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Case Report

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New-onset systemic sclerosis and scleroderma renal crisis under docetaxel

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Abstract

Systemic sclerosis is a rare systemic autoimmune disease characterized by microvascular impairment and fibrosis of the skin and other organs with poor outcomes. Toxic causes may be involved. We reported the case of a 59-year-old woman who developed an acute systemic sclerosis after two doses of adjuvant chemotherapy by docetaxel and cyclophosphamide for a localized hormone receptor + human epithelial receptor 2—breast cancer. Docetaxel is a major chemotherapy drug used in the treatment of breast, lung, and prostate cancers, among others. Scleroderma-like skin-induced changes (morphea) have been already described for taxanes. Here, we report for the first time a case of severe lung and kidney flare with thrombotic microangiopathy after steroids for acute interstitial lung disease probably induced by anti-RNA polymerase III + systemic sclerosis after docetaxel.

Keywords

Docetaxel, chemotherapy, scleroderma, drug-induced autoimmune disease, systemic sclerosis, paraneoplastic

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Introduction

Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterized by microvascular impairment and fibrosis of the skin and other organs with poor outcomes. Toxic causes may be involved.

Case report

We reported the case of a 59-year-old woman who developed an acute SSc after two doses of adjuvant chemotherapy by docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2) (DC) for a localized hormone receptor

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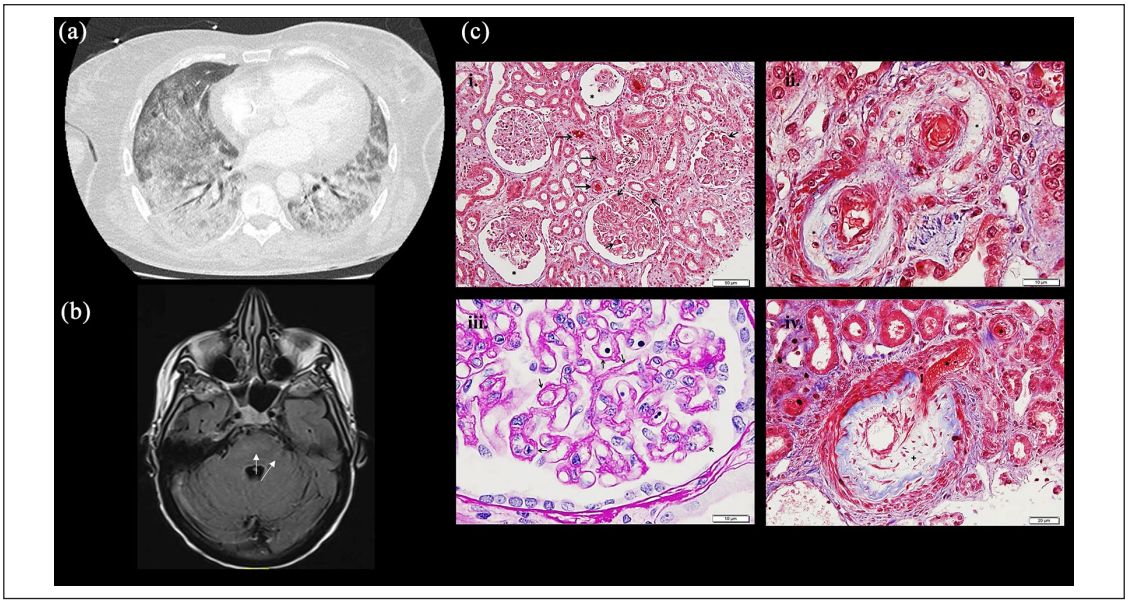

Figure 1. Capture of different clinical manifestations: (a) Chest CT scan: Bilateral interstitial diffuse syndrome on the CT (lung window), (b) brain MRI (Flair axial) with evidence of hypersignal in the right cerebellar hemisphere axial plan of Flair sequence, (c) renal biopsy ((i)–(iv)): (i) Glomeruli show ischemic features with thickening of the glomerular capillary basement membranes and/or dilated urinary space (*). Many thrombosis or red blood cells are seen in arterioles and capillary lumen of glomeruli (→). (Masson's trichrome, ×200). (ii). Mucoid intimal thickening with considerable reduction of the interlobular arterial lumen (+) with red blood cells are seen in vascular luminary of small afferent arteries (*). (Masson's trichrome, ×400). (iii). Pale mucoid intimal hyperplasia of a small interlobular artery, with swelling of medial myocytes (*). (Masson's trichrome, ×1000). (iv). Thickening and wrinkling of the glomerular capillary wall with double-contour appearance (→). (Periodic-acid Schiff, ×1000).

