CASE REPORT AND LITERATURE REVIEW

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DIGITAL ULCERATION FOLLOWING GEMCITABIN PLUS CISPLATIN CHEMOTHERAPY IN A SYSTEMIC SCLEROSIS PATIENT WITH LUNG ADENOCARCINOMA

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Abstract

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by fibrosis and vascular dysfunction in the skin and visceral organ systems. Digital ulceration is one of the major cause of morbidity. Although its pathogenesis has not been fully elucidated, structural and functional disturbances in small vessels are considered one of the major mechanisms. While cold exposure is considered the most important inciting factor for the development of digital ulceration, drugs and physical trauma are other described triggering factors. Herein, we report a case with SSc diagnosis who developed digital ulcers following gemcitabine and cisplatin chemotherapy for lung adenocarcinoma.

Keywords: Systemic sclerosis, vasculopathy, chemotherapy, digital ulceration, management

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by fibrosis and vascular dysfunction in the skin and visceral organ systems. Digital ulceration is a significant organ involvement related to morbidity. Many hypotheses have been proposed for the development of digital ulceration; however, structural and functional disturbances in small vessels are considered major mechanisms (1,2). Additionally, there are disease-related and environmental factors (including drugs) that contribute to the development of digital ulceration. Here, we describe a case of a patient with a previous diagnosis of SSc who presented with digital ulceration in both hands shortly after receiving gemcitabine and cisplatin chemotherapy for lung adenocarcinoma. Our aim in this report is to draw attention to this issue and discuss management strategies in light of the literature.

CASE REPORT

A 48 year old female was admitted to the hospital with a new onset painful ulceration at the tip of both hands. She reported that this condition started suddenly five days ago and deteriorated in the last 3 days. Past medical history showed that she was diagnosed with SSc five years ago based on the presence of Raynaud's phenomenon, bilateral sclerodactyly, telangiectasis, lung involvement (non-specific interstitial pneumonia) and high titers of anti-nuclear antibody (1/640-

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1/1000) and Scl-70 positivity (4+). She was treated with cyclophosphamide and glucocorticoids for lung involvement. After completion of four cycles of cyclophosphamide, steroid was stopped at one month and maintainance treatment with azathioprine (100 mg/day) commenced as her lung parencyhma responded well to induction therapy with no symptoms of dyspnea and showed radiologic improvement on chest computed tomography (CT) control at month four of follow-up. During follow-up every three to six months under azathioprine, nifedipine, acetylsalicilic acid and lansoprazole for SSc, a cavitary lung mass was incidentally detected by CT imaging of the chest for routine control of lung involvement three years after SSc diagnosis. Positron emission tomography (PET)-CT imaging was consistent with metastatic malignancy, however, the initial biopsy examination was noncontributory. After surgical excision, histopathologic examination confirmed the diagnosis of undifferentiated adenocarcinoma of the lung (PDL-1 negative and c-Erb2 positive). After unresponsiveness to combination of carboplatine and paclitaxel as the first line treatment, pemethrexed was given, but the cancer progressed. Thus, nivolumab was started, however, the drug was cessated shortly after due to drug intolerance. Lastly, combination of gemcitabine and cisplatine administered three months ago. Treatment was well-tolerated and lung mass decreased in size, however, ten days after the third cycle (10 days following gemcitabine), she presented with painful digital ulceration (Figure 1). She reported no recent infection and physical trauma. Physical examination showed necrotic digital ulcers at the tip of both hands. Radial pulses were palpable bilaterally. Modified Rodnan Skin Score was calculated 6 and lung examination was noncontributory. Microbiologic examination revealed no organisms. Thrombocyte counts, fibrinogen and D-dimer levels were normal but mild elevation in c-reactive protein (10 mg/dL; reference 0-5) was found. Doppler ultrasound imaging showed intact radial and ulnar pulses in upper extremities. During the whole cancer treatment period, no evidence of SSc organ progression was observed in terms of skin, lung and other organs. Skin scores were similar and chest CT imaging until detection of lung mass did not suggest any progression in SSc related lung involvement. After excluding these possibilities, the new onset digital ulceration was attributed to gemcitabine plus cisplatine chemotherapy. The patient was recommended for hospitalization to initiate intravenous iloprost, but she refused due to family reasons. Her nifedipine dose escalated to maximally tolerated dose (120 mg/day) and pentoxyphylline was added to acetylsalicylic acid. Moreover, she was consulted with the oncology department regarding the current complication. Gemcitabine plus cisplatine combination was replaced with another regimen as benefits overweigh risks. At one month follow-up visit, her lesions showed total recovery (Figure 1). She is currently on nifedipine, pentoxyphylline and acetylsalicylic acid for SSc and under chemotherapy for her metastatic cancer.

