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Clinicopathologic Aspects of Ecthyma Gangrenosum in Pediatric Patients: A Case Series and Review of the Literature

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Abstract

Ecthyma gangrenosum (EG) is a cutaneous lesion classically associated with potentially fatal pseudomonal septicemia in immunocompromised patients. Other bacterial and fungal pathogens have also been implicated in EG. Although EG typically occurs in neutropenic or immunocompromised patients, it can occasionally affect previously healthy children. The cutaneous findings are characteristic with small indurated papulovesicles progressing rapidly to necrotic ulcers with surrounding erythema and a central black eschar. While lesions can occur at any site, most are commonly found over the buttocks, perineum, limbs, and axillae. We describe three cases of EG in pediatric patients with a broad spectrum of clinical and histopathologic features, who responded to appropriate antibiotic treatment for *Pseudomonas* bacteremia. For patients with possible EG, it is very important to establish the diagnosis early so that appropriate systemic antibiotic therapy can be initiated to reduce morbidity and potential mortality.

Keywords: Ecthyma gangrenosum; *Pseudomonas*; Pediatrics

Introduction

Ecthyma gangrenosum (EG) is a well-described skin lesion classically associated with *Pseudomonas* septicemia in immunocompromised patients, but may also be caused by other bacterial and fungal organisms [1]. The lesions characteristically appear as small indurated papulovesicles progressing rapidly to necrotic ulcers with surrounding erythema and a central black eschar [2]. Ecthyma gangrenosum is caused by invasion of microorganisms into the media and adventitia of subcutaneous vasculature, precipitating a hemorrhagic occlusive vasculitis [2,3]. Although rare, the presence of EG is indicative of severe systemic infection with a potentially fatal prognosis. Mortality rates for EG range from 15% to as high as 77% based on reports in the literature [4-11]. Factors that are associated with higher mortality include neutropenia, septic shock, inappropriate or delayed antibiotic therapy, and resistant microorganisms [1,7-12]. We report three cases of *Pseudomonas*-associated EG that illustrate the assortment of clinical and histopathologic findings in this disease. We also review the literature on EG treatment and outcomes, which highlights the importance of timely diagnosis and appropriate antibiotic therapy.

Case 1

A 16 year-old Native American male with a four month history of seronegative viral hepatitis-associated aplastic anemia [13] was admitted to the hospital with neutropenic fever and a single 5 x 7 cm warm, erythematous, indurated plaque with a central 1 x 1 cm black eschar located on his left abdomen. The lesion had appeared the previous day as a painful red patch that the patient attributed to an insect bite. On admission he was started empirically on vancomycin and cefepime for his febrile neutropenia. Blood cultures revealed pan-sensitive *Pseudomonas aeruginosa* bacteremia and vancomycin was discontinued.

By the third day of admission the erythematous plaque on the abdomen had increased in size to 8 x 15 cm, with a central dusky portion and bulla (Figure 1). Dermatology was consulted, and a punch biopsy was performed. Microscopic examination demonstrated a spongiotic epidermis and edema of the papillary dermis. Both the superficial and deep dermis contained multifocal collections of gram-negative

rods in the interstitium as well as within vascular walls. The diagnosis of ecthyma gangrenosum was made. A tissue culture of the wound confirmed cefepime-resistant *Pseudomonas* and the antibiotic was changed to meropenem.

Figure 1: (a) Black eschar with erythema; (b-c) epidermal spongiosis with involved vessels in the dermis; (d) collections of bacteria within vascular walls.

After one month in the hospital the patient received a matched related bone marrow transplant to treat his severe aplastic anemia. The patient tolerated the transplant well and engraftment was demonstrated with a bone marrow biopsy three weeks later. The patient received meropenem up until the day of discharge on hospital day 58, at which time he was discharged home in good condition.

