CASE REPORT

Ecthyma gangrenosum caused by *Citrobacter freundii*Tyson Hawkley,¹ David Chang,² Whitney Pollard,³ David Ferraro⁴¹Department of Anesthesiology, Brooke Army Medical Center, Fort Sam Houston, Texas, USA²Department of Infectious Disease, Brooke Army Medical Center, Fort Sam Houston, Texas, USA³Department of Dermatology, Brooke Army Medical Center, Fort Sam Houston, Texas, USA⁴Department of Pulmonary and Critical Care, Brooke Army Medical Center, Fort Sam Houston, Texas, USA

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SUMMARY

A 55-year-old man undergoing chemotherapy for recurrent multiple myeloma presented with a 2-day history of bilateral lower leg rash with pain and oedema. On examination, there were numerous non-palpable retiform pruritic patches over both lower legs. Skin punch biopsy demonstrated a diffuse interstitial neutrophilic infiltrate with necrosis. Peripheral blood and skin tissue cultures both isolated *Citrobacter freundii*, consistent with a rare form of ecthyma gangrenosum. The patient responded with appropriate antibiotic therapy and removal of medical port. He made a full recovery from this infectious complication of his underlying immunosuppression.

BACKGROUND

Ecthyma gangrenosum (EG) is an uncommon skin manifestation of a systemic infection and generally occurs in the immunocompromised patient. Although often associated with *Pseudomonas aeruginosa*, EG is rarely caused by other infectious entities. Since 1969, this is the fifth known case of EG secondary to *Citrobacter freundii*. Confirmation of this diagnosis necessitated a multidisciplinary approach including dermatology, infectious disease and haematology–oncology specialties. Awareness of causes for EG alternative to *Pseudomonas* is important when initiating and tailoring antimicrobial therapy.

CASE PRESENTATION

A 55-year-old man was admitted to the hospital for fever, tachycardia and a new, painful purpuric rash over both lower legs. He was undergoing chemotherapy with carfilzomib, pomalidomide and dexamethasone for relapsed multiple myeloma, complicated by persistent pancytopenia. On initial presentation, the cutaneous eruption was predominantly a non-palpable retiform purpura with associated oedema and tenderness to palpation. The skin findings were isolated to the lower legs. Over the next 2 days, enlargement of the purpura was noted with development of superimposed bullae and necrosis (figure 1). Examination of the patient's medical port was notable for painless erythema without fluctuance over the device.

INVESTIGATIONS

Complete blood count (CBC) was notable for pancytopenia and predominance of band neutrophils. The white blood cell count was 3.3×10^3 with 13% neutrophils and 45% bands. The haemoglobin was 8.7 g/dL and platelet count 90×10^3 . Serum

erythrocyte sedimentation rate was 117 mm/hour (upper limit of normal 20 mm/hour), C reactive protein was 28.4 mg/dL (upper limit of normal 0.49 mg/dL) and lactate was 4.5 mmol/L (upper limit of normal 2.2 mmol/L). Serum cryoglobulins, antineutrophil circulating antibody (ANCA) and complement levels were unremarkable. There was no evidence for haemolysis or disseminated intravascular coagulopathy. Tissue punch biopsy from the left leg revealed superficial and deep interstitial neutrophilic inflammation and Gram-negative rods on initial stain, suggestive of an inflammatory infectious retiform purpura. Blood cultures from two peripheral sites and a skin tissue culture all recovered *C. freundii*.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient with bilateral painful leg purpura and sepsis is broad, secondary to the increased aggregate degree of immunosuppressive host factors from his underlying multiple myeloma, pancytopenia and chemotherapy agents carfilzomib, pomalidomide and dexamethasone.¹ Given his net increased immunosuppression, his presentation of painful bilateral lower extremity purpura, fever, tachycardia and elevation of inflammatory markers and serum band-neutrophil percentage was concerning for an infectious origin. The differential included necrotising soft-tissue infection, cellulitis, vasculitis, vasculopathy to include cryoglobulinaemia, infectious purpura fulminans and EG.

Broad-spectrum antibiotics and aggressive supportive therapy was initiated early while diagnostic testing was performed. This included blood cultures in addition to serum cryoglobulins, ANCA and complement levels. After surgical consultation, the likelihood of necrotising soft-tissue infection seemed lower and a cutaneous punch biopsy of the retiform purpura was performed by dermatology. At this point in the patient's clinical course, some of the purpuric patches rapidly developed associated bullae and necrosis.

