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Ecthyma Gangrenosum in Pediatric Patients: A Three 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 Ecthyma gangrenosum treatment and outcomes, which highlights the importance of timely diagnosis and appropriate antibiotic therapy.

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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.

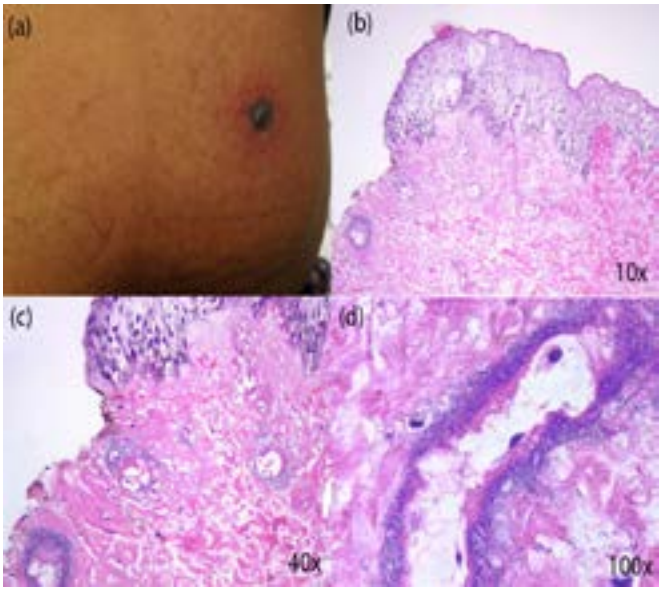


Figure 1: (a) Black eschar with erythema; (b-c) epidermal spongiosis with involved vessels in the dermis; (d) collections of bacteria within vascular walls.

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

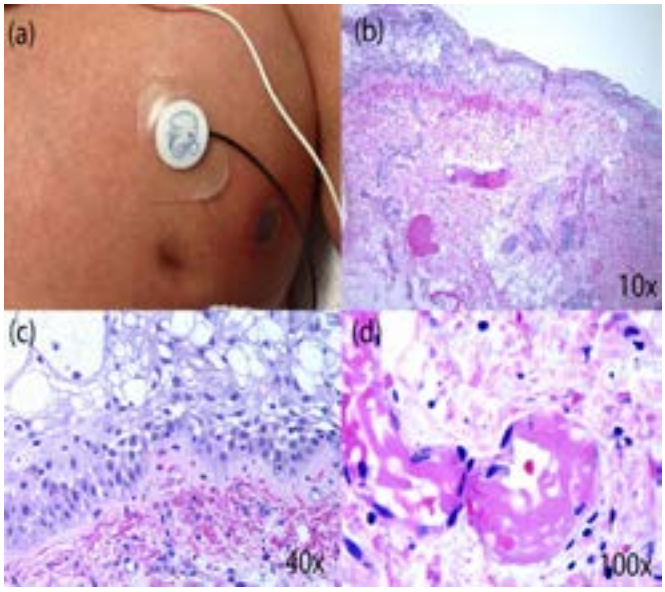


Figure 2: (a)Erythematous plaques with dusky centers; (b-c) epidermal spongiosis and extravasation of red blood cells in the superficial dermis; (d) dermal vessel thrombosis.

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

A 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 violacious to purpuric papulovesicles evolving into hemorrhagic bullae on the torso and extremities. Some of 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 negative, however, a cul-

ture of the biopsy grew 2+ Pseudomonas. An MRI revealed multiple septic emboli to her brain.

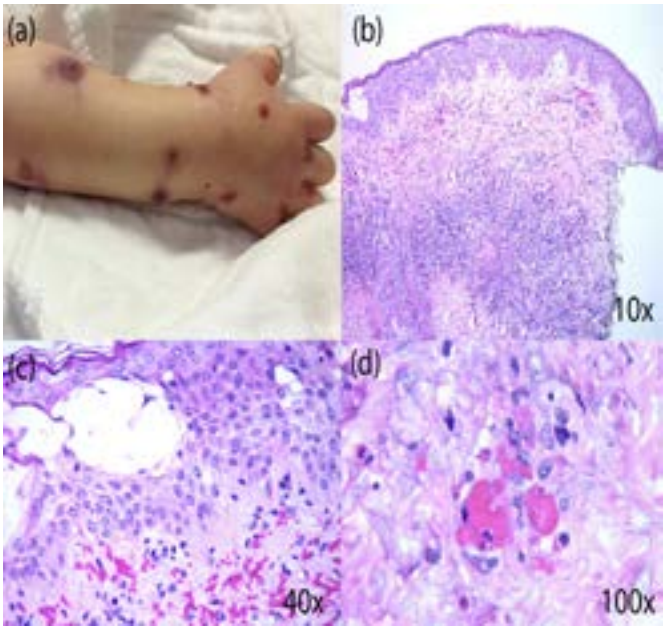


Figure 3: (a)Scabbed erythematous plaques, vesicles, and hemorrhagic bullae; (b-c) epidermal spongiosis and vesicular change with dermal lymphocytic infiltrate; (d) vasculopathy.

