Case Report

Acute febrile neutrophilic dermatosis in the setting of pembrolizumab in a patient with nonsmall cell lung cancer

Aman Nihal, MD[1a], Susan Pei, MD[2,3], Shanon Lacy, DO[2,3], Linda Serrano, MD[1,2]

[1] Aurora St. Luke's Medical Center, Milwaukee, Wisconsin, United States, [2] Aurora West Allis Medical Center, West Allis, Wisconsin, United States, [3] Great Lakes Pathologists SC, West Allis, Wisconsin, United States

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Abstract

Sweet syndrome, or acute febrile neutrophilic dermatosis is an inflammatory condition that may be idiopathic, paraneoplastic, parainflammatory, or drug associated. Recently, immune checkpoint inhibitors have been implicated in Sweet syndrome. Herein, we describe a patient with nonsmall cell lung cancer who developed Sweet syndrome in the setting of the immune checkpoint inhibitor, pembrolizumab. We also include a discussion of current literature of immune checkpoint inhibitors-induced Sweet syndrome and the histopathologic differential diagnosis of Sweet syndrome.

Introduction

Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, is an inflammatory condition characterized by fever and sterile, painful, erythematous skin lesions characterized by a dense neutrophilic infiltrate histologically.[1] SS may be idiopathic paraneoplastic, parainflammatory, or drug associated.[2] Immune checkpoint inhibitors (ICI) are monoclonal antibodies that enhance the immune system's ability to destroy tumor cells. Cutaneous immune related adverse events are common in the setting of ICI, with an incidence of 25%.[3] Common cutaneous immune related adverse events include pruritis, morbilliform eruption, and lichenoid and bullous dermatoses. However, neutrophilic dermatoses including SS are less frequently reported. Here we describe a patient who developed SS in the setting of the ICI pembrolizumab in a patient with nonsmall cell lung cancer (NSLC).

Case Synopsis

A 71-year-old woman with metastatic NSCLC with partial response to 23 cycles of 200mg pembrolizumab every three weeks over 18 months presented with one week of progressing erythematous, tender papules, and nodules that spread from the soles of the feet to the bilateral legs and arms. She had no recent changes in medications. Her vitals were notable for tachycardia and transient fevers. Physical examination revealed multiple tender erythematous nodules on the arms, a mix of red to purple nodules and pustules on the legs and feet with background erythema and edema (Figure 1). The face, chest, abdomen, and back were spared. Laboratory workup was significant for leukocytosis of 30.5 x 10^9/l, elevated procalcitonin (2.02ng/ml), lactate (1.3mmol/l), and C-reactive protein (22.0mg/l). Bacteria, mycobacteria, fungal blood and tissue cultures, varicella zoster virus, herpes simplex virus, hepatitis C, rapid plasma reagin test, and tick-borne illness testing were negative. A punch biopsy of the right arm demonstrated dense dermal and subcutaneous neutrophilic inflammation, and a punch biopsy of the right leg revealed a subcorneal, intradermal pustule with focal dermal mixed inflammation and prominent neutrophils (Figure 2). Direct immunofluorescence testing was negative. Biopsies were consistent with SS in the setting of pembrolizumab therapy. Pembrolizumab was discontinued and the patient was treated with prednisone with rapid improvement. She had notable skin improvement during her four-week follow-up (Figure 3). No new no metastatic disease was noted 11 weeks postdiscontinuation of pembrolizumab, though there was mild progression in abdominal lymphadenopathy.

Discussion

Sweet syndrome is an inflammatory condition classically characterized by sterile, painful, erythematous skin le-

a Corresponding Author: Aman Nihal MD, 2900 West Oklahoma Ave, Milwaukee, WI 53715, Tel: 608-658-0229, Email: amannihal1@gmail.com

