DERMATOLOGY PRACTICAL & CONCEPTUAL
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Proton pump inhibitor-induced Sweet's syndrome: report of acute febrile neutrophilic dermatosis in a woman with recurrent breast cancer

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Key words: acute, breast, cancer, dermatosis, esomeprazole, febrile, inhibitor, neutrophilic, omeprazole, proton, pump, Sweet, syndrome

Citation: Cohen PR. Proton pump inhibitor-induced Sweet's syndrome: report of acute febrile neutrophilic dermatosis in a woman with recurrent breast cancer. Dermatol Pract Concept 2015;5(2):23. doi: 10.5826/dpc.0502a23

Received: September 18, 2014; **Accepted:** December 30, 2014; **Published:** April 30, 2015

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

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ABSTRACT

Background: Sweet's syndrome, also referred to as acute febrile neutrophilic dermatosis, can either occur as an idiopathic disorder or associated with another condition, including cancer, or induced by exposure to a drug. Proton pump inhibitors selectively inhibit gastric parietal cell H+-K+-adenosine triphosphatase and are most commonly used for the treatment of gastroesophageal reflux disease.

Purpose: Proton pump inhibitor-associated Sweet's syndrome is described in a woman with recurrent breast cancer.

Methods: PubMed was used to search the following terms, separately and in combination: acute febrile neutrophilic dermatosis, breast cancer, malignancy, paraneoplastic, proton pump inhibitor, and Sweet's syndrome. All papers were reviewed and relevant manuscripts, along with their reference citations, were evaluated.

Results: Proton pump inhibitors have previously been associated with cutaneous adverse reactions including maculopapular rash, subacute cutaneous lupus erythematosus and toxic epidermal necrolysis. However, drug-induced Sweet's syndrome has not been observed in patients receiving proton pump inhibitors. The reported woman developed Sweet's syndrome after initial exposure and subsequent repeat challenge to proton pump inhibitors; subsequent studies also observed recurrence of her breast cancer presenting as metastases to her stomach and bone.

Conclusions: Drug-induced Sweet's syndrome has most commonly been associated with granulocyte colony stimulating factor in oncology patients. Malignancy-associated Sweet's syndrome has been observed in patients with solid tumors, including breast cancer. Confirmation of proton pump inhibitor-induced Sweet's syndrome, by repeat challenge with another medication in the same class of drug, was observed in a woman with breast cancer; although the subsequent discovery of recurrent breast cancer presenting as gastric mucosa and vertebral metastases also raises the possibility of concurrent paraneoplastic Sweet's syndrome, her Sweet's syndrome symptoms and lesions resolved without recurrence while her recurrent metastatic visceral malignancy persisted. In summary, medication-associated Sweet's syndrome can occur in oncology patients and proton pump inhibitors should be added to the list of medications associated with the potential to cause drug-induced Sweet's syndrome.

Introduction

Sweet's syndrome is an acute febrile neutrophilic dermatosis typically characterized by the sudden onset of pyrexia, increased number or percent of neutrophils, and painful red skin lesions that consist of a diffuse dermal infiltrate of neutrophils; in addition, the symptoms and lesions promptly respond to systemic corticosteroids [1]. The condition can occur in an idiopathic setting, most commonly in young women associated with a streptococcal pharyngitis [2]. Alternatively, its onset can be associated with either other conditions—such as pregnancy, inflammatory bowel disease or cancer—or drugs [3]. A woman with recurrent breast cancer who developed her first episode of Sweet's syndrome after an initial exposure to omeprazole and a recurrence of the dermatosis immediately after receiving a single dose of esomeprazole is described.

Case report

An 86-year-old Hispanic woman presented for evaluation of tender lesions on her hands. Her past medical history was significant for invasive lobular carcinoma (grade 2, T3N3 with lymphatic vessel invasion, estrogen receptor positive, progesterone receptor negative, and Her2/neu negative) of the left breast that was diagnosed 1 year earlier. Her initial treatments included mastectomy of the left breast with axillary lymph node dissection and 6 weeks of adjuvant radiation therapy; thereafter, 20 mg of tamoxifen citrate daily was started. Follow up evaluation, 9 months after diagnosis, showed no evidence of disease.

