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R-CHOP-Induced Diffuse Scleroderma in Adults. The First Reported Case with Literature Review

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ABSTRACT

Chemotherapy regimens can be associated with a rare side effect in the skin that mimics limited or diffuse scleroderma. Limited scleroderma involves fibrosis of the hands, arms, and face along with Raynaud's phenomenon and pulmonary hypertension. Diffuse scleroderma involves extensive sclerosis of the skin and a higher risk of renal, cardiac, and lung involvement with the main diagnostic criteria being skin sclerosis proximal to the wrists. Anti-centromere and Anti-scl-70 antibodies can be associated with either diffuse or limited scleroderma. We present a 48-year old female with worsening shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea associated with palpitations. She had a past medical history of sickle cell trait and stage III diffuse large-cell lymphoma diagnosed 11 years ago with successful completion of 6 rounds of R-CHOP. Examination showed clubbing in the hands and toes and sclerodactyly. Our case presents possible complications of drug-induced diffuse scleroderma with a positive anti-Scl-70 antibody that developed shortly after the completion of chemotherapy. This is the first reported case of drug-induced diffuse scleroderma in an adult induced by doxorubicin or cyclophosphamide (RCHOP).

BACKGROUND

Advanced stage diffuse B-cell-lymphoma (Ann Arbor stage III or IV) is treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy and has a good prognosis in patients less than 60 years with a 73% event-free survival rate and a 93% overall survival rate after three years [1]. Even with favorable remission and survival rates for diffuse B-cell-lymphoma, clinicians should monitor for potential side effects related to the medications in the R-CHOP regimen.

Doxorubicin in a dose-dependent relationship causes dilated cardiomyopathy which results in congestive heart failure [2]. An uncommon side effect of chemotherapy regimens is scleroderma-like changes in the skin that mimics limited or diffuse scleroderma [3]. Limited scleroderma involves fibrosis of the hands, arms, and face along with Raynaud's phenomenon, pulmonary hypertension. Diffuse scleroderma has extensive sclerosis of the skin with the main diagnostic criteria involving skin sclerosis proximal to the wrists with a higher risk of renal, cardiac and lung involvement [4]. Anti-centromere and Anti-scl-70 antibodies can be associated with either diffuse or limited scleroderma [5-7]. Case reports link taxanes to scleroderma and there are three case reports linking doxorubicin or cyclophosphamide to chemotherapy-induced limited scleroderma [3,8,9]. One case report links chemotherapy-induced diffuse scleroderma vincristine, cisplatin, doxorubicin, cyclophosphamide use to systemic scleroderma in a 13-year-old child [10]. We are unaware of any case reports linking chemotherapeutic agents in the R-CHOP

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regimen to chemotherapy-induced diffuse scleroderma in an adult. Hereby we report the first case of diffuse scleroderma induced by the R-CHOP regimen in adults.

CASE PRESENTATION

A 48-year old African-American female presented to the emergency room (ER) with a few months history of worsening shortness of breath, orthopnea, paroxysmal nocturnal dyspnea and palpitations. She could walk only 10 to 30 feet before she got short of breath versus one block 3-4 months ago. She also felt a knot in the retrosternal area that is painful for 3 to 4 months. She had a past medical history of sickle cell trait and stage III diffuse large-cell lymphoma diagnosed 11 years ago with successful completion six rounds of rituximab and CHOP 2 years later. She had swelling and tenderness of her fingertips with difficulty flexing her hands and wrist since 9 years ago after her chemotherapy ended. She had come to the ER 2 times previously with shortness of breath symptoms - once 6 months ago and once 3 years ago. Six months ago, she was discharged with albuterol nebulizer, but the nebulizer treatment did not relieve the shortness of breath when she came into the ER today. She lived with her husband and son and worked at a fast-food chain. Abnormal vital signs included a respiratory rate of 34. On physical exam the patient had mild shortness of breath, and loud P2 crackles in the bilateral basilar lungs. The patient also had bilateral digital clubbing in her fingernails and sclerodactyly in the hands and toes. The patient on her fingers had scaling, excoriations, and digital ulcers. The patient reported cold finger extremities and used gloves frequently. She also had tightness of skin in her arms and trace edema in her lower extremities. The patient was admitted to the floor as an inpatient (Figure 1).

Figure 1: This picture of the right hand of the patient showing sclerodactyly, 'salt and pepper' pigmentation, scaling, excoriations and digital ulcers.

