



Case Report

Ecthyma gangrenosum secondary to methicillin-sensitive *Staphylococcus aureus*



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ABSTRACT

Ecthyma gangrenosum (EG) is a well-described skin manifestation of *Pseudomonas aeruginosa* septicemia in immunocompromised patients. However, it can be seen in association with other bacteria, viruses, and fungi. We report a case of a 54-year-old African American female with metastatic gastric adenocarcinoma and recent chemotherapy and neutropenia who developed EG-like lesions due to methicillin-susceptible *Staphylococcus aureus*. We also review the literature to evaluate all reported cases of *S aureus*-associated EG and their clinical presentation, diagnosis, and treatment.

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Introduction

Ecthyma gangrenosum (EG) is a well-described skin manifestation of *Pseudomonas aeruginosa* septicemia in immunocompromised patients. EG is most commonly seen in *Pseudomonas* septicemia. However, it may be seen in association with infections caused by other gram-negative bacteria and fungi and can rarely be caused by gram-positive organisms such as *Staphylococcus* and *Streptococcus* species. We report a case of a 54-year-old African American female with neutropenia in the setting of metastatic gastric adenocarcinoma and recent chemotherapy who developed EG-like lesions due to methicillin susceptible *Staphylococcus aureus*. In addition, we also review the literature and discuss all reported cases of *S aureus*-associated EG manifestation, diagnosis, and treatment.

Case report

A 54-year-old African American female with a medical history significant for systemic lupus erythematosus on chronic therapy with systemic steroids and hydroxychloroquine was recently diagnosed with gastric adenocarcinoma with metastatic liver lesions. She presented to our hospital with fever and painful skin lesions. The patient had received a first round of chemotherapy with 5-fluorouracil, cisplatin, and trastuzumab. Seven to ten days after the last dose of chemotherapy she noted multiple painful skin lesions.

On admission, the patient's blood pressure was 86/52 mmHg, heart rate 122 bpm, and temperature 103.7 °F. The patient was alert, oriented, and not in any acute distress. Skin examination revealed three 3–12–mm, tender, indurated, and erythematous papules and plaques with violaceous-gray centers located on the left popliteal fossa, right anterolateral knee, and right external ear canal. Additionally, there were 4–5–mm vesicles at the right mandibular angle and right arm, and pustules scattered on the mid chest (see Figs. 1 and 2).

Admission laboratory studies revealed pancytopenia and elevated erythrocyte sedimentation rate and C-reactive protein. Additional results are shown in Table 1.

Three sets of blood cultures obtained prior to administration of antibiotic therapy showed no growth. Fungal blood cultures were negative. Chest imaging did not reveal any pathology. Transthoracic and transesophageal echocardiograms showed normal valvular function without vegetations.

The patient's initial therapy with intravenous cefepime, vancomycin, and metronidazole was changed to intravenous acyclovir, vancomycin, and double *Pseudomonas* coverage with meropenem and amikacin after evaluation by the infectious disease and dermatology teams.

Cutaneous punch biopsies were obtained from the violaceous-gray lesion on the left popliteal fossa and a pustule from the chest. Histopathology of the violaceous-gray lesion revealed prominent edema and numerous gram-positive cocci in the superficial dermis (see Figs. 3 and 4). Additionally, there was a perivascular inflammatory cell infiltrate in the superficial and deep dermis composed of lymphocytes, histiocytes, and neutrophils, as well as dilated blood vessels with extravasated erythrocytes. Special stains for acid fast bacilli and fungal organisms were negative. The chest pustule histologically

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Fig. 1. Indurated, erythematous papule with violaceous-grey center.



Fig. 2. Indurated, erythematous plaque with central edema.

demonstrated an intraepidermal pustular dermatitis with gram-positive cocci. Tissue cultures from both specimens grew methicillin-susceptible *Staphylococcus aureus*, with an oxacillin minimum inhibitory concentration of 0.5 mcg/ml.

Acyclovir, meropenem, and vancomycin were discontinued. All blood cultures remained negative throughout hospitalization, and the patient was discharged home to complete 2 weeks of intravenous oxacillin.

Discussion

Ecthyma gangrenosum (EG) is a well-described skin manifestation of *P aeruginosa* septicemia in immunocompromised patients. EG lesions usually are round, indurated, ulcerated papules progressing into plaques with a central gray-black eschar and surrounding erythema. Lesions may evolve from initial vesiculobullous lesions and rapidly become hemorrhagic.

