



Case report

Sweet syndrome with bitter outcomes in cervical cancer: A case report

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ABSTRACT

Background: Sweet Syndrome, or acute febrile neutrophilic dermatosis, is a non-infectious, painful rash accompanied by fever, leukocytosis and skin biopsy showing neutrophilic dermal inflammation. It is either idiopathic, drug-induced or malignancy associated (MASS). MASS is uncommon in cervical cancer, and usually signals diagnosis, progression or recurrence.

Clinical Course: Two months following chemoradiation for stage IIIC2(r) squamous cell carcinoma (SCC) of the cervix, a 55-year-old female developed painful papules and plaques on her left toes. One week later she developed fever and the rash spread to her body. Labs revealed leukopenia and an elevated erythrocyte sedimentation rate. Punch biopsy showed neutrophilic dermal inflammation with papillary dermal edema and was negative for infectious immunohistochemistry. The clinical presentation and histopathological features were consistent with, and met diagnostic criteria for Sweet Syndrome. One month following Sweet Syndrome diagnosis and four months following chemoradiation, positron emission tomography scan revealed recurrence in the pelvic lymph nodes. At this time, she had residual rash on her thighs that responded to oral methylprednisolone. She declined further chemotherapy for recurrent SCC and opted for palliative care.

Conclusion: We present a rare case of MASS in cervical cancer associated with recurrence two months after chemoradiation.

1. Introduction

Sweet Syndrome, or acute febrile neutrophilic dermatosis, was first described by Dr. Robert Douglas Sweet in 1964 as a non-infectious eruption of erythematous plaques accompanied by fever, neutrophilic leukocytosis and skin biopsy demonstrating neutrophilic infiltration (Sweet, 1964). Diagnosis requires two major and two minor criteria (Table 1). Sweet Syndrome is classified into three forms— classic/idiopathic, drug-induced, or malignancy-associated (MASS). Epidemiological studies reveal a female predominance and typical onset in the 4th or 5th decade of life (Nelson et al., 2018b).

Sweet Syndrome typically presents as tender papules or nodules on the arms, face or neck that develop into asymmetric plaques, vesicular bullae, pustules or ulcerative lesions lasting for 2–3 months (Cohen, 2007; Sweet, 1964). Extra-cutaneous involvement can include almost any other organ leading to acute kidney injury (AKI), arthralgias, myalgias, and conjunctival lesions (Cohen, 2007; Paydas, 2013). Labs often

demonstrate a non-specific leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate (ESR) (Cohen, 2007). These symptoms and lab results lead to a large differential diagnosis of dermatoses including vasculitides, autoimmune diseases, infections, lymphomas, leukemias and a fixed drug eruption. Histopathology demonstrates a mature, non-infectious, neutrophilic infiltrate in the upper dermis with papillary dermal edema (Villarreal-Villarreal et al., 2016).

MASS is estimated to account for 3–67% of Sweet Syndrome cases in retrospective studies, with increasing incidence reported in recent years due to heightened awareness (Nelson et al., 2018b). In patients without a known malignancy, Sweet Syndrome diagnosis should prompt a workup to exclude cancer including physical exam, routine screenings and laboratory studies (Villarreal-Villarreal et al., 2016). MASS is largely associated with hematologic malignancies, particularly acute myeloid leukemia (Nelson et al., 2018a). When MASS occurs in solid tumors, it is usually associated with adenocarcinomas of the breast, genitourinary system, or gastrointestinal tract (Cohen et al., 1993). In

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Table 1
Diagnostic Criteria for Sweet Syndrome [3]

Major Criteria	(1) acute onset of tender, erythematous cutaneous lesions (2) histopathology of the dermis showing dense neutrophilic infiltrate without leukoclastic vasculitis
Minor Criteria	(1) Preceding infection, malignancy, inflammatory disorder, or drug exposure, recent vaccination or pregnancy (2) Fever (3) Leukocytosis (4) Response to systemic corticosteroids