Interpretation of the skin biopsy was notable for diffuse neutrophilic infiltration and stained for Gram-negative rods. Vasculitis and cryoglobulinaemia were ruled out. Confirmation of the diagnosis EG was made when bacterial cultures of both peripheral blood and skin isolated *C. freundii*, further supported by the characteristic nature of gross and microscopic inspection of the skin lesions.

TREATMENT

Broad-spectrum antibiotics were initiated early and chemotherapy agents were discontinued.

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Figure 1 Well-demarcated white indurated retiform plaque with central duskiness and surrounding erythema overlying the left medial ankle.

With confirmation of EG and source control with medical port removal, antibiotics were narrowed to meropenem.

Citrobacter and other Gram-negative bacteria in the Enterobacteriaceae family can possess an inducible AmpC gene. This gene codes for a beta-lactamase resulting in potential antibiotic failure to beta-lactamase inhibitor/beta-lactam combinations as well as cephalosporins, especially when there is inadequate source control and a higher inoculum of bacteria.^{2 3} Carbapenems are the preferred antibiotic and prompt source control is necessary to reduce the inoculum effect.

OUTCOME AND FOLLOW-UP

The patient completed a 3-week course of meropenem and eventually made a full recovery from his skin lesions and Citrobacter bloodstream infection with the aid of aggressive wound care and debridement. After full resolution of this infection, chemotherapy was safely resumed.

DISCUSSION

EG is an uncommon skin manifestation resulting from either systemic or local infection. Classically, EG is characterised by bacterial invasion of the venule which then leads to secondary arteriole thrombosis, tissue oedema and separation of the epidermis. This results in formation of characteristic lesions associated with EG—vesicles or blisters surrounded by an erythematous or violaceous halo that can progress to haemorrhagic bullae with black necrotic centres.⁴ Usual skin sites of infection include the buttocks and lower extremities (66%), although a significant number of cases have resulted in involvement with the face, head and neck (8%).⁵

Two forms of EG can occur: bacteraemic and non-bacteraemic. The bacteraemic form results from haematogenous spread of the organism and the presence of positive blood cultures while the non-bacteraemic variety stems from local skin infection without evidence of a bloodstream infection.⁶ The majority of patients with EG have an underlying immunodeficiency. In one study of 167 cases of EG from 1975 to 2014, 62% were immunocompromised, including underlying malignancy, specific infectious diseases, connective tissue diseases, diabetes and AIDS.⁵

Traditionally, this disease has been pathognomonic for infection caused by *Pseudomonas aeruginosa*, occurring in 74% of cases.⁵ In the last few decades, however, more cases have emerged suggesting that other Gram-negative bacteria, Gram-positive bacteria, non-tuberculous mycobacteria and fungi can cause

EG.^{5 7 8} Some viruses including HIV and herpes simplex have also been implicated as the causative organism for EG, but their connection remains unconfirmed.⁵

C. freundii is a rare Gram-negative bacterial cause of EG and has only been reported in four previous cases, including three adults and one infant dating back to 1969.^{8–11} All four patients were immunocompromised from either lymphoma or leukaemia. Citrobacter represents normal intestinal flora and is seldom a cause of dermatological disease. Our patient has experienced the fifth known case of EG secondary to *C. freundii*. His underlying immunocompromised status was multifactorial from multiple myeloma, persistent pancytopenia and ongoing use of chemotherapy and corticosteroids. The presence of a medical port likely contributed to his sustained bacteraemia which fostered EG through skin dissemination manifesting as non-contiguous sites.

There is increasing recognition that EG can be caused by a variety of infectious organisms, including *P. aeruginosa* as well as other Gram-negative bacteria, Gram positives, non-tuberculous mycobacteria, fungi and viruses. Although the mainstay of treatment is source control and appropriate antimicrobial therapy, the variety of offending organisms necessitates a therapy directed by culture results from skin tissue biopsy and bloodstream. As *C. freundii* is a rare cause of an already uncommon skin infection, it is important to foster awareness of this pathogen as an aetiology for EG.

Learning points

- ▶ Ecthyma gangrenosum (EG) is an uncommon skin infection, typically pathognomonic for *Pseudomonas aeruginosa*.
- ▶ This is the fifth known case of *Citrobacter freundii* causing EG.
- ▶ Awareness of the spectrum of causative pathogens for EG is important as antimicrobial therapy must be tailored to the specific organism.

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