Case 2

A 23 month-old male on chronic immunosuppressive therapy was transferred to our hospital for management of his abdominal wound infection. The patient had a complicated medical history including premature birth at 24 weeks gestational age and a triple visceral transplant for liver, pancreas and small bowel at 12 months of age due to necrotizing enterocolitis in addition to liver and pancreatic failure. Culture of the abdominal wound grew mixed organisms including *pseudomonas*, vancomycin-resistant *enterococcus*, and other gram-negative bacilli, for which he was treated with a 14 day course of daptomycin. On hospital day 18, he became septic and blood cultures grew Pseudomonas aeruginosa. The day prior to his sepsis onset the patient had developed erythematous papules on the left cheek, left upper chest, and right medial leg. Dermatology was consulted. A punch biopsy was performed to reveal thrombotic vasculopathy in the superficial and deep dermis without significant bacteria in the blood vessel walls (Figure 2). Stains for AFB and GMS were negative. A tissue culture of the biopsy specimen grew *Pseudomonas aeruginosa*, confirming the diagnosis of ecthyma gangrenosum.

Figure 2: (a)Erythematous plaques with dusky centers; (b-c) epidermal spongiosis and extravasation of red blood cells in the superficial dermis; (d) dermal vessel thrombosis.

Repeat blood cultures demonstrated co-infection with two strains of *Pseudomonas*, one of which was resistant to piperacillin-tazobactam and the other resistant to ciprofloxacin. A combination of the two antibiotics provided adequate coverage and his condition gradually improved. The patient recovered from pseudomonal sepsis, but later developed post-operative complications after an emergent repair of his enterocutaneous fistula and expired despite aggressive resuscitation.

Case 3

An 11 month-old previously healthy female developed rhinorrhea, sore throat, and low-grade fever five days prior to admission while her family was vacationing in Mexico. She was treated with an unknown cephalosporin at a hospital in Mexico. Subsequently, she developed nausea and diarrhea, and the concerned parents stopped administering the antibiotics. The infant developed worsening diarrhea and a rash resembling arthropod bites on her trunk, arms, and legs. Upon admission to our facility she was in a state of septic shock and received aggressive fluid resuscitation, which precipitated pulmonary edema. She was sedated and intubated, a central line was placed, and she was started on vasopressors. Labs and blood cultures were drawn and empiric therapy with ceftriaxone and vancomycin was initiated.

Upon initial examination her skin was notable for numerous rapidly evolving violaceous to purpuric papulovesicles progressing to hemorrhagic bullae on the torso and extremities. Some of the larger purpuric lesions had a retiform configuration. A CBC revealed pancytopenia with a white blood cell count of 2,700 cells/μL. Blood cultures grew pan-sensitive *Pseudomonas aeruginosa*. A punch biopsy of a lesion on the upper abdomen was performed and histologic evaluation revealed spongiosis, vesicular changes, and a mixed infiltrate in the superficial and deep dermis (Figure 3). Vasculitis and extravasated red blood cells were also observed, but no organisms were identified microscopically. A tissue gram stain was nega-

tive; however, a culture of the biopsy grew 2+ *Pseudomonas*. An MRI revealed multiple septic emboli to her brain.

Figure 3: (a)Multiple purpuric papulovesicles evolving into hemorrhagic bullae; (b-c) epidermal spongiosis and vesicular change with dermal lymphocytic infiltrate; (d) vasculopathy.

The patient was diagnosed with ecthyma gangrenosum as a manifestation of fulminant *Pseudomonas* sepsis with pneumonia as the primary source of infection. She was started on cefepime and showed gradual improvement in her condition. Her skin lesions progressed from macules and patches to bullous lesions, and then to eschars which in time spontaneously desquamated. Unfortunately, the patient's left lower extremity showed progressive ischemic changes, becoming mottled, cool, and pulseless.

One week after admission her blood cultures again became positive for *Pseudomonas* which was found to be resistant to cefepime. She was switched to gentamicin and meropenem after which she continued to improve. Her skin lesions and septic emboli showed steady resolution, however, her ischemic left extremity worsened despite daily treatment with nitroglycerin ointment.

