Acute inflammatory edema: A mimicker of cellulitis in critically ill patients

Elizabeth M. Marchionne, MD,[a] Timothy H. McCalmont, MD,[a,b] Laura B. Pincus, MD,[a,b] Philip E. LeBoit, MD,[a,b] and Lindy P. Fox, MD[a]
San Francisco, California

Background: Inpatient dermatology consultations for treatment-refractory or atypical cellulitis are common. In critically ill patients, differentiating cellulitis from its mimickers can be challenging.

Objective: We describe acute inflammatory edema, a likely underrecognized variant of pseudocellulitis.

Methods: We reviewed the charts of 15 patients with this diagnosis, seen by the inpatient dermatology consultation service at the University of California at San Francisco between 2009 and 2017.

Results: The cohort consisted of 9 women and 6 men with an age range of 52-73 years. Acute inflammatory edema presents as bilateral, erythematous, and edematous plaques, most commonly involving the thighs and lower abdomen, sparing areas of increased pressure on the skin. There is a predilection for patients with high body mass index and those with clinical or quantitative findings of fluid overload.

Conclusion: We propose a 3-part pathogenesis of acute inflammatory edema: 1) acute-onset volume overload 2) in patients with impaired lymphatic return 3) leads to dermal edema, microtears in connective tissue, and an influx of inflammation. (J Am Acad Dermatol 2019;81:931-6.)

Key words: acute inflammatory edema; cellulitis; fluid overload; inpatient dermatology; lymphatic return; pseudocellulitis.

Inpatient dermatology consultations are often requested for patients with suspected cellulitis, especially in those with an atypical presentation or lack of response to standard treatment.[1] Differentiating pseudocellulitis, a noninfectious inflammation of the dermis and subcutis, from authentic cellulitis can be challenging, especially in a complex patient population.[2,3] Misdiagnosis of cellulitis has been shown to lead to inappropriate antibiotic exposures, longer patient hospitalizations, unnecessary patient morbidity, and substantial avoidable health care spending.[4,5]

Here, we present 15 cases of acute inflammatory edema, a likely underrecognized variant of pseudocellulitis encountered in critically ill patients. Clinically, this entity presents as erythematous and edematous plaques involving the thighs and abdomen, characteristically sparing areas of increased pressure on the skin.

METHODS

We reviewed the charts of 15 patients with acute inflammatory edema who were seen by the inpatient dermatology consultation service at the University of California at San Francisco between 2009 and 2017. Before the use of *acute inflammatory edema* as a unifying term, several patients' presentations were initially described as "erythema of edema," "inflammatory edema," and "inflammatory edema of the ICU [intensive care unit]." Cases were excluded when the inpatient dermatology team documented

From the Department of Dermatology[a] and Department of Pathology, University of California San Francisco, San Francisco, California.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
A portion of this work was presented at the American Academy of Dermatology Annual Meeting, Washington, DC, March 2, 2019, in the "Consultative Dermatology for the Hospitalized Patient" session.

Accepted for publication May 29, 2019.
Reprints not available from the authors.
Correspondence to: Lindy P. Fox, MD, 1701 Divisadero St, 3rd Floor, Box 0316, San Francisco, CA 94115. E-mail: lindy.fox@ucsf.edu.
Published online June 1, 2019.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.05.083

an ongoing differential diagnosis or suspicion for other processes. Patients were evaluated for age, sex, reason for admission, reason for consultation, past medical history, fluid status, laboratory values, microbiology results, physical examination, and histopathology results. The Committee on Human Research (institutional review board) at the University of California San Francisco reviewed and approved this study (no. 11-05526).

