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REVIEW ARTICLE

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Atypical presentation of Sweet syndrome with nodular erythema and oral ulcerations provoked by Ad26.COV2.S SARS-CoV-2 vaccination and review of literature

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Abstract

The aim of this article is to present the case of acute febrile neutrophilic dermatosis (Sweet syndrome—SS) after Ad26.COV2.S vaccination against SARS-CoV-2. To the best of our knowledge, this is the second case of SS provoked by this specific vaccine. What is more, the mildly symptomatic beginning of the disease, later followed by typical SS manifestation with a variety of symptoms including nodular erythema of the feet and oral ulcerations, made it very challenging to establish the diagnosis. The article focuses on the current literature on the acute febrile neutrophilic dermatosis, along with the coexistence with other neutrophilic dermatoses and anti-SARS-CoV-2 vaccinations as provoking factors. It emphasizes the necessity for sharing the knowledge and experience on the subject of SS's clinical manifestations and underlying causes to facilitate prompt diagnosis and introduction of appropriate treatment.

KEYWORDS

acute febrile neutrophilic dermatosis, erythema nodosum, oral ulcerations, Sweet syndrome, vaccination

1 | INTRODUCTION

Acute febrile neutrophilic dermatosis (Sweet Syndrome—SS) is a prototoplast of neutrophilic dermatoses, characterized by an infiltrate of polymorphonuclear leukocytes in the skin, however the extracutaneous localizations may be encountered. This autoinflammatory disease, described for the first time in 1964 by Sweet, was defined by painful erythematous edematous plaques with a presence of systemic symptoms.[1] The first diagnostic criteria for classical SS were proposed by Su and Liu in 1986,[2] then modified by Driesch in 1994.[3] The diagnosis is currently established on meeting diagnostic criteria: two major (abrupt onset of painful erythematous plaques or nodules; histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis) and at least two out of four minor criteria (pyrexia >38°C; association with an underlying hematological or visceral malignancy, inflammatory disease, or pregnancy, or preceded by an upper respiratory or gastrointestinal tract infection or vaccination; excellent response to systemic corticosteroids or potassium iodide; elevation of three of the four laboratory values: erythrocyte sedimentation rate >20 mm/h, positive C-reactive protein, leukocyte count >8000 G/L, neutrophils >70%). However, the second major criterium raises controversies, since many cases of SS with vasculitis were described since the publication of the criteria. Some authors suggest that the presence of vasculitis in histopathologic examination should not exclude the diagnosis of SS.[4] In 1996 criteria for drug-induced SS were introduced by Walker and Cohen.[5] SS is most often described in females aged between 30 and 60 years, however, it can occur at any age.

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2 | CASE PRESENTATION

A 44-year-old female without any concomitant diseases, referred from Emergency Department, was admitted to Dermatology, Sexually Transmitted Diseases and Clinical Immunology Clinic for a febrile mucous and skin eruption. The first symptoms occurred 2.5 months prior to the admission and included sore throat and painful lesions within the oral mucosa. The patient was treated with topical antiseptics, antifungals, and NSAIDs, as well as systemic antibiotics and antifungals—without remission. Five days before the hospitalization, the patient additionally developed fever (up to 38.9°C), pain of the joints and muscles, painful nodular erythema (Figure 1A) of the feet and scattered skin lesions within the limbs.

The physical examination revealed tender purulent vesicles and well demarcated edematous plaques consisting of papules and vesicles on the limbs (Figure 1B,C). In the oral cavity erosions on the sides of the tongue and in the vestibule were present and the tongue was covered with yellowish coating (Figure 2A–C). In the laboratory results the C-reactive protein (CRP) level was 92 mg/dl, white blood cell count (WBC) was 9.72 $\times$ 10^3/μl with neutrophilia 87.1%. The patient also suffered from mild microcytic anemia. Infectious causes were excluded prior to admission. The cultures (pustule, oral cavity and urine) were negative. The skin biopsy was taken from edematous plaque and nodular erythema of the feet. The histopathologic report confirmed the diagnosis of SS (acute febrile neutrophilic dermatosis).