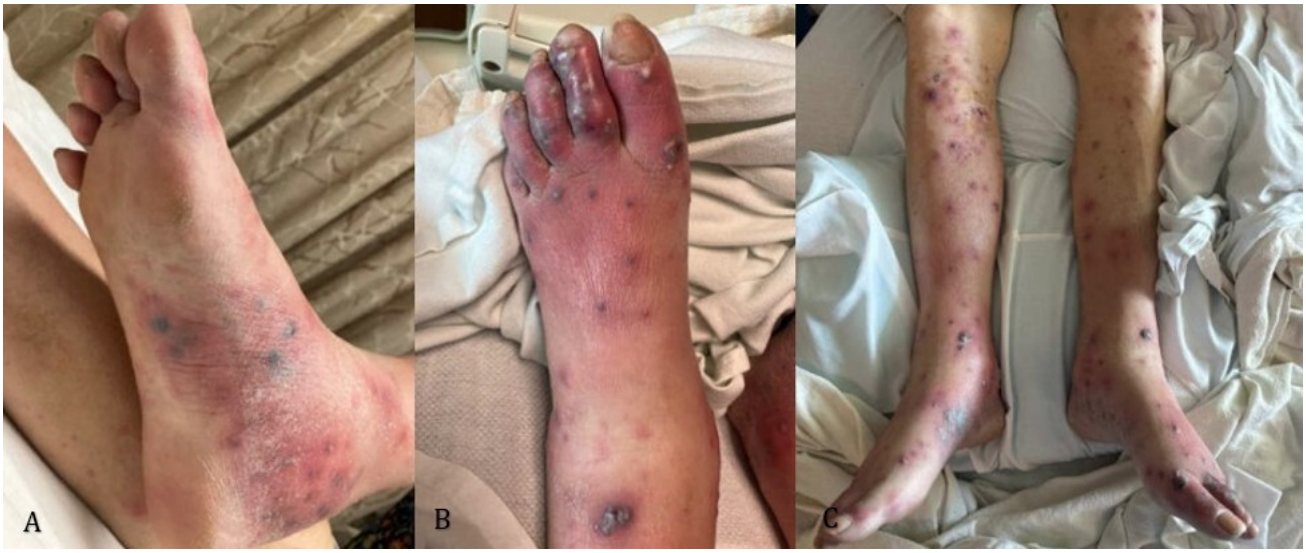

Figure 1. ***A-C)*** *A mix of tender, red to purple nodules and pustules on the legs and feet, and pustules scattered on toes with background erythema and edema.*

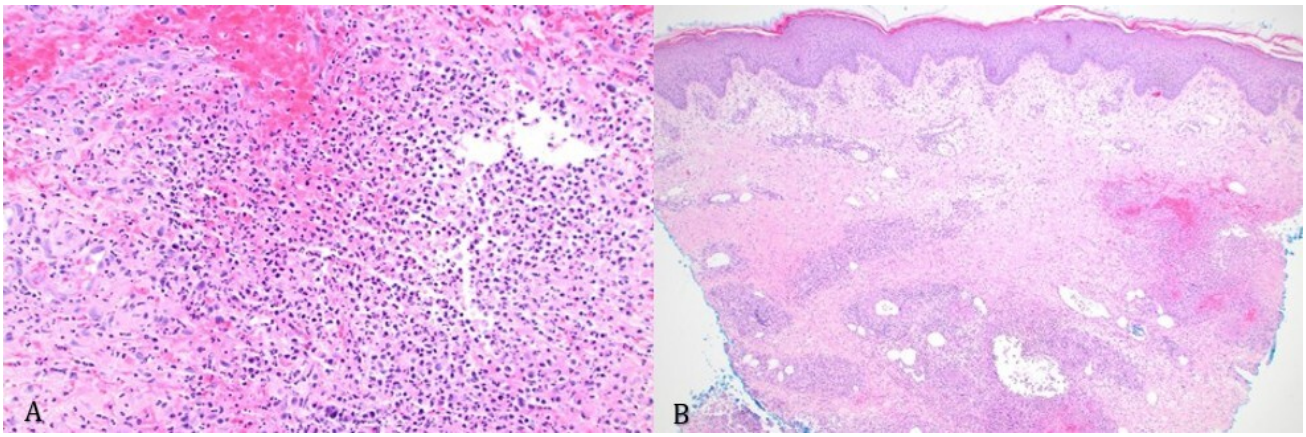

Figure 2. ***A-B)*** *Punch biopsy of the right arm demonstrated dense dermal and subcutaneous neutrophilic inflammation (hematoxylin and eosin, 40x and 200x, respectively).*