REPRESENTATIVE CASE REPORT

A 62-year-old woman was hospitalized after complications from a gastric bypass procedure. Her hospital course was prolonged and complicated by septic shock due to a gastrointestinal source, recurrent pneumonia, and acute tubular necrosis resulting in hemodialysis dependence. The dermatology department was consulted on hospital day 63 for evaluation of suspected cellulitis of the abdomen and lower extremities. The patient was critically ill, with fever and persistent leukocytosis. At the time of consultation, the patient was receiving multiple antimicrobials (meropenem, ciprofloxacin, trimethoprim/sulfamethoxazole, vancomycin, and caspofungin) for several possible sources of infection, including presumed cellulitis of the abdomen and thighs.

Physical examination showed an ill-appearing woman in the ICU. There was diffuse 3+ pitting edema of the trunk and extremities. There were bilateral, symmetric, blanchable, ill-defined, erythematous plaques on the pannus, mons pubis, and thighs. There was sparing of areas where skin was in apposition with other skin, such as the folds of the abdomen, inguinal area, and medial thighs. There was a sharp demarcation of uninvolved skin of the back and buttocks, where the bed was applying pressure to the skin. The patient had a body mass index (BMI) of 41.7 kg/m^2, and input/output data showed that she was 29 L net positive since admission. A skin biopsy sample from the right thigh showed edema of the dermis, with numerous extravasated erythrocytes and neutrophils. The result of a Brown-Brenn stain for bacterial organisms was negative. Test results for tissue cultures from the same site were negative for bacterial, fungal, and mycobacterial organisms. A diagnosis of acute inflammatory edema was made. Reassurance was provided, and no further workup or antibiotic therapy was recommended.

CAPSULE SUMMARY

- Acute inflammatory edema should be considered in the differential diagnosis of pseudocellulitis.
- Acute inflammatory edema presents as bilateral, erythematous, and edematous plaques, involving areas of dependence and sparing those of pressure.
- Recognizing and naming this entity allows for a bedside diagnosis and avoidance of a broad, costly workup and treatment.

RESULTS

Clinical features

Clinical characteristics are summarized in Table I. The cohort consisted of 15 patients, 9 women and 6 men. The average age was 63 years, with a range of 52-73 years. Twelve of the patients (80%) were in the ICU at the time of consultation. Two of the remaining patients had recent ICU stays (<2 weeks prior), and the third had decompensated cirrhosis and was receiving transplant services. The majority of admissions were for life-threatening diagnoses, including septic shock, respiratory failure, colon perforation, necrotizing pancreatitis, and surgical complications.

The average duration from admission to dermatology consultation was 20 days, with a range of 1 to 63 days. Dermatology consultation was requested for evaluation of suspected cellulitis in 5 patients. Nine consultations were requested for a new rash of unknown cause, and 1 was for an inflamed cyst (with acute inflammatory edema incidentally diagnosed).

All 15 patients were receiving antibiotics at the time of consultation. One patient was receiving antibiotics specifically for cellulitis, and the remainder of the patients were receiving antibiotics primarily for other known infectious sources (9 patients) and empiric treatment of sepsis of unknown source (5 patients).

Clinical morphology

Acute inflammatory edema presents as bilateral, blanchable, erythematous, and edematous plaques. The distribution is primarily localized to areas where fluid accumulates in a supine patient, such as the thighs, lower abdomen, and flanks (Fig 1). Notably, there is sparing of areas of pressure on the skin, including the folds, appositional skin and where external objects are in contact with the skin (e.g. bed, tubes/catheters, sequential compression devices) (Fig 2). There is often generalized edema or anasarca. Other observed findings within the inflammatory plaques include peau d'orange changes (3 patients),

Abbreviations used:

BMI: body mass index
ICU: intensive care unit

pseudovesiculation (2 patients), cobblestoning (1 patient), and edema bullae (1 patient).

The thighs were the most commonly affected area, involved in all 15 patients. The abdomen and lower legs were involved in 9 and 5 patients, respectively (Fig 3). Other less frequent areas of involvement included the back, flanks, buttocks, scrotum, forearms, and breasts.

