

CASE REPORT

Pembrolizumab induced scleroderma

Reem Alkilany*, Stanley Ballou

Department of Rheumatology, CaseWestern Reserve University/MetroHealth Medical Center, Cleveland, Ohio, USA

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ABSTRACT

Systemic sclerosis (SSc) is a rare connective tissue disorder. It is a chronic multisystem disease characterized by vascular dysfunction and progressive fibrosis of tissue, with skin hardening and thickening (known as scleroderma) being the hallmark of the disease. It tends to affect females more than males and has a higher prevalence in African American population with earlier onset and more severe disease. While scleroderma can be a manifestation of conditions other than SSC, the presence of skin thickening of the fingers, extending proximally to metacarpophalangeal joints is sufficient to classify a patient as having SSC. SSc treatment is challenging given the heterogeneity of the disease, multiple organ involvement, different subtypes and poorly understood etiology and pathogenesis. Yet, systemic immunosuppressive therapy is often the treatment of choice. Here we present a 60-year-old white female who developed skin thickening of her fingers extending to the forearms and of her proximal thighs after being treated with pembrolizumab for metastatic non-small cell lung cancer. It was difficult to determine internal organ involvement given her history of metastatic lung cancer, but scleroderma specific autoantibodies were negative. Her symptoms improved after treatment with methotrexate and stopping pembrolizumab. This is one of the first case reports of scleroderma secondary to pembrolizumab.

Key Words: Pembrolizumab, Immune check point inhibitor, Scleroderma, Systemic sclerosis, Sclerodactyly, Scleredema diabeticorum

1. INTRODUCTION

Systemic sclerosis (SSc) is a rare connective tissue disorder characterized by excessive tissue fibrosis^[1,2] with scleroderma (skin fibrosis) being the hallmark of the disorder.^[1] There are a few scleroderma-like syndromes associated with long-term diabetes such as diabetic sclerodactyly and diabetic scleroderma.^[3] Moreover, there have been few reported cases of scleroderma and scleroderma-like skin changes induced by immune checkpoint inhibitors (ICIs) used in treatment of different types of cancer.^[4] Here we present a patient with poorly controlled insulin-dependent diabetes mellitus (IDDM) and non-small cell lung cancer (NSCLC) on pem-

broilizumab who developed scleroderma 2 years following treatment.

2. CASE PRESENTATION

A 60-year-old white female with past medical history of high blood pressure, dyslipidemia, hypothyroidism, poorly controlled IDDM, carpal tunnel syndrome, Stage IV NSCLC of the right hilum with bone and right pleural metastasis, was referred to rheumatology for right hand stiffness, swelling and pain of 1-month duration.

The patient reported that her pain fluctuated but was worst in the morning. She reported stiffness in her hands through-

*Correspondence: Reem Alkilany, MD; Email: ralkilany@metrohealth.org; Address: Department of Medicine, Division of Rheumatology, 2500 MetroHealth Drive, Cleveland, Ohio 44109-1998, USA.

out the day and was unable to make a fist or flex at the wrist. She had swelling over the left hand that had improved. She had a history of carpal tunnel syndrome for which she wears a splint. She denied sicca symptoms, history of eye inflammation, difficulty swallowing, heart burn, Raynaud’s phenomena or skin rashes.

She was diagnosed with IDDM in her teens, without complications, and had been on insulin with moderate control, yet it became poorly controlled after the diagnosis of cancer and its management. She was diagnosed with NSCLC in 2017 and was treated with chemotherapy (Carboplatin/Pemetrexed) and immunomodulators (Pembrolizumab). Single pembrolizumab was re-introduced on 11/27/17 due to liver metastasis and left supraclavicular adenopathy that had resolved. She received 30 cycles total over the past 32 months with some interruption, now with stable disease.

She quit smoking 6 years ago after smoking over 30 pack-years, and drinks two glasses of wine a day. There is a possible family history of lupus in her sister.

Vital signs were stable. Musculoskeletal exam was significant for limited range of motion of the right wrist, tenosynovitis over bilateral metacarpophalangeal joints (MCPs) more severe on the right, mild tenderness over 2nd and 3rd left MCPs. She was noted to have tightness and thickening of skin over her fingers extending to the forearms and over the thighs bilaterally (see Figure 1). She was able to open her mouth > 3 fingerbreadth. She didn’t have any skin rashes or telangiectasia. she had decreased basilar breath sounds. Otherwise her exam was unremarkable.

When further questioned, patient recalled that over the past few months (3-6 months) she was having difficulty pinching

the skin of her thighs when she attempted injecting insulin but didn’t pay much attention to it.



Figure 1. a. Right hand and forearm upon presentation to rheumatology clinic, patient had hardening and thickening of the skin of the fingers extending to forearms. b. Thickening and difficulty in pinching the skin over the distal forearm.