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 leg left 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]. EG 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 ecthyma gangrenosum 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 gonorhheae* [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 also 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 5 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 of 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.

References

1. Patel JK, Perez OA, Viera MH, Halem M, Berman B (2009) Ecthyma gangrenosum caused by Escherichia coli bacteremia: a case report and review of the literature. Cutis 84: 261-267.

2. Greene SL, Su WP, Muller SA (1984) Ecthyma gangrenosum: report of clinical, histopathologic, and bacteriologic aspects of eight cases. J Am Acad Dermatol 11: 781-787.

3. Goolamali SI, Fogo A, Killian L, Shaikh H, Brathwaite N, et al. (2009) Ecthyma gangrenosum: an important feature of pseudomonal sepsis in a previously well child. Clin Exp Dermatol 34: e180-e182.

4. Zomorrodi A, Wald ER (2002) Ecthyma gangrenosum: considerations in a previously healthy child. Pediatr Infect Dis J 21: 1161-1164.

5. Huminer D, Siegman-Igra Y, Morduchowicz G, Pitlik SD (1987) Ethyma gangrenosum without bacteremia: report of six cases and review of the literature. Arch Intern Med 147: 299-301.

6. Osmon S, Ward S, Fraser VJ, Kollef MH (2004) Hospital mortality for patients with bacteremia due to Staphylococcus aureus or Pseudomonas aeruginosa. Chest 125: 607-616.

7. Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, et al. (2003) Pseudomonas aeruginosa bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. Clinical Infectious Diseases 37: 745-751.

8. Peña C, Suarez C, Gozalo M, Murillas J, Almirante B, et al. (2011) Prospective multicenter study of the impact of carbapenem resistance on mortality in Pseudomonas aeruginosa bloodstream infections. Antimicrobial Agents and Chemotherapy 56: 1265-1272.

9. Marra AR, Pereira CA, Gales AC, Menezes LC, Cal RG, et al. (2006) Bloodstream infections with metallo-beta-lactamase- producing Pseudomonas aeruginosa: epidemiology, microbiology, and clinical outcomes. Antimicrob Agents Chemother 50: 388-390.

10. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH, et al. (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting Chest 118: 146-155.

11. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, et al. (1989) Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 87: 540-546.

12. Bodey GP, Jadeja L, Elting L (1985) Pseudomonas bacteremia: retrospective analysis of 410 episodes. Arch Intern Med 145: 1621-1629.

13. Cudillo L (2009) Aplastic anemia and viral hepatitis. Mediterr J Hematol Infect Dis 1: e2009026.

14. Pechter PM, Marchione R, Milikowski C, Berman B (2012) Ecthyma gangrenosum secondary to Staphylococcus aureus in an infant with transient neutropenia. Pediatr Dermatol 29: 320-323.

15. Koo SH, Lee JH, Shin H, Lee JI (2012) Ecthyma gangrenosum in a previously healthy infant. Arch Plast Sur 39: 673-675.

16. Huang YC, Lin YT, Wang CH (2002) Community-acquired Pseudomonas aeruginosa sepsis in previously healthy infants and children: analysis of forty-three episodes. Pediatr Infect Dis J 21: 1049-1052.

17. Viola L, Langer A, Pulitano S, Chiaretti A, Piastra M, et al. (2006) Serious Pseudomonal aeruginosa infection in healthy children: case report and review of the literature. Pediatrics International 48: 330-333.

18. Reich HL, Williams Fadeyi D, Naik NS, Honig PJ, Yan AC (2004) Nonpseudomonal ecthyma gangrenosum. J Am Acad Dermatol 50: S114-S117.

19. Francis YF, Richman S, Hussain S, Schwartz J (1982) Aerumonas hydrophila infection: ecthyma gangrenosum with aplastic anemia. N Y State J Med 82: 1461-1464.