Associated diseases and laboratory findings

Abnormal white blood cell count (average, 17.4 $\times$ 10^9/L; reference range, 3.4-10 $\times 10^9$/L) was present in 11 of 15 patients. Four patients had abnormal body temperature at the time of consultation (2 >38°C and 2 <36°C), as defined by systemic inflammatory response syndrome guidelines.[6] Twelve patients had active liver, cardiac, or renal dysfunction at the time of consultation.

Eighty-seven percent (13 of 15 patients) had a BMI of 25 kg/m^2 or greater and thus were classified as overweight or obese according to the National Institutes of Health clinical guidelines.[7] There were 2 patients with normal BMI (18.5-24.9 kg/m^2), 2 patients were overweight (BMI, 25.0-29.9 kg/m^2), 7 patients were obese (BMI, 30.0-39.9 kg/m^2), and 4 patients were extremely obese (BMI, $\geq$ 40 kg/m^2). The average BMI was 34.8 kg/m^2.

Fluid overload was judged based on clinical examination (description of anasarca) and quantitative input/output data. Based on this, 93% (14 of 15) of patients had findings of fluid overload. Detailed inpatient fluid input and output measurements could be obtained from 8 of 15 patients (others were limited by transition to the updated electronic medical record system or consultation on day of hospital admission). Of these 8 patients, 7 had a net positive fluid status on the day of consultation, and 1 had net negative status. However, despite having a net negative fluid status, this patient was still described as anasarcous in the physical examination. Interpretation of these data are complicated, given that several patients were receiving continuous renal replacement therapy or hemodialysis. Of the remaining 7 patients for whom full quantitative fluid status was not available, 6 were described as anasarcous on physical examination.

Data on serum albumin were collected and included if obtained within 5 days of the initial dermatology consultation. All of the 13 patients for whom these data were available had low values (range, <1-3.2 g/dL; reference range, 3.5-4.8 g/dL).

Table I. Patient characteristics, associated diseases, and laboratory findings

Characteristics	Values
Total number of patients	15
Male	6
Female	9
Age in years	
Mean	63
Range	52-73
ICU stay, n (%)	12 (80)
Hospital day of consultation	
Mean	20
Range	1-63
Reason for consultation, n	
Cellulitis	5
Rash	9
Other	1
BMI in kg/m^2, n (%)	
18.5-24.9	2 (13)
25.0-29.9	2 (13)
30.0-39.9	7 (47)
≥40	4 (27)
Organ dysfunction, n (%)	
Liver	3 (20)
Renal	9 (60)
Cardiac	3 (20)
Fluid overload, n (%)	
Clinical anasarca	11 (73)
Net positive based on in/out data*	7 (88)
Leukocytosis	11 (73)
Abnormal body temperature, n (%)	
≥38°C	2 (13)
≤36°C	2 (13)
Low serum albumin, n (%)†	13 (100)

BMI, Body mass index; *ICU,* intensive care unit.
*These data were available for 8 patients.
†These were data available for 13 patients.

Histopathologic findings

Three patients had skin biopsy for histopathologic examination. All of the biopsy samples showed marked papillary dermal edema. Edema in the upper reticular dermis was also noted in 2 of the specimens, and purpura was noted in 1 biopsy specimen. The inflammatory infiltrate consistently included scattered neutrophils and lymphocytes with varying numbers of admixed histiocytes, including pale edema-phages with bubbly cytoplasm, which were prominent in 1 biopsy specimen. All histochemical stain results for infective microbes were negative.

