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Sweet Syndrome: A Paraneoplastic Syndrome Related to Ovarian Cancer: A Case Report

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Abstract

Background: Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm, although exact pathogenesis remains unclear for most cases. Symptoms may occur in any organ or physiological system. Up to 20% of cancer patients can experience paraneoplastic syndromes, but these syndromes are often difficult to recognize.

Sweet's syndrome or, acute febrile neutrophilic dermatosis, is an uncommon cutaneous inflammatory disorder characterized by the abrupt appearance of painful, edematous and erythematous papules, plaques or nodules on the skin. These lesions typically show an upper dermal infiltrate of mature neutrophils. Fever and leukocytosis are also frequently present. In addition, involvement of the eyes, musculoskeletal system and internal organs may occur.

Methods and Results: We report a case of a 57-year-old woman in which Sweet Syndrome precedes and heralds the diagnosis of ovarian cancer.

Conclusion: Sweet syndrome may precede, follow or appear concurrently with a malignancy. The search for a neoplasm should be emphasized in patients with Sweet syndrome without a prior diagnosis of malignancy.

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Introduction

Sweet's syndrome is a reactive phenomenon and should be considered a cutaneous marker of systemic disease, including underlying malignancy.

We present a case of a 57-year-old woman who was diagnosed with serous epithelial ovarian cancer after starting with painful erythematous papules and plaques on her chest and extremities. We also reviewed the literature regarding Sweet syndrome and gynecologic tumors.

Case Presentation

We report a case of a 50-year-old woman who consulted a dermatologist because of painful and erythematous plaques spotted on her skin (Figure 1).

The patient also presented unintentional weight loss. The dermatologist performed a skin biopsy with the result of neutrophilic dermatosis. Figure 2a and 2b show dense dermal infiltrate of neutrophils compatible with Sweet Syndrome. Once infectious disease and associated drugs were excluded as the cause of these lesions, a wide range of screening tests were performed to search for underlying neoplasm.

Colonoscopy and gastroscopy were negative for malignity. The blood test showed only anemia, Ca 125 500, CEA 4.3 and Ca 19.9 6.11. A CT scan revealed peritoneal carcinomatosis, omental cake and pelvic ascites. The PET-CT also identified a 15 mm nodular lesion in the right ovary suggesting primary tumor.

The patient started treatment with high dose oral prednisolone and colchicine with good control of the cutaneous symptoms.

With the suspected diagnosis of advanced ovarian cancer with peritoneal carcinomatosis, an exploratory laparoscopy was performed consisting of double annexectomy, epiplon biopsy and peritoneal lavage. Intraoperatively, the pathologist informed of high grade serous carcinoma. Our multidisciplinary committee decided upfront surgery. Although that was the initial plan, at the same

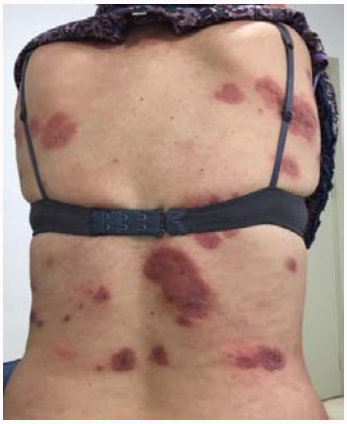

Figure 1: Elevated erythematous plaques.

surgical act, surgeons found an extensive carcinomatosis not allowing optimal surgery with complete resection (clinical stage IIIC).

The patient underwent neoadjuvant chemotherapy. The patient started carboplatin AUC6-paclitxel 175 mg/m^2 every three weeks. After 3 cycles the CT scan showed partial response and the Ca 125 levels went back to normal. During this period, the cutaneous lesions fluctuated, with a new outbreak just right before the interval debulking surgery. At that moment, she was still treating Sweet syndrome with oral prednisolone and colchicine without any break otherwise Sweet Syndrome lesions continue to appear.

Interval debulking surgery was performed with histerectomy, pelvic and paraaortic lymphadenectomy, and omentectomy, also recquiring extensive pelvic peritonectomy and small bowel resection in order to achieve complete cytoreduction.

