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Malignancy-associated Sweet syndrome: acute febrile neutrophilic dermatosis associated with recurrence of metastatic cervical cancer

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Abstract

We present a rare case of acute febrile neutrophilic dermatosis, also known as Sweet syndrome, associated with recurrence of metastatic cervical cancer. This report highlights similar reports and serves as an important reminder of the relationship between Sweet syndrome and cervical cancer. Increasing awareness of Sweet syndrome assists clinicians in recognizing characteristic findings and encourages evaluation of patients for new-onset or recurrent neoplastic disease. Additionally, we discuss the typical presentation of the syndrome, the proper workup and treatment, and a common pitfall encountered in the diagnosis of Sweet syndrome.

Keywords: Sweet syndrome, acute febrile neutrophilic dermatosis, malignancy, cervical cancer

Introduction

The first patient with acute febrile neutrophilic dermatosis, also known by the eponym Sweet syndrome (SS), was described in 1964 [1]. Since the initial description, several hundred reports of SS associated with infections, malignancies, autoimmune diseases, drugs, or vaccines have been published throughout the primary literature [2, 3]. Approximately 10-20% of patients with SS have an associated malignancy, which may be hematologic or a solid tumor [4]. Only a few patients have been reported on the association with cervical cancer. Our report highlights a rare patient with SS associated with recurrence of metastatic cervical cancer. The purpose of this report is to increase awareness of a rare but important association.

Case Synopsis

A 54-year-old woman had a history of stage 2B metastatic cervical squamous cell carcinoma treated with chemoradiation one year prior and tumor debulking. She was admitted from the emergency department for one week of worsening chronic right inguinal and abdominal pain, a new extensive rash, and a fever to 38.1°C. The eruption started on her arms and progressed to her legs and torso, sparing her face, mouth, palms, and soles. Recent PET and computed tomography scans revealed recurrence and progression of her cervical carcinoma. She was not exposed to new systemic or topical medications and had no history of recent travel.

On examination, the patient was febrile (38°C) but other vital signs were unremarkable. She had symmetrically distributed brightly erythematous, tender, infiltrated plaques that blanched, approximately 1-3 cm in diameter, on the arms, anterior thighs, and trunk (**Figure 1**). Additionally, some lesions had central umbilication and were fluid filled vesicles or pustules, with confluent pustules in a curvilinear fashion. There were distinct borders to the erythema. There were no mucous membrane lesions.

Laboratory testing revealed a normal white blood cell (WBC) count of 9.5 K/mm3 (range 4.5-11.0 K/mm3) with neutrophil predominance (7.80 K/mm3,range 1.8-7.7 K/mm3), red blood cell count 3.4 m/mm3 (reference 4.0-5.2 m/mm3), platelet

