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A striking presentation of pustular Sweet syndrome induced by trimethoprim-sulfamethoxazole

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The patient discussed gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Please print all figures in color.

Key words

Sweet Syndrome

Trimethoprim, Sulfamethoxazole Drug Combination

Drug eruptions

Drug hypersensitivity

Potassium Iodide

Neutrophils

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Abstract

We describe a strikingly robust presentation of trimethoprim-sulfamethoxazole (TMP-SMX)-induced pustular Sweet syndrome and discuss how to distinguish it from iododerma and other neutrophil-rich conditions. Review of the literature indicates that TMP-SMX-induced Sweet syndrome (SS) may have higher rates of neutrophilia and greater ocular, mucosal, and musculoskeletal involvement compared to SS from other drugs. Recognizing these features and identifying the offending agent are critical to correctly diagnosing TMP-SMX-induced SS in a timely manner.

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Introduction

Sweet syndrome (SS), also known as acute febrile neutrophilic dermatosis, is a hypersensitivity reaction characterized by tender, erythematous papules that may coalesce into edematous plaques and nodules with a pseudovesicular appearance. Histologically, it is characterized by a dense dermal neutrophilic infiltrate with variable edema. SS is classically triggered by infection, inflammatory bowel disease, pregnancy, or malignancy, but can also be drug-induced. In this report, we share a strikingly robust presentation of trimethoprim-sulfamethoxazole (TMX-SMX)-induced pustular SS and highlight the features of drug-induced Sweet syndrome (DISS). This report was deemed exempt by our institutional review board. The patient gave full consent to publish his medical information and photographs.

Case Report

A 53-year-old healthy male presented to the emergency department with a one-day history of scattered pustules that developed on the face and rapidly progressed to other areas of the body. Ten days prior to presentation, the patient had started TMP-SMX for a methicillin-resistant *Staphylococcus aureus*-positive abdominal furuncle, which had since resolved after incision and drainage. He had never taken TMP-SMX before and had no known drug allergies. He denied fever, chills, unexplained weight loss, arthralgias, chest pain, dyspnea, odynophagia, dysphagia, bloody stools, or diarrhea. He had no recent travel, sick contacts, exposure to iodinated contrast or other sources of iodine, history of renal insufficiency, malignancy, or immunodeficiency.

On evaluation, the patient was tachycardic (110 beats/minute), but afebrile and non-toxic in appearance. On the face, neck, and chest were pustules coalescing into clusters of purulent

nodules with central yellow-brown crusting, imparting a targetoid appearance (Figure 1A). The nodules were markedly edematous with erythematous rims. Smaller pustules with surrounding erythema and edema were scattered on the abdomen and upper and lower extremities. We noted coalescing pustules on his palate (Figure 1B), as well as yellow conjunctival drainage (Figure 1C). A square-shaped erythematous plaque studded with pustules was present on the abdomen, suggesting pathergy from an adhesive bandage (Figure 1D). Our differential diagnosis included SS, infection, iododerma, subcorneal pustular dermatosis (SPD), and IgA pemphigus. We also considered pyoderma gangrenosum and pemphigus vegetans.

Laboratory evaluation was remarkable for leukocytosis (19.4 K/ul) with neutrophilia (90.2%, Absolute Neutrophil Count 17.5 K/ul). A punch biopsy from a facial lesion revealed a robust, dermal neutrophilic infiltrate with numerous follicularly-based pustules and overlying intraepidermal spongiform pustules (Figure 2A and 2B). Special stains for microorganisms were negative. A second punch biopsy taken from the abdomen for tissue culture was negative for bacterial, mycobacterial, and fungal organisms. A third punch biopsy taken from perilesional abdominal skin for direct immunofluorescence was negative for immunoreactants.

Based on clinical and histological findings, we rendered a diagnosis of pustular SS secondary to TMP-SMX. We discontinued TMP-SMX and placed the patient on a 4-week prednisone taper starting at 1 mg/kg with rapid resolution of his cutaneous, oral, and ocular lesions. Artificial tears and prednisolone ophthalmic drops were used as needed.

