Case Report

Digital Necrosis Related to Carboplatin and Gemcitabine Therapy in Systemic Sclerosis

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ABSTRACT. We present a woman with scleroderma who developed multiple ischemic digits after chemotherapy for lung cancer. The ischemia started during treatment with carboplatin and gemcitabine and required amputation of the affected digits. A review of the literature shows that thrombotic episodes coinciding with chemotherapy are not uncommon, though venous thrombosis occurs more frequently than arterial. Scleroderma patients are at particular risk for digital infarction because of their underlying vascular disease and associated Raynaud's phenomenon. This case illustrates the risk of severe digital ischemia and digital loss in patients with scleroderma during chemotherapy with carboplatin and gemcitabine. (J Rheumatol 2003;30:1341–3)

Key Indexing Terms:
SCLERODERMA NECROSIS ANTINEOPLASTIC AGENTS
CARBOPLATIN GEMCITABINE

Systemic sclerosis (scleroderma, SSc) is characterized by arterial vascular disease. Patients with SSc have Raynaud's phenomenon and are at increased risk for painful digital ulcers and catastrophic ischemic digital loss. Therapeutic interventions that promote vasoconstriction or thrombosis, including arterial vascular access and medications, compound the risk for severe ischemia. We present a case in which carboplatin and gemcitabine directly preceded multiple severe digital infarcts in a patient with SSc, highlighting the potential risks of these chemotherapeutic agents.

CASE REPORT

A 50 year old Caucasian woman was diagnosed with SSc in 1996. The patient met American College of Rheumatology criteria[1] for SSc with digital ulcers and sclerodactyly. She also had carpel tunnel syndrome, Raynaud's phenomenon, sicca syndrome, and mild dysphagia. Laboratory analysis revealed an antinuclear antibody titer of 1:640 with a centromere pattern. Alhough she had no symptomatic pulmonary complaints and was a non-smoker, pulmonary function tests showed restrictive lung disease with a vital capacity 69% of predicted and a diffusion capacity 80% of predicted.

A screening chest radiograph in August 2000 uncovered hilar adenopathy and bilateral pulmonary nodules. A bronchoscopy in November 2000 found pseudohyphae and she was treated with itraconazole for histoplasmosis. A computed tomographic (CT) scan in December 2000 showed enlargement of the pulmonary lesions and lymphadenopathy. Mediastinoscopy biopsy revealed poorly differentiated carcinoma, negative for melanoma, neuroendocrine, and lymphoid tumor markers.

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The patient was evaluated January 2001 by oncologists at Johns Hopkins Hospital who recommended treatment with carboplatin and gemcitabine. Prior to chemotherapy, they noted a small ulcer on her first finger but no cyanosis or signs of critical ischemia. Her medications prior to the commencement of chemotherapy were armour thyroid, gingko, grape seed, and a multivitamin. She received carboplatin on day 1 and gemcitabine on days 1 and 8, repeated in 21 day cycles. After the first chemotherapy cycle, the patient noted some right hand and left foot swelling that resolved without treatment, but no signs of critical ischemia. On March 1, 2001, day 1 of her second cycle, she noted a blue hue and pain in one finger. The cyanosis and pain progressively worsened. She was treated with a calcium channel blocker, prednisone, cephalexin, gabapentin, and 2 stellate ganglion blocks, without significant improvement.

Her first visit to the Johns Hopkins and University of Maryland SSc Center was on April 9, 2001. Her general examination revealed a weight of 110 lb, blood pressure of 140/86 mmHg, and resting pulse of 100 beats/min. SSc skin changes and telangectasias were noted over her hands, forearms, face, and both upper and lower legs. Critical ischemia with advanced gangrenous changes had developed in multiple fingers (Figure 1). She had symmetric strong radial pulses and normal Allen's tests, no ischemic changes in her feet, and no evidence of large vessel disease. She was referred to the Plastic Surgery Department for management and on April 15, 2001 her right 2nd, 4th, and 5th fingers and her left 3rd finger were amputated.

Laboratory studies revealed normal serum electrophoresis panel, Russell's viper venom time, complement levels, complete blood count, partial thromboplastin time (PTT), and prothrombin time (PT). Her Anti-Scl-70 antibody, pANCA, cANCA, anticardiolipin antibodies, and cryoglobulin screen were all negative. Her erythrocyte sedimentation rate was 40 mm/hour.

