ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

SCIENTIFIC-CLINICAL LETTER

[Translated article] Giant Cellulitis-like Sweet Syndrome: Contribution of a New Case and Medical Literature Review

Síndrome de Sweet tipo celulitis gigante: aporte de un nuevo caso y revisión de la literatura

To the Editor,

A 53-year-old male with a past medical history of hypertension, gout, obesity, and prior endoscopic ureteral lithotripsy consulted for painful skin lesions localized over the entire left thigh, ipsilateral flank and buttock, and the lumbosacral region. He reported having a fever and general malaise. Over the past 6 years, he had experienced similar episodes in the same location lasting 3 up to 7 days. Over the past 2 years, the outbreaks recurred every 4 to 8 weeks. Although, at times, he had been treated with systemic antibiotics due to suspected infectious cellulitis, this had no impact on the course of the disease. He said he did not have any other symptoms, constitutional syndrome, relevant family history, or association with drug intake. He did not meet any other criteria for familial Mediterranean fever either.

Upon examination, a large, well-demarcated, indurated, warm and painful erythematous plaque was revealed covering the above-mentioned areas (fig. 1A and B). A blood test revealed the presence of leukocytosis (11.98 x 10^9/L), neutrophilia (9.6 x 10^9/L; 80%), and an elevation of C-reactive protein (196 mg/L). Other blood tests during remission periods showed no elevation in acute phase reactants. The remaining tests (tumor markers, autoimmunity, or serologies) revealed no significant findings.

Histological examination of a biopsy taken from the affected area (fig. 1C-E) revealed the presence of skin with mild papillary edema and superficial and periadnexal perivascular lymphocytic inflammation, also with the presence of neutrophils. No vasculitis or leukocytoclastic phenomena were reported. Although histology proved atypical, the clinicopathological correlation suggested the diagnosis of giant cellulitis-like Sweet syndrome (GCSS).

Initial treatment with oral corticosteroids and colchicine proved ineffective. Dapsone at a dose of 50 mg daily was then administered, resulting in excellent control of the outbreaks. After gradually tapering the dose over a 9-month period, treatment was eventually discontinued. To date, no new outbreaks have occurred, and no associated comorbidities have appeared. An endoscopic ureteral lithotripsy—laterality consistent with the lesions—performed 1-2 months before symptom onset could have acted as a trigger.

Multiple clinical and histological variants of Sweet syndrome (SS) have been described to date. Surovy et al. described a rare variant in 2013, which they called ''GCSS''.[1] In our review (Pubmed/other sources), we found 9 articles and 1 poster, representing an exceptional SS subtype (Table 1).[1–9] The articles report on 9 women and 4 men (N = 13) aged between 36 and 90 years (median, 62). Notable past medical histories include the presence of neoplasms and obesity. Possible triggers described include hematological and solid organ neoplasms, trauma, or bacterial infection.

Disease is characterized by outbreaks—lasting days to weeks—featuring large, confluent, well-demarcated erythematous-edematous plaques, associated with fever and general malaise. Lesions can be warm, painful, and pruritic. They may begin in a localized area and then spread locally or affect multiple areas. Initially, lesions can mimic bacterial cellulitis, so patients are sometimes hospitalized and treated with antibiotics, or surgical treatment. The most widely affected areas are the lower limbs, buttocks, and trunk. Regarding the duration and frequency of the outbreaks, 2 forms of presentation seem to emerge. One shows a recurrent pattern,[7] with multiple episodes over months or even years. The second form has an episodic pattern,[6] with 1 or 2 self-limited episodes over a period of weeks to months.

Blood tests during outbreaks show leukocytosis, neutrophilia, or elevated acute phase reactants. Histological features are shown in Table 2.

The diagnosis of GCSS is one of exclusion, and differential diagnosis should include the following entities: bacterial cellulitis, eosinophilic cellulitis, thrombophlebitis,

DOI of original article:
https://doi.org/10.1016/j.ad.2023.04.038

https://doi.org/10.1016/j.ad.2024.10.047

Table 1 Conceptual table summarizing the epidemiological, clinical, and analytical characteristics of GCSS cases described in the current literature.