The possible neoplastic causes were examined (CA 125, CEA, CA 19-9, CA 15-3), not revealing any abnormalities. Low level of β-hCG excluded pregnancy. HIV, lupus anticoagulant, pANCA, cANCA, anticardiolipin antibodies were negative. Antinuclear antibodies titer occurred to be 1:640, however immunoblot was negative. Direct immunofluorescence has not revealed any pathologic deposits. Thorough examination of medical history of the patient led to the conclusion that the disease was triggered by Ad26.COV2.S SARS-CoV-2 vaccination (Johnson & Johnson, Janssen) taken 7 days prior to the first symptoms. The patient was treated with oral prednisone 0.6 mg/kg/day and intravenous doxycycline 200 mg/day. The pain was relieved with s.c. tramadol 200 mg/day and 3% ichthyol solution was applied topically on nodular erythema. After 3 days of treatment there was a spectacular improvement in terms of both signs and symptoms, which additionally confirmed the diagnosis. Therefore, the patient met two major and four minor diagnostic criteria of SS.[3] An informed consent on publication of anonymized description of the case was obtained from the patient.

3 | DISCUSSION

The history of neutrophilic diseases started with a first description of an acute febrile neutrophilic dermatosis in 1964.[1] Sweet presented series of eight patients with skin lesions resembling erythema

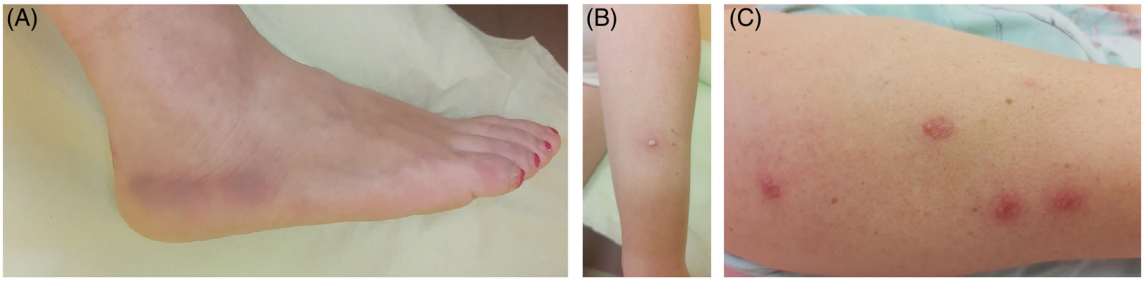

FIGURE 1 The manifestations of Sweet syndrome on the limbs. (A) Painful nodular erythema of the feet. (B) Pustule on the upper limb. (C) Edematous plaques on the upper limb

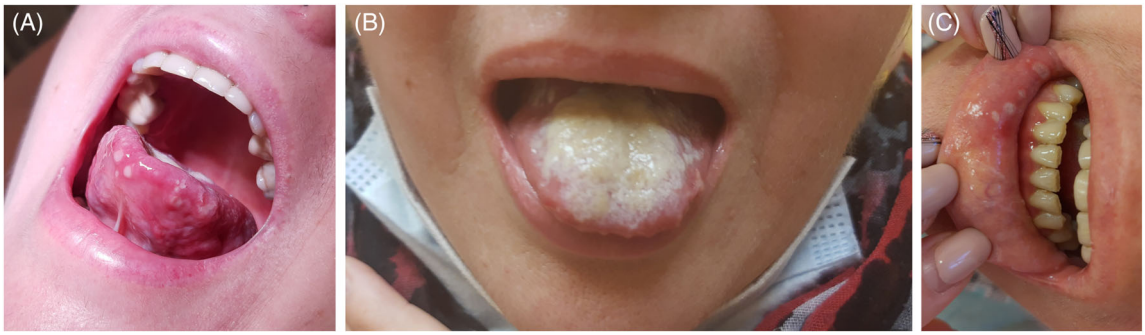

FIGURE 2 The manifestations of Sweet syndrome in the oral cavity. (A) Ulcerations on the sides of the tongue. (B) Yellowish coating of the tongue. (C) Ulcerations in the vestibule of the oral cavity

multiforme located on the face, neck and limbs. They were characterized by dense neutrophil infiltration in the dermis, the presence of fever and lack of infection. Over the years, the spectrum of the symptoms of SS occurred to be much wider—erythema nodosum-like nodules on the limbs, oral ulcerations, arthralgia, myalgia (all present in the described case), erythematous, edematous plaques, pustules, bullae, as well as nausea, diarrhea, headache, and other neurological symptoms.[6–11] In rare cases of SS, myocardium may be involved.[12]

Over the years, numerous new clinical variants were described: necrotizing SS, cellulitis-like SS, generalized pustular SS, subcutaneous SS as well as novel histological variants: histiocytoid-like, cryptococcoid, eosinophilic, lymphocytic and normolipemic xanthomized SS.[11] In 1999 the term "Neuro-Sweet Disease" was proposed for a variant with recurrent neurologic symptoms.[13] Considering extracutaneous involvement—ophthalmological, pulmonary, coronary, gastrointestinal, muscular, otorhinolaryngological symptoms were reported.[11,14]

There has been a considerable number of descriptions of coexisting different diseases from the spectrum of neutrophilic dermatoses, especially in light of rare occurrence of these conditions.

