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Single Case

Nanoparticle Albumin-Bound Paclitaxel- and/or Gemcitabine-Induced Scleroderma Accompanied by Acanthosis Nigricans-Like Skin Changes

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Keywords
Nanoparticle albumin-bound paclitaxel · Gemcitabine · Scleroderma · Acanthosis nigricans

Abstract
We herein present the first case of nanoparticle albumin-bound paclitaxel (nab-paclitaxel)- and/or gemcitabine-induced scleroderma accompanied by acanthosis nigricans-like skin changes in a 54-year-old Japanese male. He was diagnosed with pancreatic cancer and received 17 courses of nab-paclitaxel and gemcitabine chemotherapy. Edema and skin sclerosis in his legs appeared after the first and third course, respectively. Histological examination of the hyperkeratotic lesion of the ankle revealed hyperkeratosis, acanthosis, papillomatosis, increased number of melanocytes in the basal layer, and dermal fibrosis. Awareness of the clinical characteristics of nab-paclitaxel- and/or gemcitabine-induced scleroderma accompanied by acanthosis nigricans-like skin changes is important for dermatologists to establish an accurate diagnosis.

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Introduction

It has been reported that both taxanes, including nanoparticle albumin-bound paclitaxel (nab-paclitaxel), and gemcitabine induce scleroderma-like skin changes. Acanthosis nigricans is a disease that may occur with diabetes mellitus, cancer, endocrine disorders, and collagen diseases. However, there have been no reports that acanthosis nigricans-like skin changes occur in the skin lesion of nab-paclitaxel- and/or gemcitabine-induced scleroderma. We hereby describe the first case of nab-paclitaxel- and/or gemcitabine-induced scleroderma accompanied by acanthosis nigricans-like skin changes.

Case Report

A 54-year-old Japanese man was admitted to our hospital in August 2018 with a 7-month history of skin sclerosis of extremities. He was diagnosed with pancreatic cancer in February 2016 and received 17 courses of nab-paclitaxel and gemcitabine chemotherapy. Edema and skin sclerosis in his legs appeared after the first and third course, respectively. He had also been previously diagnosed as having diabetes mellitus. Physical examination revealed edema and skin sclerosis of the bilateral forearms, hands, lower legs, and feet, as well as flexion contracture of the fingers (Fig. 1a, b). Symmetrical dark-brownish pigmentation with hyperkeratosis was observed in the ankle joints and dorsum of the feet (Fig. 1c–e). Laboratory tests revealed an elevated γ-GTP and HbA_{1c}; however, tests were negative for antinuclear antibodies and scleroderma-specific autoantibodies. Raynaud's phenomenon and abnormal nailfold capillaries were not observed. Lung fibrosis and pulmonary hypertension were not detected by computed tomography and echocardiography. Histological examination of the leg revealed prominent fibrosis and lymphocyte infiltration around the blood vessels and among collagen fibers in the dermis (Fig. 1f, g). Histological examination of the hyperkeratotic lesion of the ankle revealed hyperkeratosis, acanthosis, papillomatosis, increased number of melanocytes in the basal layer, and dermal fibrosis (Fig. 1h). Based on clinical and pathological findings, the patient was diagnosed with nab-paclitaxel- and/or gemcitabine-induced scleroderma accompanied by acanthosis nigricans-like skin changes. He stopped nab-paclitaxel and gemcitabine, and changed to combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin. Three months after discontinuing nab-paclitaxel and gemcitabine, the edema of his extremities had gradually improved; however, skin sclerosis and pigmentation of his legs were unchanged.

Discussion

Taxane-induced scleroderma-like skin changes were first reported in 1995, and clinical characteristics include preceding edema, absence of Raynaud's phenomenon, and negative scleroderma-specific autoantibodies [1–4]. The clinical course is refractory to treatment and commonly progressive even after discontinuation of the trigger drugs [1]. To our knowledge, there have been 3 cases of nab-paclitaxel-induced scleroderma-like skin changes [1, 3, 4]. It has been reported that solvents used for paclitaxel and docetaxel might not be associated with the pathogenesis of taxane-induced scleroderma-like skin changes, but that the taxanes themselves might induce them [4]. In addition, there have been case reports of skin sclerosis induced by gemcitabine [1, 5]. Verhulst et al. [1] reported that scleroderma-like lesions are most

likely induced by nab-paclitaxel or paclitaxel, rather than by gemcitabine, in the current literature. However, the possibility that skin sclerosis in our case was induced by gemcitabine cannot be excluded.

