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Ecthyma gangrenosum versus ecthyma-like lesions: should we separate these conditions?

Michael Vaiman[1]✉, Tsilia Lasarovitch[2], Lior Heller[3], Gad Lotan[4]

Abstract

Introduction: We analyzed cases of ecthyma gangrenosum (EG) and "ecthyma-like" or "ecthyma-mimicking" cases of necrotic lesions of the skin to improve current definitions of these conditions.
Methods: The retrospective analysis compared 28 cases of lesions (from 2001 to June 2015) that were identified as EG. Age, sex, lesion location, time from macule to ulcer, underlying diseases, number of lesions per patient, wound bacterial culture, blood culture, and immune status served as variables for analysis and comparison.
Results: Only in 20 cases (71.42%) was *Pseudomonas aeruginosa* the etiology of the lesion. The etiology of eight cases was various bacterial species (five cases, 17.85%) and fungal species (three cases, 10.73%). In 21 cases (75%), the lesion appeared in immunocompromised patients. In four cases (14.28%), the patients suffered from *Pseudomonas* sepsis. In four cases (14.28%), the lesion appeared in healthy individuals. There was no difference in clinical picture, lesion location, number of lesions per person, and treatment strategy between *Pseudomonas* and non-*Pseudomonas* cases.
Conclusions: Necrotic lesions resembling EG can have various microbiological etiology and can occur in immunocompetent or healthy persons. With no difference in clinical picture, two separate definitions should not be applied to *Pseudomonas* and non-*Pseudomonas* cases. We suggest accepting a broader definition of EG.

Keywords: ecthyma gangrenosum, ecthyma-like lesions, necrotic lesion, *Pseudomonas aeruginosa*

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Introduction

Ecthyma gangrenosum (EG) is a relatively uncommon condition. It has been known since 1897 and the term itself was generally accepted in the 1950s (1, 2). Until the 1970s, it was thought that this condition was pathognomonic of *Pseudomonas* septicemia (*Pseudomonas aeruginosa*) and that it should usually be seen in immunocompromised patients, particularly those with underlying malignant disease (3, 4). Since the 1980s, it has been understood that various bacteria such as *E. coli*, *Citrobacter freundii*, *Klebsiella pneumonia*, various other *Pseudomonas* species, and *Morganella morganii* may be etiologic agents for EG as well as some fungi (*Candida albicans* and others) (5–7). The infection is not necessarily a monoculture and, for example, *Candida albicans* can coexist with *Pseudomonas aeruginosa* in the same lesion (7). To make matters worse, it was then reported that EG is not specific to immunocompromised patients but can also manifest in immunocompetent patients as well (8). Finally, it was reported that EG can affect an otherwise healthy person, and the entire concept that EG is a skin manifestation of severe systemic infection was called into question (9). Cases of EG diagnosed in healthy newborn infants exacerbated this confusion (10, 11).

Although they are generally accepted, the exact clinical manifestations also have unanswered questions. For example, most authors agree that the skin lesions usually occur in the gluteal and perineal regions (57%) or extremities (30%) (12, 13). At the same time, the lesions may appear on the face, chest, arms, neck—in fact, all over the body (9, 14). Thus, currently we have no detailed knowledge about this condition. Some authors have tried to overcome this confusion by suggesting two definitions: EG and EG-like lesions (11, 15, 16), or "mimicking ecthyma gangrenosum" lesions (17).

What is definitely known is that the skin lesion begins as an erythematous nodule or hemorrhagic vesicle, which evolves into a necrotic ulcer with an eschar (4–7). An early lesion may transform into a necrotic ulcer in as little as 12 hours. The skin lesions can be single or widespread over the body, and the case fatality rate is high. If patients with EG are immunocompromised, they are usually suffering from leukemia, lymphoma, other malignant diseases, severe burns, or organ transplant, or might be receiving immunosuppressive therapy (18–20). Blood cultures and skin biopsy with culture are necessary for precise diagnosis. A second skin biopsy is usually sent for tissue culture for bacteria, fungi, yeasts, and mycobacteria. Sensitivity tests are carried out on any isolated organisms. When the etiology is established, aggressive antibiotic or anti-fungal treatment is prescribed but, because EG manifests as a necrotizing soft-tissue lesion, surgical excision is often necessary. The surgeries vary from aggressive surgical debridement and skin grafting to relatively mild plastic surgeries.