INVESTIGATIONS

Laboratory data on admission is listed in (Table 1). An EKG showed sinus tachycardia with left axis deviation. A chest x-ray (Figure 2) showed an enlarged cardiac silhouette and

Table 1: Laboratory results:

White blood cell count	4.7 x10e3/mcL
Red blood cell count	4.37 x10e6/mcL
Hemoglobin	13.3 gm/dL
Hematocrit	40 %
Platelet count	169,000 x10e3/mcL
Sodium	139 mmol/L
Potassium	3.8 mmol/L
Chloride	107 mmol/L
CO2	232mmol/L
Anion Gap	10 mmol/L
Blood Urea Nitrogen	10 mg/dL
Creatinine	0.6 mg/dL
Calcium	8.5 mg/dL
Troponin	0.01 ng/mL
D-Dimer	384 mg/L
Brain natriuretic peptide	1,418.00 pg/mL
Antiscleroderma-70 Antibody	>8.0 Ab Index

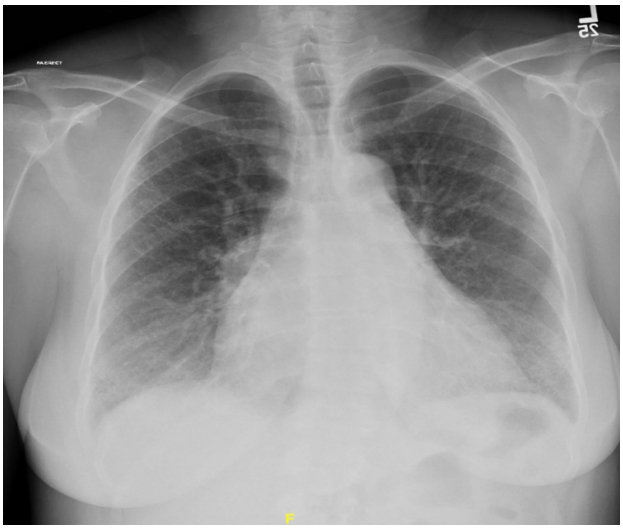

Figure.2: Chest x-ray showing a slight increase in the cardiac silhouette and the progression of pulmonary interstitial disease which may be due to the progression of the fibrotic changes.

pulmonary vascular congestion or pneumonia, superimposed on changes of interstitial pulmonary fibrosis. CT-Thorax (Figure 3) exhibited severe peripheral honeycombing/fibrotic changes very typical for idiopathic pulmonary fibrosis or usual interstitial pneumonitis with no signs of malignancy. A left heart catheterization showed no significant blockages in the left main artery, left anterior descending artery, left circumflex artery, and right coronary artery. Upon further chart review, a CT scan done 11 years ago presented some early non-significant signs of interstitial lung disease. A CT abdomen/pelvis scan done last year showed no signs of malignancy. A chest x-ray three years ago from the ER also showed findings suggestive of chronic interstitial lung disease.

A pulmonary function test resulted in an FVC of 73% predicted, FEV1 of 70% predicted, and FEV1/FVC of 95% predicted. Oxygen saturation testing on ambulation was around 90% to 99% oxygen saturation on ambulation.

Immunologic tests were remarkable for positive anti-Scl-70 >8.0 f and anticentromere (ACM) antibodies <0.2f. Serum antinuclear antibody was 1:640 for both for homogeneous and nucleolar pattern. SDNA antibodies, Smith (Sm) antibodies, ribonucleoprotein antibodies (RNP), rheumatoid factor (RF), P-ANCA/C-ANCA, antimicrosomal antibodies and Sjogren's anti-SS-B and Anti-Sjogren's SS-A all were negative. Total serum complement, C3, C4, serum immunoglobulins, and aldolase were normal. C-reactive protein was elevated at 100 mg/L (normal range, 0–6 mg/L). The thyroid panel revealed a low thyroid stimulating hormone of 0.18 uIU/mL (normal range, 0.49–4.67uIU/mL), with a normal free T4 of 1 ng/dl. A follow-up peripheral blood smear was negative for any evidence of malignancy.

The patient was diagnosed with scleroderma due to symptoms of sclerodactyly, thickening of the skin with proximal extension to the upper arm, positive anti scleroderma-70 antibody, and Raynaud's phenomenon (cold finger extremities).