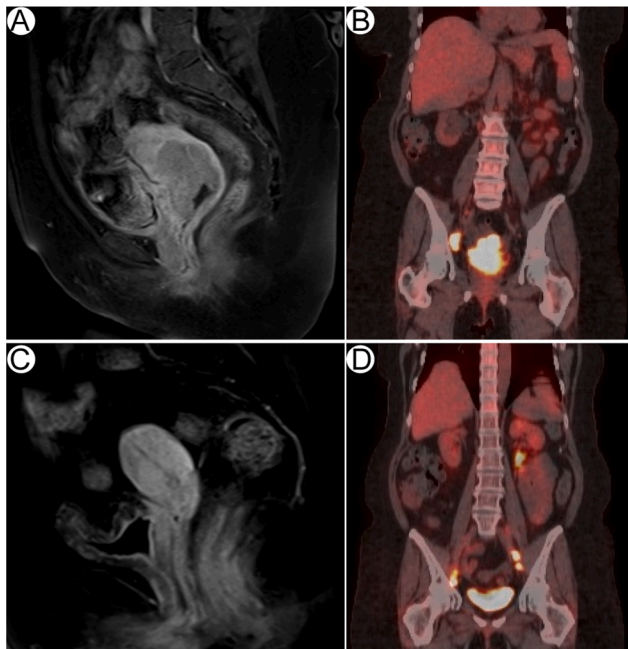


Fig. 1. A). MRI at diagnosis showing a 5.6 × 3.7 cm cervical mass with extension into the lower uterine segment, bilateral parametrial involvement, right obturator node measuring 2.0 cm and right internal iliac node measuring 0.7 cm. B). PET at diagnosis showing FDG avidity in the cervix (SUV 33.4), right external iliac nodal conglomerate (3.1 × 1.7 cm, SUV 25.5), right iliac chain node (SUV 3.44), right infrarenal para-aortic node (SUV 3.99) and left external iliac node (SUV 2.88). C). MRI obtained for brachytherapy planning after chemotherapy and EBRT showed treatment response with no definitive tumor seen, and no lymphadenopathy. D). Three weeks after Sweet Syndrome diagnosis, PET scan showed resolution at the cervix (SUV 1.9) but high metabolic activity in the right pelvic sidewall (2.3 × 1.5 cm, SUV 15.3), and new areas of avidity in the left common iliac node (1.4 × 1.2 cm, SUV 15.5) and left distal internal iliac node (1.6 × 1.2 cm, SUV 19.0).

contrast to idiopathic Sweet Syndrome, MASS is typically seen with leukopenia instead of leukocytosis, anemia, and thrombocytopenia (Nelson et al., 2018b; Paydas, 2013). In addition, MASS lesions may spare mucosal areas, and show fewer extra-cutaneous features (Cohen, 2007; Nelson et al., 2018a).

MASS has been reported in International Federation of Gynecologic Oncologists (FIGO) stage IB1 to IVA squamous cell carcinomas (SCC) of the cervix, likely due to the greater incidence of SCC versus adenocarcinoma at the cervix (Clark et al., 2017). MASS can either precede cervical cancer diagnosis, or signal its metastasis, recurrence or progression (Clark et al., 2017). Here we present a case of MASS that signaled recurrence in a patient with SCC of the cervix two months following definitive chemoradiation.