She presented to her primary care physician 3 weeks earlier with 2 months of loss of appetite, nausea, dyspepsia, and postprandial abdominal bloating. She had also lost 5 pounds. A clinical diagnosis of gastroesophageal reflux disease was made and she was started on 20 mg of omeprazole daily. Within 6 days, she developed severe neck pain; 2 days later she had "blisters on her palms."

She was evaluated in the emergency department 8 days after initiating omeprazole; the medication was stopped and she received dilaudid (and subsequently ibuprofen) for her neck pain and ondansetron 4 mg every 8 hours, as needed, for her nausea. The next day her primary care physician prescribed prednisone (40 mg daily for 5 days) for the painful blisters on her hands.

She returned for evaluation after completing the prednisone. Her neck pain had improved and the lesions on her hands had resolved. However, her gastrointestinal symptoms persisted. The ondansetron was stopped and her primary care physician prescribed 20 mg of esomeprazole daily.

Within 6 hours after she took her first dose of esomeprazole, the neck pain returned and the skin lesions on her hands recurred. Cutaneous examination showed tender, erythematous to violaceous, pustules and pseudovesicular plaques, ranging in size from 5 mm to 3 cm in diameter, predominantly on the proximal palms of both hands (Figures 1, 2 and 3). Similar lesions were also noted on the distal left palm proximal to the left second digit and the left ventral thumb (Figure 3), the lateral side of the left second digit (Figures 4 and 5), and the dorsal left thumb (Figures 4 and 6).

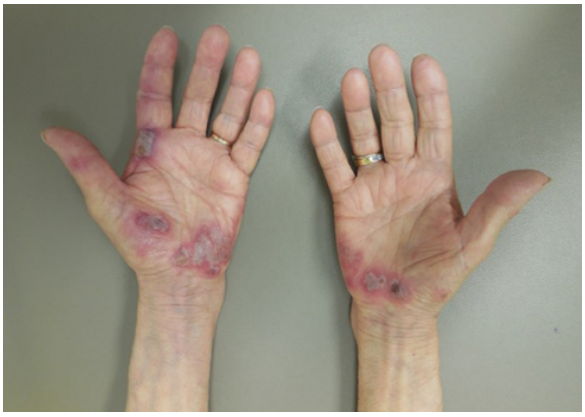

Figure 1. Distant view of the palms of an 86-year-old woman with proton pump inhibitor-induced Sweet's syndrome. The painful hand lesions appeared within 6 hours after she took an initial dose of esomeprazole. Previously, she had developed similar hand lesions on day 8 of omeprazole that resolved after a short course of oral prednisone. [Copyright: ©2015 Cohen.]

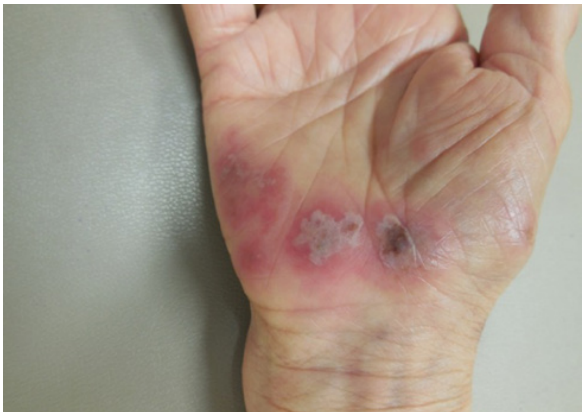

Figure 2. The right ventral hand show tender erythematous-based pustules and pseudovesicular violaceous plaques on the proximal palm. [Copyright: ©2015 Cohen.]

