Sweet syndrome in a patient with rectal adenocarcinoma and HIV following neoadjuvant chemoradiation

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INTRODUCTION

Sweet syndrome, or acute febrile neutrophilic dermatosis, is characterized by the acute onset of tender, erythematous plaques associated with fever, neutrophilia, and elevated inflammatory markers.[1] Other symptoms include myalgias, arthralgias, and glomerulonephritis.[2] While classically presenting as erythematous plaques, the morphology can be variable, leading to a vast differential diagnosis[1] including infection, leukemia or lymphoma cutis, fixed drug eruption, and interstitial granulomatous dermatitis. Etiologies of Sweet syndrome include malignancy, drug, and idiopathic.[1]

We describe a case of Sweet syndrome in a patient with rectal cancer following chemotherapy (capecitabine, oxaliplatin) and radiotherapy that probes the roles of chemotherapy, radiation, human immunodeficiency virus (HIV), and tumor progression in the development of Sweet syndrome.

Abbreviation used:

HIV: human immunodeficiency virus

CASE REPORT

A man in his 40s with well-controlled HIV on antiretroviral therapy presented to the emergency department and was admitted for a 2-day history of fever, tender, erythematous plaques and pustules, and joint swelling. Seven months prior, he had been diagnosed with Stage IIIA rectal adenocarcinoma. He completed the last of 8 cycles of neoadjuvant capecitabine, oxaliplatin, and radiotherapy 9 days prior to admission. He never received granulocyte-colony stimulating factor.

Physical exam revealed edematous dermal pink-to-red nodules studded with pustules located symmetrically on the scalp, posterior neck, and upper shoulders and back (Fig 1). Erythema, swelling, and decreased range of motion were noted most prominently in the right wrist, ankle, and knee.

The medicine team was initially concerned for septic arthritis. Blood cultures were drawn (resulted negative), and he was started on intravenous vancomycin. Initial labs revealed an elevated C-reactive protein to 135.2 (normal <3.1 mg/dL) and a hemoglobin of 10.9 (normal 13.3-17.7 g/dL). Rheumatoid factor, anti-cyclic citrullinated peptide, anti-nuclear antibodies, and uric acid levels were normal. An arthrocentesis of the right wrist did not result in any synovial fluid. Ertapenem was added due to no improvement. Infectious disease and rheumatology were then consulted with concern for an atypical

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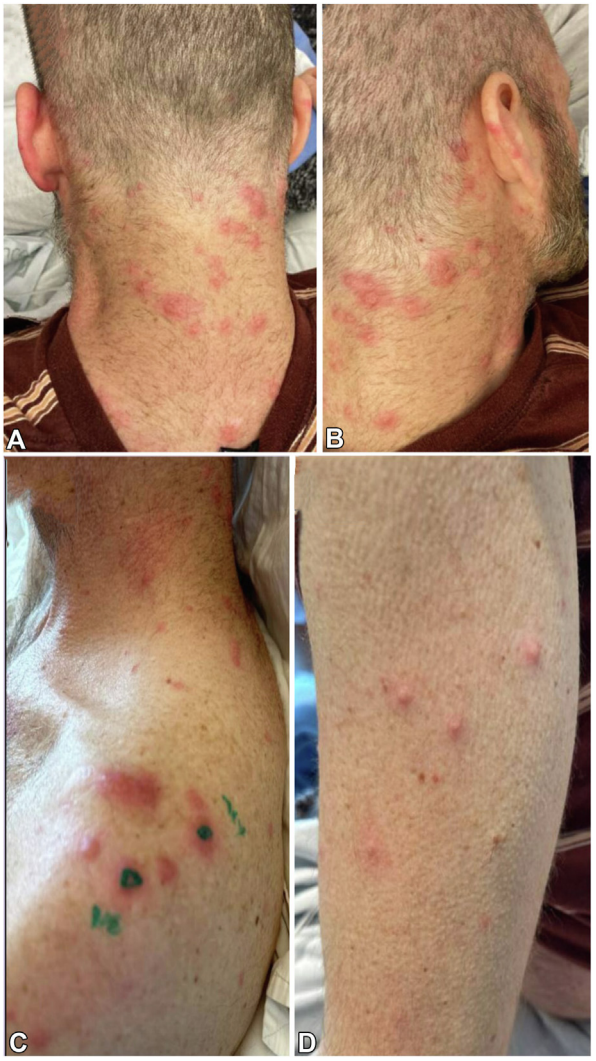