The purpose of the current research was to seek to give some order to the current situation with EG and answer whether "EG-like lesion" should be accepted as a separate definition.

Materials and methods

The methodology of the research was based on a comparative analysis between our own EG cases and cases described in the literature with respect to etiology, underlying diseases, immune status,

[1]Department of Otolaryngology – Head and Neck Surgery, Assaf Harofe Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. [2]Department of Microbiology, Assaf Harofe Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. [3]Department of Plastic Surgery, Assaf Harofe Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. [4]Pediatric Surgery Department, Assaf HaRofeh Medical Center, affiliated with the Sakler Medical School, Tel Aviv University, Zerifin, Israel. ✉**Corresponding author: vaimed@yahoo.com**

and location of the lesions. A retrospective cohort study reviewed the medical records of patients with EG that were admitted to the Emergency Department and referred to the Surgical Department or Dermatology Department at the Assaf Harofeh Medical Center from January 2001 to June 2014. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected a priori after approval by the institution's Helsinki committee.

Inclusion/exclusion criteria were as follows: tissue defects due to burns were excluded from the analysis. All other cases with an EG-specific tissue defect that were admitted and had signs of general and/or local infection and skin necrosis were included, whatever etiology was detected. The presence or absence of underlying diseases such as malignancy, specific infectious disease, connective tissue disease, diabetes, AIDS, and other immunocompromising pathologies were taken into account. In all of the cases analyzed, a differential diagnosis was performed between EG and Warfarin-induced skin necrosis, cocaine-induced skin necrosis, calciphylaxis, septic emboli, loxoscelism, diabetic microangiopathy, disseminated intravascular coagulation, necrotizing vasculitis, paraneoplastic extensive necrotizing vasculitis, pyoderma gangrenosum, livedoid vasculopathy, necrotizing fasciitis, and necrosis secondary to the use of vasoactive drugs. If the records lacked complete information on these subjects, the cases were excluded from the analysis. Records with incomplete or unclear bacteriological results were excluded from the analysis.

Results

Twenty-eight cases were identified following the inclusion/exclusion criteria. The flow was as follows: out of 49 cases, 16 were excluded because of lack of complete data on differential diagnosis, and five cases were excluded because of a lack of clear bacteriological data. All of the patients had previously untreated EG lesions. All of the patients received standard lesion inspection/sanitation/closure procedures at the Emergency Department and were then referred to the Dermatology Department, of them 23 patients (82%) with further reference to surgery. General data on the cases are presented in Table 1.

Bacteriological results, clinical picture, and treatment results were obtained for each case. On the 1st or 2nd day after admission, the blood culture and culture specimen from the skin lesion were obtained. In all identified cases, bacteriological samples were processed in the hospital's laboratory department. Specimen processing included detection of bacteria by culturing, biochemical identification, and susceptibility testing. Specimens were inoculated into the following culture media: MacConkey agar and blood agar. Cultured plates were examined after overnight incubation at 37 °C; if no growth was obtained in the plates, they were re-incubated for another 24 hours. Identification of *Pseudomonas aeruginosa* and an antibiotics susceptibility test were performed using VITEK 2 instrument, bioMerieux, according to CLSI (Clinical Laboratory Standards Institute) interpretive standards. The bacteriological data are presented in Table 2.

In 20 cases (71.42%), *Pseudomonas aeruginosa* was the etiology of the lesion. The etiology of eight cases was various bacterial species (five cases, 17.85%) and fungal species (three cases, 10.73%). In 21 cases (75%), the lesion appeared in immunocompromised patients. Only in four cases (14.28%) did the patients suffer from *Pseudomonas* sepsis. In four cases (14.28%), the lesion appeared in healthy individuals. There was no difference in clinical picture, lesion location, number of lesions per person, and treatment strategy between *Pseudomonas* and non-*Pseudomonas* cases.

