MAYO CLINIC

CASE REPORT

Scleroderma Induced by Pembrolizumab: A Case Series

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Abstract

Immune checkpoint inhibitors are approved for select cancer treatment and have shown survival benefit in patients with advanced melanoma. Adverse events, including immune-related adverse events, are common and potentially life-threatening. We describe cases of 2 patients with scleroderma (patient 1 had diffuse scleroderma, and patient 2 had limited scleroderma) that developed while they were receiving pembrolizumab therapy for metastatic melanoma. Prompt recognition and treatment of immune-related adverse events may improve tolerance to immune checkpoint inhibitors and contribute to an understanding of the manifesting autoimmune disease.

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The immune checkpoint molecules cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) are critical in controlling T-cell activation and promoting self-tolerance by down-modulation of T-cell activity upon interaction with their ligands.[1] In turn, their inhibition permits up-regulation of T-cell activation and impairs self-tolerance, which, in the cancer-bearing host, can lead to robust antitumor immunity.[1,2] Immune checkpoint inhibitors (ICIs) target CTLA-4, PD-1, and the programmed cell death ligand 1 (PD-L1) and are approved for the treatment of advanced melanoma, selected lymphomas, and advanced non–small cell lung cancer. These medications are the first to improve overall survival in patients with advanced melanoma. By virtue of their mechanism of action, ICIs are commonly associated with adverse events, including immune-related adverse events (irAEs), which manifest as systemic and organ-specific autoimmunity and pose a challenge in treatment.[3] Dermatologic adverse events are among the most commonly reported toxicities of ICI therapy. They include rash, pruritus, dermatitis, photosensitivity, urticaria, toxic epidermal necrolysis, and vitiligo.[4] Arthralgia and myalgia are the most reported rheumatic and musculoskeletal irAEs.[5] Inflammatory arthritis, sicca syndrome, vasculitis, myositis, and polymyalgia rheumatica have been reported in the past few years.[6-9]

We present 2 patients in whom scleroderma developed after treatment with pembrolizumab, a PD-1 inhibitor, of metastatic melanoma. We recently reported on patient 2 as the first published case of a sclerodermoid reaction to pembrolizumab.[10] The emergence of a second case of a sclerosing skin process induced by pembrolizumab with systemic features within the same institution warrants broad reporting to health care professionals to increase their awareness and to help improve management.

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CASE REPORTS

Patient 1

A 66-year-old man, previously treated with pembrolizumab for *BRAF* (B-Raf proto-oncogene, serine/threonine kinase)–positive stage IV metastatic melanoma, was referred to our rheumatology service for weakness, profound fatigue, and skin stiffness. Soon after the melanoma diagnosis 1 year earlier, he began therapy with pembrolizumab 2 mg/kg every 3 weeks. After cycle 13 of pembrolizumab, fatigue developed along with swelling of his joints and ankles. After cycle 14, his symptoms progressed and included skin

dryness and burning and muscle weakness. Pembrolizumab therapy was discontinued, and he began taking prednisone 1 mg/kg daily. His weakness continued to progress along with new-onset diffuse skin tightness. Review of systems was negative for Raynaud phenomenon, gastroesophageal reflux, dysphagia, diarrhea, and shortness of breath.

On physical examination, the patient was confined to a wheelchair and required considerable assistance to reach the examination table. He had marked xerosis and moderate to severe skin tightness with thickening involving the forearms, hands, fingers, thighs, legs, feet, and face (Figure 1). The modified Rodnan skin score (mRSS) was 36. He did not have nailfold capillary abnormalities. Wrist and shoulder range of motion was limited bilaterally. The patient had diminished muscle bulk with atrophy of the deltoids and quadriceps. No synovitis or tendon friction rubs were noted. Specimens from 2 skin punch biopsies (right upper forearm and right medial shin) revealed mild dermal fibrosis and sclerosis with trapping of adnexal structures and minimal lymphocytic inflammation, compatible with a sclerosing process (Figure 1).

The laboratory test results revealed a normal erythrocyte sedimentation rate, mildly elevated C-reactive protein level, and normal levels of antinuclear, anticentromere, anti-ribonucleoprotein, and anti—topoisomerase 1 (Scl 70) antibodies. Anti-RNA polymerase III (RNAP3) was not tested. Muscle enzyme levels were within the reference ranges.