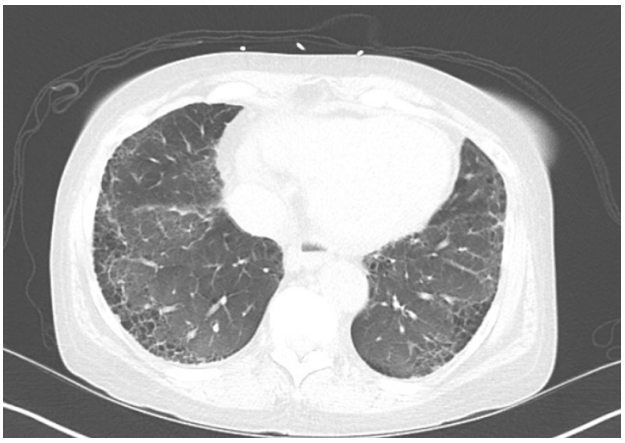

Figure 3: CT thorax, axial view, showing severe peripheral honeycombing and fibrotic changes that is worse in the bases.

DISCUSSION

Our case presented a patient with complications of drug-induced diffuse scleroderma that developed shortly after the completion of chemotherapy. The patient had a positive anti-Scl-70 antibody suggestive of diffuse scleroderma with negative anti-centromere B, anti-Jo-1, anti-myeloperoxidase, anti-proteinase 3, c-ANCA, p-ANCA, antinuclear, and anti-SSA antibodies. The patient did not follow up regularly with a primary care physician or any specialists. The patient reported shortness of breath symptoms that started months after the completion of chemotherapy and a CT scan during the course of chemotherapy showed early signs of interstitial lung disease. The patient reported shortness of breath symptoms, which suggested earlier onset of drug-induced scleroderma. The clinical onset of scleroderma-like symptoms for other chemotherapy drugs is shorter. Docetaxel has an average disease onset of 6.5 months after starting docetaxel with clinical worsening over the next 2-3 months. Paclitatxel has an average of 8.1 months after starting docetaxel with progression of disease over 3.3 months. For patients with chemotherapy including doxorubicin and cyclophosphamide, the mean time to the development of limited sclerosis is 25 months with the disease progression to final sclerosis 2 months later [3].

The mechanisms of pathogenesis of scleroderma are poorly understood. Current understanding involves a confluence of tissue injury, vascular injury, and endothelial damage. This damage leads to inflammation and the production of auto-antibodies and cell-mediated autoimmunity. Macrophages and T-cells lead to the growth of fibroblasts that cause growth of extracellular matrix proteins and collagen that cause fibrosis [11,12]. Though the complete mechanism of scleroderma is unclear, oxidative stress to endothelial cells could trigger the cascade that leads to the fibrosis of skin and internal organs seen in scleroderma. Immunomodulating effects of chemotherapy drugs could also trigger the fibroblast cascade. Levels of IL-2, IL-6, TNF and granulocyte-macrophage colony stimulating factor can increase with taxanes [13]. Doxorubicin and paclitaxel can increase levels of tumor necrosis factor-alpha, whose rising levels are linked to scleroderma linked to pulmonary fibrosis [14].

Certain drugs used in the R-CHOP chemotherapy regimen should be considered when determining the cause of the patient's drug-induced scleroderma. Vincristine was shown when used in mice to reduce the cardiotoxicity of doxorubicin by reducing oxidative stress [15]. Rituximab is currently under investigation for treatment of scleroderma. Cyclophosphamide and prednisone have also been used in the treatment scleroderma [16]. Doxorubicin is known to cause endocardial damage through oxidative stress. Additionally, doxorubicin also activates the pro-inflammatory NF-KB

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Table 2: summarizes other drug-induced scleroderma cases in the literature [3,8-10,21-34].