The patient was discharged 37 days after admission with instructions to follow up with orthopedic and plastic surgery for her left leg which was becoming mummified and showing signs of auto-amputation. Two months after her discharge the patient's mummified foot and lower leg eschar spontaneously separated. At this time the patient continues to receive follow-up care with orthopedics and plastic surgery, with plans for a future prosthesis. Despite an extensive work-up, including a hematology/oncology consultation, no immunodeficiency has been identified to date.

Discussion

Patients who develop EG generally have a known diagnosis of hematologic malignancy or immunodeficiency such as agammaglobulinemia, hypogammaglobulinemia, aplastic anemia, or AIDS [1]. Rarely, EG can present in a previously healthy patient as the first indicator of an underlying malignancy or immunocompromised state [4]. Ecthyma gangrenosum has also been described in infants and young children with transient risk factors, such as concurrent viral infection and recent antibiotic therapy [4,14,15]. It has been proposed that such factors may disrupt normal host defenses by weakening the mucosal barrier of the gastrointestinal tract or temporarily affecting neutrophil number and/or function [3,4,14-17]. Furthermore, it is thought that *Pseudomonas* organisms may directly trigger a transient neutropenic state by producing toxins that inhibit granulocyte migration and cause bone marrow suppression in immunocompetent children [4,16].

Although EG is rare it serves as a hallmark of severe systemic infection and its timely recognition is of great consequence. EG is classically considered pathognomonic for *Pseudomonas aeruginosa septicemia*; however, reports have implicated an array of other bacterial and fungal pathogens [1,18]. Reported pathogens include: *Aeromonas hydrophila* [19], *Chromobacterium violaceum* [20], *Citrobacter freundii* [18], *Corynebacterium diptheriae* [21], *Escherichia coli* [1,22], *Klebsiella pneumoniae* [23], *Morganella morganii* [24], *Neisseria gonorrhoeae* [25], *Pseudomonas cepacia* [26], *Pseudomonas maltophilia* [27], *Pseudomonas stutzeri* [28], *Serratia marcescens* [29], *Staphylococcus aureus* [30] including methicillin-resistant strains [31], *Streptococcus pyogenes* [18,30], *Xanthomonas maltophilia* [32], *Yersinia pestis* [33], *Aspergillus fumigatus* [29], *Candida albicans* [34], *Curvularia sp.* [35], *Exserohilum sp.* [36], *Fusarium solani* [37], *Meterhizium anisopliae* [38], *Mucor pusilus* [39], *Pseudallecheria boydii* [35], and *Scytalidium dimidatum* [40].

A non-septicemic variant of EG has been described, in which the lesion is located at the site of entry of the pathogen. This form of EG has a substantially reduced rate of mortality [15]. It is proposed that this form may represent either an advanced local skin infection or existence of a subclinical or transient state of bacteremia [14]. Similarly, two mechanisms of pathogenesis are proposed for the classic bacteremic type of EG. In the first mechanism bacteremia originates from a primary infection of the gastrointestinal, respiratory, or urinary tract, then disseminates hematogenously to the skin [4,14]. The presentation of fever followed by an eruption of multiple lesions, as seen in Case 3, suggests hematogenous seeding subsequent to a respiratory or gastrointestinal infection. In the second postulated mechanism septicemia is thought to occur secondary to direct inoculation of the skin, as might be seen in an advanced folliculitis or a secondary infection in a burn [4,14].

The clinical presentation of ecthyma gangrenosum is somewhat variable depending upon when the lesion is first encountered. The lesion classically begins as a painless round macule that elevates into an edematous papule. Subsequently, the papule becomes erythematous, developing into a hemorrhagic bulla or pustule [2]. Bullae eventually slough to form necrotic ulcers characterized by a black eschar with a surrounding erythematous halo [2]. This evolution from macule to eschar occurs over a period of approximately 12-24 hours [17] and may be present in different stages of development [4]. Lesions

most frequently occur on the buttocks, perineum, axillae, and/or extremities but may be observed at any site [2,4,31]. Fever and other constitutional symptoms may be present depending on the extent of the underlying infection and the patient's immune status [41]. Gastrointestinal and respiratory complaints are also commonly described [17,41].

