EJCRIM
European Journal
of Case Reports
in Internal Medicine

ACUTE ONSET OF BULLOUS SKIN RASH AND ACUTE KIDNEY INJURY AFTER EXPOSURE TO RADIOCONTRAST: SWEET'S SYNDROME

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Received: 26/01/2023 **Accepted:** 11/02/2023 **Published:** 13/03/2023

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Verbal and written consent was obtained from the patient to publish their case.

How to cite this article: Abdelnabi M, Cavazos A, Thongpiya J, Pruneda C, Yingchoncharoen P, Sullivan S, Davalos J, Tarbox M. Acute onset of bullous skin rash and acute kidney injury after exposure to radiocontrast: Sweet's syndrome. *EJCRIM* 2023;**10**:doi:10.12890/2023_003781.

ABSTRACT

Sweet's syndrome or acute febrile neutrophilic dermatosis is characterized by an acute inflammatory skin eruption of oedematous and erythematous papules, plaques or nodules, accompanied by fever, and leucocytosis with possible extracutaneous involvement. Aetiologies include infections, inflammatory bowel disease, pregnancy or malignancy, or the syndrome may be drug-induced by many classes of medications or very rarely, radiocontrast exposure. Herein, the authors report a case of radiocontrast-induced bullous Sweet's syndrome and contrast-induced acute kidney injury in a woman in her 60s with a complex medical history.

KEYWORDS

Sweet's syndrome, acute febrile neutrophilic dermatosis, radiocontrast-induced, drug-induced, acute kidney injury, oesophageal ulcers

LEARNING POINTS

- Patients with Sweet's syndrome (SS) typically present with acute-onset fever, leucocytosis, and erythematous, tender plaques with dense neutrophilic infiltration in the dermis. The condition is classified into three subtypes: classic SS, malignancy-associated SS, and drug-induced SS.
- Drug-induced SS is characterized by an abrupt onset of a painful erythematous rash, dense neutrophilic dermal infiltrate without vasculitis, a temporal relationship between exposure and onset, and resolution of symptoms after drug discontinuation and/or corticosteroid therapy.
- Treatment options include systemic corticosteroids as first-line therapy, while colchicine, dapsone, indomethacin, naproxen, clofazimine, ciclosporin, α-interferon, and potassium iodide may be considered as second-line therapies in cases resistant to corticosteroids.

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INTRODUCTION

Sweet's syndrome (SS) or acute febrile neutrophilic dermatosis is characterized by fever, leucocytosis with neutrophilia, and skin lesions including painful erythematous papules, nodules, and plaques caused by infiltration of neutrophils in the dermis. It can be classified into classic or idiopathic, malignancy-associated, and drug-induced SS[1]. Herein, the authors report a case of radiocontrast-induced bullous SS and contrast-induced acute kidney injury in a woman in her 60s with a complex medical history.

CASE DESCRIPTION

A 67-year-old woman with a medical history of hypertension, hyperthyroidism, myelodysplastic syndrome, and pyoderma gangrenosum presented for evaluation of acute onset of skin rash, 24 hours after she had undergone computed tomography (CT) scans for further evaluation of conditions associated with pyoderma gangrenosum. Upon evaluation, she complained of a progressive, painful, bloody skin rash that had started in her mouth and face and spread to her chest, arms, and legs, and which did not respond to topical emollients or topical steroids. She also complained of worsening heartburn and decreased urine output over the past 24 hours. On clinical examination, her vital signs were unremarkable with a temperature of 36.8°C, a pulse of 108/minute, blood pressure of 101/70 mmHg, respiratory rate of 16 per minute, and oxygen saturation of 98% on room air. Skin examination was significant for numerous, juicy papules with potential vesiculation, and tender haemorrhagic bullae affecting over 50% of the bilateral upper extremities with scattered foci affecting the trunk, lower extremities (inner thighs), mouth, and face *(Fig. 1)*. Laboratory work-up was unremarkable except for normocytic normochromic anaemia with a haemoglobin of 9 g/dl (normal 12.1–15.1) and acute kidney injury with a blood urea nitrogen level of 94 mg/dl (normal 6–21), creatine level of 4.9 mg/dl (normal 0.5–1.2), and potassium level of 6.2 mmol/l (normal 3.5–5.1). Based on the history, clinical course, and physical findings, bullous SS versus the less likely toxic epidermal necrolysis was the main differential diagnosis.