Microscopic examination of a biopsy from the left dorsal wrist showed parakeratosis with neutrophilic pustule formation in the epidermis. There was edema in the upper dermis and a dense interstitial inflammatory infiltrate in both the superficial and deep dermis. The infiltrate was comprised mostly of neutrophils; lymphocytes and histiocytes were also present. Stains to detect bacteria, fungi and mycobacteria were negative for organisms; a separate lesional biopsy for tissue culture was also negative for these organisms and her-

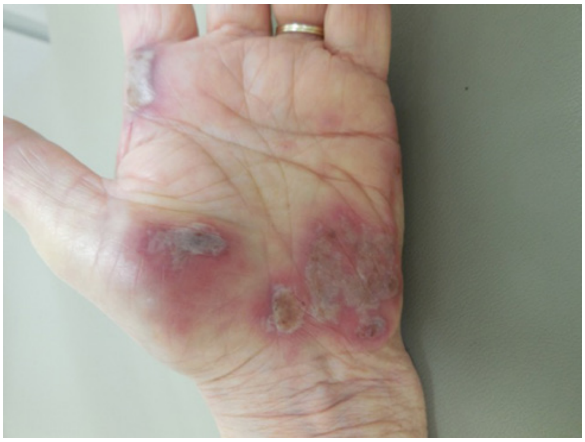

Figure 3. The left ventral hand show painful erythematous-based pustules and violaceous plaques on the proximal palm and a similar-appearing lesion on the distal palm proximal to the left second digit and the thumb. [Copyright: ©2015 Cohen.]

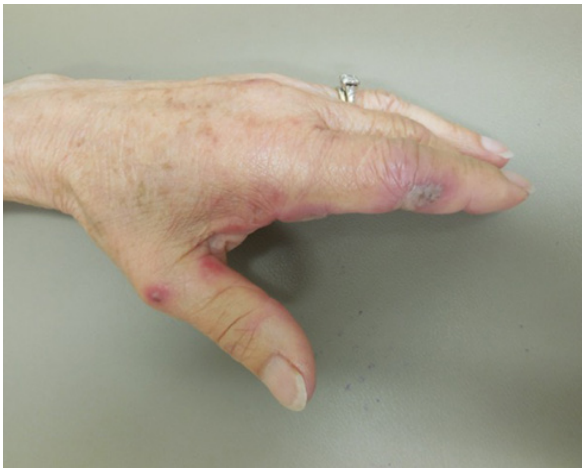

Figure 4. Distant lateral view of the left hand shows Sweet's syndrome lesions on the index finger and thumb. [Copyright: ©2015 Cohen.]

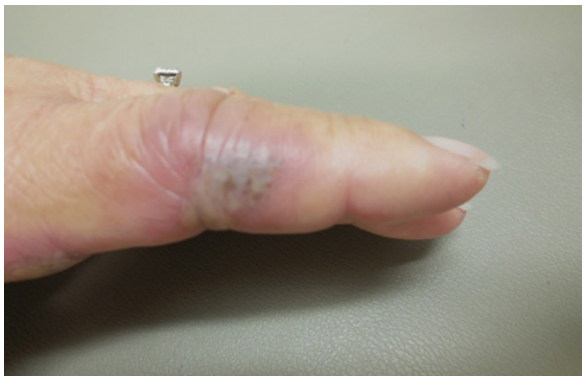

Figure 5. Closer view of the lateral left index finger shows a Sweet's syndrome lesion presenting as a pustule with surrounding erythema. [Copyright: ©2015 Cohen.]

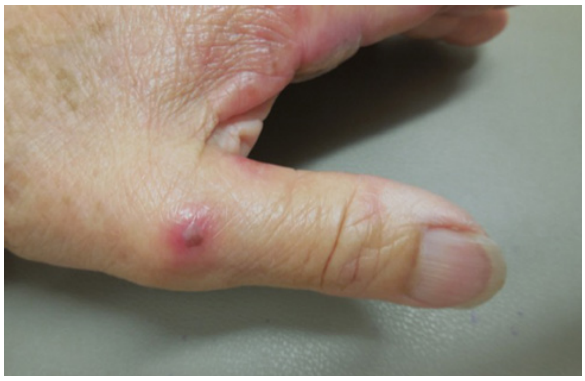

Figure 6. Closer view of the dorsal left thumb shows an erythematous-based pustular Sweet's syndrome lesion. [Copyright: ©2015 Cohen.]

pes virus infection. In summary, the pathology findings were those of a neutrophilic dermatosis.