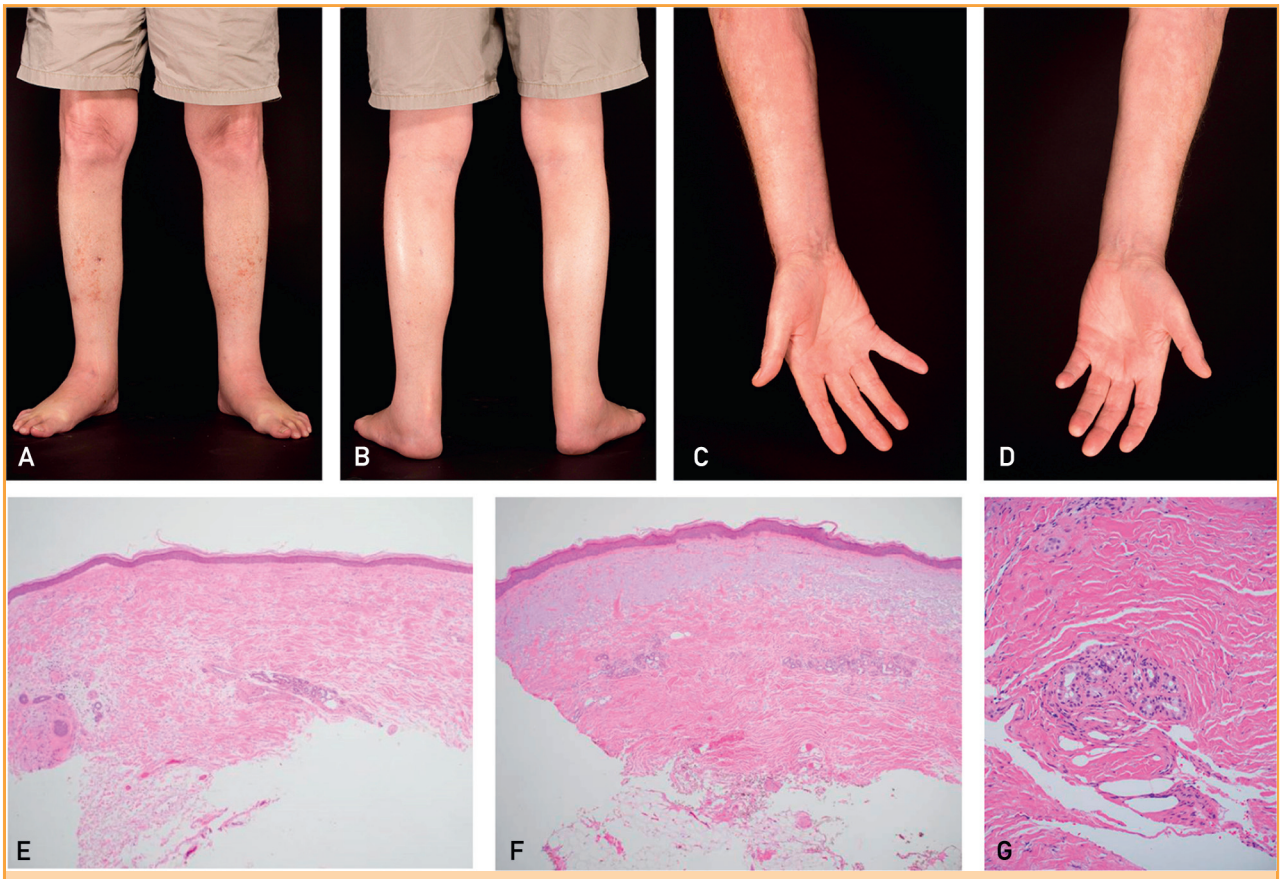

FIGURE 1. Bilateral skin tightening, consistent with scleroderma, is shown on the lower extremities and feet (A and B) and on the forearms and hands (C and D) of patient 1. Skin histology from the right medial shin (E) and right upper forearm (F) revealed mild dermal sclerosis with trapping of adnexal structures and minimal inflammation (hematoxylin-eosin, original magnification ×4). Higher magnification of the right upper forearm specimen (G) revealed deep dermal sclerosis (hematoxylin-eosin, original magnification ×20).