Table 1 | **General data on 28 observed cases of ecthyma gangrenosum.**

Case no.	Age	Sex	Lesion location	Macule to ulcer	Diseases	No. of lesions
1	5	M	arm	in 12 hours	leukemia	single
2	18	M	buttock	in 18 hours	healthy	single
3	54	M	buttock, leg	in 2 days	rheumatoid arthritis	multiple
4	38	F	face	in 2 days	multinodular goiter	single
5	33	F	back, leg	in 1.5 days	cancer treatment	multiple
6	12	F	forearm	in 12 hours	leukemia	single
7	87	M	back	in 2 days	cancer treatment	single
8	65	F	leg	in 3 days	diabetes mellitus	single
9	52	M	buttock	in 2 days	cancer treatment	single
10	43	M	leg	in 24 hours	leukemia	single
11	19	F	leg	in 24 hours	rheumatoid arthritis	single
12	45	F	buttock	in 1.5 days	leukemia	single
13	45	F	leg	in 3 days	cancer treatment	single
14	38	F	back	in 24 hours	healthy	single
15	29	M	buttock	in 2 days	cancer treatment	single
16	74	M	back, leg, foot	in 2 days	cancer treatment	multiple
17	69	M	face	in 5 days	lymphoma	single
18	7	F	leg, arm	in 24 hours	leukemia	multiple
19	24	M	chest	in 24 hours	rheumatoid arthritis	single
20	83	M	leg	in 24 hours	cancer treatment	single
21	65	F	leg	in 2 days	cancer treatment	single
22	66	M	abdomen	in 4 days	lymphoma	single
23	38	M	leg	in 7 days	leukemia	single
24	44	F	back	in 24 hours	abscess	single
25	71	F	buttock, leg	in 24 hours	leukemia	multiple
26	57	F	face	in 2 days	healthy	single
27	18	M	buttock	in 24 hours	leukemia	single
28	53	M	buttock	in 2 days	healthy	single

Table 2 | **Microbiology lab data on 28 observed cases of ecthyma gangrenosum.**

Case no.	Age	Culture in wound	Culture in blood	Immunocompromised?
1	5	*P. aeruginosa*	*P. aeruginosa*	Yes, leukemia
2	18	*P. aeruginosa*	none	No
3	54	*P. aeruginosa*	none	Yes, rheumatoid arthritis
4	38	*P. aeruginosa*	none	No
5	33	*A. hydrophila*	none	Yes, cancer treatment
6	12	*P. aeruginosa*	*P. aeruginosa*	Yes, leukemia
7	87	*P. aeruginosa*	none	Yes, cancer treatment
8	65	*P. aeruginosa*	none	No
9	52	*A. hydrophila*	none	Yes, cancer treatment
10	43	*P. aeruginosa*	none	Yes, leukemia
11	19	*P. aeruginosa*	none	Yes, rheumatoid arthritis
12	45	*P. aeruginosa*	*P. aeruginosa*	Yes, leukemia
13	45	*P. aeruginosa*	none	Yes, cancer treatment
14	38	*P. aeruginosa*	none	No
15	29	*Fusarium solani*	none	Yes, cancer treatment
16	74	*P. aeruginosa*	none	Yes, cancer treatment
17	69	*Candida albicans*	none	Yes, lymphoma
18	7	*P. aeruginosa*	none	Yes, leukemia
19	24	*P. aeruginosa*	none	Yes, rheumatoid arthritis
20	83	*P. aeruginosa*	none	Yes, cancer treatment
21	65	*P. aeruginosa*	*P. aeruginosa*	Yes, cancer treatment
22	66	*P. aeruginosa*	none	Yes, lymphoma
23	38	*P. stutzeri*	none	Yes, leukemia
24	44	*P. aeruginosa*	none	No
25	71	*E. coli*	none	Yes, leukemia
26	57	*A. hydrophila*	none	No
27	18	*Fusarium solani*	none	Yes, leukemia
28	53	*P. aeruginosa*	none	No

In 18 cases, the buttocks and/or lower extremities were affected (64.5%), but the rest of the ten cases presented lesions in various parts of the body, including the face (three cases, 10.7%).

During the period from 2001 to 2014, empiric antibiotic therapy experienced some changes. Ceftazidime, ampicillin, and conventional amphotericin B were used more often. Specific therapy was administered upon availability of results from the microbiology department. There was no uniformity in these results. For

example, 10 isolates (50% of *P. aeruginosa* cases) were resistant to cefazolin, and another 10 isolates (50%) were resistant to ampicillin but susceptible to cefazolin. Following bacteriological results, the antibiotic treatment was changed to gentamicin (two cases), ampicillin (10 cases), ceftazidime (one case), ciprofloxacin (two cases), doxorubicin + vincristine (one case), cefazolin (three cases), and clindamycin + ciprofloxacin (two cases) that were administered as standard protocols require. Standard wound care included wet to dry dressing changes.