A repeated chest CT scan on March 21, 2001 revealed a marked decrease in the size of her lymph nodes and the pulmonary nodules compared to January 2001. The gemcitabine and carboplatin was stopped because of the digital ischemia and the patient was lost to followup.

DISCUSSION

This case illustrates the potential risk of using carboplatin and gemcitabine in a patient with SSc and is the first report of digital loss in a patient with SSc related to the combina-

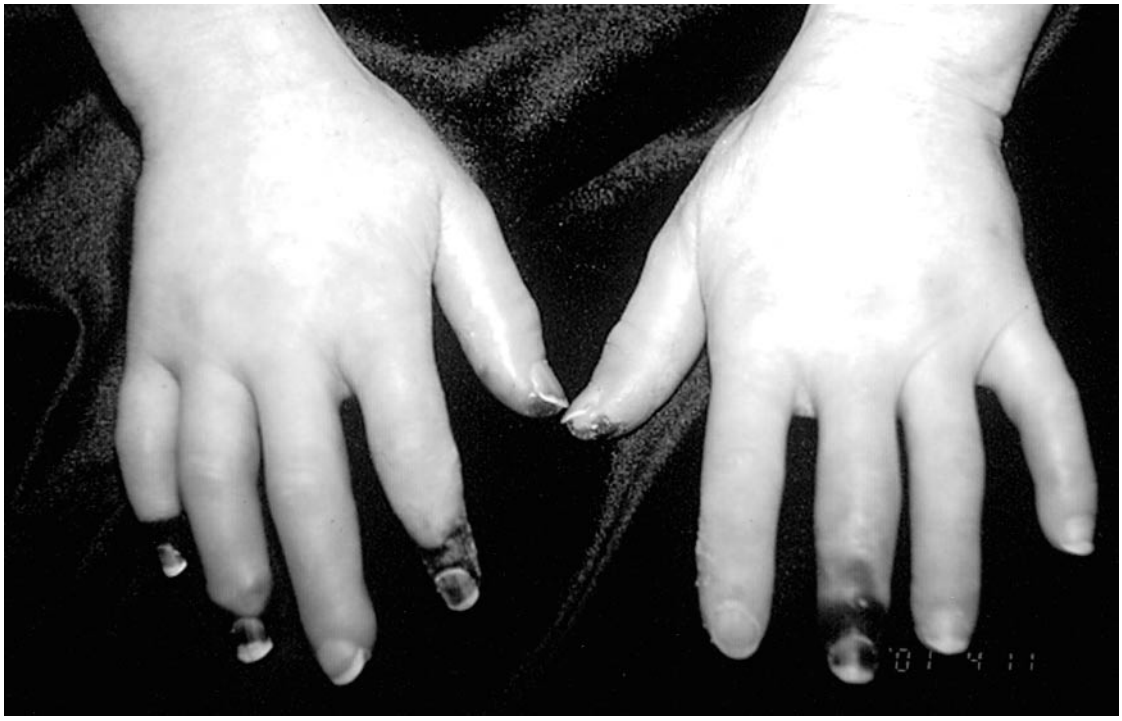

Figure 1. Dry gangrene on multiple digits prior to amputation.

tion of these medications. SSc patients are at increased risk for digital ischemia because of increased smooth muscle contractility, vessel narrowing, endothelial damage, and platelet activation. Over 90% of SSc patients have Raynaud's phenomenon usually accompanied by recurrent digital ulceration[2]. Endothelial cell dysfunction is associated with intimal thickening and vascular narrowing of the small and medium size arteries. Limited SSc (CREST syndrome) as well as the presence of anticentromere antibody, antiendothelial cell antibody, and antibody directed toward granzyme B cleaved autoantigens increases the risk for peripheral vascular occlusive disease and digital loss[2,3].