Fig 1. Sweet syndrome. *Pink*, *red* plaques, and nodules on the posterior neck and scalp (**A** and **B**) and shoulders (**C**) with pustules on the *upper* arms (**D**) in a patient with Sweet syndrome.

infection or an adverse reaction to vancomycin. Antibiotics were switched to daptomycin and ceftriaxone and an arthrocentesis of the right knee was performed (bland fluid, negative culture, no crystals). X-ray of the bilateral hands/wrist and feet/ankles did not show signs of erosive changes. Despite antibiotics, the patient had persistent fevers, new erythematous plaques and pustules on his arms, and a rising C-reactive protein to 158.

Dermatology was consulted. The clinical differential based on morphology included an acute febrile neutrophilic dermatosis, infectious process, or drug reaction. Two punch biopsies were performed from lesions on the left shoulder and sent for tissue culture (bacteria, fungal, and mycobacterial) and Gram, hematoxylin and eosin (H&E), and periodic acid–Schiff–diastase (PAS-D) staining. Histopathologic examination demonstrated a brisk inflammatory infiltrate centered in the upper dermis, associated with prominent papillary dermal edema (Fig 2, *A* and *B*). Higher power views were notable for a perivascular and interstitial infiltrate of neutrophils with admixed histiocytes and lymphocytes (Fig 2, *C*). Tissue cultures were negative.

With the abrupt onset of painful erythematous nodules, histopathologic features, fever, and underlying visceral malignancy, this case met diagnostic criteria for malignancy-associated Sweet syndrome.[3] Prednisone 60 mg/day was started for 7 days and then tapered over 2 weeks. The patient reported significant improvement and continued to have full resolution of lesions at follow-up 1 week after prednisone completion. With the resolution of lesions following prednisone and temporal relationship between neoadjuvant chemotherapy and disease onset, diagnostic criteria for drug-induced Sweet syndrome were also met.[4] A few weeks later, the patient's oncology team diagnosed progression of his rectal cancer with new liver and lung metastases.

DISCUSSION

Malignancy-associated Sweet syndrome can appear before, concurrent with, or after a diagnosis of malignancy, most often in the setting of acute myeloid leukemia and rarely with solid tumors.[1] Literature review demonstrated 4 reported cases of malignancy-associated Sweet syndrome in the context of anal cancer or rectal adenocarcinoma (Table I).[5-8] We considered whether Sweet syndrome was due to malignancy or triggered by recent neoadjuvant chemoradiation.

Capecitabine is an oral chemotherapy agent used to treat several solid tumors. Common side effects include hand-foot syndrome, diarrhea, and fatigue.[9] A drug reintroduction test could have provided definitive proof of capecitabine as the causative agent but would have been unethical in light of other treatment options. Khan et al reported a patient with Stage III rectal adenocarcinoma who developed Sweet syndrome 4 weeks after completion of concurrent chemoradiation with capecitabine.[6] Lesions resolved after prednisone treatment and did not recur with transition to FOLFOX (no capecitabine). Although the mechanisms remain to be elucidated, it is possible that capecitabine induced localized cytotoxicity,[9] leading to secondary tissue infiltration by neutrophils, thereby causing Sweet syndrome.

Radiotherapy causes increased tumor antigen release from cancer cells.[10] Some hypothesize that Sweet syndrome is a hypersensitivity immune