Her presentation prompted further workup for an underlying autoimmune disorder including scleroderma and rheumatoid arthritis (RA). Lab workup was significant for leukopenia, mildly elevated rheumatoid factor (RF), and elevated inflammatory markers, otherwise unremarkable (see Table 1), right hand X-ray as in Figure 2.

For further evaluation of SSc, patient had an echocardiogram that showed hyperdynamic left ventricular (LV) systolic function with ejection fraction (LVEF) of 80%.

Table 1. Laboratory results

Test	Value	Normal	Test	Value	Normal	Test	Value	Normal
WBC	2.9 K/ μ l	4.5-11.5 K/ μ l	ESR	43 mm/hr	< 30 mm/hr	HBsAb	< 3.1	Non-Reactive
HB	13.7 g/dl	12.0-15.0 g/dl	CRP	2.2 mg/dl	< 0.8 mg/dl	HBcAb	Nonreactive	Non-Reactive
Platelet	288 K/ μ l	150-400 K/ μ l	Autoimmune Panel	Negative	Negative	HBsAg	Non-Reactive	Non-Reactive
Creatinine	0.88 mg/dl	0.50-1.10 mg/dl	Anti RNA Pol III	< 20F	< 20F	Hepatitis C Ab	Non-Reactive	Non-Reactive
ALP	131 IU/L	40-200 IU/L	RF	13 IU/ml	< 10 IU/ml	TB	Negative	Negative
ALT (SGPT)	12 IU/L	7-40 IU/L	CCP IgG	2.2 U/ml	nl < 3.0 U/ml	HbA1C	10.4	0-5.6%
AST (SGOT)	23 IU/L	7-40 IU/L	CK	36 IU/L	57-374 IU/L			

Note. ALP: Alkaline Phosphatase, CCP: Cyclic Citrullinated Peptide Ab,IgG, CRP: C-Reactive Protein, CK: Creatine Kinase, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, HBsAb: Hepatitis B Surface Ab, HBcAb: Hepatitis B Core Ab Total, HBsAg: Hepatitis B Surface Antigen, IF: immunofluorescence, WBC: white blood cell.



Figure 2. Osteoarthritic changes most severely involving the radial carpometacarpal joint, focal erosion of the distal third metacarpal and deformity of the fifth finger including exaggerated concavity with molding at the proximal aspect middle phalanx.

The case was concerning for possible Rheumatoid arthritis and/or SSc in the setting of Pembrolizumab. The presence of skin thickening of the fingers that extended proximally to the forearms and bilateral thighs in addition to very low RF titer and negative anti CCP antibodies favored systemic sclerosis. A decision was made to stop pembrolizumab and start methotrexate (MTX) 15 mg once a week. Patient started to notice improvement in her skin manifestations and joint symptoms after the third dose of MTX.

Unfortunately, it wasn't possible to obtain skin biopsy as patient's skin thickening has resolved by the time she was evaluated by dermatology. She had been off Pembrolizumab for 1 month and on MTX for 2 months.

3. DISCUSSION

Systemic sclerosis is a rare connective tissue disorder most commonly affecting middle-aged women and characterized by tissue fibrosis, vascular dysfunction and autoimmunity.^[1] According to EULAR/ACR 2013 SSc classification criteria, skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints is sufficient for

classification as SSc in the absence of SSc-like disorders that better explain the skin manifestations.^[2] SSc is divided into two major subgroups: limited cutaneous SSc and diffuse cutaneous SSc. In limited cutaneous scleroderma, fibrosis is mainly restricted to the hands, arms, and face. Raynaud's phenomenon often precedes fibrosis by several years, and anticentromere antibodies occur in 50%-90% of patients. Diffuse cutaneous scleroderma affects a larger area of skin and often compromises one or more internal organs.^[5]

Published studies demonstrate an increased risk of all cancers in SSc. Autoantibody production has been shown to appear years before cancer diagnosis in this context, especially anti-RNA-Pol III antibodies. Nevertheless, the connection is complex, as immunosuppressive therapy can also be associated with cancer development. Furthermore; the temporal clustering observed in some patients raises the possibility of SSc as a paraneoplastic syndrome.^[1,6]

Recently, ICIs used for cancer treatment have been associated with several immune related adverse events (IrAEs) including very few reported cases of scleroderma.^[4,7] ICIs are monoclonal antibodies that increase T-cell activity by blocking Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or PD-1, PD-L1. IrAEs manifest as systemic and organ-specific autoimmunity, with pruritis, skin rash, arthralgia and myalgia being the most often reported cutaneous and rheumatologic IrAEs. Most IrAEs develop within 3 to 6 months of the initiation of ICI therapy and are responsive to systemic corticosteroids or immunosuppressive therapies (Disease modifying antirheumatic drugs) in refractory cases.^[4]