There was no history of sore throat, mucosal lesions, or other skin lesions. Her leukocyte count was 8,400 cells per cubic millimeter with 72% neutrophils (upper limit of normal = 71%). The remainder of her complete blood counts, serum chemistries, thyroid function tests, urinalysis were normal. Direct fluorescent antibody studies for herpes (simplex and varicella zoster) virus and urine culture were negative.

Correlation of her clinical history, lesion morphology, biopsy pathology and laboratory studies were consistent with the diagnosis of Sweet's syndrome. An association between her exposure to omeprazole and the initial episode of her skin lesions was retrospectively considered. The recurrence of her dermatosis within hours after receiving esomeprazole (a chemically-related proton pump inhibitor), confirmed the suspected diagnosis of drug-induced Sweet's syndrome.

Additional laboratory studies showed an elevated CA153 of 435.7 U/m (normal < 25.0 U/ml). CA153 is a tumor marker used for monitoring a breast cancer patient's response to treatment and to detect cancer recurrence. Elevation of this marker is seen in oncology patients with therapy-resistant breast cancer or raises concern regarding the possibility of recurrent carcinoma in individuals with previously treatment-responsive disease.

Computerized tomography scan of the abdomen with contrast showed a large gastric fundus and body with circumferential wall thickening at the antrum; these findings were compatible with metastatic cancer and postulated to be responsible for her clinical manifestations of gastric outlet obstruction and abdominal symptoms. There was also mild diffuse nodularity of the omentum consistent with peritoneal carcinomatosis. Her computerized tomography scan of the chest showed sclerotic lesions in the T8 vertebral body consistent with thoracic skeletal metastases.

Biopsy of the stomach lining showed sheets of cohesive malignant cells with enlarged atypical nuclei and foamy cytoplasm invading into the gastric mucosa. Immunohisto-

chemistry stains showed that the tumor cells were positive for BRST-2—a monoclonal antibody that detects gross cystic disease fluid protein 15 (GCDFP-15) which is a specific marker for breast cancer in surgical specimens—and weakly positive (in approximately 10% of tumor cells) for estrogen receptor and progesterone receptor; the cells were negative for Her2/neu. These findings established a diagnosis of metastatic carcinoma and were consistent with a breast primary.

Treatment for the hand lesions included topical soaks—using a mixture of white vinegar (1 cup) and water (4 cups)—three times daily, followed by applying a thin layer of 0.05% clobetasol cream; topical application of a high potency corticosteroid cream was used for treatment of her skin lesions since she had experienced nausea and gastrointestinal irritation when she had previously received oral prednisone. The clinical presentation of her hand lesions raised the possibility of infection or impetiginization by a bacterial pathogen; therefore, prior to receiving negative tissue cultures from her skin biopsy, empiric therapy (capable of treating methicillin susceptible Staphylococcus aureus) with oral cefdinir (300 mg twice daily for 10 days) was also initiated. Within 1 week there was significant improvement of the skin lesions: they were no longer painful and had begun to heal. After an additional 7 days, the hand lesions had nearly resolved and the frequency of topical corticosteroid cream applications was progressively decreased and the medication was subsequently discontinued. There was no recurrence of the dermatosis.

Her metastatic breast cancer was treated with fulvestrant, 500 mg intramuscularly, every 2 weeks. She was also started on denosumab, 120mg subcutaneously, every month to prevent skeletal events. After 3 courses of antineoplastic therapy, her computerized tomography scans did not show any decrease in tumor and her CA153 had increased to 1098.0 U/ml (normal < 25.0 U/ml). In spite of the progression of her metastatic breast cancer, new lesions of Sweet's syndrome had not appeared.