Discussion

Drug-induced Sweet syndrome (DISS) is an uncommon subtype of SS, comprising less than 5% of cases.⁶ Granulocyte colony-stimulating factor (G-CSF) is the most common culprit, but other drugs have been implicated, including TMP-SMX.^{1,6} It may be challenging to distinguish DISS from other SS subtypes, as patients often have prior or concurrent infections or neoplastic disorders.¹¹

As observed in our patient, the distribution of skin lesions in DISS most often includes the upper extremities, trunk, face, and neck.¹¹ Pathergy, also observed in our patient, is a common feature.¹ Our patient's cutaneous morphology of crusted plaques and pustules is consistent with the neutrophilic dermal infiltration and overlying spongiform pustules seen on histology. In conventional (non-drug-induced) cases, pustular SS, in which pus-filled lesions are the predominant presentation, is a rare variant. It has been associated with ulcerative colitis (UC).^{1,7} Likewise, drug-induced pustular SS is rare. To our knowledge, in addition to our patient, there are five prior reports of TMP-SMX-induced DISS with pustular lesions.^{2,4,8-10} The presence of follicularly-based pustules was not noted in any of these reports, but has been mentioned in an isolated report of pustular SS associated with UC.⁷

Ocular involvement, which was observed in our patient, has been described in DISS.^{1,11} Bilateral conjunctivitis is the most common manifestation.¹¹ Oral mucosal lesions, also observed in our patient, and musculoskeletal involvement (e.g., arthralgias), have been reported in DISS.¹¹

Interestingly, the literature suggests that TMP-SMX-induced DISS tends to have greater ocular,

mucosal, and musculoskeletal involvement, compared with DISS induced by other medications.^{3,4,9-11} Further studies are necessary to confirm these observations.

Regarding time to onset of lesions from drug exposure, our patient's time to onset was 10 days, similar to that presented in a DISS case series (7.5 days).¹¹ While fever is classically considered one of the required diagnostic criteria for both classic SS and DISS,¹¹ a recent study reported fever in only 56% of its DISS cohort.⁵ Interestingly, although our patient was afebrile, most reported cases of TMP-SMX-induced DISS are associated with fever.^{2-4,8-11} In terms of laboratory abnormalities, peripheral leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate are common in classic SS.¹ Compared with classic (80%) or paraneoplastic (47-60%) SS¹, neutrophilia is reportedly less common in DISS (38%).¹¹ However, a review of the literature suggests that neutrophilia may be more common in TMP-SMX-induced cases, compared with other DISS cases.^{3,4,8,9,11}

Clinically, many of our patient's lesions were iododerma-like. Iododerma is another neutrophilic dermatosis, often presenting with pustular acneiform papules and vegetative plaques, as well as oral and ocular involvement. Histologically, it is characterized by variable epidermal hyperplasia with intraepidermal neutrophilic microabscesses and a dermal neutrophilic infiltrate.⁶ Iododerma may mimic pustular SS both clinically and histologically. To differentiate it from pustular SS, the patient must have known exposure to iodine, such as iodinated contrast, amiodarone, oral iodine supplements, or potassium iodide wound irrigation. Our patient lacked such exposures.

In addition to iododerma, the differential diagnosis for DISS includes infection, pustular vasculitis, and other neutrophilic dermatoses. Tissue culture for microorganisms can exclude infection. Histologic evidence of vasculitis suggests pustular vasculitis. Other considerations include acute generalized exanthematous pustulosis (AGEP), subcorneal pustular dermatosis (SPD), and pemphigus vegetans. AGEP does not usually present with large, crusted pustular nodules, but rather, pinpoint pustules on a background of erythema. While our patient's lesions appeared vegetative and might make one consider pemphigus vegetans, SPD and pemphigus vegetans usually present in intertriginous areas, with the latter demonstrating a pemphigus pattern with direct immunofluorescence testing. A final consideration is pyoderma gangrenosum which can start as follicularly-based pustules; however, compared with SS, lesions of pyoderma gangrenosum usually develop more slowly into ulcers with violaceous, undermined borders in typical locations, such as the legs.