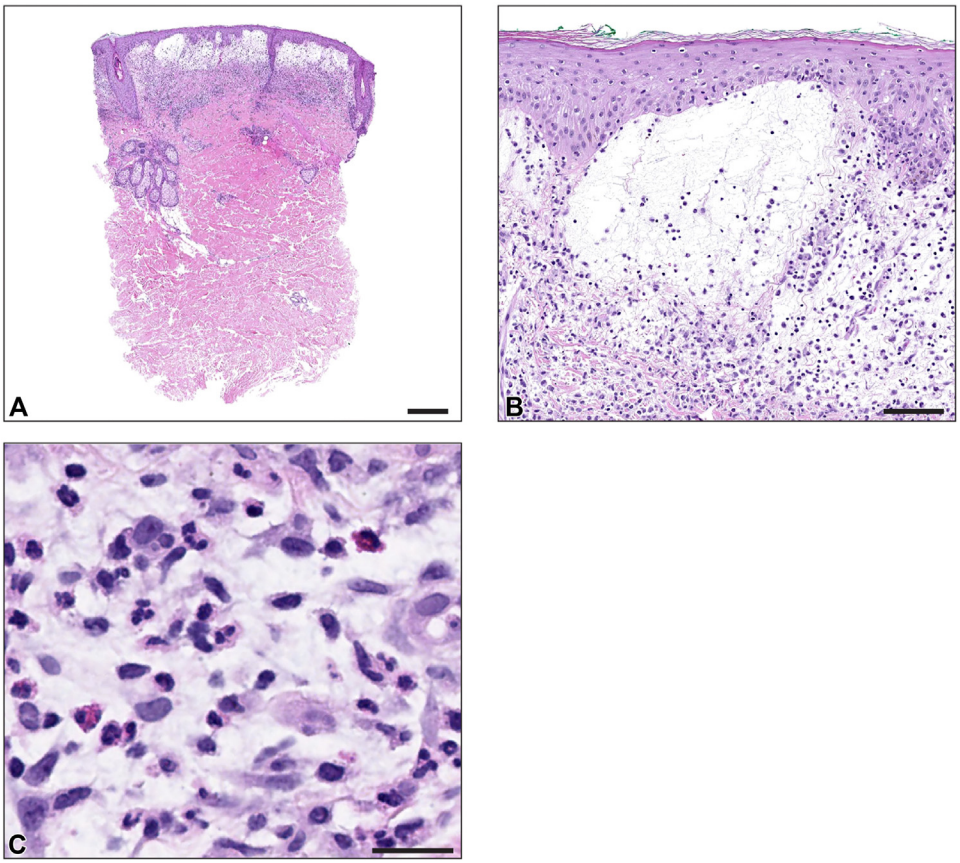

Fig 2. Histopathology of Sweet syndrome. **A,** Low power hematoxylin and eosin (*H&E*) photomicrograph of a punch biopsy showing an *upper* dermal inflammatory infiltrate and prominent papillary dermal edema (bar = 500 μm). **B,** Medium power H&E photomicrograph demonstrating marked papillary dermal edema and an infiltrate of lymphocytes, histiocytes, and neutrophils (bar = 100 μm). **C,** High power H&E photomicrograph showing a perivascular and interstitial infiltrate of neutrophils with multilobed nuclei and histiocytes in an edematous dermis (bar = 20 μm).

reaction to bacterial, viral, or tumor antigens.[11,12] It is hypothesized that the release of tumor-associated antigens following radiotherapy can induce Sweet syndrome.[5,13]

Our patient's cancer progression was discovered a few weeks after his Sweet syndrome diagnosis. A malignancy-associated Sweet syndrome could be linked to tumor progression.[11,13,14] In Sweet syndrome associated with hematologic malignancies such as acute myeloid leukemia, studies have found that the neutrophils within skin lesions have the same genetic abnormalities as malignant myeloblasts.[15] One hypothesis suggests a common progenitor leading to dysfunctional neutrophils that accumulate in the dermis.[15] In solid organ malignancy, however, the model of Sweet syndrome pathogenesis is more uncertain. Some postulate that the tumor cells create a proinflammatory state, leading to the secretion of cytokines involved in neutrophil activation, localization, and subsequent infiltration in the dermis.[15]

Finally, an alternative hypothesis is that the growing tumor and the capecitabine acted synergistically to promote an inflammatory state leading to neutrophil maturation, proliferation, and localization to the dermis in a multifactorial pathway.[15] We cannot exclude that our patient's HIV could play a role as immune dysregulation is observed even in treated HIV infection.[16] Our understanding of the pathogenesis and associations of Sweet syndrome remains limited and evolving. Future basic and translational studies may help to elucidate the pathogenesis of this condition, such as transcriptomic analyses of immune pathways activated in patients with Sweet syndrome.

Conflicts of interest

None disclosed.