The patient underwent two 4 mm punch skin biopsies from her right upper arm. The skin biopsy samples showed diffuse neutrophilic dermatosis in the dermis. No vasculitis was noted, and the infiltration was not cantered on follicles. No organisms were seen with routine staining. Direct immunofluorescence of IgG, IgA, IgM, and C-3 tested uniformly negative, consistent with SS *(Fig. 2)*. A diagnosis of radiocontrast-induced bullous SS was made and the patient was started on methylprednisolone 80 mg IV daily and 0.05% clobetasol ointment twice daily. Her hospital course was complicated with worsening kidney injury due to contrast-induced acute kidney injury requiring renal replacement therapy. Also, she had an episode of haematochezia for which esophagogastroduodenoscopy (EGD) and colonoscopy were performed, revealing a few superficial oesophageal ulcers with the largest measuring 4 mm in the proximal esophagus *(Fig. 3)* and a few 3 mm ulcers in the rectum with no active source of bleeding *(Fig. 4)*. Biopsy results showed superficial mild and chronic inflammation with vascular congestion and focal erosion without dysplasia. The patient's condition eventually resolved, with a gradual improvement in her skin lesions after 48 hours of corticosteroid therapy. She was discharged with a tapering dose of oral prednisone therapy.

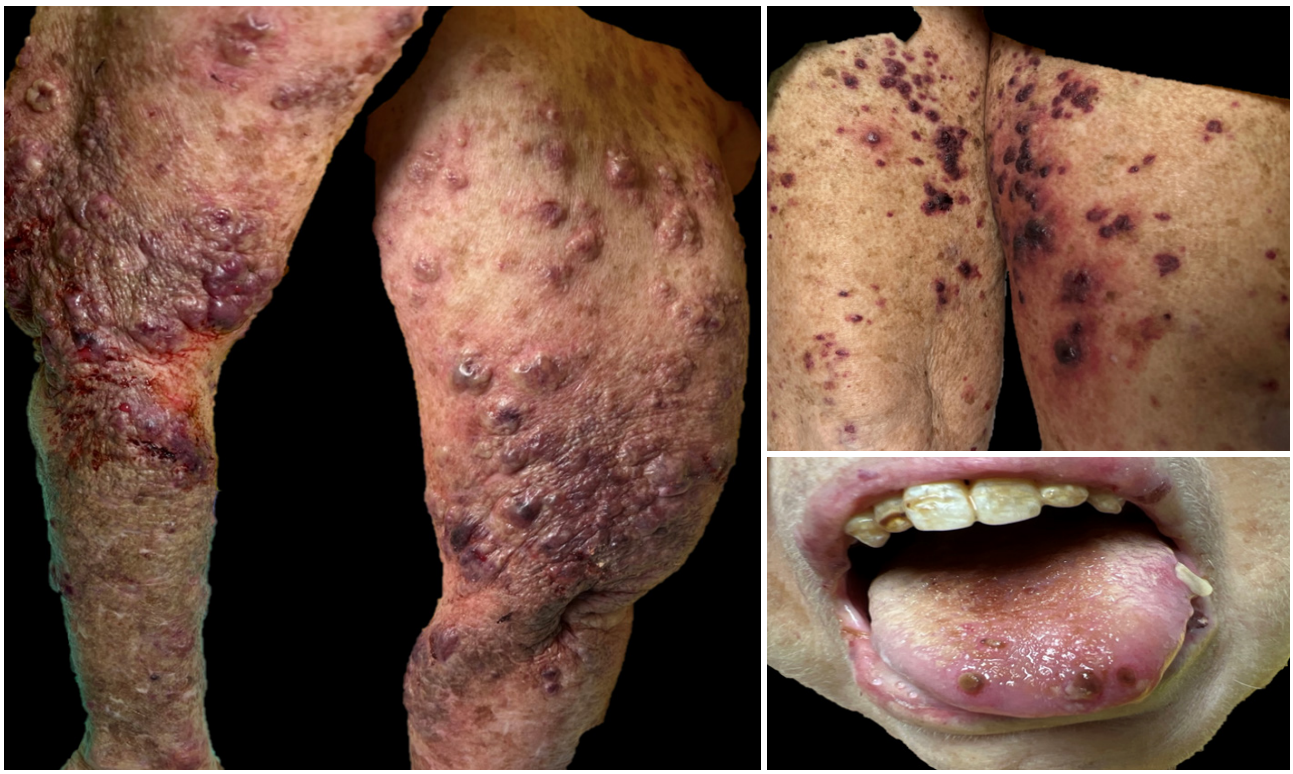

Figure 1. Tender haemorrhagic bullae on both arms, inner thighs, and mouth

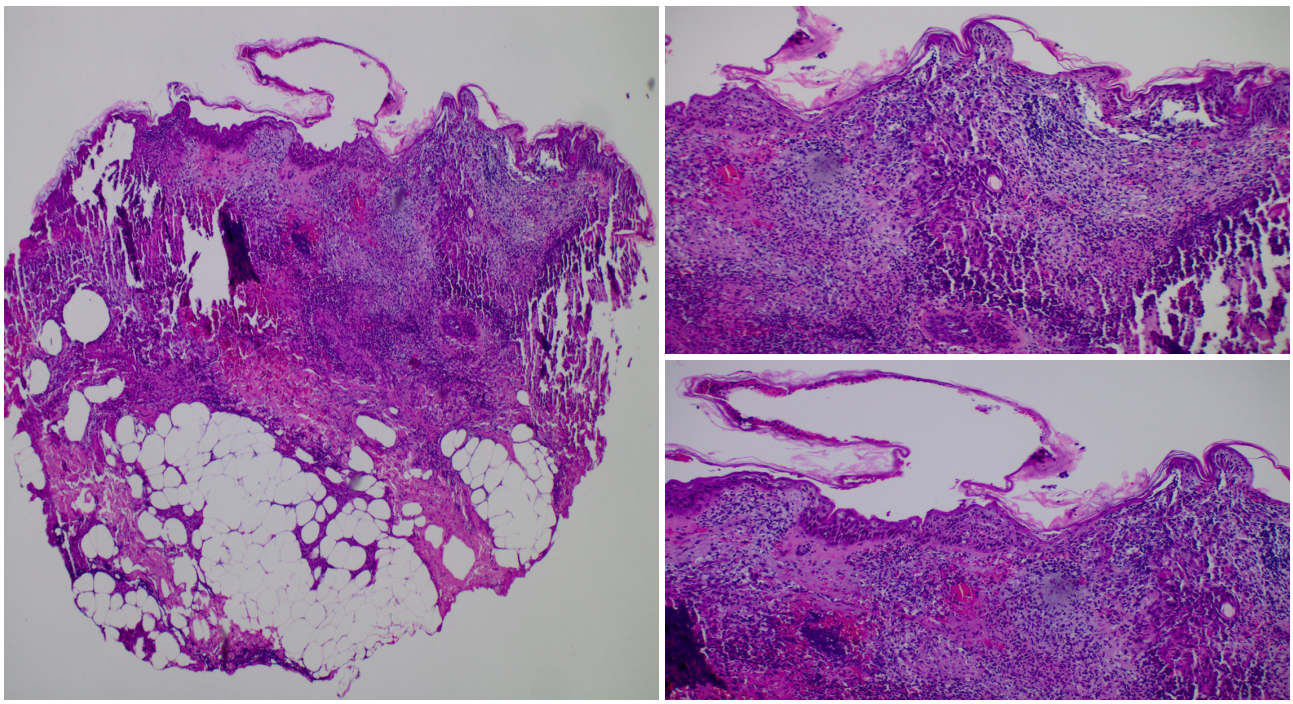

Figure 2. Skin biopsy showing diffuse neutrophilic infiltration in the dermis with no evidence of leukocytoclastic vasculitis, consistent with Sweet's syndrome

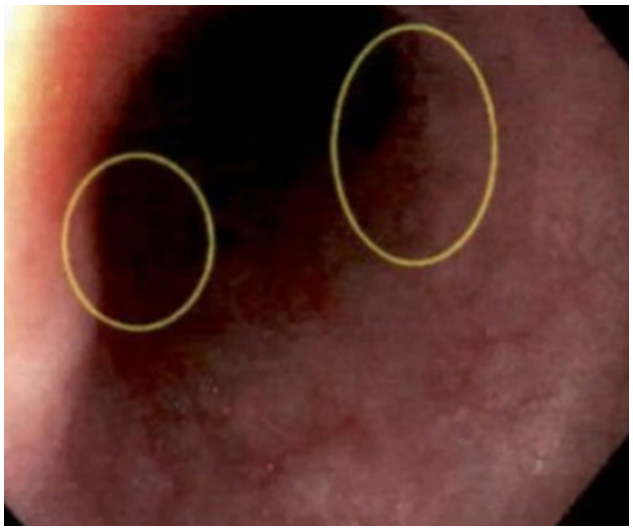

Figure 3. Esophagogastroduodenoscopy showing oesophageal ulcers (marked by circles)

