

# Ecthyma gangrenosum in Saudi Arabia

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## ABSTRACT

We report a diagnosis of ecthyma gangrenosum (EG) in 4 females of mean age 54.8 (range 43-64) years, within 10 months. Severe drug reaction treated with high dose systemic corticosteroids in patient one, acute myelocytic leukemia treated with high dose dexamethasone, and multiple broad-spectrum antibiotics in patient 2 preceded the onset of EG. Patients 3 and 4 had vasculitic purpura and hemodialysis. In addition, patient 3 was receiving multiple broad-spectrum antibiotics plus anti-tuberculosis (TB) drugs for gastric TB, while patient 4 was on melphalan and high dose systemic corticosteroids. *Pseudomonas aeruginosa* was isolated from blood culture of the first 3 patients, and skin culture of patient one. Blister aspirate from patient 4 yielded *Candida albicans*. Factors enhancing skin invasion by pathogenic organisms in our patients were breached skin integrity, therapy with high dose corticosteroids and multiple broad-spectrum antibiotics, hematologic malignancies and chemotherapy with severe neutropenia

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Ecthyma gangrenosum (EG) is a skin manifestation of *Pseudomonas aeruginosa* (*P. aeruginosa*) bacteremia. It occurs in immuno-compromised patients, in those on chemotherapy with hematological malignancies, neutropenia on prolonged therapy with broad-spectrum antibiotics, and in diabetes mellitus (DM). The aim of this report is to create awareness of the clinical features of EG as seen at King Khalid Hospital, Jeddah, Kingdom of Saudi Arabia (KSA).

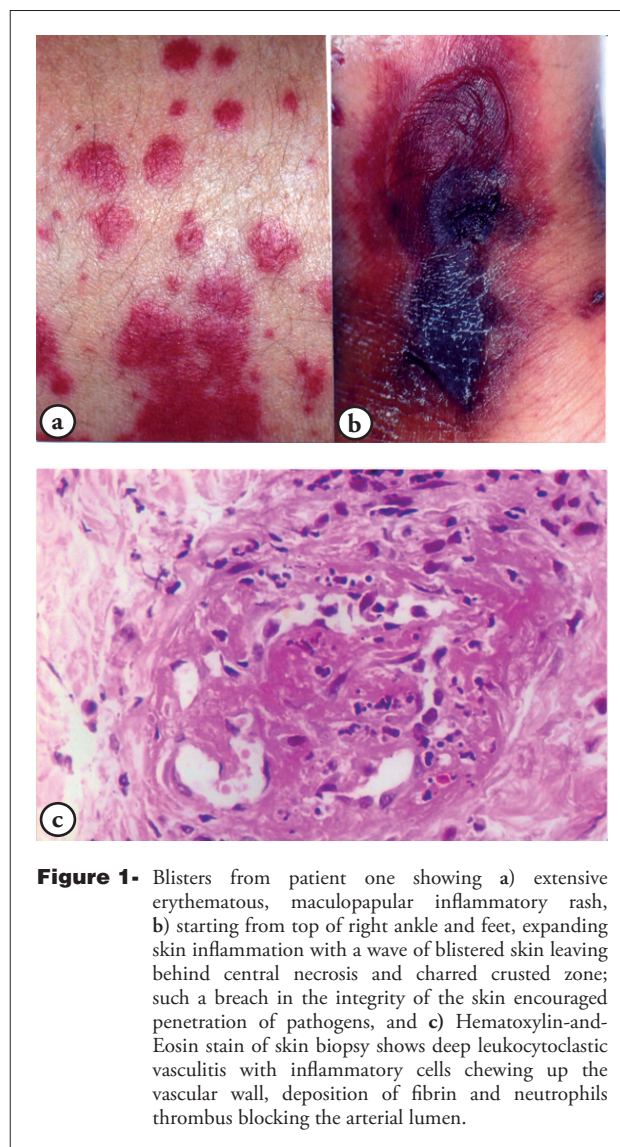
**Case Report.** *Patient 1.* A 43-year-old female presented with generalized itchy rash and painful swelling