The clinical differential diagnosis in our case included EG associated with invasive pathogens: *Pseudomonas*, *Staphylococcus* sp., fungal infection such as *Aspergillus* sp., *Fusarium* sp., disseminated varicella zoster virus, and herpes simplex virus; noninfectious entities such as vasculitis were also considered. Ecthyma (“deep impetigo”) was not considered in our differential diagnosis, as clinically the skin lesions in our patient did not start as superficial epidermal erosions and crusting that progressed deeper into the dermis to create crusted ulcers.

EG is most commonly seen in *Pseudomonas* septicemia; however, it may be seen in association with infections caused by other gram-negative bacteria, such as *Aeromonas hydrophilia*, *Klebsiella pneumonia*, *Escherichia coli*, *Neisseria gonorrhoea*, *Citrobacter freundii*, *Serratia*

marcescens, and fungi including *Candida albicans*, *Aspergillus fumigatus*, *Fusarium solani*, *Pseudallescheria boydii* and *Curvularia* sp. The viral pathogens herpes simplex viruses 1 and 2 and varicella-zoster virus can be associated with EG as well. Rarely, EG can be caused by gram-positive organisms such as *Staphylococcus* and *Streptococcus* species (Kao et al. 2001; Reich et al. 2004).

A review of English literature in PubMed between January 1, 1990, to January 31, 2016, was performed using the following keywords: non-pseudomonal ecthyma gangrenosum, methicillin-resistant *Staphylococcus aureus*, and methicillin-susceptible *Staphylococcus aureus*. This search revealed 5 other reported cases of EG associated with *S aureus* infection. EG usually occurs in the patients with underlying immunodeficiency. Predisposing factors include neutropenia,

Table 1
Blood Test Performed on Admission.

Blood test	Patient's results	Normal reference range
White blood cell count	$0.8 \times 10^3/\mu\text{L}$	$3.6\text{--}11.0 \times 10^3/\mu\text{L}$
Absolute neutrophil count	$0.4 \times 10^3/\mu\text{L}$	$1.4\text{--}6.3 \times 10^3/\mu\text{L}$
Platelet count	$78 \times 10^3/\mu\text{L}$	$150\text{--}440 \times 10^3/\mu\text{L}$
Hemoglobin	7.7 g/dL	12.0–16.0 g/dL
Erythrocyte sedimentation rate	150 mm/h	0–20 mm/h
C-reactive protein	132.9 mg/L	<1.0 mg/L
Creatinine	0.9 mg/dL	0.6–1.2 mg/dL
Blood urea nitrogen	10 mg/dL	8–24 mg/dL
Beta-D glucan	31 pg/mL	<31 pg/mL is negative, >80 pg/mL positive
Aspergillus Galactomannan index by EIA	0.08	index equal to or greater than 0.5 positive

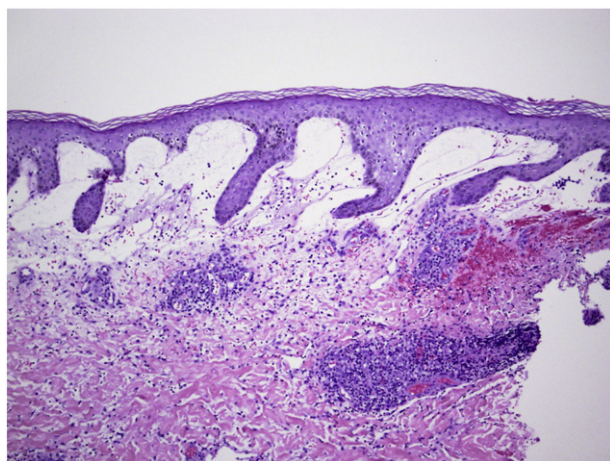


Fig. 3. Prominent superficial dermal edema and a dense perivascular inflammatory infiltrate with neutrophils.