As for non-*Pseudomonas* cases, *Aeromonas hydrophila* (three cases) had different antibiotic sensitivities and were treated with cephalosporin. The case caused by *Pseudomonas stutzeri* was successfully treated with chlorhexidine. *Escherichia coli* (one case) was sensitive to ampicillin. Two cases due to *Fusarium solani* were treated with local debridement and topical amphotericin B. Another fungal case, in which *Candida albicans* was involved, was successfully treated with amphotericin B and caspofungin.

In 23 cases (82.14%), various surgical treatment was needed, mainly surgical debridement (in all 23 cases) followed by minor plastic surgery in five cases (17.85%). In two cases, both on the back, the lesions were more than 10 cm in diameter and skin grafting was performed. Among these 23 surgical cases, acute inflammatory cell infiltration and vascular proliferation were seen in the dermis in 17 cases, but in six cases the process also involved the subcutaneous tissue. The surgical approach to *Pseudomonas* and non-*Pseudomonas* cases was similar.

The treatment of EG was successful in all 28 cases in our series, but five patients died afterwards because of their main diseases.

Discussion

The generally accepted definition of EG states that this condition is a bacterial skin infection usually caused by *Pseudomonas aeruginosa*, which appears in the context of *P. aeruginosa* sepsis in immunocompromised patients (2–4, 18, 21). When it was understood that P. aeruginosa is not the only etiological agent for EG, an attempt was made to separate "real" EG from "EG-like" or "EG-mimicking" lesions. At that point, the first definition was applied to P. aeruginosa EG cases and the second definition to all EG cases of different etiology. The term "nonpseudomonal ecthyma gangrenosum" was also suggested (22).

As stated in the introduction, continuous description of EG cases of various etiology, in immunocompetent and even healthy individuals, started in the 1960s and 1970s. The majority of these descriptions are presented as case reports and number of these reports is growing every year. The recently published review on EG literature indicates that *P. aeruginosa* was detected in 73.65% of cases; of them, there were only 72 cases (58.5%) with sepsis (23).

Comparing our series of cases with the cases that have been described in the literature, we did not find any clinical difference between *Pseudomonas* and non-*Pseudomonas* EG cases. To illustrate our point, we present two cases (Figs. 1 and 2). In both cases, the face was affected at approximately the same location. Some case reports state that EG is extremely rare in the face, but in fact it is not so rare. In the first case (case 4, 38, F), *P. aeruginosa* was the etiology of the lesion. In the second case (case 17, 69, M), *Candida albicans* caused similar skin necrosis. Both cases were successfully treated by the same protocol, which is indicated below.

If an etiological approach is warranted, one can define *Pseudomonas EG*, other-bacteria EG, fungal EG, and so on. Clinically, one sees the same disorder. If a clinical approach is warranted, the conditions should not be separated on the basis of possible

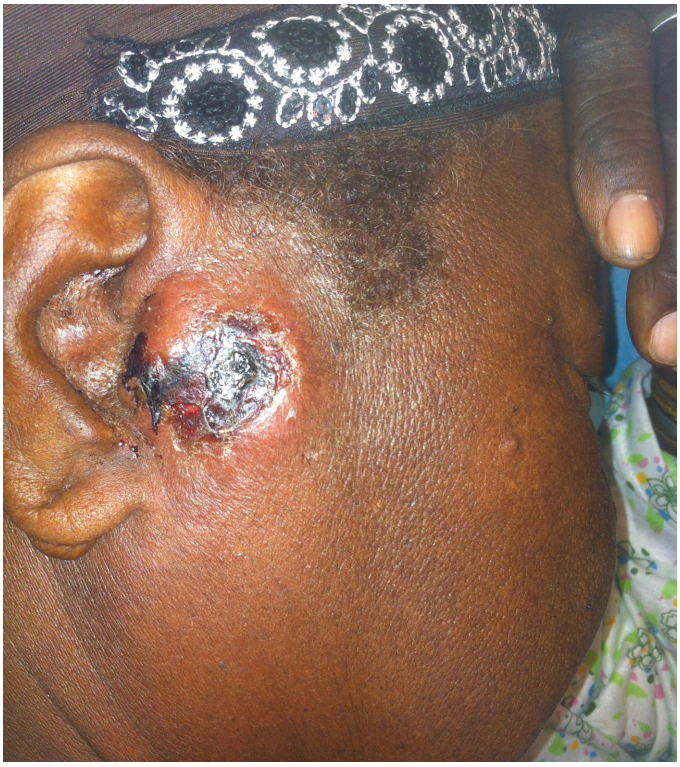

Figure 1 | A case of facial EG (case 4, 38, F) with *P. aeruginosa* as the etiology of the lesion.