sions, ranging from vesicles to plaques in the setting of fevers.[1] Histopathology reveals dense neutrophilic infiltrates in the dermis with papillary dermal edema and absence of primary vasculitis. Sweet syndrome is most common in women ages 30 to 60 but can occur in patients of all ages.[2] Sweet syndrome is often idiopathic but may occur secondary to autoimmune disorders, pregnancy, malignancies, or medications. The most common drugs implicated in drug-induced SS include granulocyte colony stimulating factor, antibiotics, nonsteroidal anti-inflammatory drugs, antiepileptics, and anticancer drugs.[1] ICIs are a relatively new class of anticancer medications approved for treatment of various cancers, ranging from melanoma to NSCLC. Immune checkpoint inhibitors are monoclonal antibodies that enhance the immune system's ability to destroy tumor cells via blockade of the programmed cell death (*PD-1*) receptor, its ligand (*PD-L1*), or cytotoxic T-lymphocyte-associated antigen 4 (*CTLA4*) and are infrequently associated with neutrophilic dermatoses.[4]

Ipilimumab, which targets *CTLA4*, is the most reported ICI to cause neutrophilic dermatosis.[5] In contrast, there have been rare reports of neutrophilic dermatosis secondary to pembrolizumab, a *PD-1* inhibitor.[6] Cutaneous immune related adverse events may occur within two to three weeks of therapy initiation, and the median onset is 113 days although onset has been reported up to 38 months or after discontinuation of ICI.[7] The average latency period of SS secondary to ipilimumab is 8.9 weeks.[8] In this case, SS developed 18 months after initiation of pembrolizumab. Our case reports the greatest delayed onset of ICI associated neutrophilic dermatoses but is consistent with prior studies reporting a wide range of delayed onsets of cutaneous immune related adverse events.

Although SS may occur as a paraneoplastic dermatosis in the absence of ICI, several factors support pembrolizumab as the etiology in our case. First, malignancy-associated SS is commonly related to hematologic malignancies and is rarely reported in solid-organ

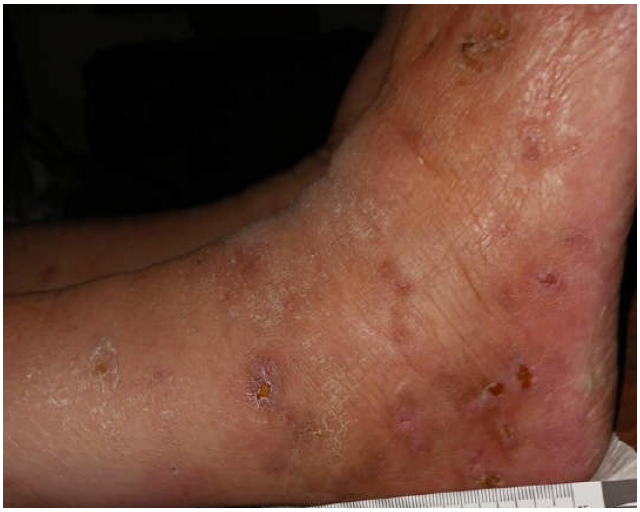

Figure 3. *Notable improvement in nodules and pustules four weeks after cessation of pembrolizumab and initiation of prednisone taper.*

malignancies such as adenocarcinoma of the lung.[9,10] Moreover, in cases of malignancy-associated SS, SS is often the initial symptom of a new malignancy or is a sign of recurrence or disease progression.[11] Our patient's malignancy had been stable for many months prior to developing SS and remained stable after discontinuation of pembrolizumab.

Besides infection, the differential diagnosis of SS includes neutrophilic dermatoses such as acute generalized exanthematous pustulosis and pyoderma gangrenosum. Acute generalized exanthematous pustulosis is distinguished from SS by typical presence of numerous, small, sterile, nonfollicular pustules on the trunk and intertriginous areas, with histopathology showing intraepidermal pustules, papillary dermal edema, and mixed dermal infiltrate of neutrophils and eosinophils.[12] Pyoderma gangrenosum presents typically with solitary or few folliculocentric nodules and pustules that enlarge and ulcerate with undermined violaceous border. On histopathology, pyoderma gangrenosum may show overlap with SS by presence of dense dermal neutrophilic infiltrate.[13] The above neutrophilic dermatoses including SS all require exclusion of infectious etiologies with special stains and tissue cultures.

Conclusion

It is important to recognize ICI associated SS may have a delayed onset of over a year. Herein, we present a case of SS with delayed onset in the setting of pembrolizumab in a patient with NSCLC. This case contributes to growing literature that in addition to *CTLA* inhibitors, *PD-1* inhibitors may be associated with SS.

Potential conflicts of interest

The authors declare no conflicts of interest.

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