As far as we could perceive, after the surgery the skin lesions nearly disappeared. After surgical recovery, she received 3 more cycles of chemotherapy. Yet again, during chemotherapy, despite the fact that Ca 125 was still in the normal range, Sweet Syndrome came up with erythematous plaques again highly depending on corticoid treatment. Germline BRCA status was analyzed with a negative result.

At the time of publication, the patient is free from recurrence and undergoing CT scan control every 3 months. The progression free survival is now 7 months from last chemotherapy cycle. Although only residual crust lesions persist on her skin, she is still up to oral corticoid dose reduction treatment in order to avoid another regrowth of lesions due to drug withdrawal.

Discussion

Sweet syndrome may occur as a cutaneous paraneoplastic syndrome. To our knowledge, less than 5 cases have been reported in the literature associated with ovarian cancer [1,2], and there are two more associated with cervical cancer [3,4].

First case report associated with ovarian cancer was in 1983 but Sweet syndrome originally was described in 1964 by Dr. Robert Douglas Sweet.

Approximately 10% to 20% have an associated neoplasm. Sweet syndrome is more likely to occur in association with hematological malignances than in solid tumors, 85% *vs.* 15% approx. Acute myeloid leukemia is the most common malignancy associated with Sweet syndrome [5]. Among solid cancers, carcinomas of the genitourinary tract, breast, and gastrointestinal tract are most commonly linked to Sweet syndrome.

In 1993 Cohen et al. [6] reviewed retrospective data from 15 studies of patients with Sweet's syndrome (each study containing 10 to 48 patients) in order to define the incidence of malignancy associated Sweet's syndrome. They found that 21% of the patients had either hematologic or solid malignancy.

The pathogenesis of Sweet syndrome is not well understood; factors theorized to contribute include hypersensitivity reactions--due to an immune reaction to bacterial, viral, tumor or other antigens that could influence the development of Sweet syndrome through stimulating the production of cytokines that promote neutrophils activation and infiltration motivating the clinical response to corticosteroids, cytokine dysregulation principally IL-1 (fever, increased levels of acute-phase proteins, increased circulating neutrophils) and genetic susceptibility. Increased production of G-CSF by tumor cells and by activated monocytes and fibroblasts has also been proposed as a potential factor in malignancy-associated Sweet syndrome disease [5-8].

Clinical manifestations include cutaneous lesions typically presenting as tender, edematous, and inflamed papules, plaques and nodules, exhibiting bright erythematous or violaceous color. Sometimes skin lesions develop a central yellowish hue. In contrast to patients with idiopathic Sweet syndrome, individuals with malignancy-associated syndrome often have vesicular, bullous or ulcerative skin lesions and demonstrate some of the more severe cutaneous features of the disorder [8]. The upper extremities are the most common site of involvement regardless of the cause of the Sweet Syndrome. Yet, malignancy-associated lesions also frequently

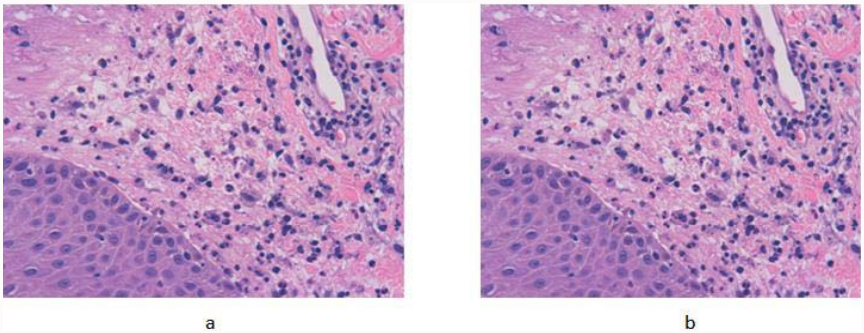

Figure 2: a) and b) Microscopic examination of the skin lesion shows a diffuse dense neutrophilic dermic infiltrate within the edematous upper dermis. (H&E, original magnification × 40X and 20X).

develop on the trunk, lower extremities, head and neck [5]. Patients usually complain about pain related to the lesions sometimes with a burning sensation.