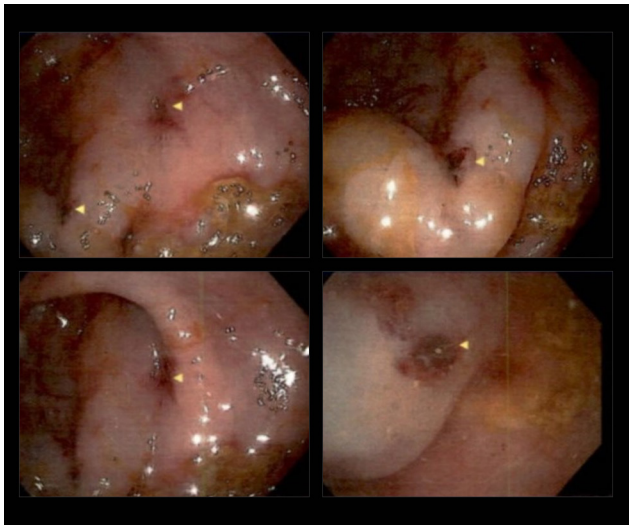

Figure 4. Colonoscopy showing rectal ulcers (marked by arrowheads)

DISCUSSION

Skin manifestations related to sensitivity to radiocontrast agents are relatively common and include acute or delayed urticaria, morbilliform rash and Stevens-Johnson syndrome, while SS, originally described as 'acute neutrophilic dermatosis', has rarely been reported as a complication following radiocontrast exposure. Neutrophilic dermatoses are a group of disorders characterized by skin lesions, histological examination of which reveals intense epidermal, dermal or hypodermal infiltrates composed primarily of neutrophils with no evidence of infection, or true vasculitis including SS, pyoderma gangrenosum, neutrophilic eccrine hidradenitis and Behçet's disease[2]. Each disease is distinguished by disease chronicity, tissue involvement, and clinical appearance, but there is some overlap in disease pathophysiology.

Classic SS is responsible for most cases, although drug-induced SS is not uncommon[3]. The most frequently reported drug associations are with granulocyte-colony stimulating factor (G-CSF), azathioprine, and all-trans retinoic acid (ATRA)[4]. The diagnostic criteria for drug-induced SS include: (a) abrupt onset of painful erythematous plaques or nodules; (b) histopathological evidence of dense neutrophilic infiltrates without evidence of leukocytoclastic vasculitis; (c) pyrexia >38°C; (d) a temporal relationship between exposure and clinical presentation; and (e) temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids[1]. Fever is considered the most frequent clinical sign of SS and may even precede skin lesions, but it can be absent in 10–20% of cases. Gastric ulcers have been previously reported in conjunction with Sweet's syndrome, and in this setting, contrary to typical gastric ulcers, systemic steroids may improve the skin, oral mucosa, and gastric mucosa[5]. Neutrophilia can be seen in drug-induced SS but is more common in idiopathic SS.

Author (year)	Alper et al., 2008[7]	Fok et al., 2014[8]	Bhat et al., 2018[9]	Abdelnabi et al., 2023 (this case)
Sex/age	Male/77	Male/78	Male/73	Female/67
Comorbidities	Diabetes mellitus, hypertension	Hypertension, chronic kidney disease, diabetes mellitus, hypothyroidism	Antineutrophil cytoplasmic antibody vasculitis, end-stage renal disease	Hypertension, hyperthyroidism, myelodysplastic syndrome, pyoderma gangrenosum
Onset after radiocontrast exposure	8 hours	16 hours	24 hours	24 hours
Fever	Present	Present	Present	Absent
Leucocytosis	Present	N/A	Present	Absent
Neutrophilia	Present	N/A	N/A	Absent
Morphology	Well-demarcated reddish plaques with vesicles and flaccid bullae filled with colourless fluid and superficial erosions	Dark purplish nodules, followed by blisters	Bullous haemorrhagic rash	Numerous, juicy papules with potential vesiculation and haemorrhagic bullae
Distribution	Trunk and proximal limbs	Scalp, followed by palms and fingers	Face, neck, chest and back	Bilateral upper extremities, trunk, lower extremities, face and mouth
Skin biopsy results	Marked oedema in the papillary dermis and a dense dermal infiltrate of neutrophils intermixed with a few eosinophils. A subcorneal cleft filled with neutrophils was present in the upper epidermis.	Heavy dermal neutrophil infiltration with superficial dermal oedema and early vesicle formation in the papillary dermis. The epidermis was acanthotic and hyperkeratotic with focal spongiosis. Eosinophils and dermal microabscesses were not seen.	Neutrophils admixed with nuclear debris and collagen degeneration spanning throughout the dermis with focal degeneration and separation of the epidermis from the underlying papillary dermis	Diffuse neutrophils in the dermis without vasculitis. The infiltrate was not centred on follicles. Negative direct immunofluorescence of IgG, IgA, IgM and C-3
Treatment	Hydrocortisone 100 mg and chlorpheniramine 2 mg and supportive care	Prednisolone 50 mg	High-dose prednisone 40 mg/day for 1 week	Methylprednisolone 80 mg IV daily with oral prednisone taper
Response	Marked improvement at 12 hours	Marked improvement on the second day of treatment	Complete resolution within 48 hours	Marked improvement