Table I. Review of the literature of Sweet syndrome in the setting of rectal and anal cancers

PMID	Country, y	Type of cancer	Delay of onset of Sweet	Progression of the cancer
PMID: 28011887	US, 2016	Rectal adenocarcinoma	Four weeks after completed neoadjuvant concurrent chemoradiation with capecitabine	No mass seen after therapy
PMID: 31617491	France, 2019	Anal canal cancer	Thirty-nine days after treatment initiation during concomitant radiochemotherapy with mitomycin and 5-FU	(No comment in the report)
PMID: 3214949	US, 1988	Rectal adenocarcinoma	Three months after radiotherapy began during the last week of radiotherapy schedule	No signs of tumor recurrence 4 mo after therapy
Hilder R, Simmons L Jr, Damm S. Sweet's syndrome: a case report. *Journal of the Association of Military Dermatologists.* 1979;5:17-20.	US, 1979	Rectal adenocarcinoma	One month after cancer diagnosis during course of radiotherapy	(No comment in the report)

REFERENCES

1. Cohen PR. Sweet's syndrome — a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007;2:34. https://doi.org/10.1186/1750-1172-2-34
2. Nofal A, Abdelmaksoud A, Amer H, et al. Sweet's syndrome: diagnostic criteria revisited. *J Dtsch Dermatol Ges*. 2017;15(11): 1081-1088. https://doi.org/10.1111/ddg.13350
3. von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol*. 1994;31(4):535-556; quiz 557-560. https://doi.org/10.1016/s0190-9622(94)70215-2
4. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol*. 1996;34(5 Pt 2):918-923. https://doi.org/10.1016/s0190-9622(96)90080-8
5. Mali-Gerrits MG, Rampen FH. Acute febrile neutrophilic dermatosis (Sweet's syndrome) and adenocarcinoma of the rectum. *Clin Exp Dermatol*. 1988;13(2):105-106. https://doi.org/10.1111/j.1365-2230.1988.tb00669.x
6. Khan U, Rizvi H, Ali F, Lebovic D. Sweet syndrome: a painful reality. *BMJ Case Rep*. 2016;2016:bcr2016217606. https://doi.org/10.1136/bcr-2016-217606
7. Moreau E, Peiffert D, Schmutz JL, Granel-Brocard F, Bursztejn AC. Sweet syndrome and erythema nodosum in a case of anal canal cancer during concomitant radiochemotherapy. *Eur J Dermatol*. 2019;29(5):539-540. https://doi.org/10.1684/ejd.2019.3628
8. Hilder R, Simmons L Jr, Damm S. Sweet's syndrome: a case report. *Journal of the Association of Military Dermatologists*. 1979;5:17-20.
9. Saif MW, Katirtzoglou NA, Syrigos KN. Capecitabine: an overview of the side effects and their management. *Anti Cancer Drugs*. 2008;19(5):447-464. https://doi.org/10.1097/CAD.0b013e3282f945aa
10. Spiotto M, Fu YX, Weichselbaum RR. The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. *Sci Immunol*. 2016;1(3):EAAG1266. https://doi.org/10.1126/sciimmunol.aag1266
11. Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: review of the world literature. *J Clin Oncol*. 1988;6(12):1887-1897. https://doi.org/10.1200/JCO.1988.6.12.1887
12. Voelter-Mahlknecht S, Bauer J, Metzler G, Fierlbeck G, Rassner G. Bullous variant of Sweet's syndrome. *Int J Dermatol*. 2005;44(11):946-947. https://doi.org/10.1111/j.1365-4632.2004.02287.x
13. Cohen PR, Kurzrock R. Sweet's syndrome and cancer. *Clin Dermatol*. 1993;11(1):149-157. https://doi.org/10.1016/0738-081X(93)90112-P
14. Cohen PR, Holder WR, Tucker SB, Kono S, Kurzrock R. Sweet syndrome in patients with solid tumors. *Cancer*. 1993;72(9): 2723-2731. https://doi.org/10.1002/1097-0142(19931101)72:9<2723::aid-cncr2820720933>3.0.co;2-f
15. Heath MS, Ortega-Loayza AG. Insights into the pathogenesis of sweet's syndrome. *Front Immunol*. 2019;10:414.
16. Boyd MA, van Bockel D, Munier CML, Kelleher AD. Navigating the complexity of chronic HIV-1 associated immune dysregulation. *Curr Opin Immunol*. 2022;76:102186. https://doi.org/10.1016/j.coi.2022.102186