Three patients also had skin biopsy for tissue culture, which was sent for microbiological analysis seeking conventional bacteria, fungi, and

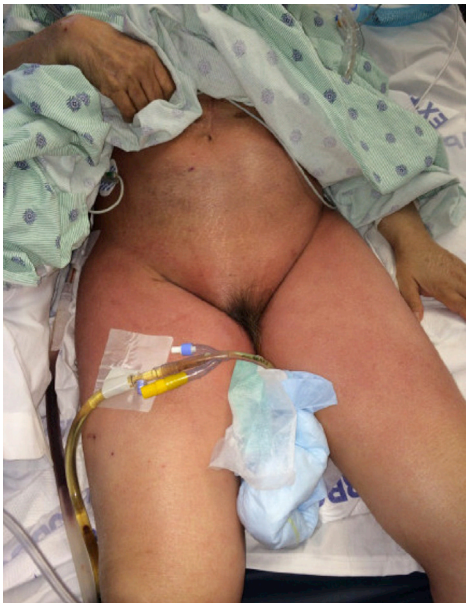

Fig 1. Representative case of acute inflammatory edema involving the bilateral thighs.

mycobacteria. There was no growth from any of these samples.

Treatment

Treatment for acute inflammatory edema involves reassurance. Helpful interventions include decreasing the fluid burden on the tissue by improving the patient's fluid status (with diuretics, dialysis, etc), compression, frequent repositioning, and increased mobility. Antibiotics should be discontinued if they are used solely for a cellulitis indication.

DISCUSSION

Acute inflammatory edema presents as bilateral, erythematous, and edematous plaques, most commonly on the thighs and abdomen, in critically ill patients. These plaques favor dependent areas of the supine patient and characteristically spare areas where there is increased pressure on the skin. Patients who are fluid overloaded and have a high BMI are preferentially affected.

Acute inflammatory edema is a form of pseudocellulitis. It is important to distinguish this entity from true cellulitis and other infectious causes such as erysipelas, pyomyositis, and necrotizing fasciitis. Unlike cellulitis, which is most often unilateral, acute inflammatory edema is bilateral and spares areas of pressure. The presence of systemic leukocytosis is likely related to the cause of the critically ill state rather than a feature of acute inflammatory edema. The histopathologic characteristics may also be mistaken for those of cellulitis or other infectious cause, given the presence of neutrophils. In addition to infection, other main diagnostic considerations include drug eruptions, irritant and allergic contact dermatitis, stasis dermatitis, and lipodermatosclerosis. Other inflammatory conditions, such as Sweet syndrome (specifically giant cellulitis type), panniculitis, and vasculitis could be considered as well based on patient history and clinical findings.

Evaluation of a patient with suspected acute inflammatory edema should include a complete skin examination, particularly focused on areas of increased pressure to detect sparing, such as the skin folds, appositional skin, areas in contact with external devices (lines, tubes, catheters, underneath sequential compression devices), and the sacrum and medial back, where edematous fluid is pushed away to areas of decreased resistance. Acute inflammatory edema is primarily a clinical diagnosis. In classic cases with high clinical suspicion, biopsy may not be required.

We propose the pathogenesis of acute inflammatory edema to be due to a 3-part process: 1) acute-onset volume overload 2) in patients with impaired lymphatic return 3) leads to dermal edema, microtears in connective tissue, and an influx of inflammation.

Fluid homeostasis is a tightly regulated physiologic system, where movement of fluid between the capillary and interstitium is dependent on oncotic and hydrostatic pressure.[8] In states of increased intravascular hydrostatic pressure and/or decreased intravascular oncotic pressure, fluid moves from the intravascular space into the interstitial space, and edema occurs.[8]

Edema may occur in a hospitalized patient through several mechanisms. Increased intravascular hydrostatic pressure is induced in states of fluid overload, such as volume overresuscitation and organ dysfunction (cardiac, liver, renal).[9] Decreased intravascular oncotic pressure occurs in low-protein states, which may occur after acute dilution with rapid administration of fluids, malnutrition, liver failure, or nephrotic syndrome.[9] Sepsis unleashes a systemic inflammatory response, with peripheral vasodilation and an increase in vascular permeability.[10]

Lymphatics maintain volume homeostasis by returning filtrate to the circulation.[9] Lymphedema develops with decreased fluid resorption, which can occur with excessive body fat.[11] Because 87% of our patients had a BMI of 25 kg/m^2 or greater (classified as overweight and obese), we hypothesize that our patient population had a predisposition to obesity-associated impairment in lymphatic return. The