Discussion

Malignancy-associated Sweet's syndrome can occur in patients with either hematologic cancer or solid tumors [4]. Sweet's syndrome in oncology patients can be idiopathic or related to a medication they are receiving either to treat the cancer or to manage a drug-induced neutropenia and/or associated with the discovery of a previously undiagnosed malignancy or recurrence of an established neoplasm [5]. Paraneoplastic Sweet's syndrome is most commonly observed in patients with acute myelogenous leukemia [6].

Solid tumor-associated Sweet' syndrome has most frequently been described in patients with carcinomas of the genitourinary organs, breast, and gastrointestinal tract [7]. However, Sweet's syndrome has also been described in breast cancer patients—either in a paraneoplastic setting [7-14] or as an incidental dermatosis occurring in the individual's lymphedematous arm following ipsilateral mastectomy and lymph node dissection [15-20]. The currently described woman had an established diagnosis of metastatic breast cancer that had been treated; she had achieved a clinical remission. However, the development of Sweet's syndrome and persistent symptoms suggestive of gastroesophageal reflux disease prompted additional investigation that discovered biopsy-confirmed recurrence of her breast cancer presenting with metastasis to the gastric mucosa [21-25].

Diagnostic criteria for drug-induced Sweet's syndrome were introduced in 1996 [26]. Subsequently, an increasing number of medications have been associated with the development of Sweet's syndrome [27]. Granulocyte colony stimulating factor is the most frequently described agent to elicit the dermatosis; as expected, this usually occurs in patients with new or recurrent malignancy who are being treated with antineoplastic therapy and receive the granulocyte colony stimulating factor for treatment-related neutropenia [1,14].

The proton pump is a term that refers to the gastric parietal cell H+-K+-adenosine triphosphatase (ATPase); proton pump inhibitors selectively inhibit this enzyme and thereby inhibit gastric acid secretion [28,29]. Agents in this class of drugs include dexlansoprozole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, and tenatoprazole [29,30]. The drugs are primarily used to treat gastroesophageal reflux disease in children and adults [31,32].

Cutaneous adverse reactions to proton pump inhibitors are uncommon [33]. A retrospective study performed in Thailand discovered a prevalence of skin reactions ranging from three to 20 per 100,000 of the treated population. A "maculopapular rash" was the most frequently observed proton pump inhibitor-induced skin reaction [34].

Proton pump inhibitor-associated subacute cutaneous lupus erythematosus was initially described in 2005 and its recognition is increasing [35]. A recently published retrospective series of 24 patients from Denmark noted the skin rash was widespread with a tendency to bullous lesions and focal skin necrosis and that most individuals had anti-Ro/Sjogren syndrome A antibodies. Twelve and a half percent (3/24) of the patients who developed drug-induced subacute cutaneous lupus erythematosus reacted to more than one proton pump inhibitor, similar to the described patient [36].

Life threatening dermatoses secondary to proton pump inhibitors have also been described, albeit rarely [30,37,38]. To the best of my knowledge, proton pump inhibitor-induced Sweet's syndrome has not previously been observed. The currently reported woman had never previously been exposed to proton pump inhibitors; she experienced her initial episode of Sweet's syndrome 8 days after starting omeprazole and

TABLE 1. Adverse drug reaction probability scale [a-e]

Question	PA	PS
Are there previous conclusive reports on this reaction? Answer score: Yes = +1; No = 0	No	0
Did the adverse event appear after the suspected drug was administered? Answer score: Yes = +2; No = -1	Yes	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? Answer score: Yes = +1; No = 0	Yes	1
Did the adverse reaction reappear when the drug was readministered? Answer score: Yes = +2; No = -1	Yes	2
Are there alternative causes (other than the drug) that could on their own have caused the reaction? Answer score: Yes = -1; No = +2	No [f]	2
Did the reaction reappear when a placebo was given? Answer score: Yes = -1; No = +1	No [g]	1
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? Answer score: Yes = +1; No = 0	DNK	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Answer score: Yes = +1; No = 0	DNK	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Answer score: Yes = +1; No = 0	Yes	1
Was the adverse event confirmed by any objective evidence? Answer score: Yes = +1; No = 0	Yes	1
Total score		10

[a] Abbreviations: DNK, do not know; PA, patient answer; PS, patient score

[b] Answer all questions and determine score to assess the adverse drug reaction.