Other associated symptoms are fever >38°C, but in malignancy-associated rarely does increased temperature appear. Arthralgias, headache, malaise and myalgias could be also referred to. The absence of fever or neutrophilia does not exclude the diagnosis.

Extracutaneous disease such as the involvement of eyes, muscles, lung, bone, liver, spleen, heart, or kidneys, happens in a significant proportion (near 50%) of the malignancy-associated [8], most frequently myalgias and arthralgias as mentioned above. Ocular inflammation and musculoskeletal system are the most common extracutaneous manifestation.

Laboratory findings like peripheral neutrophilia, anemia, platelet abnormalities, elevated erythrocyte sedimentation rate and C-reactive protein level are present in the vast majority of patients' malignancy-associated disease. Only between half and up to two thirds of malignancy-associated syndrome have an elevated neutrophil count [5,9].

The diagnosis of Sweet syndrome is based upon the recognition of clinical and laboratory findings. In addition, the knowledge that a patient has a condition known to occur in association with Sweet syndrome (e.g., recent infection, malignancy, pregnancy, or inflammatory bowel disease) raises clinical suspicion for the diagnosis [10].

Moreover, a rapid and dramatic response to systemic glucocorticoid therapy also supports the diagnosis because sweet syndrome is characterized by rapid response to corticosteroid therapy regardless of the response of the associated neoplasm to tumor-directed therapy.

Biopsy is a diagnostic criterion for Sweet Syndrome. Thus, a skin biopsy should be performed whenever feasible. In patients with inflammatory papules or plaques, a 4 mm punch biopsy is usually sufficient for obtaining a tissue specimen for histological examination. The most characteristic histological features of Sweet syndrome include: prominent edema in the superficial dermis, dense infiltrate of neutrophils in the upper and mid-dermis with sparing of the epidermis, leukocytoclasis and endothelial swelling. A dense infiltration, primarily composed of mature neutrophils, located predominantly in the mid- and upper-dermis, is the pathognomonic histologic finding. Importantly, bacterial, mycobacterial, and fungal organisms, tumor cells and histological features of vasculitis are absent [5].

Corticosteroid therapy is the treatment of choice in all Sweet syndrome causes. The lesions usually start to heal rapidly after 1-2 days of treatment. Oral treatment is preferred combined or not with topical treatment [5]. Other modalities are in combination with colchicine or indomethacin with the purpose to relieve the symptoms. Antibiotics have no effect.

Nearly all undiagnosed solid tumors are discovered within 12 months after the onset of Sweet syndrome. It is a challenging task for clinicians to suspect an underlying malignancy and perform the consequent studies in previously cancer-free patients with Sweet syndrome. Workup recommendations are complete history and physical examination including examination of thyroid, lymph nodes, oral cavity and skin. Breast, ovary and pelvic examination in women and prostate and testicle examination in men must be performed. Gastrointestinal endoscopies must be performed in patients older than 50 years of age. Additional studies, if needed, should be directed by the findings from these preliminary tests.

Conclusion

Sweet syndrome may precede, follow or appear concurrently with a malignancy [6]. In patients with a previous history of cancer, the development of Sweet syndrome may predict or herald the disease recurrence such as the elevation of Ca 125 marker in ovarian cancer. A skin biopsy is mandatory for the diagnosis.

It is a challenging task for clinicians to suspect an underlying malignancy and perform the consequent studies in previously cancer-free patients with Sweet syndrome.

Glucocorticoid systemic therapy should be administered. If not enough response is achieved, physicians may try immunosupressors. It is also important to initiate the specific treatment for the neoplasm as early as possible, although patients should respond to corticoid treatment regardless of the specific oncologic treatment.

Recurrent episodes are frequent when patients have associated neoplasm as ours did and in some cases corticoid treatment may be difficult to stop.

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