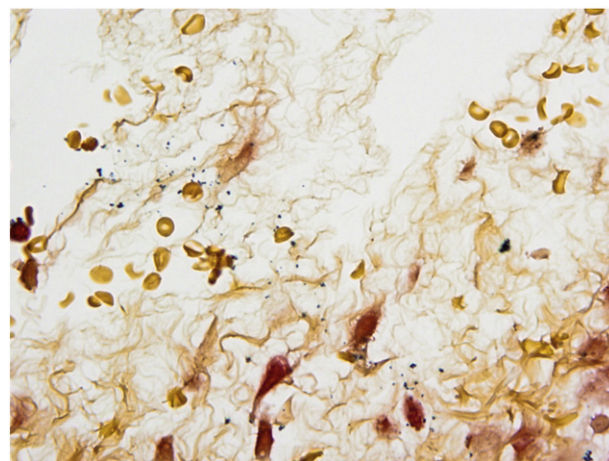


Fig. 4. Numerous gram-positive cocci in the upper dermis.

malignancy, burns, malnutrition, and tuberculosis. Most of the patients described in the literature had underlying immunosuppression (Song et al. 2015).

EG can occur in association with bacteremia or in patients with sterile blood cultures (Huminer et al. 1987; Reich et al. 2004). Skin lesions in patients with bacteremia represent hematogenous dissemination of organisms from distant sites, and blood cultures are positive in these patients. In those patients with sterile blood cultures and EG, skin lesions are thought to be associated with direct pathogen inoculation into the skin. However, as previously discussed, this would not explain the simultaneous presence of multiple discrete, distant skin lesions. Blood cultures were negative in five out of six reported *Staphylococcus* cases, including our case (Table 2). Our patient had multiple sterile blood cultures but had organisms cultured from three different skin lesions. This could be explained by transient bacteremia that was undetected in cultures. Interestingly, in the case presented by Song et al., organisms were not found in tissue stains, and skin lesions were therefore thought to be associated with toxins produced by *S aureus* (Song et al. 2015). However, *Staphylococcus* was cultured from tissue culture.

Upon review of all published case reports, methicillin resistance was more commonly associated with EG lesions, as only two patients out of six had methicillin-susceptible *Staphylococcus* cultured from skin lesions. Lesions had a wide anatomic distribution but were more commonly seen on the trunk and upper and lower extremities and less commonly on the face. Lesions may be macular, papular, plaque-like, ulcerated, bullous, and/or vesicular. All lesions had necrotic-appearing centers with surrounding erythema and soft tissue induration (see Table 2).

Histopathologic evaluation of skin biopsies revealed dermal edema with neutrophil infiltration and gram positive cocci in most of the reported *S aureus*-associated cases. Extensive dermal and epidermal necrosis was reported only in 2 cases (Table 2). Histopathologic evaluation of skin biopsies from our patient did not reveal the typical findings of EG, such as blood vessel invasion, vasculitis, and necrosis. However, given the wide anatomic distribution of multiple skin lesions, typical clinical appearance and systemic symptoms that are not generally seen with deep impetigo, the lesions in our patient are most consistent with EG.

As opposed to other infections caused by *S aureus*, written treatment guidelines for staphylococcal EG do not exist. Given skin and soft tissue involvement, one could consider treating patients based on Skin and Soft Tissue Infection Guidelines (Liu et al. 2011), which

would comprise 5 to 10 days of therapy, individualizing based on the patient's clinical response. Clindamycin, trimethoprim-sulfamethoxazole, tetracycline (doxycycline or minocycline), or linezolid could be used to treat methicillin-resistant *S aureus* infection (Liu et al. 2011). For methicillin-susceptible strains, dicloxacillin, cephalexin, nafcillin, or cefazolin can be employed.

In a hospitalized patient, especially in patients with febrile neutropenia and complicated skin and soft tissue infections, surgical debridement plus intravenous antibiotic therapy is recommended. According to the Skin and Soft Tissue Infection Guidelines, treatment duration in febrile neutropenic patients should be 7 to 14 days with intravenous therapy. Given the wide distribution of skin lesions and possibility of disseminated infection, we recommend that treatment be prolonged to the duration recommended to treat noncomplicated blood stream infections.

Treatment should be initiated with intravenous vancomycin, daptomycin, cefazolin, nafcillin, or oxacillin for at least 2 weeks depending on the susceptibility pattern for uncomplicated bacteremia (Liu et al. 2011; Stevens et al. 2014). Empiric therapy with broader spectrum antibiotics, such as vancomycin, daptomycin, or linezolid should be considered pending culture data. Duration of the pathogen-directed therapy in case reports ranged from 14 to 28 days, with intravenous as opposed to oral therapy being the delivery of choice (Song et al. 2015). Our patient received 2 weeks of intravenous oxacillin.