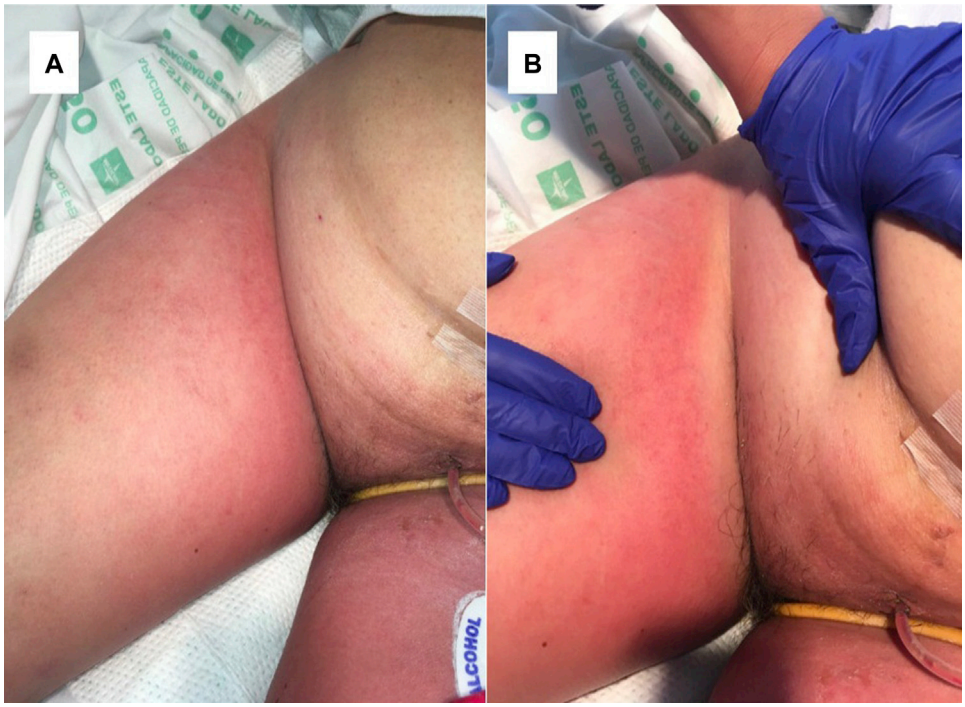

Fig 2. A, Erythema and edema of the thighs and mons pubis in a patient with acute inflammatory edema. **B**, Examination shows sparing of the inguinal fold.

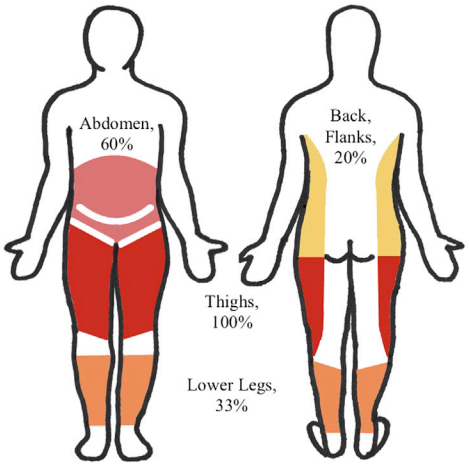

Fig 3. Distribution of acute inflammatory edema.

pathogenesis of the lymphatic dysfunction in obesity is thought to be due to several mechanisms, including an increase in lymphatic fluid production due to larger tissue mass, a decrease in ambulation and muscle contraction, and collapse of the vessels due to increased pressure from the tissue.[12] Accumulation of lymphatic fluid leads to fibrosis, adipose deposition, and tissue hypertrophy.[13,14] Furthermore, in bedridden patients, the lymphatic flow is slowed due to immobility.[15]