We were able to find 4 cases of ICI-induced SSc reported in the English literature. Three of these were reported as scleroderma induced by pembrolizumab (PD-1),^[4,8] and one as scleroderma like skin changes induced by ICIs.^[7] Skin histology from 2 patients disclosed mild dermal sclerosis with trapping of adnexal structures and minimal inflammation in one case, and a sclerodermoid reaction with deep dermal sclerosis and mild perivascular lymphocytic inflammation in the other.^[4]

Scleroderma skin changes were noted to develop after 5, 14 and 20 cycles of pembrolizumab (2 mg/kg every 3 weeks) respectively,^[4,8] and after 16 cycles of nivolumab in one case.^[7,8] Skin Biopsy was consistent with sclerosis. It was noted that none of the cases developed autoantibodies specific to systemic sclerosis or had involvement of other systems. An exception was one case of Raynaud's phenomena that followed skin manifestations.^[4,7] Scleroderma skin changes improved significantly in one patient after 12 weeks of ICI cessation and initiation of prednisone and hydroxychloroquine, and after starting prednisone in another

case.^[4,7] Follow up was limited in one case due to early death from other comorbidities and there was no comment on treatment in the fourth case.^[4,8]

Our case is more complicated as the patient had long term, poorly controlled diabetes which can result in scleroderma-like skin syndromes. Of these is diabetic sclerodactyly, also referred to as diabetic cheiroarthropathy, with a prevalence ranging from 8% to 50%, it manifests as skin thickening and hardening involving the dorsal part of hands, particularly the fingers, with limited joint mobility and contractures.^[3] And diabetic scleroderma (scleredema diabeticorum) which occurs in approximately 2.5%-3% of patients with diabetes, manifesting as skin hardening involving the face, neck, shoulders, upper parts of the trunk, and upper arms.^[2,3]

We also considered other inflammatory arthropathies such as RA given tenderness and limitation in range of motion over MCPs. However; the asymmetry, absence of effusion, low titer RF and negative anti CCP antibodies test argued against this diagnosis. While there was evidence of tenosynovitis

on exam, the absence of historical or current psoriatic skin lesions and the normal appearance of finger and toenails argued against psoriatic arthritis. In addition, the presence of skin thickening extending to forearm favored scleroderma or scleroderma-like syndromes stated above.

The major diagnostic dilemma in our patient was differentiating between diabetic scleroderma-like skin syndromes, scleroderma as a paraneoplastic syndrome and Pembrolizumab-induced scleroderma. Several factors favored the later, including the temporal relation between initiation of Pembrolizumab and the emergence of skin hardening, the more diffuse skin involvement of the proximal thighs and arms, significant improvement of scleroderma after initiation of MTX and Pembrolizumab cessation. Also, our patient had negative autoantibodies, including anti-RNA-Pol III antibodies which typically precede cancer diagnosis.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

REFERENCES

- [1] Maria ATJ, Partouche L, Goulabchand R, et al. Intriguing Relationships Between Cancer and Systemic Sclerosis: Role of the Immune System and Other Contributors. *Front Immunol.* 2019; 9: 3112. PMID:30687318. <https://doi.org/10.3389/fimmu.2018.03112>
- [2] van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis.* 2013; 72(11): 1747-55. PMID:24092682. <https://doi.org/10.1136/annrheumdis-2013-204424>
- [3] Wielosz E, Kurowska M, Suszek D, et al. Coexistence of diabetes mellitus type 1 with diffuse systemic sclerosis - case report and literature review. *Reumatologia.* 2017; 55(2): 104-107. PMID:28539684. <https://doi.org/10.5114/reum.2017.67607>
- [4] Barbosa NS, Wetter DA, Wieland CN, et al. Scleroderma Induced by Pembrolizumab: A Case Series. *Mayo Clin Proc.* 2017; 92(7): 1158-1163. PMID:28599746. <https://doi.org/10.1016/j.mayocp.2017.03.016>
- [5] Gilbane AJ, Denton CP, Holmes AM. Scleroderma pathogenesis: a pivotal role for fibroblasts as effector cells. *Arthritis Res Ther.* 2013; 15(3): 215. PMID:23796020. <https://doi.org/10.1186/ar4230>
- [6] Shah AA, Casciola-Rosen L. Cancer and scleroderma: a paraneoplastic disease with implications for malignancy screening. *Curr Opin Rheumatol.* 2015; 27(6): 563-70. PMID:26352736. <https://doi.org/10.1097/BOR.0000000000000222>
- [7] Tjarks BJ, Kerkvliet AM, Jassim AD, et al. Scleroderma-like skin changes induced by checkpoint inhibitor therapy. *J Cutan Pathol.* 2018; 45: 615-618. PMID:29740855. <https://doi.org/10.1111/cup.13273>
- [8] Board RE, Nathan P, Newsom-Davis T, et al. Problem solving in cancer immunotherapy. *Evidence-based Networks Ltd.* 2019. 140 p.