20. Brown KL, Stein A, Morrell DS (2006) Ecthyma gangrenosum and septic shock syndrome secondary to Chromobacterium violaceum. J Am Acad Dermatol 54: S224-S228.

21. Hofler W (1991) Cutaneous diphtheria. International Journal of Dermatology 30: 845-847.

22. Rajan RK (1982) Spontaneous bacterial peritonitis with ecthyma gangrenosum due to Escherichia coli. J Clin Gastroenterol 4: 145-148.

23. Rodot S, Lacour JP, van Elslande L, Castanet J, Desruelles F, et al. (1995) Ecthyma gangrenosum caused by Klebsiella pneumoniae. Int J Dermatol 34: 216-217.

24. Del Pozo J, Garcia-Silva J, Almagto M, Martínez W, Nicolas R, et al. (1998) Ecthyma gangrenosum-like eruption associated with Morganella morganii infection. Br J Dermatol 139: 520-521.

25. Glicksman JM, Short DH, Knox JM, Freeman RG, et al. (1967) Gonococcal skin lesions: report of a case of gonococcal ecthyma. Arch Dermatol 96: 74-76.

26. Sanlangue J, Brissaud O, Labreze C (2006) Clinical features of Pseudomonas aeruginosa infections. Arch Pediatr 13: S13-S16.

27. Mudet RR, Yu VL, Dummer JS, Vinson C, Lumish RM (1987) Infections caused by Pseudomonas maltophilia: expanding clinical spectrum. Arch Intern Med 147: 1672-1674.

28. Puzenat E, Chirouze C, Khayar N, Aubin F, Estavoyer JM, et al. (2004) Rev Med Interne 25: 315-318.

29. Musher DM (1980) Cutaneous and soft-tissue manifestations of sepsis due to gram-negative enteric bacilli. Rev Infect Dis 2: 854-866.

30. Hurwitz RM (1987) Ecthyma gangrenosum without bacteremia or necrotic cellulitis: a localized form of septic vasculitis. Archives of Internal Medicine 147: 1513.

31. Chang AY, Carlos CA, Schuster M, Xu X, Rosenbach M, et al. (2012) Nonpseudomonal ecthyma gangrenosum associated with methicillin-resistant Staphylococcus aureus: a case report and review of the literature. Cutis 90: 67-69.

32. Bottone EJ, Reitano M, Janda JM, Troy K, Cuttner J, et al. (1986) Pseudomonas maltophilia exoenzyme activity as correlate in pathogenesis of ecthyma gangrenosum. J Clin Microbiol 24: 995-997.

33. Welty TK. Grabman J, Kompare E, Wood G, Welty E, et al. (1985) Nineteen cases of plague in Arizona: a spectrum including ecthyma gangrenosum due to plague and plague in pregnancy. West J Med 142: 641-646.

34. File TM Jr, Manna OA, Flowers FP (1979) Necrotic skin lesions associated with disseminated candidiasis. Arch Dermatol 115: 214-215.

35. Bonduel M, Santos P, Turienzo CF, Chantada G, Paganini H, et al. (2001) Atypical skin lesions caused by Curvularia sp. and Pseudallescheria boydii in two patients after allogeneic bone marrow transplantation. Bone Marrow Transplant 27: 1311-1313.

36. Levy I, Stein J, Ashkenazi S, Samra Z, Livni G, et al. (2003) Ecthyma gangrenosum caused by disseminated Exserohilum in a child with leukemia: case report and review of the literature. Pediatr Dermatol 20: 495-497.

37. Prins C, Chavaz P, Tamm K, Hauser C (1995) Ecthyma gangrenosum-like lesions: a sign of disseminated Fusarium infection in the neutropenic patient. Clin Exp Dermatol 20: 428-430.

38. Burgner D, Eagles G, Burgeos M, Procopis P, Rogers M, et al. (1998) Disseminated invasive infection due to Metarrhizium anisopliae in an immunocompromised child. J Clin Microbiol 36: 1146-1150.

39. Kramer BS, Hernandez AD, Reddick RL, Levine AS (1977) Cutaneous infarction: manifestation of disseminated mucormycosis. Arch Dermatol 113: 1075-1076.

40. Benne CA, Neeleman C, Bruin M, de Hoog GS, Fleer A (1993) Disseminating infection with Scytalidium dimidiatum in a granulocytopenic child. Eur J Clin Microbiol Infect Dis 12: 118-121.

41. Fink M, Conrad D, Matthews M, Browning JC (2012) Primary ecthyma gangrenosum as a presenting sign in a child. Dermatol Online J 18: 3.