Similar to other cases of DISS, our patient's lesions resolved rapidly with oral steroid treatment. Literature review suggests that there are no obvious differences in prognosis of pustular TMP-SMX-induced DISS, compared with DISS induced by other agents.^{2-6,8-11}

Conclusion

Trimethoprim-sulfamethoxazole is well known to cause cutaneous reactions such as morbilliform eruption, urticaria, fixed drug eruption, photosensitivity, SS, drug rash with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome. We wish to remind the clinician that, while rare, drug-induced Sweet syndrome may be secondary to TMP-SMX. It can have a florid clinical presentation with abrupt onset of cutaneous lesions that may

be pustular, mimicking iododerma and other neutrophil-rich conditions. Similar to conventional SS, it may be accompanied by fever and peripheral leukocytosis. In addition, ocular and mucosal involvement is not uncommon among TMP-SMX cases. Recognition of these features and identifying the offending agent are critical to correctly diagnosing TMP-SMX-induced DISS in a timely manner.

Abbreviations and Acronym List (in order of appearance)

Sweet Syndrome (SS)

Trimethoprim-sulfamethoxazole (TMX-SMX)

Drug-induced Sweet syndrome (DISS)

Subcorneal pustular dermatosis (SPD)

Immunoglobulin A (IgA)

Thousand per microliter (K/uL)

Milligram per kilogram (mg/kg)

Granulocyte colony-stimulating factor (G-CSF)

Ulcerative Colitis (UC)

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

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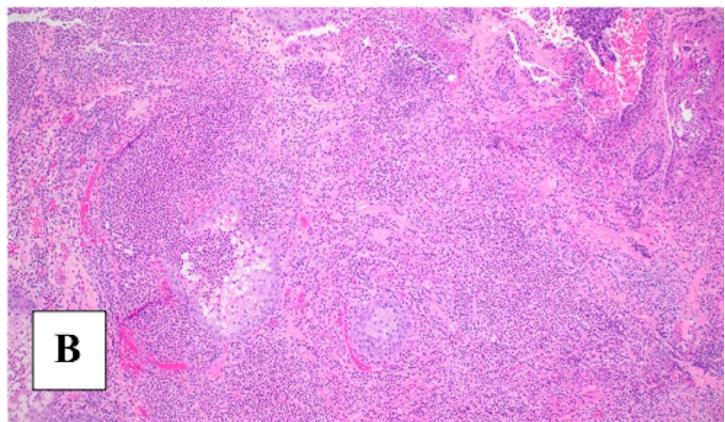
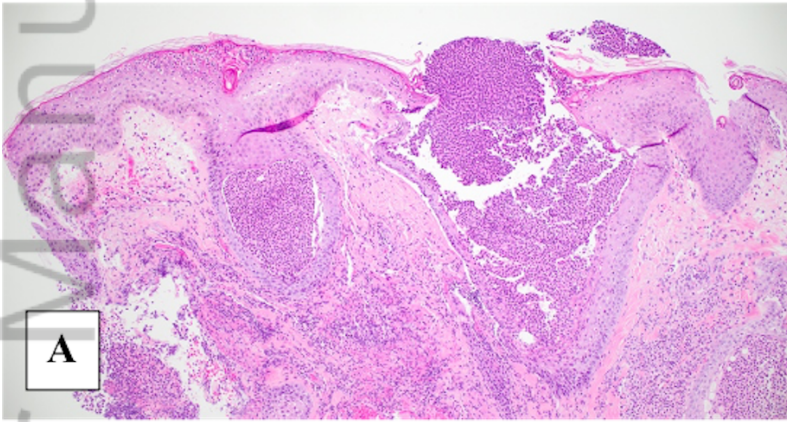
Figures Legends

Figure 1. Clinical presentation of a 53-year-old male with trimethoprim-sulfamethoxazole-induced pustular Sweet syndrome. A) Clusters of pus-filled, edematous papules and nodules with central crusting, imparting a targetoid appearance, especially on the face. B) Coalescing pustules on the palate. C) Yellow conjunctival drainage. D) A square-shaped erythematous plaque studded with pustules on the abdomen, consistent with pathergy from an adhesive bandage.

Figure 2. Histological findings in trimethoprim-sulfamethoxazole-induced pustular Sweet syndrome. A biopsy of lesional skin on the face demonstrated A) large follicularly-based pustules (hematoxylin-eosin, original magnification 100x) and B) dense diffuse dermal neutrophilic infiltrate (hematoxylin-eosin, original magnification 100x).



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