Acanthosis nigricans is a disease that may occur with diabetes mellitus, cancer, endocrine disorders, and collagen diseases, and is characterized by symmetric, skin-colored or brownish, velvety lesions resulted from growth factor stimulation of keratinocytes and dermal fibroblasts [6]. The region of acanthosis nigricans-like change in our case is different from that of typical acanthosis nigricans. However, we called this lesion "acanthosis nigricans-like change," because the histopathological finding was consistent with acanthosis nigricans. This is the first case of nab-paclitaxel- and/or gemcitabine-induced scleroderma accompanied by acanthosis nigricans-like skin changes. It has been reported that the taxane enhanced the production of various cytokines, including tumor necrosis factor-α, interleukin-2 (IL-2), IL-6, and interferon-γ which are also relevant in systemic sclerosis [2, 3]. Changes in the cytokine and/or growth factor profiles due to the use of taxanes may induce scleroderma and acanthosis nigricans-like skin changes. It is thought that the acanthosis nigricans-like changes were caused by nab-paclitaxel and/or gemcitabine because diabetes mellitus was diagnosed before and was not aggravated, pancreatic cancer was not aggravated, and acanthosis nigricans-like changes occurred simultaneously with scleroderma. Further accumulation of patients with similar symptoms is required.

Statement of Ethics

The authors have no ethical conflicts to disclose. Informed consent was obtained from the patient. The study complied with the Declaration of Helsinki.

Disclosure Statement

The authors declare that no competing interests exist.

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Author Contributions

M. Ishikawa, S. Motegi, and A. Sekiguchi took care of the patient. M. Ishikawa, S. Motegi, and O. Ishikawa wrote the manuscript, and contributed to the conception and design, and the analysis and interpretation of the data. All authors gave final approval of the version to be published.

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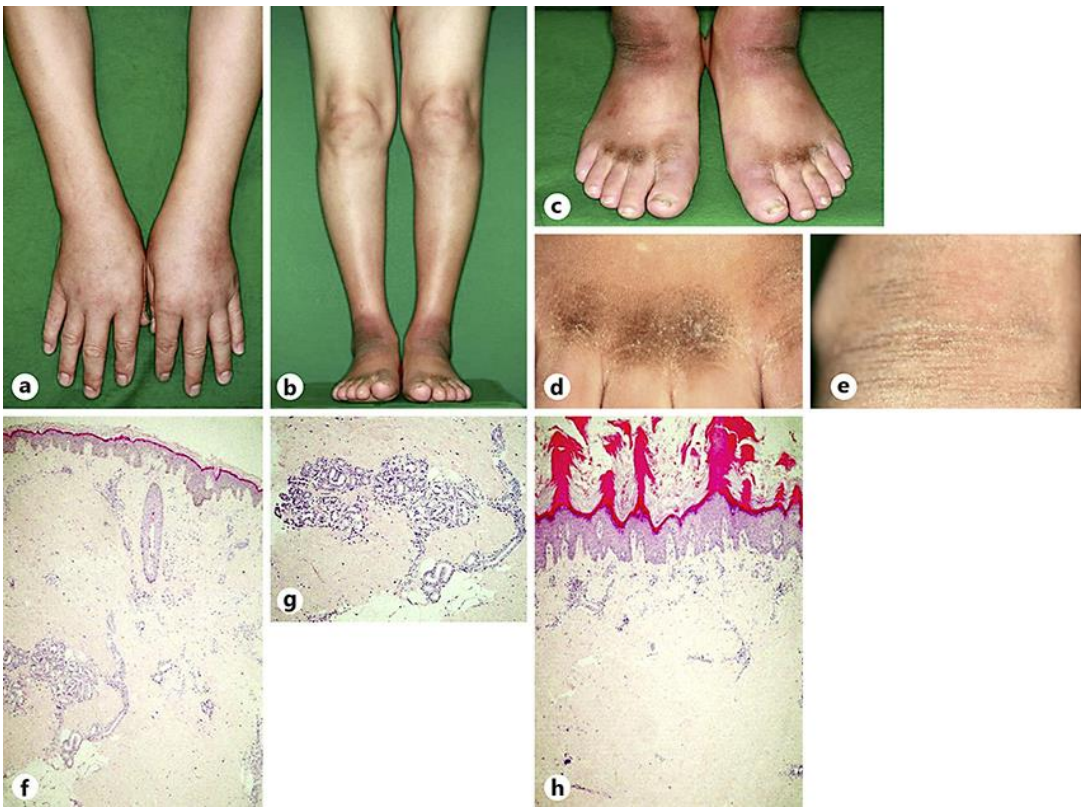

Fig. 1. **a** Edema and skin sclerosis of bilateral forearms and hands. **b** Skin sclerosis and pigmentation of bilateral lower legs and feet. **c–e** Symmetrical dark-brownish pigmentation with hyperkeratosis in the ankle joints (**d**) and the dorsum of feet (**e**). **f**, **g** Histological examination of the left leg. Fibrosis and lymphocytes infiltration around blood vessels and among collagen fibers in the dermis. Hematoxylin-eosin (HE). Original magnification, ×40 (**f**), ×100 (**g**). **h** Histological examination of the hyperkeratotic pigmented lesion in left ankle. Hyperkeratosis, acanthosis, papillomatosis, increased number of melanocytes in the basal layer, and dermal fibrosis. HE. Original magnification, ×40.