2. Case description

A 55-year-old Caucasian nulliparous female with history of

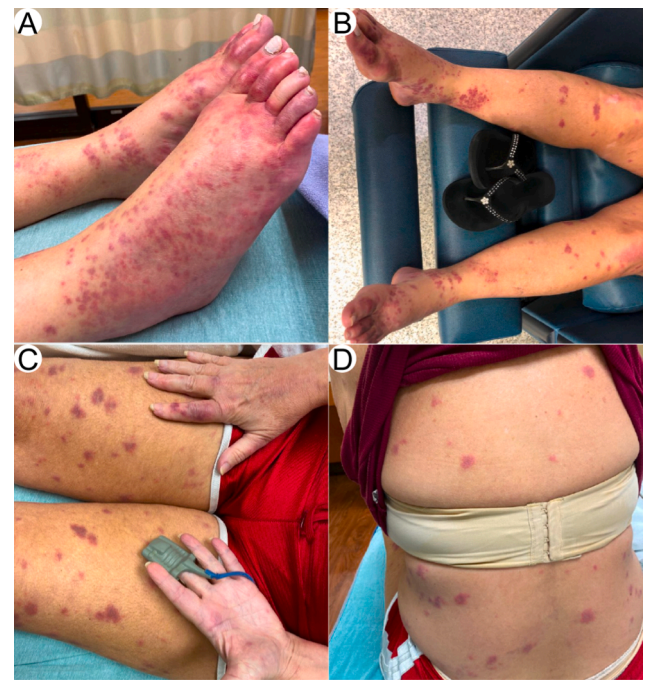


Fig. 2. Rash on admission for workup showing involvement of all four extremities and the trunk, sparing only the face, soles and right palm.

hypertension presented to our gynecology department with nine-months of post-menopausal bleeding and Pap smear showing atypical squamous cells cannot exclude high grade squamous intraepithelial lesion (ASC-H) and human papillomavirus (HPV) infection. She was a former smoker with six pack years' history. Pelvic examination in clinic was limited by pain, so she consented for an exam and biopsies under anesthesia. This revealed a firm, nodular, retracted cervix flush against the posterior vagina with edematous vaginal tissue surrounding and protruding past the cervix. Biopsies showed moderately differentiated SCC of the cervix. Magnetic resonance imaging (MRI) revealed a 5.6 × 3.7 cm cervical mass extending into the anterior lower uterine segment and bilateral parametria, a right obturator node measuring 2.0 cm and a right internal iliac node measuring 0.7 cm (Fig. 1A). Positron emission tomography (PET) scan revealed FDG avidity in the cervix with a standardized uptake value (SUV) maximum of 33.6, a right external iliac nodal conglomerate (3.1 × 1.7 cm, SUV 25.5), a right iliac chain node (SUV 3.44), a right infrarenal para-aortic node (SUV 3.99) and a left external iliac node (SUV 2.88) (Fig. 1B). She was staged IIIC2(r) by the 2018 FIGO system and received definitive treatment with five cycles of weekly cisplatin and concurrent radiation over 64 days. There was a one-week treatment delay after cycle 5 due to a circumstance requiring patient travel. A sixth cycle of cisplatin was held due to neutropenia. Radiation treatment consisted of extended field pelvic external beam radiation therapy (EBRT), with three-dimensional conformal radiation boosts to the parametria, para-aortic nodes, bilateral PET-avid pelvic nodes and high dose rate (HDR) brachytherapy. The low dose rate (LDR) equivalent dose of her HDR procedures was 36.17 Gy and the cumulative external beam with LDR equivalent was 86.57 Gy to the paracentral disease. MRI obtained for brachytherapy planning after chemotherapy and EBRT showed treatment response with no definitive residual tumor, no lymphadenopathy and decreased parametrial extension (Fig. 1C).

Two months following chemoradiation she developed erythematous, purpuric, painful, non-pruritic plaques and papules on three left toes associated with left ankle edema. She was seen by internal medicine, diagnosed with cellulitis and treated with cephalixin. This resolved the swelling, but the rash spread to her right toes. One week later, she developed fever, fatigue, anosmia, anorexia and the rash spread to all