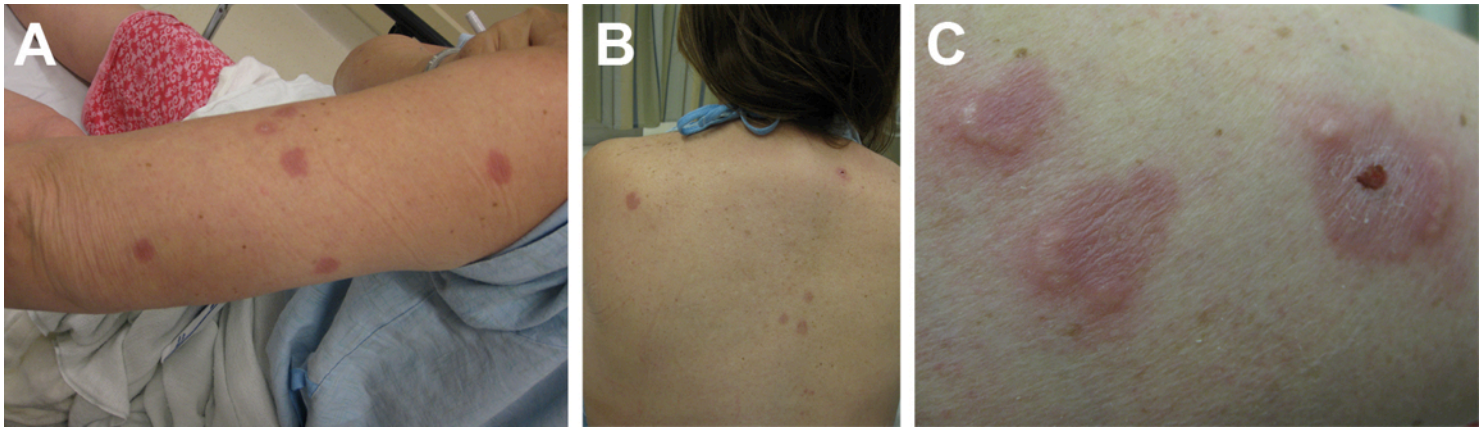

Figure 1. *(A) Multiple red-violet, well-demarcated, indurated, and edematous papules and plaques on the left arm and back (B). (C) Closer inspection of the papule revealed focal areas of pseudovesiculation and focal ulceration.*

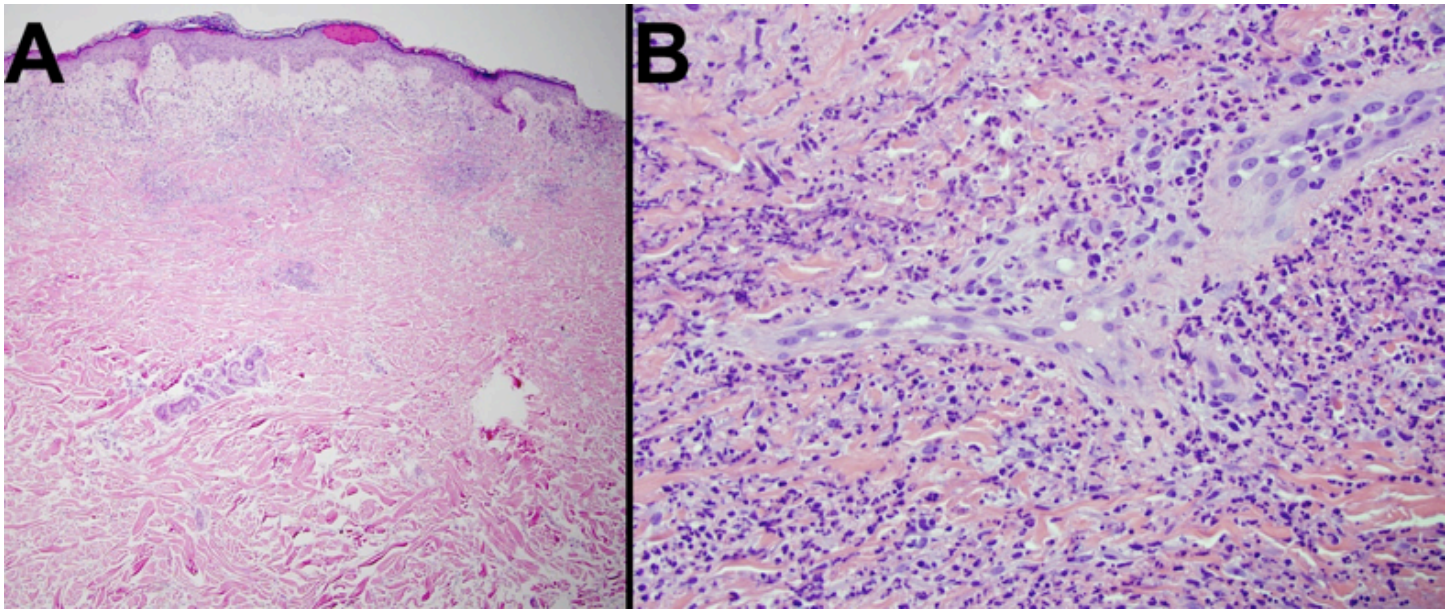

Figure 2. *(A) Histological examination revealed a diffuse inflammatory infiltrate associated with edema of the papillary dermis. (B) Higher magnification shows diffuse neutrophilic infiltrate in the dermis without vasculitic changes.*

count of 306 K/mm3 (reference 130-400 K/mm3), and urinalysis with moderate leukocyte esterase, 9 WBC/HPF (reference 0-3 WBC/HPF), and many bacteria. Serum chemistry and liver function were within normal limits. A punch biopsy from the right posterior arm of the most indurated plaque revealed a dense predominantly neutrophilic infiltrate within the dermis, leukocytoclasis (nuclear "dust"), and no significant vasculitis (**Figure 2**). A biopsy for culture was not performed as the patient did not appear acutely septic and appeared to have a urinary tract infection.