Case report	*Culprit drug*	*Patient age*	*Cancer type*	*Time from the first dose*	*Diffuse or Localized S.D.*	*Improved after stopping chemo?*
Cleveland et al. 2000	5-Fluorouracil, doxorubicin, docetaxel	39/F	Breast cancer	3 months	limited	Yes
Battafarano et al. 1995, case 1	doxorubicin, docetaxel	46/M	Leiomyosarcoma of duodenum	7 months	limited	Partial
Battafarano et al. 1995, case 2	docetaxel and radiation therapy	63/M	Melanoma	4 months	limited	Partial
Battafarano et al. 1995, case 3	docetaxel	67/F	Bronchoalveolar carcinoma	4 months	limited	Yes
Hassett et al. 2001	tamoxifen, cyclophosphamide, methotrexate, 5-Fluorouracil, docetaxel	59/F	Breast cancer	3 months	diffuse	Partially
Kupfer et al. 2003	paclitaxel/paraplatin, cyclophosphamide/ paraplatin, paclitaxel/ paraplatin	63/F	Primary peritoneal carcinoma	4 months	limited	Partially
Läuchli et al. 2002	paclitaxel/carboplatin	66/F	Primary peritoneal carcinoma	6 months	limited	Partially
De Angelis et al. 2002	carboplatin, doxorubicin, etoposide; paclitaxel; paclitaxel/ carboplatin	56/F	Ovarian cancer	1 year	diffuse	Partially
Haviv et al. 1998	adiramycin, bleomycin, vinblastine (ADV) and cyclophosphamide, hydroxydaunorubicin , vincristine, predisone (CHOP)	58/M	Hodgkin disease	8 years	diffuse	No
Fraschini et al. 1988	vincristine, doxorubicin, cyclophosphamide	50/F	Breast cancer	2 months	limited?	No
Emir et al. 2001	vincristine, cisplatin, doxorubicin, cyclophosphamide	13/F	Thymic carcinoma	9 months	diffuse	No
Alexandrescu et al. 2005	doxorubicin, cyclophosphamide	45/F	breast cancer	11 months	limited	No
Konishi et al. 2010	paclitaxel/carboplatin	67/F	Ovarian cancer	3 months	limited	Not reported
Kawakami et al. 2009	paclitaxel	48/F	breast cancer	10 months	limited	Partially
Garcia-Martinez et al. 2012	hydroxycarbamide	67/M	polycythaemia vera	10 years	limited	Yes
Winkelmann et al. 2016	paclitaxel/carboplatin	64/F	Ovarian cancer	6 months	diffuse	Yes
Park et al. 2017	docetaxel/ cyclophosphamide	49/F	breast cancer	1 year	diffuse	No
Kilic et al. 2015	docetaxel/doxorubicin/ cyclophosphamide	59/F	breast cancer	Not reported	limited	Partially
Byun et al. 2013	docetaxel	57/F	breast cancer	7 months	limited	Yes
Verhulst et al. 2018	paxlitaxel/gemcitabine	63/M	pancreatic cancer	1 year	limited	Not stopped

pathway in cardiac cells, renal cells, and endothelial cells [17]. Our team suggested that the doxorubicin or cyclophosphamide combined with immunomodulation were the likely causes of the scleroderma symptoms. Other drugs have been reported to cause scleroderma-like endothelial injury including cisplatin, bleomycin, and vincristine who can present as hemolytic uremic syndrome that can require emergent dialysis and plasmapheresis [18,19].

The patient did not follow up with specialists or a primary care physician when she came into the ER 4 years later, but our imaging and tests showed no progression in the patient's scleroderma and even some improvement. A repeat CT angio scan showed no progression of the patient's interstitial lung disease or pulmonary hypertension. The patient's skin thickening was similar, and fewer signs of calcinosis were seen clinically. The patient was also not on any medications specific for treating scleroderma; she was only on medications for management of the chronic heart failure symptoms. The lack of patient follow up raises the question of if the symptoms of scleroderma were present in the milder form in the past but the lack of progression makes it less likely. Additionally it is possible that the scleroderma could be a neoplastic syndrome associated with a hematological malignancy which has been described in the literature [20]. However, a follow-up peripheral blood smear after the patient was discharged was negative for any hematological malignancy making this association less likely. Regardless, it is important for the patient to follow-up with a physician on a regular basis but insurance issues make this difficult for the patient.

This case is unique because after an extensive review for the reported cases in literature we could not find any reports of diffuse drug-induced scleroderma in adults which makes it the first case to be reported (Table 2).

LEARNING POINTS/TAKE HOME MESSAGES

- We report a first-known case of drug-induced diffuse scleroderma in an adult induced by doxorubicin or cyclophosphamide.
- Physical exam of the patient provided important clues pointing towards scleroderma and should not be ignored on initial presentation.
- Four years later, the patient's scleroderma symptoms were unchanged even after poor outpatient follow-up by the patient.
- Interstitial lung disease could be seen as a rare complication due to rituximab. Clinicians should maintain a high index of suspicion to recognize this complication.(35,36)

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