Suspicion for EG warrants a prompt punch biopsy of the lesion with cultures and sensitivities performed on blood and tissue specimens [1,2]. The histological finding of occlusive vasculitis secondary to bacteremia is characteristic of EG [3]. Histologic analysis classically reveals acute or mixed inflammation and vascular proliferation within the dermis as well as abundant gram-negative rods concentrated in the media and adventitia of vessels [2]. Necrosis of the epidermis, dermal infarction, and spongiosis are common findings [2]. These histopathologic findings are not universal, however, as illustrated by the spectrum of histologic findings in our three cases. The degree and type of inflammation as well as the presence of organisms, tissue necrosis, red blood cell extravasation, and spongiosis are highly variable. These findings are dependent upon the evolutionary stage of the lesion, which may be affected by temporal, therapeutic, and/or host factors. Correlation with the clinical picture, tissue culture, and blood culture is essential.

In combination with supportive measures, empiric therapy with broad-spectrum systemic antibiotics should be initiated as soon as blood cultures and skin biopsy are collected [2]. Typically a combination of anti-pseudomonal beta-lactam penicillin such as piperacillin with an aminoglycoside or fluoroquinolone is recommended [1,15]. Pechter et al. [14] advocate the addition of vancomycin to the empiric regimen to cover rare cases of methicillin-resistant *Staphylococcus aureus* (MRSA). If a fungal etiology is suspected systemic antifungal medication should be included. Once the pathogen has been identified and sensitivities performed, antibiotic therapy should be tailored to target the specific organism. Consultation with an infectious disease specialist is also recommended for proper treatment [2]. Surgical debridement of necrotic tissue and drainage of localized abscesses may be necessary to prevent further spread of infection [1]. Patients with immunodeficiencies such as severe neutropenia, hypogammaglobulinemia, or agammaglobulinemia may benefit from administration of granulocyte-stimulating factor or immunoglobulin [1]. In previously healthy patients a thorough work up should be performed to rule out an underlying immune deficiency or malignancy [3].

Even with appropriate therapy the mortality for Pseudomonas septicemia in the immunocompromised remains high, ranging from 38-77% [4-11], with septic shock and multisystem organ failure commonly occurring. The prognosis for patients with the non-septicemic variant of EG is much better, with a reported mortality rate of 15% [5]. Other factors negatively affecting prognosis include underlying malignancy, neutropenia, bacteremia, infection originating in the lung or abdomen, and delay of greater than 1 day in the administration of appropriate antibiotic therapy [1,7-12].

Conclusion

These three reported cases highlight the diversity of clinical presentations in ecthyma gangrenosum among pediatric patients with life-threatening *Pseudomonas* septicemia. Although EG classically occurs in immunocompromised patients, the same entity may arise in otherwise healthy children with transient risk factors such as recent viral infection, as demonstrated by our third case. As the appearance of ecthyma gangrenosum can be highly variable, EG should always be considered in the differential diagnosis for septic patients presenting with neutropenia and a new skin lesion.

Suspicion for EG warrants prompt collection of blood and tissue cultures, a skin biopsy, and broad-spectrum empiric antibiotic therapy to include anti-pseudomonal coverage. While a skin biopsy showing occlusive vasculopathy with gram-negative rods in venule walls is virtually diagnostic of EG, the histopathologic appearance is affected by many variables, including lesion evolution and antibiotic therapy. Since biopsy findings may be non-specific it is imperative to correlate histopathologic appearance of the lesion with tissue and blood cultures as well as the clinical presentation.

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