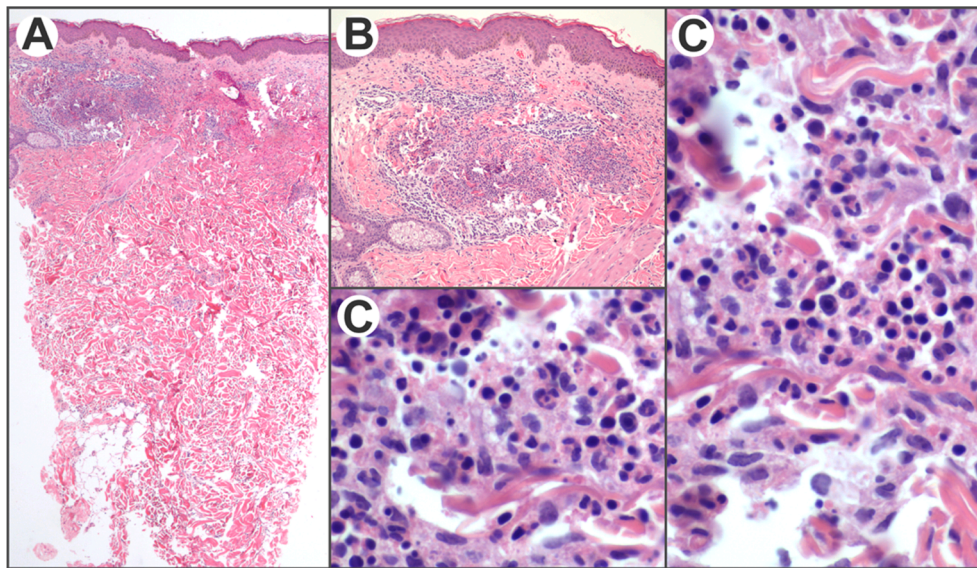


Fig. 3. Histopathology of skin punch biopsies obtained from left leg and back. A). Low Power (40 \times) and B). Medium power (100 \times) microscopic images: Superficial nodular dermal predominately neutrophilic infiltrate with mild papillary dermal edema C). High Power 600 \times microscopic images: Chiefly neutrophilic dermal inflammation with associated leukocytoclasia and accompanying lymphohistiocytic inflammation.

four extremities and trunk, sparing the face, soles and right palm (Fig. 2A–D). She had no recent travel or new dietary exposures, had no history of vasculitis or autoimmune disorders, and tested negative for COVID-19. She was admitted for workup where dermatology and rheumatology were consulted. Labs revealed normocytic anemia, elevated fibrinogen, leukopenia with a normal absolute neutrophil count, elevated ESR, and AKI. Immunoglobulins were positive for cytomegalovirus and parvovirus. She tested negative for sexually transmitted diseases, anti-neutrophil cytoplasmic autoantibody, anti-nuclear antibody, cyclic citrullinated protein, murine typhus, anti-dsDNA antibodies, anti-SSA, and thiopurine methyltransferase. Computed tomography (CT) scan ruled out hepatosplenomegaly but was not able to well characterize the pelvis. Punch biopsies revealed nodular and interstitial neutrophilic dermal infiltrate with focal leukocytoclastic vasculitis and mild papillary dermal edema consistent with Sweet Syndrome (Fig. 3). She was followed conservatively without treatment.

One month after Sweet Syndrome diagnosis and four months following chemoradiation, a PET scan revealed resolution of the FDG avidity at the cervix (SUV 1.9) signaling good localized response to chemoradiation, but high metabolic activity in the right pelvic sidewall (2.3 \times 1.5 cm, SUV 15.3), and new areas of avidity in the left common iliac node (1.4 \times 1.2 cm, SUV 15.5) and left distal internal iliac nodes (1.6 \times 1.2 cm, SUV 19.0) consistent with recurrence (Fig. 1D). A persistent leg rash resolved with oral methylprednisolone. She was offered a biopsy to confirm radiographic suspicion, further cancer therapy with carboplatin, paclitaxel and bevacizumab and the possibility of enrollment into clinical trials. She declined further workup or cancer treatment and sought palliative care only.