of the left hand after using diclofenac sodium for 13 days. On examination, she was in pain with a tender swollen left hand, extensive erythematous maculopapular, and plaque rash (**Figure 1a**). A diclofenac-related drug reaction was diagnosed. Skin biopsy showed focal neutrophilic vasculitis, focal acanthosis, and moderate perivascular mixed inflammatory infiltrates, large numbers of neutrophils, few lymphocytes, and histiocytes. A hand x-ray and laboratory tests results were normal except for high erythrocyte sedimentation rate 35 mm/hr (normal range [nr]: 0-20mm/hr) and gamma glutamic transaminase (GGT) 104 iu/L (nr: 7-32iu/L). Her medications were stopped. Betamethasone dipropionate 25% cream twice per day, methylprednisolone 30 mg once daily, ranitidine 150 mg twice per day, and loratadine 10 mg once daily was started. The rash began fading within a week. On the 8th day, a dose of diclofenac prescribed by an on-call physician started fresh rashes at multiple sites. There were target-like lesions, acute arthritis of the right ankle and hands, mouth ulcers, and pain on swallowing. Stevens Johnson's syndrome was suspected. The methylprednisolone and dipropionate cream were stopped. Meloxicam 15 mg once daily, azathioprine 2 mg/kg/day, valacyclovir 500 mg twice per day, lignocaine oral gel, and lorazepam 1 mg at bed time were started. Repeat laboratory tests showed blood urea 113 mmol/L (nr: 1.7- 8.3mmol/L), GGT 104 iu/L (nr: 7-32 iu/L), fasting blood glucose 21.5mmol/L (nr 3.9-6.1mmol/L), rheumatoid factor 55, and antistreptolysin O titer 1600 iu/ml (nr <200 iu/ml). Other tests were normal. Steroid-induced hyperglycemia was controlled with insulin. On the third week, severe polyarthrititis, tender erythematous plaques appeared on the upper and lower limbs. Intravenous methylprednisolone 1 gm daily for 5 days followed by prednisolone 60 mg once daily, one-Alpha (alfacalcidol) and Ca-Caltrate were given. Her condition stabilized and initial rash began to fade. On day 24, the tender erythematous plaques increased centrifugally. Skin biopsy was repeated. Dapsone 100 mg daily were

added, followed with prednisolone. On day 30, the patient developed low-grade fever and central necrosis of the plaques covered by black eschar, first starting on the right ankle and at other sites. Thin superficial blisters were leading the advancing margin of the plaques (**Figure 1b**). A diagnosis of EC was suspected. Blood and skin specimens were sent out immediately. The second skin biopsy showed superficial and deep leukocytoclastic vasculitis, subcutaneous fat necrosis, fibrin, and neutrophil thrombosis within the vascular walls (**Figure 1c**). Blood culture and swab from the floor of the thin blister yielded heavy growth of *P. aeruginosa* and *Acinetobacter*, the skin also grew *Citrobacter freundii* and *Acinetobacter*. She was treated with ceftazidime, ciprofloxacin, and gentamicin according to the sensitivity results. The ulcers later healed and she was discharged, and was well at the next follow-up.

**Patient 2.** A 48-year-old female, receiving treatment for acute myelocytic leukemia type M3, presented with a large bruise on the right breast. Her medications were ciprofloxacin, amikacin, vancomycin, ceftazidime, gentamicin, dexamethasone, and all-trans-retinoic acid. On examination, she was very ill and lethargic. On her right breast were 2 adjacent erythematous indurated plaques with central necrosis covered by a black-green crust. On her right calf was an early, erythematous plaque with mild central darkening. The clinical features fitted those of EG. A review of her laboratory results showed hemoglobin (Hb) 9.5 g/dl, severe neutropenia (neutrophils  $0.7 \times 10^9/L$ , (nr  $7.5 \times 10^9/L$ )), white blood cell (WBC)  $1.5 \times 10^9/L$  (nr:  $4.0-11.0 \times 10^9/L$ ), and platelets  $5 \times 10^9/L$  (nr:  $150 \times 450 \times 10^9/L$ ). Blood and skin cultures showed heavy growth of *P. aeruginosa*, *Klebsiella pneumoniae* (*K. pneumoniae*), and methicillin resistant *Staphylococcus aureus* (MRSA). Antibiotic therapy was chosen in accordance to sensitivity tests. Her condition improved and she was discharged home after one month.