[c] An answer of "Do not know" = 0 score.

[d] From the total score, the adverse drug reaction is assigned a probability category: definite (greater than or equal to 9), probable (5 to 8), possible (1 to 4), doubtful (less than or equal to 0).

[e] Drug = proton pump inhibitor: omeprazole and esomeprazole.

[f] Although the detection of recurrent breast cancer raised the possibility of paraneoplastic Sweet's syndrome, the dermatosis remained in remission: (1) after withdrawal of the proton pump inhibitor and either systemic or topical corticosteroid treatment and (2) as the patient's CA153 tumor marker increased in association with the persistence of her antineoplastic therapy-treated metastatic malignancy.

[g] The patient received oral medications for neck pain and nausea following the initial episode of Sweet's syndrome without recurrence of the dermatosis: dilaudid, ibuprofen, and ondansetron.

her second episode within 6 hours after receiving a single dose of esomeprazole.

Naranjo et al developed a method for estimating the probability of adverse drug reactions [39]. They not only created and studied an adverse drug reaction probability scale (Table 1), but also found that their scale was reliable and valid for: (1) assessing a potential adverse drug reaction and (2) assigning a probability category. According to Naranjo et al's adverse drug probability scale, Sweet's syndrome developing as an adverse drug reaction induced by proton pump inhibitors would be assigned to a definite probability category in the reported patient (Table 1).

In summary, the temporal relationship between initially receiving a proton pump inhibitor and the onset of Sweet's syndrome suggests the possibility of a drug-induced etiology. The subsequent prompt recurrence of the dermatosis within hours after a non-intentional repeat challenge with a different proton pump inhibitor established the diagnosis of medication-associated Sweet's syndrome. The initial episode cleared after a short treatment course of oral corticosteroid and her recurrence resolved after stopping the proton pump inhibitor and topical treatment with a high potency corticosteroid cream. Although the detection of an unsuspected recurrence of her breast cancer with documented new metastatic disease to her stomach and bone raised the possibility of concurrent paraneoplastic Sweet's syndrome, the dermatosis remained in remission while her CA153 tumor marker increased and the antineoplastic therapy-treated metastatic tumor persisted.

Conclusion

Drug-induced Sweet's syndrome has been associated with antibiotics, antivirals, biotherapeutics, granulocyte growth factors, nonsteroidal anti-inflammatory drugs, psychotropes, vaccines, and other miscellaneous medications. Cancer-associated Sweet's syndrome had been observed in oncology patients with not only hematologic malignancies but also solid tumors; the dermatosis may be either idiopathic, medication-related or paraneoplastic. The reported patient, a woman with a history of treated breast cancer, had never previously taken any proton pump inhibitors; she developed Sweet's syndrome after initial exposure and subsequent repeat challenge to proton pump inhibitors. The first episode of Sweet's syndrome occurred 8 days after starting omeprazole and promptly cleared following the oral administration of corticosteroid whereas the second episode of the dermatosis erupted within hours after a single dose of esomeprazole and gradually resolved after initiating topical treatment with a high potency corticosteroid cream. The diagnosis of Sweet's syndrome, associated with her symptoms of gastroesophageal reflux disease, prompted additional studies that resulted in the unexpected discovery of metastatic breast cancer to her stomach and vertebrae. Therefore, in addition to drug-induced Sweet's syndrome associated with proton pump inhibitors (which was confirmed by rechallenging the patient with the same class of medication), the woman described in this report may also coincidentally have concurrent paraneoplastic Sweet's syndrome; however, her symptoms and lesions of Sweet's syndrome have not recurred and her metastatic breast cancer has persisted in spite of antineoplastic therapy.

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