As soon as in 1983, a concomitant pyoderma gangrenosum (PG) and SS were described.[15] Another disease from the spectrum of neutrophilic dermatoses, neutrophilic dermatosis of the dorsal hands (NDDH) is a localized variant of SS.[16] However, in case of PG localized on the dorsa of the hands it might be impossible to distinguish between these two entities.[17] The presence of clinical manifestations of SS and erythema nodosum was reported by few authors.[6] Evans et al. reports a case of overlapping SS and erythema elevatum diutinum with necrotizing periodontitis.[18] There is a discussion whether rheumatoid neutrophilic dermatosis is a form of SS with extracutaneous involvement or a different entity.[19] Wilson et al. presents a case of a patient with rheumatoid arthritis who developed PG, Sweet's syndrome and pustular vasculitis (however, not simultaneously).[20] The analysis of biopsy specimens taken from patients with SS led to the conclusion that vasculitis can be present in case of longer course of the disease and should not exclude the diagnosis of acute febrile neutrophilic dermatosis.[21] The literature mentions also coexistence of SS and Behçet's disease, and subcorneal pustular dermatosis, aseptic abscesses syndrome and neutrophilic eccrine hidradenitis.[22–25]

Having the longest history among neutrophilic dermatoses, SS has been associated with many triggering factors. Some authors distinguish three subtypes of the dermatosis—*classical*, *malignancy-associated*, and *drug-induced SS*.[14,26] The classical one is related to upper respiratory tract and gastrointestinal infections, pregnancy, inflammatory bowel disease (IBD).[27] It may be also associated with common variable immunodeficiency (CVID).[28] Among the most commonly described causes of malignancy-associated SS are hematologic neoplasms like acute myeloid leukemia and myelodysplastic syndrome, but also large B-cell lymphoma, Hodgkin lymphoma, and others like clonal hematopoiesis of indeterminate potential and solid tumors of a gastrointestinal tract, breast, or testicular carcinoma.[14,29] In some cases SS precedes the malignancy, thus acts as a paraneoplastic syndrome. The medications causing the onset of the disease are very often anti-cancer agents: granulocyte-colony stimulating factor (G-CSF), bortezomib, azacitidine, decitabine, but also other drugs—antibiotics: minocycline, trimethoprim-sulfamethoxazole, antiepileptics: carbamazepine, diazepam, and others.[11] Additionally, drug-induced variant may be provoked by vaccinations: pneumococcal, influenza, BCG, smallpox, SARS-CoV-2, and others.[30–35]

Due to the large number of patients vaccinated in the last 2 years, respectively many adverse effects were observed. Among them, SS cases were reported after vaccination with agents of different companies (Table 1). The search in Google Scholar and Medline/PubMed databases was conducted using combinations of keywords including "SS," "acute febrile neutrophilic dermatosis," "neutrophilic," "COVID," "SARS-CoV-2," "coronavirus," "vaccine," and "vaccination." No restriction was applied to the time range and to the type of the article included.

Fourteen cases of SS provoked by SARS-CoV-2 vaccinations were identified. Most of them occurred after Pfizer-BioNTech (6) and AstraZeneca/Vaxzevria (4), only one case of SS was reported after both Moderna and Sinovac. Among the identified cases four reports include classical acute febrile neutrophilic dermatosis without any additional symptoms.[31,36,37,46] Seven publications describe wide spectrum of coexistent conditions concerning musculoskeletal system:

TABLE 1 Case reports of Sweet syndrome provoked by SARS-CoV-2 vaccinations

Type of vaccine	Description of the case	Number of cases
BNT163b2 (Pfizer-BioNTech)	1. Three cases of classical Sweet syndrome[31,36,37] 2. Sweet syndrome with phalanges' pain and dysesthesias[38] 3. Cellulitis-like Sweet syndrome[39] 4. Necrotizing Sweet Syndrome[40]	6
AZD1222/ChAdOx1 nCoV-19 (AstraZeneca, Vaxzevria)	1. Sweet syndrome with arthritis, pitting edema, muscle weakness and neuropathic foot pain[32] 2. Two cases of Sweet syndrome with joints' pain[41,42] 3. Bullous Sweet Syndrome[43]	4
mRNA-1273 (Moderna)	1. Acute encephalitis, myoclonus and Sweet syndrome[44]	1
Ad26.COV2.S (Janssen)	1. Generalized Sweet syndrome with vasculitis and transient IgA monoclonal gammopathy[45] 2. Sweet syndrome with nodular erythema of the feet and oral ulcerations (this report)	2
CoronaVac (Sinovac)	1. Classical Sweet syndrome[46]	1

joint pain and arthritis, muscle weakness and pain, myoclonus; nervous system: dysesthesias, neuropathic pain, acute encephalitis.[32,38,41,42] The skin and mucous membranes involvement not typical for classical SS was also reported: pitting edema, nodular erythema of the feet and oral ulcerations.[32] What is more, Janssen vaccination has been linked to generalized SS with vasculitis and transient IgA monoclonal gammopathy.[45] Other types of reported acute febrile neutrophilic dermatosis comprise cellulitis-like SS and bullous SS.[39,43] In the latest publication concerning acute skin reaction after Pfizer-BioNTech vaccine included in this review, the authors settle the diagnosis of neutrophilic dermatosis with necrobiotic changes.[40] However, the patient meets the diagnostic criteria for SS, therefore this case was incorporated into the analysis.

Apart from the case presented in the article, there is only one description of SS, triggered by Janssen Ad26.COV2.S vaccine. It was accompanied by vasculitis and transient IgA monoclonal gammopathy and occurred 9 days after the administration.[45] Of note, both vaccination and SARS-CoV-2 infection may provoke SS.[47]

The pathogenesis of neutrophilic diseases still is still not fully understood. In terms of pathogenesis, the available data points to elevated levels of IL-1a, IL-1b, IL-2, IL-6, IL-8, IL-17, TNF-α, and interferon-γ as well as to increased expression of CD3 (T cell marker), CD163 (macrophage marker), vascular endothelial growth factor, Toll-like receptors, C-type lectin innate immunity receptors.[48] Apart from elevated levels of cytokines and markers, impaired neutrophil function may be observed in SS.[49] The literature highlights the role of genetic predisposition to neutrophilic diseases, namely human leukocyte antigen HLA-B54.[50] Mutations in the MEFV gene were also identified in SS.[51] In case of drug induced SS, the most common factor, granulocyte-colony stimulating factor, in straightforward manner induces neutrophils.[11] Other agents activate these white blood cells via various mechanisms. Further research is necessary to fully explain the mechanisms behind neutrophilic diseases.

The management of the patients with SS requires the exclusion of infectious diseases and thorough examination in search of extracutaneous manifestation as well as underlying causes. In treatment of SS, most authors report excellent response to the systemic corticosteroids, however, depending on concomitant diseases potassium iodide, dapsone, colchicine, indomethacin, clofazimine, rituximab, tumor necrosis factor α inhibitors and others are successfully applied.[11] However, neutrophilic dermatoses lack appropriate guidelines and recommendations in terms of management of the patient due to insufficient data.

4 | CONCLUSIONS

The article presents the second known case of SS after Janssen Ad26.COV2.S vaccine and the 14th case of SS after anti-SARS-CoV-2 vaccine.

The described clinical case of SS depicts a wide range of skin and mucous lesions that may be present in acute febrile neutrophilic dermatosis (nodular erythema, edematous plaques, pustules, and erosions in oral cavity), yet its initial picture limited to mucous membranes, made it very challenging to settle the diagnosis.

Early diagnosis of SS is of great importance—it allows to avoid incorrect treatment and associated adverse effects, especially due to the fact that the proper therapy leads to very quick resolution of the skin changes.

What is more, the possible causes should be thoroughly examined—in the first place a neoplastic disease should be excluded. In case of drug-related SS, the patient is able to avoid future exposition, knowing the trigger factor. Together with introduction of new drugs and new vaccines, its adverse events should be researched and described in detail.

Of note, some of the conditions should be taken into consideration both in differential diagnosis and as a trigger factor, which makes the management of the disease even more demanding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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