The patient was diagnosed with acute febrile neutrophilic dermatosis (Sweet syndrome, **Table 1**). Owing to the patient's concurrent urinary tract infection the dermatology team did not begin corticosteroid treatment and recommended follow-up in the dermatology clinic. A few days after the biopsy, the patient was contacted with the results. She felt her skin eruption was spontaneously improving and did not desire treatment. The patient subsequently canceled her follow-up dermatology visit.

One month later, the patient had a re-exacerbation of her rash. Skin examination showed scattered purplish plaques ranging from 1 to 2 cm that were round and well circumscribed, mostly on the bilateral knees and elbows. She was seen by a nurse practitioner and treated with 300 mg clindamycin.

Two months following her original presentation, her skin examination continued to demonstrate

Table 1. *Diagnostic Criteria for Sweet's Syndrome and Patient's concordance*

		Present Case
Major Criteria	Abrupt onset of painful plaques or nodules	✔
	Pathology: dense neutrophilic infiltrate in the absence of leukocytoclastic vasculitis	✔
Minor Criteria	Fever	✔
	Association with: inflammatory disease, malignancy, pregnancy, upper respiratory or gastrointestinal infection, or vaccination	✔
	Response to systemic steroids or potassium iodide	No Treatment
	Abnormal labs: Elevated ESR, C-reactive protein, elevated white blood cell count, or a preponderance of neutrophils (>70%)	✔

Reference: Su et al. [14].

scattered plaques on her knees and elbows. She was started on 300 mg clindamycin four times per day for 10 days for the second time. Her lesions subsequently resolved. Three months after her hospitalization for uncontrolled pain and rash, her cancer progressed despite chemotherapy and she was transitioned to hospice care and expired 2 months afterwards.

Case Discussion

Malignancy-associated Sweet syndrome (MASS) can occur as a paraneoplastic syndrome and has been most commonly reported in acute myelogenous leukemia (AML) [4]. Additionally, MASS has been associated with myeloproliferative, lymphoproliferative, and myelodysplastic disorders [5]. On the other hand, carcinomas of the breast, genitourinary, and gastrointestinal tracts are the most frequently reported solid tumors associated with MASS [6]. The cutaneous findings can precede, follow, or appear concurrently with the underlying malignancy. Hence, SS may indicate a malignancy in a previously cancer-free individual or recurrence of the disease in a patient with history of cancer [2].

The first two patients with SS associated with cervical cancer were published in 1982 by Shinoda et al. in a Japanese journal [7] (**Table 2**). Subsequently, in 1985, a brief abstract from the French Society of Dermatology Spring Meeting discussed a patient with SS associated with carcinoma of the cervix [8]. Unfortunately, very little information was provided from these initial patients.

Fifteen years later, a 44-year-old woman presented with pelvic pain and postcoital bleeding and was found to have a cervical mass measuring 8 x 10 cm. A biopsy revealed poorly differentiated carcinoma. Eight months later, the patient presented with a small bowel obstruction and bullous pustular lesions on the hand. She was found to have recurrence of her disease and metastases. This patient is the most similar to our patient as the lesions developed with recurrence of cervical cancer.

The fifth patient described in the literature is a 61-year-old woman who presented with erythematous plaques and bullous pustular lesions over her body. She was subsequently diagnosed with SS after biopsy and correlation with clinical and laboratory findings. In pursuit of a cause, imaging detected a 6 x 6 cm tumor of the uterus. Biopsy confirmed a poorly differentiated cervical carcinoma with metastases. In contrast to the previous patient, this woman presented with cutaneous lesions prior to her diagnosis of cervical cancer and led to a primary diagnosis of cervical cancer. Serirat et al. discussed a 34 year old with SS who subsequently developed cervical cancer three years later [9]. These are the only two known patients with SS lesions preceding the diagnosis of cervical cancer.