Epidemiological, clinical and analytical characteristics of GCSS	Gender/Age	Relevant history	Possible trigger	Skin lesions	Location	Fever, malaise, others	Leukocytes/ Neutrophils and %/CRP (units as per article)	Disease duration	Episodic/ Recurrent	Flare duration	Treatment	Surgical debridement
Case #1 (Surovy et al., 2013)	Male/62	Obesity	Synchronous multiple myeloma	Large, erythematous, warm, well-demarcated plaque associated with other faint erythematous plaques	Left leg, buttocks, thighs, trunk	Yes	Leukocytes: 10,600/μL / CRP: 279 mg/L	2 years	Recurrent (8 flares)	3 weeks	Prednisone	No
Case #2 (Surovy et al., 2013)	Female/48	Obesity	Not identifiable	Painful, warm erythematous infiltrated plaques. Some with blister-purpuric appearance	Right leg and knee, left arm, buttocks, trunk	Yes	Leukocytes: 24,000/μL / CRP: 429 mg/L	8 years	Recurrent (multiple)	Not specified	Prednisone	No
Case #3 (Surovy et al., 2013)	Female/68	Obesity	Synchronous breast cancer	Large, well-demarcated erythematous plaques. Some with blister-purpuric appearance	Suprapubic region, right thigh, leg, and foot	Yes	Leukocytes: 11,300/μL / CRP: 235 mg/L	3 months	Recurrent (3 flares)	Not specified	Prednisone, breast cancer surgery	No

Table 1 (*Continued*)

Epidemiological, clinical and analytical characteristics of GCSS	Gender/Age	Relevant history	Possible trigger	Skin lesions	Location	Fever, malaise, others	Leukocytes/ Neutrophils and %/CRP (units as per article)	Disease duration	Episodic/ Recurrent	Flare duration	Treatment	Surgical debridement
Case #4 (Koketsu et al., 2014)	Female/60s	Not relevant	Not identifiable	Erythematous macules and indurated, painful erythemato-edematous plaques	Right thigh and flank	Yes	Leukocytes: 10,300/μL / Neutrophils: 8,755/μL	3 years	Recurrent (multiple)	Not specified	Dapsone + colchicine + prednisone	No
Case #5 (Kaminska et al., 2014)	Female/54	Sjögren's disease, morbid obesity, PBC with liver transplant	Escherichia coli bacteremia (1 month prior)	Erythemato-edematous, indurated, confluent papules and plaques. Progression with a tendency to generalize	Buttocks, limbs, trunk, head, neck	Yes	Leukocytes: 4.1 K/μL / Neutrophil percentage: 77%	Not specified	Episodic (1)	2 days	Prednisone	No
Case #6 (So et al., 2015)	Female/72	Gastric cancer	Synchronous unclassifiable myelodysplastic syndrome	Large, well-demarcated, warm erythematous plaque, preceded by recurrent fevers and pain in the ipsilateral foot	Left thigh and flank	Yes	Leukocytes: 73.5 cells/μL / Neutrophil percentage: 66%	2 years	Recurrent (multiple flares)	2 weeks	Clobetasol propionate cream	No

Table 1 (*Continued*)

Epidemiological, clinical and analytical characteristics of GCSS	Gender/Age	Relevant history	Possible trigger	Skin lesions	Location	Fever, malaise, others	Leukocytes/ Neutrophils and %/CRP (units as per article)	Disease duration	Episodic/ Recurrent	Flare duration	Treatment	Surgical debridement
Case #7 (Buendía et al., 2019)	Female/62	Obesity	Not identifiable	Large, warm, indurated erythematous plaque followed by flares with a tendency to generalize	Buttocks, trunk, upper limbs	Yes	Leukocytes: 10,900/mm^3 / Neutrophils: 10,000/mm^3 / CRP: 306.8 mg/L	Not specified	Recurrent (at least 3 flares)	10 days	Prednisone, colchicine → dapsone	No
Case #8 (Okuyama et al.)	Female/56	Gastric cancer	Lower limb trauma or synchronous acute myeloid leukemia	Cellulitis-like erythematous plaques with pain and edema. Unilateral onset with bilateral progression	Legs	Yes	Leukocytes: 10-15$\times10^3/\mu L$ / CRP 20 mg/dl	At least 2 months	Episodic (2)	Not specified	Prednisone	Yes
Case #9 (Mitaka et al.)	Female/90	Breast cancer	Not identifiable	Erythematous, warm, well-demarcated, pruritic plaques	Breast and axilla (post-surgical/RT area), right flank, and lower limb	Yes	Leukocytes: 29,100/μL / Neutrophil percentage: 78%	2 weeks	Episodic (1)	2 weeks	Prednisone	No
Case #10 (Zhao et al., 2022)	Male/52	Not relevant	Bone marrow biopsy in sternum (postsurgical) or synchronous myelodysplastic syndrome	Erythema around puncture site associated with edema, heat, pain, and blister formation. Progressive local extension	Anterior chest (trauma site)	Yes	Leukocytes: 1.82$\times10^9$/L / Neutrophils: 1.07$\times10^9$/L / CRP: 351 IU/L	1 week	Episodic (1)	1 week	Prednisone	No