3. Discussion

Systemic corticosteroids are the first line treatment for Sweet Syndrome, although some patients experience resolution in 2–3 months without treatment (Cohen, 2007). Delayed diagnosis or misdiagnosis is common in Sweet Syndrome due to its rarity, dramatic cutaneous presentation, and non-specific laboratory markers. Many patients will initially receive antibiotics for presumed skin infection or undergo workup for more common etiologies (Villarreal-Villarreal et al., 2016). Resolution occurs after time, starting corticosteroids, removing the instigating drug, or treating the underlying malignancy (Cohen, 2007).

When corticosteroids are contraindicated, colchicine, dapsone, and potassium iodide are alternatives. Sweet Syndrome recurrence is rare and has not been reported in cervical cancer.

In our patient, several findings were consistent with previous reports of MASS in cervical cancer with a few notable differences. As with most cases, she was initially misdiagnosed with cellulitis and given antibiotics. Her rash began in an atypical location for Sweet Syndrome on the lower extremities as opposed to the more common location on the face, upper extremities and neck. When the rash progressed, she was admitted for workup, and then met diagnostic criteria for Sweet Syndrome. Compared to previous reports of MASS in cervical cancer, our patient had the shortest reported time frame of only two months between the completion of chemoradiation and the development of the Sweet Syndrome rash. The malignant association of the syndrome was confirmed at four months after chemoradiation when PET scan revealed recurrence at sites that showed good treatment response just prior to brachytherapy. Other cases report 3 months to 3 years between initial cervical cancer treatment and the development of MASS (Clark et al., 2017).

While the pathogenesis of Sweet Syndrome is unknown, serum cytokine studies point to a Th1-mediated autoimmune response that leads to neutrophil recruitment (Giasuddin et al., 1998). Upregulation of serum interleukin 1 (IL-1), IL-2, IL-3, IL-6, IL-8, interferon gamma (IFN- γ), granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) have been observed in Sweet Syndrome (Giasuddin et al., 1998; Paydas, 2013). This Th1 immune mediated theory is supported by iatrogenic cases of Sweet Syndrome, which have occurred after treatment with G-CSF, GM-CSF, IFN- γ , all trans retinoic acid, angiogenesis inhibitors, antimetabolites, BRAF inhibitors, FMS-like tyrosine 3 inhibitors, hypomethylating agents, proteasome inhibitors, topoisomerase inhibitors, and tyrosine kinase inhibitors (Nelson et al., 2018b; Paydas, 2013).

In cervical cancer, Sweet Syndrome is an ominous sign. Cisplatin, a common first-line chemotherapy agent in cervical cancer has not been associated with iatrogenic cases of Sweet Syndrome. In fact, many of the known drug triggers of iatrogenic Sweet Syndrome are not typically used in cervical cancer. Thus, when Sweet Syndrome occurs in cervical cancer, it is most often associated with recurrence, progression or metastasis. Independent of MASS, elevations of IL-1 and IL-6 are associated with invasion, progression and poor prognosis in cervical cancer (Song et al., 2016). Activation of proinflammatory Th1 cytokines during Sweet

Syndrome could create a cytokine environment that promotes cervical cancer tumorigenesis, recurrence or progression. More research is warranted in this area to determine the effects of systemic activation of the Th1 immune response on the tumor microenvironment in cervical cancer.

4. Conclusion

In our case, the diagnosis of Sweet Syndrome was associated with cervical cancer recurrence just two months following chemoradiation and MRI showing no definitive residual tumor. When the characteristic rash and fever are seen, clinicians must recognize the potential link between the physical findings and malignancy. Routine cancer screenings should be emphasized, and full physical exam should be performed. If Sweet Syndrome is missed, an opportunity for cancer diagnosis or recurrence may also be missed, resulting in poor oncologic outcomes. For our patient, Sweet Syndrome diagnosis allowed for earlier cancer evaluation with PET scan, which provided her more time to make decisions about future therapy.

5. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRedit authorship contribution statement

Kelly Lamiman: Conceptualization, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Justine Sheu:** Writing - review & editing. **Brandon Goodwin:** Writing - review & editing, Visualization. **Sandra Hatch:** Writing - review & editing. **Gwyn Richardson:** Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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