The association between arterial thrombosis, cancer, and chemotherapy has been demonstrated in several studies and case series (Table 1). Gemcitabine has been implicated in several cases of myocardial infarction (MI), hepatic veno-occlusive disease, and microangiopathic hemolytic anemia[5,6,9,12]. Moreover, MI, cerebral vascular accidents, and severe digital ischemia requiring amputation have been reported in patients treated with cisplatin and gemcitabine[10,11]. A case similar to ours by Marie, *et al* describes a woman with diffuse SSc who developed digital necrosis after treatment with cisplatin and gemcitabine for bronchoalveolar carcinoma[4].

The pathogenesis of thrombosis caused by chemotherapy includes endothelial damage and hypercoagulability. Bleomycin, nitrosourea, and vincristine all cause endothelial cells to retract *in vitro*, exposing the subendothelial matrix. Platelets easily adhere to this exposed matrix inducing aggregation and thrombosis[16]. Chemotherapeutics also can induce a hypercoagulable state by decreasing fibrinolytic activity, lowering levels of proteins C and S, and shortening the PT and PTT[17,18].

This case highlights the interaction of chemotherapy toxicity and SSc vascular disease leading to digital ischemia requiring amputation. SSc patients' risk for digital ischemia is compounded by the risk of arterial thrombosis following chemotherapy. Although it is possible that our patient's ischemic digits were solely secondary to SSc, we think that the dramatic presentation of the digital ischemia at the time of chemotherapy strongly suggests that the chemotherapy was an aggravating factor. We suggest that the combination of carboplatin and gemcitabine should be avoided in SSc patients if possible. Similar caution should be used when prothrombotic agents like cisplatin or bleomycin are used. This case also highlights the importance of maintaining a high level of suspicion for venous or arterial thrombosis when treating SSc patients undergoing chemotherapy.

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Table 1. Chemotherapy associated with thrombotic events: literature review.

Chemotherapy	Study, Reference	Thrombosis
Cisplatin and gemcitabine	Case report of a woman with diffuse scleroderma treated for broncho-alveolar carcinoma[4]	Digital nercrosis after chemotherapy
Gemcitabine	Case report of man with pancreatic cancer[5]	MI 6 hours after 5th cycle of gemcitabine; ischemic EKG changes on next gemcitabine infusion
Gemcitabine	Case report of woman with non-small cell lung cancer[6]	Hepatic veno-occlusive disease after 11th treatment of gemcitabine; resulted in death
Bleo, Vcr	Case report of non-Hodgkins lymphoma[7]	Cynanosis then gangrenous digits after second course of chemotherapy
Carbo, Etop	Case report of man with small cell lung cancer[8]	MI from vasospastic angina during chemotherapy
Gemcitabine	Case series of 3 patients on longterm gemcitabine[9]	Thrombotic microangiopathy after one year of gemcitabine therapy
Cisplatin-based therapy	Case series of 4 young men with testicular cancer[10]	2 had MI and 2 had CVA
Cisplatin and gemcitabine	Case series of 4 patients with lung cancer[11]	Distal ischemia with 2 requiring amputation of their extremity
Gemcitabine	Phase II trial of non-Hodgkin's lymphoma with 36 patients[12]	3 patients with vascular complications, one each: microangiopathic hemolysis, hepatic veno-occlusive disease, and MI
C, Dox, F, Vcr, MTX, Thio, Fl, Pred	Cohort study of 1,014 breast cancer patients from 2 cancer and leukemia Group B protocols[13]	13 patients developed arterial thrombosis; 12 occurred during chemotherapy
C, MTX, F, Pred, Tam, Dox, Fl, thio, Vbl	Cohort study of 2,673 patients in 7 ECOG studies of breast cancer therapy: chemotherapy vs observation[14]	Venous and arterial thrombosis incidence was 5.4% in chemotherapy patients, vs 1.6% in observed patients
C, MTX, F, Vcr, Pred, Dox, Tam	Randomized trial of 205 women with stage II breast cancer[15]	14 patients developed thrombosis (1 arterial) during chemotherapy

Bleo: bleomycin; C: cyclophosphamide; Carbo: Carboplatin; Cis: cisplatin; Dox: doxorubicin; Etop: Etoposide; F: fluorouracil; Fl: fluoxymesterone; MTX: methotrexate; Pred: prednisone; Tam: tamoxifen; Thio: thiotepa; Vbl: vinblastine; Vcr: Vincristine; MI: myocardial infarction; CVA: cerebrovascular accident

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