DISCUSSION

Digital ulceration in SSc remains a major problem in clinical practice. The primary pathogenesis is considered to be alterations in the vasculature of extremities. Vasculopathy in SSc consists of endothelial dysfunction, defective angiogenesis, and altered vasculogenesis (2). While environmental factors such as persistent exposure to cold weather are major determinants of ulcer development, other causes have also been described, including trauma, thrombosis, and drugs (2). Notably, serious thrombotic complications in various organs have been reported in patients after gemcitabine plus platinum-based regimens, mainly associated with increased cumulative doses (3). Digital ulceration and necrosis have also been reported following gemcitabine in SSc patients (4,5). Indeed, in our case we can not ignore the possiblity of that this incident might occur as solely

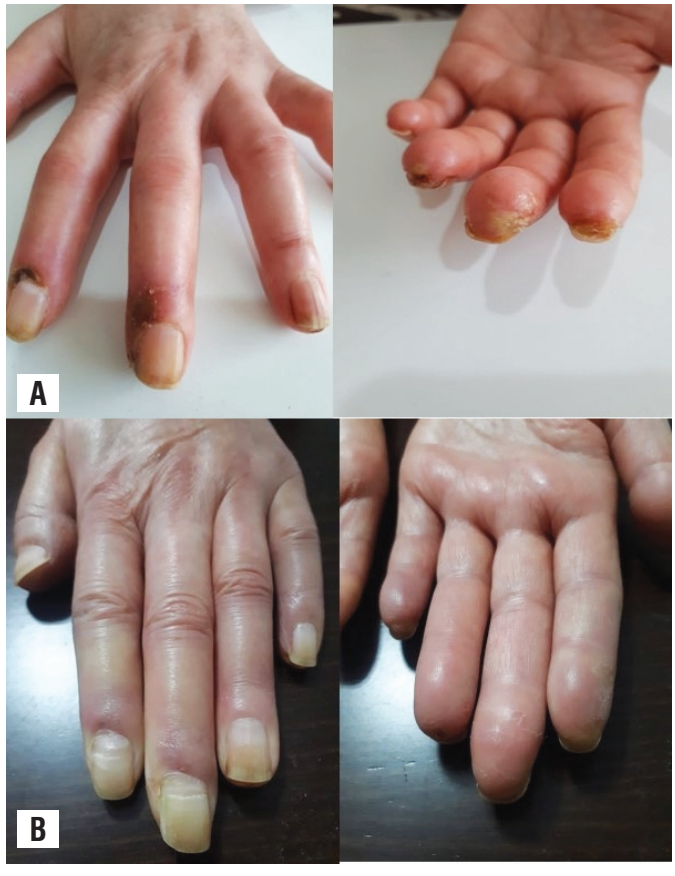

Figure 1. A) Digital ulcerations at the fingertips tip and at the edges of the nails, B) Follow-up examination at 1 month revealed fully recovered lesions

disease related, which can be considered as a limitiation however, recent usage of these agents and no SSc related vascular events for a long time are supporting that there is a strong relationship between these agents and the incident.

It is well known that SSc patients have endothelial dysfunction and a microvascular environment sensitive to hypoxia, procoagulant activity, and external stimuli. This microenvironment might explain the contribution of gemcitabine and cisplatin in developing digital ulceration in our case. Management includes intravenous prostacyclin analogues, calcium channel blockers, and other vasodilators, as well as wound care and prevention of infectious complications (3). Moreover, there is no consensus on prophylaxis in those maintaining their same anti-cancer regimens. It is of great importance that physicians are aware that gemcitabine and cisplatin might increase the tendency for microvascular thrombotic complications in SSc patients. The cessation and/or continuation of cancer drugs should be tailored in collaboration with the oncology department according to the activities and benefits of both diseases.

CONCLUSION

SSc patients are prone to developing vascular complications, leading to digital ulcerations. Potential risk factors should be minimized for better outcomes. Clinicians should keep in mind that some chemotherapeutic agents can induce vasculopathy in this population if cancer is concomitantly present. In the case of a chemotherapy-related vascular event in an SSc patient, treatment should be discussed with oncology with the patient's best interest in mind.

Footnote

Informed Consent: Written informed consent has been obtained from the patient to access and collect data from the medical record to be used in scientific publications.

Authorship Contributions

Surgical and Medical Practices: H.O., R.Y., Concept: H.O., R.Y., N.Ş.Y.B., T.K., Design: H.O., R.Y., N.Ş.Y.B., T.K., Data Collection or Processing: H.O., R.Y., N.Ş.Y.B., T.K., Analysis or Interpretation: H.O., R.Y., N.Ş.Y.B., T.K., Literature Search: H.O., R.Y., N.Ş.Y.B., T.K., Writing: H.O., R.Y., N.Ş.Y.B., T.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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