(HR) + human epithelial receptor 2 (HER2)—breast cancer.

After 2.5 months of partial mastectomy and after 2 cycles of DC, the patient was hospitalized for severe hypoxemia (PaO_2 = 48 mmHg) with interstitial syndrome on the computed tomography (CT) scan and right heart failure (Figure 1). The bronchial fibroscopy with broncho-alveolar lavage found an inflammatory alveolitis made of numerous neutrophils (300,000 cells/mL with 83% of neutrophils). Echocardiography showed an elevated mean pulmonary arterial pressure (mPAP) of 44 mmHg and left ejection function (LEF) of 64%. Infectious causes were eliminated, and steroids therapy (1 mg/kg/day) was started. Under steroids, she developed an acute renal failure with creatinine value of 273 µmol/L (glomerular filtration rate (DFG) = 16 mL/min/1.73 m^2) and hemolytic anemia with 2.5% circulating schistocytes, ADAMTS13 activity at 33% (normal = 50%–150%), low haptoglobin rate at 0.4 g/L, and thrombopenia at 50G/L, and a diagnosis of thrombotic microangiopathy (TMA) was made. The patient was admitted to the intensive care unit (ICU) because of increased need of oxygen with 70% of FiO_2 ($PaP0_2/FiO_2$ = 115) and intermitted hemodialysis for KDIGO III (Kidney Disease: Improving Global Outcomes) renal organic failure due to TMA. A renal biopsy was performed and showed lesions of acute TMA and medium-caliber interlobular arterioles with a myxedema appearance referring to SSc (Figure 1). In hypothesis of scleroderma renal crisis provoked by glucocorticoids, this therapy was reduced and completed with plasma exchanges. While patient was out of ICU, she developed confusion with transient loss of consciousness. The analysis of cerebrospinal fluid did not find any infectious or paraneoplastic etiology, but brain magnetic resonance imaging (MRI) showed intense multiple signals in the white matter of two pyramidal tracks (Figure 1). A PRES (posterior reversible encephalopathy syndrome) associated with hypertension associated with SSc renal crisis was diagnosed. The patient developed sphincter disorders in link with suspected central involvement and pyramidal syndrome for several weeks.

The diagnosis of SSc was made retrospectively and complete with the presence of severe Raynaud's syndrome and a megaesophagus. Rodnan score at this time was 11/51. The diagnosis of toxic docetaxel–related SSc was retained after serological results: the antinuclear antibodies (ANA) were positive at 1/1280 with the aspect of type 1 anti-pseudo-PCNA antibodies (associated with cancer).[1] Interestingly, the anti-RNA polymerase III (anti-RNA pol III) antibodies became positive at 28 U/mL (N < 20 U/mL) in the second time and stay positive thereafter. It should be noted that the analysis of serum collected before chemotherapy did not find anti-RNA pol III antibodies, but only ANA with same speckled fine pattern of type 1 anti-pseudo-PCNA.

The patient depended on hemodialysis three times a week. Concerning her breast cancer, the 18F-FDG-PET-CT did not show any recurrence. The adjuvant radiation was excluded because of scleroderma skin involvement. As

Table 1. Drugs associated with the occurrence of scleroderma and scleroderma-like syndromes.