**Patient 3.** A 64-year-old female was seen on dermatology consultation, after an emergency hospital admission, with watery diarrhea, vomiting, and purpura on her legs and trunk. Her other medical problems were type II diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, gastric tuberculosis, and chronic renal failure on hemodialysis. Her medications were flucloxacillin 500 mg 6 hourly, ceftazidime 1 g hourly, ciprofloxacin, isoniazid 150 mg, rifampicin 300 mg, and pyrazinamide 1.5 g daily. Henoch-Schönlein purpura was diagnosed, and skin biopsy showed leukocytoclastic vasculitis. The *P. aeruginosa* was isolated from her blood and atrio ventricular fistula on 2 occasions. Purpura (**Figure 2a**) was still present when she was reviewed a fortnight later, and she had black-colored superficial bulla with marginal erythema on the dorsum of her right

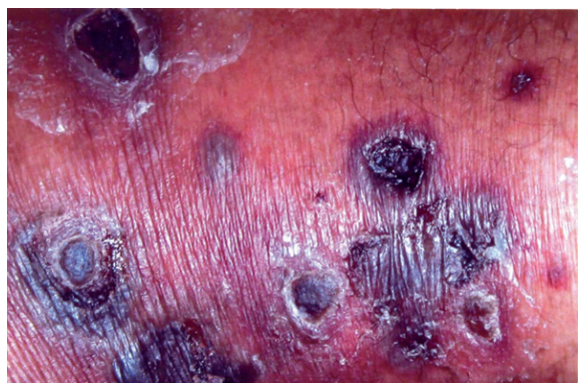


**Figure 1** - Blisters from patient one showing a) extensive erythematous, maculopapular inflammatory rash, b) starting from top of right ankle and feet, expanding skin inflammation with a wave of blistered skin leaving behind central necrosis and charred crusted zone; such a breach in the integrity of the skin encouraged penetration of pathogens, and c) Hematoxylin-and-Eosin stain of skin biopsy shows deep leukocytoclastic vasculitis with inflammatory cells chewing up the vascular wall, deposition of fibrin and neutrophils thrombus blocking the arterial lumen.



**Figure 2** - Lesions from patient 3 showing a) erythematous maculopapular purpuric lesions with 2 excoriated papules at the upper zone on upper and lower limbs, and b) Ecthyma gangrenosum lesion as a large irregular black superficial bulla with marginal erythema on the dorsum of right hand.





**Figure 3** - Close-up view of multiple deep ulcers on both ankles and contiguous dorsum of feet of patient 4. They have raised margins and central thick black crusts. An established deep ulcer is on the right lower zone.

hand (**Figure 2b**). A diagnosis of EG was made. Blister fluid grew coagulase negative *S. aureus*. Antibiotics were unchanged. Her condition later improved, and the ulcer healed. She was discharged home. Subsequently, she was in and out of hospital for 9 months and died from extensive purpura, fungal sepsis, candida endocarditis, and cerebral vascular accident.

**Patient 4.** A 64-year-old female was presented with 6-week-history of painful ulcers, with blister formation on both feet and ankles. She previously had 2 preceding episodes of purpura affecting both lower limbs. Skin biopsy then showed leukocytoclastic vasculitis. Multiple myeloma was diagnosed, and treatment with melphalan 10 mg daily, prednisolone 50 mg daily, and hemodialysis for chronic renal failure was started. She received intravenous vancomycin 1 gm, and ceftazidime 2 gm 4 hourly prior to this consultation. On examination, multiple ulcers covered with a thick gray-black crust, slight erythematous halo and thin superficial blisters (**Figure 3**) were seen on the anterior aspects of her ankles and dorsum of feet. A diagnosis of EG was made. Blister aspirate yielded scanty growth of *Candida albicans* (*C. albicans*). Urine examination showed antibacterial substances, and grew *C. albicans* ( $>10^5$  CFU/ml, nr:  $<1000$  col/ml). Her blood count showed pancytopenia, hemoglobin 8.6 g/dl (nr: 13.0-18.0 g/dl), WBC 2.7 (nr:  $4.0 - 11.0 \times 10^9/L$ ); lymphocytes 0.07 (nr:  $1.5 - 4.0 \times 10^9/L$ ), neutrophils  $1.5 \times 10^9/l$  (nr:  $2.0 \times 7.5 \times 10^9/L$ ). She was lost to follow up.