Table 1 (*Continued*)

Epidemiological, clinical and analytical characteristics of GCSS	Gender/Age	Relevant history	Possible trigger	Skin lesions	Location	Fever, malaise, others	Leukocytes/ Neutrophils and %/CRP (units as per article)	Disease duration	Episodic/ Recurrent	Flare duration	Treatment	Surgical debridement
Case #11 (Díez-Madueño et al., 2023)	Male/53	Obesity	Postsurgical ureteral endoscopic lithotripsy	Large, well-demarcated erythemato-edematous plaque associated with heat and pain	Left thigh, buttock, flank, and lumbosacral region	Yes	Leukocytes: 11.98×10^{9}/L / Neutrophils: 9.6×10^{9}/L / Neutrophil percentage: 80% / CRP: 198 mg/L	6 years	Recurrent (multiple flares)	1 week	Prednisone, colchicine → dapsone	No
Case #12 (Hingtgen et al., 2023)	Male/36	Obesity, chronic myeloid leukemia, heart failure	Not identifiable	Large, painful erythematous plaques. Local progression	Right axilla and flank. Some discontinuous lesions on the thorax	Yes	White series: 172,000/mL / Neutrophil percentage: 64% / Band percentage: 34%	1 week	Episodic (1)	1 week	Prednisone	Yes
Case #13 (Kyung Nam et al., 2023)	Female/69	Cervical cancer, adjuvant radiotherapy	Postsurgical saphenectomy	Erythematous, edematous plaques; tender but not very painful. Associated pseudovesicles	Right thigh (postsurgical area)	Yes	Neutrophil percentage: 88.8% / CRP: 9.14 mg/dL	2 weeks	Episodic (1)	2 weeks	Prednisone	No