Table 1. Summary of contrast-induced Sweet's syndrome cases

Many pathophysiological mechanisms have been proposed to explain SS. First, high levels of cytokine involvement (specifically G-CSF) promote neutrophil proliferation and maturation, and further inhibit neutrophil apoptosis as in the many cases of SS reported after the initiation of G-CSF therapy. Second, additional dysfunctional immune mediators including the adaptive immune system (specifically type 1 helper T cells with their cytokines) have been recognized as facilitating neutrophil migration and localization in the dermis. Last, exposure to stimuli causes an immune reaction to drugs and results in a cytokine cascade resulting in SS that responds to corticosteroids[3,6]. To date, only three other cases with similar presentations of radiocontrast-induced SS have been reported; these are summarized in *Table 1*[7–9].

Treatment for drug-induced SS consists of the administration of topical or systemic corticosteroids together with withdrawal of the drug. The average time until skin lesions improved with systemic treatment was 8 days. The time for clinical improvement with topical treatment varied from 3 to 30 days. In rare cases of corticosteroid failure, alternative therapies such as colchicine, dapsone, indomethacin, naproxen, clofazimine, ciclosporin, α-interferon, and

Question	Yes	No	Don't know	Score
1. Are there previous conclusive reports on this reaction?	Yes			+1
2. Did the adverse event appear after the suspected drug was administered?	Yes			+2
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	Yes			+1
4. Did the adverse reaction reappear when the drug was readministered?			Don't know (since the drug was not readministered)	0
5. Are there alternative causes (other than drug) that could on their own have caused the reaction?		No		+2
6. Did the reaction reappear when a placebo was given?			Don't know (a placebo was not given)	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?			Don't know (concentration was not measured but could be elevated since the patient presented with acute kidney injury)	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?			Don't know (radio-contrast was only given once)	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?		No		0
10. Was the adverse event confirmed by any object of evidence	Yes			+1
Total score				**+7**

Table 2. Adverse Drug Reaction Probability Scale

potassium iodide may be utilized. Recurrence is uncommon in drug-induced SS after discontinuation of the medication[4]. The authors have presented a case of radiocontrast-induced bullous SS and contrast-induced acute kidney injury in a woman with a complex medical history. There was a direct temporal relationship between contrast exposure and the abrupt onset of bullous skin lesions. A review of her medications showed she had not been previously exposed to any drugs associated with SS. Local bacterial infection of her skin lesions was also ruled out by negative tissue cultures. De novo or recurrent malignancies such as haematological malignancies or solid tumours such as adenocarcinoma[1] were excluded by negative CT scans. A skin biopsy confirmed the diagnosis and the skin lesions improved with corticosteroid therapy and discontinuation of the offending agent. The Adverse Drug Reactions Probability Scale[10] score was 7, indicating a probable association between exposure to radiocontrast and the onset of SS *(Table 2)*. However, there were some limitations to this calculation as applied to our patient since some of the parameters could not be tested, such as whether the adverse reaction reappeared if the contrast was readministered or with placebo, whether the adverse reaction was more or less severe with higher or lower doses, or whether it was detected in known toxic concentrations. Consequently, the score might have been falsely low; nevertheless, our patient met all five diagnostic criteria for drug/contrast-induced SS[11].

CONCLUSIONS

This report has described a case of radiocontrast-induced haemorrhagic bullous SS associated with contrast-induced acute kidney injury. History, clinical examination with abrupt onset of a painful erythematous rash, dense neutrophilic dermal infiltrate without vasculitis after drug/contrast exposure, and resolution of symptoms after urgent cessation and early initiation of high-dose steroids all suggested a diagnosis of SS.

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