**Discussion.** The diagnosis of 4 cases of EG in 10 months may suggest that the condition is common in this region. On the contrary, a literature search covering a period of 10 years found no previous report of EG from KSA. The reason for this may be lack of awareness

of this condition on the part of clinicians. Pseudomonas bacteremia occurred in 3 of our 4 patients. The *C. albicans* was the only isolate from the fourth patient. A swab was taken after she received ceftazidime and vancomycin. However, it is unclear whether or not *C. albicans* was the only pathogen involved. Pathogens associated with EG in our patients were *P. aeruginosa*, Acinetobacter species, *K. pneumoniae*, MRSA, coagulase-negative *S. aureus* and *C. albicans*. The EG is most commonly associated with *P. aeruginosa*<sup>1</sup> bacteremia in up to 28% of cases. Candida<sup>2</sup> and *Aeromonas hydrophilia*<sup>3,4</sup> cause skin lesions clinically and histologically resembling EG. Other pathogens<sup>1</sup> that cause EG-like lesions include *Aspergillus*, *Mucor*, *S. aureus*, *Serratia marcescens*, *Yersinia*, *Fusarium solani*<sup>5</sup> and *Escherichia coli*, *Morganella*, and *K. pneumoniae*.<sup>6</sup> In view of the wide range of varied pathogens linked to EG or to EG-like lesions, it has been suggested<sup>7</sup> that EG may be a final common pathway in some forms of sepsis. Histopathologic features of EG<sup>8-10</sup> include vasculitis, septic thromboses in the vascular lumen, and necrosis of the epidermis, dermis and subcutaneous fatty layer.

The diagnosis of EG requires a high index of suspicion, especially when an erythematous, warm, tender or non-tender nodule or macule develops central necrosis with black-green or gray-black eschar, surrounding erythematous halo and marginal superficial blister. Microbiology of the blister fluid, necrotic ulcer or tissue biopsy is of utmost importance in the recognition of the pathogenic organisms associated with EG. The EG may occur without bacteremia.<sup>11,12</sup> Principles of management include good nursing care, frequent monitoring of the patient's clinical condition, early commencement of antibiotic therapy based on bacterial sensitivity as well as necessary general measures. The *P. aeruginosa* rarely causes disease in a healthy subject. Host factors,<sup>13,14</sup> which encourage tissue colonization by pathogens include a breach in normal cutaneous barrier function as in inflammatory dermatoses, and burns, pressure ulcers and intravenous line in some of our patients. Other factors are prolonged therapy with high dose systemic corticosteroids, multiple broad spectrum antibiotics, hematologic malignancies, chemotherapy-induced neutropenia, DM, sepsis, chronic renal failure, and hemodialysis, hypogammaglobulinemia and immunodeficiency states such as HIV.<sup>15</sup> Most pseudomonas infections are hospital-acquired. The *P. aeruginosa* starts with superficial attachment to cutaneous or mucosal, surfaces, followed by localized bacterial invasion and damage to underlying tissues. It may also gain entry into the dermis and subcutaneous tissue through adnexal epidermal structures. The *Pseudomonas* releases a number of host-tissue destroying enzymes, cytotoxin, elastase, phospholipase, alkaline protease,

exoenzymes or exotoxins A and S, which aid bacterial proliferation, host tissue invasion and injury, with or without blood stream invasion, dissemination, systemic inflammatory response syndrome, multiple organ dysfunction and ultimate death.<sup>16</sup> The clinical course of EG can be very rapid, from onset to completion may take only from 12-24 hours.<sup>17</sup>

In conclusion, this report may stimulate clinicians to look for and report more cases of EG from Saudi Arabia.

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