developed sclerodermic skin lesions in their extremities after starting treatment with paclitaxel and nabpaclitaxel respectively.*

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**Key words:** Drug Related Side Effects and Adverse Reactions; Scleroderma, Localized; Taxoids; Antineoplastic Agents.

## Esclerodermia inducida por taxanos. Informe de dos casos

*Los taxanos son agentes quimioterapéuticos cuyo uso se asocia a problemas dermatológicos tales como hiperpigmentación, síndrome manos-pies, paroniquia y onicolisis. La esclerodermia inducida por taxanos es rara, con pocos casos informados en la literatura. Informamos los casos de dos pacientes con cáncer de mama en estado IV, de 66 y 71 años, que desarrollaron lesiones esclerodérmicas en las extremidades después de ser tratadas con paclitaxel y nabpaclitaxel, respectivamente.*

**Palabras clave:** Antineoplásicos; Efectos Colaterales y Reacciones Adversas Relacionadas con Medicamentos; Esclerodermia Localizada; Taxoides.

**T**axanes are a class of chemotherapeutic agents with common associated dermatologic adverse events, such as skin hyperpigmentation, hand-foot skin syndrome, paronychia and onycholysis. Taxane-induced scleroderma is rare, with only a few reported cases with skin findings resembling systemic sclerosis, occurring after the administration of agents on this class.

Here we describe two cases of this rare condition and discuss the most important clinical, laboratory and histological findings.

## Case reports

A 66-year-old male with stage IV breast carcinoma was treated with neoadjuvant tamoxifen, followed by letrozole and radiotherapy with progressive disease after 2 years. He was then initiated on paclitaxel. Four months later he started to develop edema on the extremities, evolving to skin induration/thickening with a distal to proximal progression (Figure 1 A-B). Histology revealed dermal fibrosis with thickened collagen bundles

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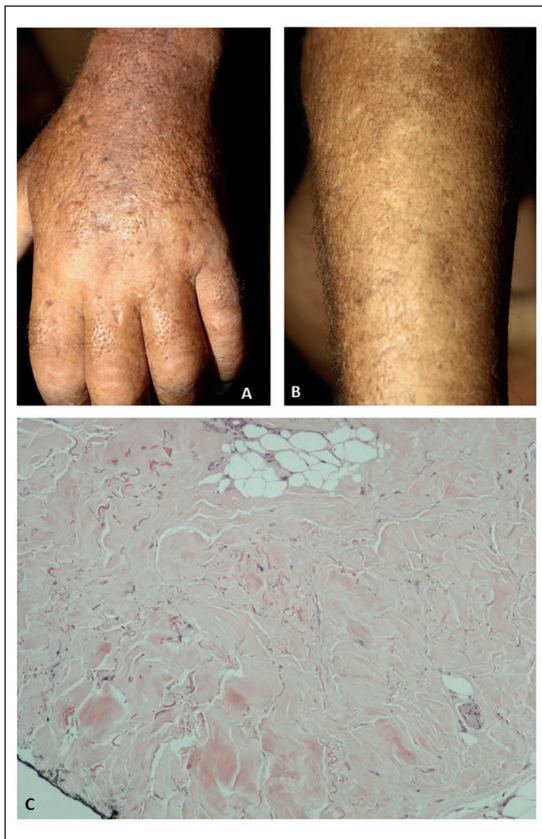
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**Figure 1.** Case 1: skin sclerosis on the dorsum of the hands (A) and forearms (B). (C) On histology (HE, 200x), dermal fibrosis with thickened collagen bundles and scarce inflammatory infiltrate.

and scarce inflammatory infiltrate without mucin deposition (Figure 1 C). Laboratory investigations were negative for antinuclear antibody (ANA), anti-Scl-70 and rheumatoid factor; protein electrophoresis, complement levels, thyroid stimulating hormone (TSH) were within normal range. X-ray of the esophagus and nail fold capillaroscopy were normal and thorax computed tomography revealed no alterations suggestive of systemic sclerosis. Phototherapy (PUVA) was planned, but patient died before starting skin-directed treatment due to disease progression.

Second case is of a 71-year-old female with stage IV breast carcinoma who started treatment in a clinical trial with Nabpaclitaxel +/- Atezolizumab/placebo. Shortly after treatment initiation, patient developed edema on the left distal arm,



**Figure 2.** Case 2: skin sclerosis and hyperpigmentation on the anterior (A) and posterior (B) aspects of the hands and forearms. (C) Clinical improvement two months after taxane therapy was suspended. (D) On histology (HE, 200x), dermal fibrosis with thickened collagen bundles, discrete adnexal atrophy and absence of inflammatory infiltrate.

evolving 4 months later with limbs dysesthesias and skin hyperpigmentation, followed by skin induration/thickening of the extremities with a distal to proximal progression (Figure 2 A-B). Histology revealed dermal fibrosis with thickened collagen bundles, discrete adnexal atrophy, presence of dendrocytes and absence of inflammatory infiltrate, fibroblasts and mucin deposition (Figure 2 D). Laboratory findings were only positive for a low titer anti-Ro and were negative for ANA, Anti-RNP/Sm, Sm, La, Scl-70, Jo-1. TSH levels and renal function were normal. Due to disease progression, protocol was suspended and capecitabine was started with good response and improvement of skin sclerosis (Figure 2 C).

## Discussion

Taxanes are a group of chemotherapeutic agents widely used to treat solid tumors such as ovarian, breast, lung, among others. The two main representatives are docetaxel and paclitaxel. Nab-paclitaxel is an albumin-bound paclitaxel. The main related dermatological adverse events are skin hyperpigmentation, hand-foot skin syndrome, paronychia and onycholysis<sup>1,2</sup>.

Taxane-induced scleroderma is a rare event, with approximately 25 cases reported in the literature, most of them related to paclitaxel. Even though many patients had received other chemotherapeutic agents, a time correlation is suggestive of taxanes as the causative agent. Lesions start from weeks to several months after drug initiation (most cases around 3-6 months), usually with edema on the extremities, evolving to skin tightening and sclerosis, with a distal to proximal progression. There is no relationship with a specific type of tumor, with cases of breast, ovarian, endometrium and peritoneum being described<sup>1-6</sup>.

Differently from classic systemic sclerosis (SSc), ANA antibodies are negative or, less often, positive with no specific SSc pattern; vascular phenomenon such as Raynaud or nail fold changes are usually absent, and no esophagus or pulmonary involvement is usually detected.

Mechanisms are still poorly understood, but it is believed they are mainly induced by a toxic and non-immunomediated mechanism. They are usually dose-dependent, and dose reductions or even discontinuation of the taxane is sometimes necessary<sup>1-6</sup>. Other treatments reported are corticosteroids (topical or systemic), PUVA and methotrexate, with variable responses<sup>6</sup>.

## Conclusion

Even though rare, taxane-induced scleroderma might cause important morbidity. It is important for dermatologists and oncologists to be aware of this possible association, since early identification and management are critical for maintaining quality of life in cancer patients.

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