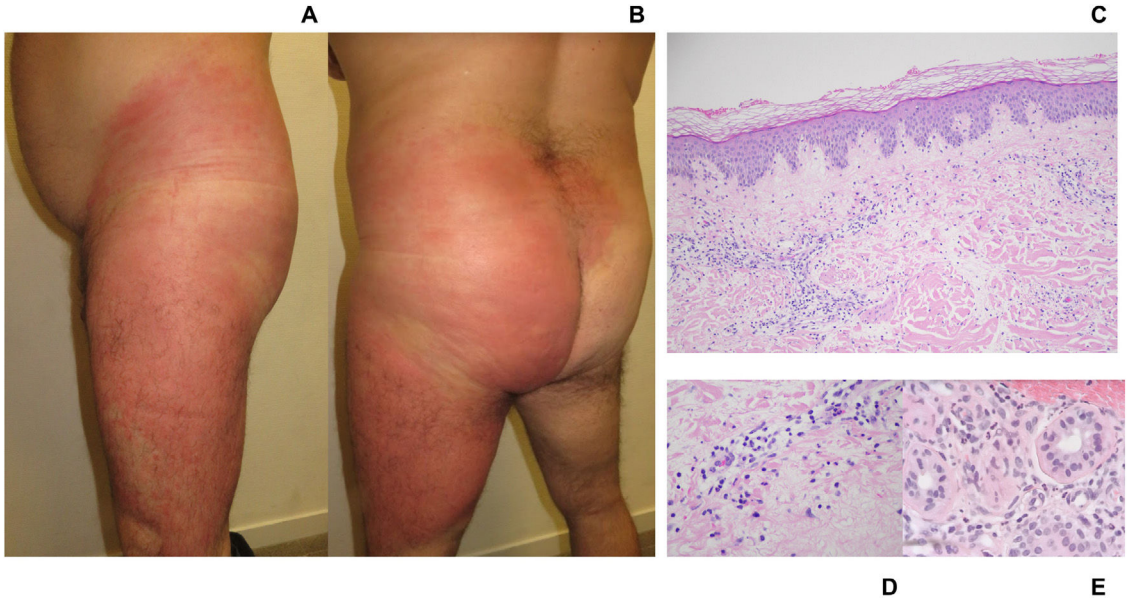

Figure 1 **A:** clinical image. Left lateral view. Large erythematous plaque covering the entire left thigh and ipsilateral flank. Well-demarcated, indurated, and warm plaque. **B:** clinical image. Posterior view. Erythematous-edematous plaque. Left thigh, buttock, and flank involvement; confluent toward the lumbosacral region. **C:** histological image. Overview. Skin with superficial perivascular lymphocytic inflammation with neutrophils. Mild papillary dermal edema and preserved epidermis. No evidence of panniculitis or vasculitis. No eosinophils seen. Original Image 4X. Hematoxylin-eosin stain. **D:** histological image. Detail of inflammatory infiltrate. Papillary dermis with perivascular lymphocytic infiltrate. Presence of neutrophils. Original Image 20X. Hematoxylin-eosin stain. **E:** histological image. Detail of periadnexal infiltrate. Periadnexal inflammatory infiltrate composed of lymphocytes and neutrophils. Original Image 20X. Hematoxylin-eosin stain.

Table 2 Table summarizing the histological characteristics of GCSS cases described in the current literature.

Sweet syndrome resembling giant cellulitis	Histopathological examination
Case #1 (Surovy et al., 2013)	Edema in the papillary dermis with an inflammatory infiltrate in the upper dermis composed mainly of mature neutrophils. No vasculitis.
Case #2 (Surovy et al., 2013)	Edema of the papillary dermis with a dense inflammatory infiltrate in the upper dermis consisting of mature neutrophils. No vasculitis.
Case #3 (Surovy et al., 2013)	Prominent edema of the papillary dermis with a dense inflammatory infiltrate of mature neutrophils in the papillary dermis. No vasculitis.
Case #4 (Koketsu et al., 2014)	Papillary dermal edema. Superficial and mid-dermal inflammatory infiltrate, perivascular and interstitial, composed of lymphocytes and numerous neutrophils. No vasculitis.
Case #5 (Kaminska et al., 2014)	Prominent papillary dermal edema with a mixed inflammatory infiltrate composed of abundant neutrophils intermingled with lymphocytes, histiocytes, and eosinophils.
Case #6 (So et al., 2015)	Superficial dermal edema with a perivascular and interstitial inflammatory infiltrate of predominantly histiocytoid and immature granulocytic cells, along with neutrophils, eosinophils, and lymphocytes. Staining with CD68 and myeloperoxidase highlighted most interstitial cells (histiocytoid).
Case #7 (Buendía et al., 2019)	Polymorphonuclear-predominant infiltrate in the dermis, with perivascular accentuation and slight edema of the dermal papillae. No vasculitis.
Case #8 (Okuyama et al., 2019)	Neutrophil infiltration in the dermis and adipose tissue, with superficial dermal edema. No vasculitis. / Neutrophil infiltration in the dermis and adipose tissue, superficial dermal edema, intact epidermis, and absence of vasculitis or massive necrotic changes.
Case #9 (Mitaka et al., 2020)	Dense neutrophilic infiltration in the dermis. No vasculitis.

Table 2 (*Continued*)

Sweet syndrome resembling giant cellulitis	Histopathological examination
Case #10 (Zhao et al., 2022)	Edema in the papillary dermis and dense inflammatory infiltration in the dermis composed of myeloperoxidase-positive and CD163-negative mononuclear cells with twisted vesicular nuclei and scant eosinophilic cytoplasm. No vasculitis (histiocytoid).
Case #11 (Díez-Madueño et al., 2023)	Superficial perivascular and perianexial lymphocytic infiltration with presence of neutrophils. Mild edema in the papillary dermis. Intact epidermis. No vasculitis.
Case #12 (Hingtgen et al.)	Dermal edema with a perivascular and interstitial neutrophilic infiltration spreading towards the subcutaneous tissue.
Case #13 (Kyung Nam et al., 2023)	Prominent upper dermal edema and diffuse neutrophilic infiltrates with histiocytoid mononuclear cells. No vasculitis.

autoinflammatory syndromes, or atypical SS subtypes (e.g., necrotizing fasciitis-type SS).[10] The presentation of large plaques with atypical characteristics, asymmetrical distribution affecting multiple areas, negative cultures, and the lack of response to antibiotics help distinguish it from bacterial cellulitis.

Treatment is similar to that used to treat classic SS, often responding to corticosteroids. In non-responsive cases, dapsone is considered an effective drug.

Localized neutrophilic dermatosis triggered by tissue injury (LNDT) is a recently described umbrella term used to unify cases of SS triggered by trauma, surgery, lymphedema, or chronic venous insufficiency (whether primary or secondary).[11] In our opinion, both GCSS and LNDT share traits that suggest they could be presentations of the same autoinflammatory syndrome. The 2 entities exhibit skin lesions, fever, and general malaise occurring in episodic or recurrent outbreaks, which can affect a localized area or become generalized. Differently, in LNDT, the lesions are predominantly limited to the affected tissue or area—usually the lower limb or postoperative region—with multi-territory involvement being less frequent. GCSS, therefore, remains a concept still under definition. New publications are necessary to properly define this entity.