Acute-onset dermal edema likely causes microtears in connective tissue, which in turn can release mediators of inflammation, resulting in an influx of neutrophils and other inflammatory cells. This mechanism is similar to that proposed in inflammatory solar purpura, in which shearing forces acting on fragile elastotic material cause clefts and result in an accumulation of neutrophils.[16] Other factors, such as impaired removal of toxins due to the increased distance for oxygen and nutrient diffusion, as well as distribution of systemic leukocytosis, may also play a role in the inflammatory infiltrate.[17]

Limitations to this study include a low rate of biopsy and retrospective single-center reporting. After recognizing that acute inflammatory edema was a benign entity with distinct clinical manifestations, histopathologic examination became a less valuable resource and, thus, biopsy was pursued less frequently in classic cases. This scenario is similar to stasis dermatitis in the outpatient setting.

Identifying acute inflammatory edema allows for a bedside diagnosis and avoidance of a costly workup and treatment. Importantly, in the critically ill patient population, recognizing this condition as a noninfectious entity provides support that these skin findings are not the source of an unknown sepsis and allows discontinuation of antibiotics if used for a cellulitis indication. Treatment of acute inflammatory edema is primarily reassurance and decreasing fluid burden on the tissues.

REFERENCES

1. Kroshinsky D, Cotliar J, Hughey LC, Shinkai K, Fox LP. Association of Dermatology consultation with accuracy of cutaneous disorder diagnoses in hospitalized patients: a multicenter analysis. *JAMA Dermatol*. 2016;152(4):477-480.
2. Korniyenko A, Lozada J, Ranade A, Sandhu G. Recurrent lower extremity pseudocellulitis. *Am J Ther*. 2012;19(4):e141-e142.
3. Strazzula L, Cotliar J, Fox LP, et al. Inpatient dermatology consultation aids diagnosis of cellulitis among hospitalized patients: a multi-institutional analysis. *J Am Acad Dermatol*. 2015;73(1):70-75.
4. Weng QY, Raff AB, Cohen JM, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis. *JAMA Dermatol*. 2017;153(2):141-146.
5. Li DG, Xia FD, Khosravi H, et al. Outcomes of early dermatology consultation for inpatients diagnosed with cellulitis. *JAMA Dermatol*. 2018;154(5):537-543.
6. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992; 101(6):1644-1655.
7. *NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report*. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2003/.
8. Guyton AC, Hall JE. The microcirculation and the lymphatic system: capillary fluid exchange, interstitial fluid, and lymph flow. In: Guyton AC, ed. *Textbook of Medical Physiology*. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006:181-194.
9. Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest*. 2014;124(3):915-921.
10. Lee WL, Slutsky AS. Sepsis and endothelial permeability. *N Engl J Med*. 2010;363(7):689-691.
11. Mehrara BJ, Greene AK. Lymphedema and obesity: is there a link? *Plast Reconstr Surg*. 2014;134(1):154e-160e.
12. Greene AK. Diagnosis and management of obesity-induced lymphedema. *Plast Reconstr Surg*. 2016;138(1):111e-118e.
13. Cucchi F, Rossmeislova L, Simonsen L, Jensen MR, Bülow J. A vicious circle in chronic lymphoedema pathophysiology? An adipocentric view. *Obes Rev*. 2017;8(10):1159-1169.
14. Savetsky IL, Torrisi JS, Cuzzone DA, et al. Obesity increases inflammation and impairs lymphatic function in a mouse model of lymphedema. *Am J Physiol Heart Circ Physiol*. 2014; 307(2):H165-H172.
15. Lira A, Pinsky MR. Choices in fluid type and volume during resuscitation: impact on patient outcomes. *Ann Intensive Care*. 2014;4:38.
16. Wood BA, Leboit PE. An 'inflammatory' variant of solar purpura: a simulant of leukocytoclastic vasculitis and neutrophilic dermatoses. *Pathology*. 2013;45(5):484-488.
17. Scallan J, Huxley VH, Korthuis RJ. Capillary fluid exchange: regulation, functions, and pathology. In: *Pathophysiology of Edema Formation*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53445/.