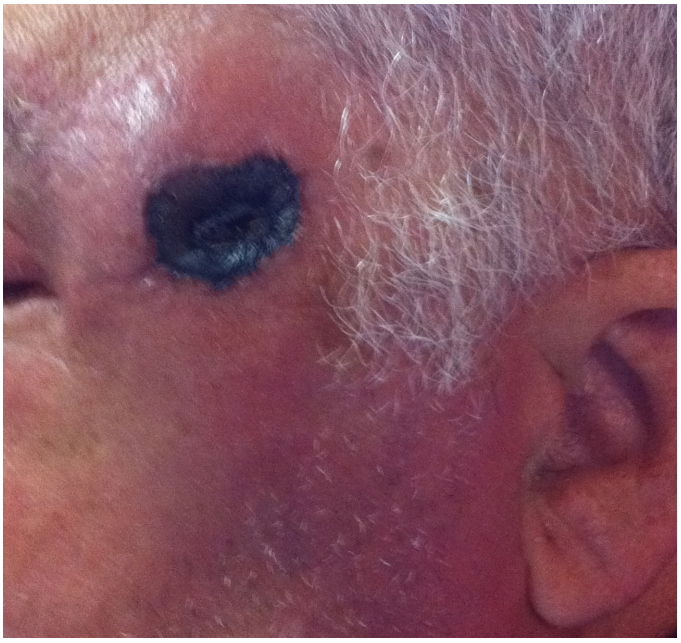

Figure 2 | A case of facial EG (case 17, 69, M) with *Candida albicans* as the etiology of the lesion.

microbiological causes that vary broadly. EG is a reaction pattern of the skin to compromised local blood flow, and this reaction generally occurs irrespective of the bacterial or non-bacterial agent. In all cases, whatever the etiology is, the protocol to manage a patient remains the same:

1. Recognize the necrotic skin lesion as EG, perform differential diagnosis;
2. Send samples for bacteriological investigation;
3. Administer empiric antibiotic therapy;
4. Obtain results from the microbiology department;
5. Change the antibiotic or antifungal treatment accordingly;
6. Apply surgery as needed.

A Wood's lamp (Wood's light, black lamp) can be used to speed up this process. By using this diagnostic tool, a physician can see the green fluorescence if there is *Pseudomonas aeruginosa*, allow-

ing proper antibiotic therapy before culture results are obtained from the laboratory (24, 25).

In our series, we had numerous variations of the disorder: EG due to *P. aeruginosa* in an immunocompromised patient (cases 1, 3, 6, 10, 11, etc.), EG due to *P. aeruginosa* in an immunocompetent patient (cases 2, 4, 8, etc.), EG due to *P. aeruginosa* in a healthy patient (cases 14, 28), EG due to various bacterial infection in an immunocompromised patient (cases 5, 9, 23, 25), and fungal EG (cases 15, 17, 27). We observed cases with and without septicemia. *P. aeruginosa* etiology and immunocompromised status prevailed, but were not obligatory.

Any attempt to change the definition is open to further discussion. Analyzing our experience and reports in the emerging literature, we suggest defining EG as a bacterial skin infection of various etiology that leads to vasculitis and further local skin necrosis. The disorder is more likely to appear in the presence of *P. aeruginosa* and immunocompromised status of a patient. However, only a minority of patients are septic and other organisms can be associated with ecthyma-like lesions.

Conclusion

Necrotic lesions resembling ecthyma gangrenosum can have various microbiological etiology, and can occur in immunocompetent or even healthy persons. Although there is no difference in the clinical picture, we do not think that two separate definitions should be applied to *Pseudomonas* and non-*Pseudomonas* cases. Instead, we suggest accepting a broader definition of ecthyma gangrenosum.

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