Understanding GCSS helps in the early suspicion of the disease, distinguishing it from bacterial cellulitis, thus avoiding multiple hospital admissions, prolonged antibiotic use, and unnecessary surgical interventions.

Conflicts of interest

None declared.

References

1. Surovy AM, Pelivani N, Hegyi I, Buettiker U, Beltraminelli H, Borradori L. Giant cellulitis-like Sweet Syndrome, a new variant of neutrophilic dermatosis. JAMA Dermatol. enero de. 2013;149:79–83, http://dx.doi.org/10.1001/2013.jamadermatol.548.
2. Koketsu H, Ricotti C, Kerdel FA. Treatment of giant cellulitis-like Sweet syndrome with dapsone. JAMA Dermatol. 2014;150:457–9, http://dx.doi.org/10.1001/jamadermatol.2013.7814.
3. Kaminska ECN, Nwaneshiudu AI, Ruiz de Luzuriaga A, Tsoukas M, Bolotin D. Giant cellulitis-like Sweet syndrome in the setting of autoimmune disease. J Am Acad Dermatol. 2014;71:e94–5, http://dx.doi.org/10.1016/j.jaad.2014.03.025.
4. So JK, Carlos CA, Frucht CS, Cohen PR. Histiocytoid giant cellulitis-like Sweet's syndrome: Case report and review of the literature. Dermatol Online J. 2015;21, http://dx.doi.org/10.5070/D3213024175.
5. Okuyama S, Nito T, Yanagawa N, Tajima K. Giant cellulitis-like Sweet syndrome as an initial clinical presentation of acute myeloblastic leukemia with t(6;9)(p23;q34): DEK-CAN and internal duplications of FMS-like tyrosine kinase 3. Ann Hematol. 2019;98:787–8, http://dx.doi.org/10.1007/s00277-019-03613-1.
6. Zhao DW, Ni J, Sun XL. Histiocytoid giant cellulitis-like Sweet syndrome at the site of sternal aspiration: A case report and review of literature. WJCC. 2022;10:9768–75, http://dx.doi.org/10.12998/wjcc.v10.i27.9768.
7. Buendía Castaño D, Molins Ruiz M, Fernandez-Nieto D, Pindado Ortega, Fernández-González P, Fernández Guarino M, Jaén Osasolo P. Libro de Resúmenes de Comunicaciones Orales y Pósteres del 47 Congreso Nacional de Dermatología y Venereología, Barcelona. AEDV. 2019: 103, 1889-5352.
8. Bae KN, Shin K, Kim HS, Ko HC, Kim BS, Kim MB. Giant cellulitis-like Sweet syndrome following varicose vein surgery: A rare variant of sweet syndrome mimicking cellulitis. Ann Dermatol. 2023;35:151, http://dx.doi.org/10.5021/ad.20.129.
9. Hingtgen G, Mojica R, Motaparthi K. Giant cellulitis-like Sweet syndrome in association with chronic myeloid leukemia. JAAD Case Rep. 2023;34:1–4, http://dx.doi.org/10.1016/j.jdcr.2023.01.023.
10. Kroshinsky D, Alloo A, Rothschild B, Cummins J, Tan J, Montecino R, et al. Necrotizing Sweet syndrome: A new variant of neutrophilic dermatosis mimicking necrotizing fasciitis. J Am Acad Dermatol. 2012;67:945–54.
11. Imstepf VA, Schlapbach C, Benzaquen M, Feldmeyer L, Lipsker D, Borradori L. Localized aseptic neutrophilic dermatoses of the extremities triggered by stasis and tissue damage: Two case reports of an unrecognized condition misdiagnosed as bacterial cellulitis. JAAD Case Reports. 2022;28:14–7, http://dx.doi.org/10.1016/j.jdcr.2022.07.036.

K. Díez-Madueño[a], D. Buendía Castaño[a], D. Roldán Cortés[b], P. de la Cueva Dobao[a,*]

[a] *Servicio de Dermatología, Hospital Universitario Infanta Leonor, Madrid, Spain*
[b] *Servicio de Anatomía Patológica, Hospital Universitario Infanta Leonor, Madrid, Spain*

* Corresponding author.
E-mail address: pdelacueva@yahoo.com
(P. de la Cueva Dobao).