Another report depicted a patient with SS localized to the fingers found three years after chemoradiation therapy in a 56-year-old woman with a history of cervical cancer [10]. However, no recurrence of the cancer was found and the SS was believed to be

Table 2. *Summary of Sweet's Syndrome Case Reports in association with cervical cancer*

Author (Year)	Number of Patients	Age/ Date of Onset of Cervical Cancer	Stage of Cervical Cancer at Onset of SS (FIGO)	Age/ Date of Onset of SS	WBC (PMNL)	Fever	Treatment of Cancer	Treatment of SS	Response & Follow-up
Shinoda et al. (1982)	2	?	?	?	?	?	?	?	?
Hogan DJ, Zeide DA (1985)	1	?	?	?	?	?	Radiotherapy	Systemic steroids	Responded to steroid treatment
Culp et al. (2004)	1	44-year-old May of 2000	III B	45-year-old, January 2001	?	?	Concurrent chemotherapy (cisplatin) and radiation	None	Developed ARDS post-operatively after small bowel obstruction, patient was made DNR. She expired on postoperative day 3
Loehberg et al. (2006)	1	61-year-old, 2006	IV A	61-year-old, 2006	11,400/ uL (77.4%)	?	Concurrent chemotherapy (cisplatin) and radiation	Methylprednisolone	Patient's symptoms remitted after 10 days. There was no recurrence. The patient is still living.
Lee et al. (2009)	1	56-year-old	I b1	59-year-old	11,400/ uL (88.1%)	38.1°C	Concurrent chemotherapy (cisplatin and 5-FU) and radiation	None	The lesions resolved spontaneously over the following 2 weeks.
Serirat (2011)	1	37-year-old	?	34-year-old	34,900/ uL (80.0%)	High grade fever	?	Cirprofloxacin and systemic steroid	Initially treated with Ciprofloxacin with no resolution. Resolution of skin lesions with steroids.
Clark et al. (2016)	1	53-year-old, March 2010	III B	54-year-old, June 2011	9,500/uL (84.6%)	38.1°C	Concurrent chemotherapy (cisplatin) and radiation. Recurrence treated with clinical trial of Taxol and Topotecan	None	Three months after presentation she was transitioned to hospice care. She died 2 months later.

Abbreviations: WBC=White blood cell, PMNL=Polymorphonuclear leukocyte, SS=Sweet's syndrome, FIGO=International Federation of Gynecology and Obstetrics

secondary to radiation treatment since the lesions were only found in the irradiated area.

In the current report, only the eighth published, our patient had SS in association with metastatic recurrence of a previously treated cervical cancer.

The laboratory findings of SS include an elevated ESR, leukocytosis with a neutrophil predominance, anemia, abnormalities in platelet counts, and elevated C-reactive protein [3]. The WBC count is said to be greater than 8,000 in 80% of affected individuals. The presence of anemia and thrombocytopenia are most commonly seen in MASS [1]. In the present report, the patient developed a WBC count greater than 8,000 with a dominance of neutrophils, and anemia. Her platelet count, however, was within normal limits. An ESR and C-reactive protein were not obtained.

Misdiagnosis is common and biopsy is necessary to detect characteristic changes consistent with SS. Furthermore, bacterial, mycobacterial, fungal, and some parasitic infections can mimic SS and should be considered in the differential diagnosis for SS based on the travel and exposure history. A biopsy for culture should be considered as well to exclude infectious etiologies if no nidus for infection is found otherwise.

Systemic corticosteroids are considered the gold standard of treatment and typically lead to rapid improvement in symptoms [11]. However, various other therapeutic options including immunomodulatory agents, intralesional corticosteroid, oral potassium iodide, indomethacin, dapsone, or colchicine have been used for relief of symptoms and cutaneous lesions [11-13]. It is noteworthy that cutaneous lesions associated with SS may spontaneously resolve without treatment [3]. In our patient, systemic corticosteroids were not initiated owing to an underlying infection and the rash spontaneously resolved over the following week.

Sweet syndrome is often mistaken for an infectious process given the fevers and general appearance of the cutaneous lesions. Antibiotics are commonly administered with no improvement in symptoms [3]. This occurred in our patient, who was given two separate courses of clindamycin for her MASS.

Conclusion

Our case report features a rare finding of SS in association with the recurrence of metastatic cervical cancer. This report provides an important reminder of the relationship between SS and cervical cancer, the typical presentation, the proper workup and treatment, and common pitfalls for practitioners. In future practice, clinicians will be more likely to recognize the characteristic findings of SS, make the diagnosis, and begin the evaluation of the patient for new-onset or recurrent neoplastic disease.

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