Conclusion

EG is most commonly seen in septicemia caused by *P aeruginosa* in an immunocompromised host. However, in the presence of neutropenia and immunosuppression, EG lesions can be caused by gram-positive bacteria such as *S aureus*. These patients may have negative blood cultures. Gram positive coverage should be considered early in patients without clinical improvement.

Conflicts of interest

none

Funding

none

Table 2
Case Reports of Patients with *Staphylococcus aureus* Ecthyma Gangrenosum.

Author (location)	Song et al. 2015 (PA)	Sen et al. 2009 (Turkey)	Ungprasert et al. 2013 (Japan)	Chang et al. 2012 (PA)	Pechter et al. 2012 (FL)	UCONN, 2015 (CT) Our reported case.
Underlying medical condition	Healthy 15-month-old girl	69-year-old male with COPD	40 year old with AIDS, MRSA skin abscess 2 weeks prior the admission	35 year old with T-cell ALL, with recent chemotherapy (2 weeks prior)	8-month-old infant with transient neutropenia	54-year-old female with SLE and metastatic gastric adenocarcinoma with recent chemotherapy (7-10 days prior)
MRSA vs MSSA	MSSA	MRSA	MRSA	MRSA	MRSA	MSSA
Blood cultures positive (+) vs negative (-)	(-)	(+)	(-)	(-)	(-)	(-)
Lesion cultures (+) vs (-):GS: HP	Culture: MSSA GS: no organism HP: no organism	Cultures MRSA GS: NR HP: NR	Culture: negative GS: NR HP: NR (cultures from prior skin abscess + MRSA)	Culture: MRSA GS: GPC in clusters HP: NR	Culture: MRSA (tissue) GS: NR HP: NR	Culture MSSA GS: GPC HP: GPC
Location of the lesion(s)	Chest, axilla, and shoulders	Upper and lower extremities	Trunk, lower extremities	Buttocks, bilateral upper thighs, lower abdomen	Face, neck, back, genitalia	Face, upper and lower extremities, trunk
Description of the lesion	Eight purpuric, indurated plaques and nodules with ovoid necrotic centers	Macular lesions evolved to bullae over the 3 days with necrotic center and surrounding erythema	Multiple deep, punched-out ulcerations with necrotic base and surrounding erythema	Tender hemorrhagic bullae with surrounding erythema	Edematous papules, purplish-red with necrotic centers	Multiple vesicular lesions, necrotic macules, gunmetal gray color, indurated, tender with erythematous soft tissue edema surrounding the central necrosis
Histopathology	Dyskeratotic keratinocytes and focal spongiosis of the epidermis. Dermal infiltration with neutrophils, lymphocytes and karyorrhectic debris surrounding dermal blood vessels	No biopsy performed	No biopsy performed	Numerous bacteria in the dermis without inflammatory infiltrate, and with dermal/epidermal edema, necrosis, and hemorrhages	Large vessel vasculitis in the superficial subcutis, foci of dermal necrosis with overlying epidermal necrosis with bullae, and numerous gram-positive cocci	Necrotic eschar: edema, dilated blood vessels and superficial infiltrates of lymphocytes, histiocytes, and neutrophils were present within dermis Vesicular lesion: intraepidermal pustular dermatitis with gram-positive cocci
Treatment and duration	14 days of IV therapy with doxycycline, followed by PO cephalixin	Ampicillin/sulbactam + meropenem + teicoplanin IV	Linezolid 4 weeks PO	Vancomycin IV, (duration not reported)	Vancomycin IV 14 days Initial antibiotic therapy (vancomycin, cefepime, amikacin)	Vancomycin + nafcillin total 2 week IV therapy Initial antibiotic therapy (vancomycin, meropenem, amikacin, acyclovir)
Outcome	Was discharged	Died—septic shock	Was discharged	Was discharged	Was discharged	Was discharged

COPD, chronic obstructive pulmonary disease; MRSA, methicillin resistant *Staphylococcus aureus*; ALL, acute lymphoblastic leukemia; SLE, systemic lupus erythematosus; MSSA, methicillin sensitive *Staphylococcus aureus*; GS, gram stain; HP, histopathology stain; NR, not reported; GPC, gram positive cocci; IV, intravenous; PO, oral administration of medication.

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