Drugs	Clinical features	References
Chemotherapeutics		
Bleomycin	Scleroderma-like skin changes, pulmonary fibrosis	Haustein and Haupt,[6] Inaoki et al.[9]
Docetaxel, paclitaxel	Scleroderma-like skin changes, possible visceral involvement	Itoh et al.,[10] Winkelmann et al.[11]
Uracil-tegafur	Scleroderma-like skin changes	Kono et al.[12]
Gemcitabine	Scleroderma-like skin changes	Bessis et al.[13]
Capecitabine	Scleroderma-like skin changes, possible visceral involvement	Saif et al.[14]
Pemetrexed	Scleroderma-like skin changes	Ishikawa et al.[15]
Doxorubicine and cyclophosphamide association	Scleroderma-like skin changes	Alexandrescu et al.[16]
Hydroxyurea	Scleroderma-like skin changes	Garcia-Martinez et al.[17]
Analgesics		
Pentazocine	Localized scleroderma at the injection sites	Palestine et al.[18]
Methysergide	Scleroderma-like skin changes	Kluger et al.[19]
Ketobemidone	Localized scleroderma at the injection sites	Danielsen et al.[20]
Psychotropics		
Carbidopa and L-5-hydroxy-tryptophan	Scleroderma-like skin changes, localized scleroderma	Joly et al.[21]
Ethosuximide	Scleroderma-like skin changes associated with systemic lupus erythematosus	Teoh and Chan,[22]
Appetite suppressants		
Diethylpropion hydrochloride, mazindol, phenmetrazine, dexamphetamine-metaqualone, fenproporex, fenfluramine	SSc (typical skin lesions, Raynaud's phenomenon, ±visceral involvement, ±autoantibodies), localized scleroderma	Aeschlimann et al.,[23] Tomlinson and Jayson,[24] Korkmaz et al.[25]
Food supplements		
L-tryptophan	Eosinophilia-myalgia syndrome, eosinophilic fasciitis, scleroderma-like skin changes	Belongia et al.,[26] Varga et al.[27]
Antihypertensive drugs		
Bisoprolol	Localized scleroderma	De Dobbeleer et al.[28]
Fosinopril	SSc, eosinophilic fasciitis	Biasi et al.[29]
Immune system modulators		
Human recombinant interleukin-2	Scleroderma-like skin changes	Marie et al.[30]
Interferon alpha	SSc	Beretta et al.[31]
Anti-PD1 (pembrolizumab, nivolumab)	Scleroderma-like skin changes ± interstitial lung disease, worsening of pre-existing SSc	Tjarks et al.,[32] Barbosa et al.,[33] Terrier et al.[34]
Other		
Vitamin K_1	Localized scleroderma	Pujol et al.[35]
Penicillamine	Scleroderma-like skin changes and restrictive lung defect	Miyagawa et al.[36]
Triamcinolone	Localized scleroderma	Rodriguez Prieto et al.[37]
Bromocriptine	Localized scleroderma	Leshin et al.[7]

SSc: systemic sclerosis.

adjuvant chemotherapy was contraindicated, the complete mastectomy was realized.

Discussion

Docetaxel is a major chemotherapy drug used in the treatment of breast, lung, and prostate cancers, among others. Scleroderma-like skin-induced changes have been already described for Taxanes.[2] Sporadic cases of TMA and more frequently of docetaxel interstitial pneumopathy are reported.[3,4] However, the systemic involvement is not well established. A case report presented a case of systemic scleroderma with heart congestive failure 2 years after the diagnosis of breast cancer and treatment by DC.[5] The interesting finding in our case is the complexity of the clinical picture with multi-organ involvement, especially neurological symptoms.

Besides taxanes, many drugs have been associated with the occurrence of scleroderma and scleroderma-like disorders.[6] Although chemotherapeutic agents are most often involved, cases have also been reported with others drugs (Table 1). Most cases of drug-induced scleroderma

remained localized scleroderma with skin changes. Drug-induced SSc is rather rare. In localized scleroderma, skin involvement may display atypical features such as predominant edema, preferential axial or proximal involvement and bullous or vesicular lesions. Skin sclerosis may also be limited to a small area (localized scleroderma or morphea).[7] In systemic forms, specific autoantibodies (mainly, anticentromere, anti-RNA pol III, and antitopoisomerase 1 antibodies) are usually lacking. Finally, most cases improve after drug withdrawal. Three main mechanisms have been proposed to explain the occurrence of drug-induced scleroderma, echoing the three poles of SSc pathophysiology: (1) fibroblasts activation with increased production of collagen, (2) immune system stimulation, and (3) tissue ischemia induced by vasoconstriction or vascular thrombosis.[6]

The hypothesis of paraneoplastic SSc was consider in our case. Several types of solid tumors have been described as potentially associated with SSc, especially with anti-RNA pol III.[8] However anti-RNA pol III positivity appeared secondary. One possibility is that anti-RNA pol III antibodies were missed by the first test but that the autoimmune process had already started before the treatment of the cancer as a paraneoplastic form of SSc. In this view, the development of megao-esophagus usually needs time in SSc. Nonetheless, more than 1 year after the mastectomy and the arrest of all therapies, our patient had complete remission of her breast cancer, and SSc does not evolve anymore.

Physician should be aware about respiratory signs and renal function changes to not ignore a severe complication induced by docetaxel.

Declaration of conflicting interests

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