Ecthyma gangrenosum and ecthyma-like lesions: review article

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Abstract The generally accepted definition of ecthyma gangrenosum (EG) states that this condition is pathognomonic of Pseudomonas septicemia (Pseudomonas aeruginosa) and that it should usually be seen in immunocompromised patients, particularly those with underlying malignant disease. The cases described in the literature present a somewhat different picture. Our objective was to analyze this controversy. The review analyzes 167 cases of EG that were described in the literature from 1975 to 2014. All articles on EG cases with EG-specific tissue defect that had signs of general and/or local infection and skin necrosis were included and analyzed, whatever the etiology detected. Necrotic lesions of the skin diagnosed as EG have various microbiological etiology, can occur in immunocompetent or even healthy persons, and are not necessarily connected with septicemia. In published cases, P. aeruginosa was detected in 123 cases (73.65 %); of them, there were only 72 cases (58.5 %) with sepsis. Other bacterial etiology was detected in 29 cases (17.35 %) and fungi were detected in 15 cases (9 %). While the clinical picture of the disease and the treatment strategy remain the same, there is no need to invent two separate definitions for Pseudomonas and non-Pseudomonas cases. We suggest accepting a broader definition of EG.

Introduction

Ecthyma gangrenosum (EG) is a relatively uncommon condition. The clear description of the disease was given by L. Barker in 1897 and the term itself was generally accepted in the 1950s [1, 2]. Up to the 1970s, it was postulated that this condition is pathognomonic of Pseudomonas septicemia (Pseudomonas aeruginosa) and that it should usually be seen in immunocompromised patients, particularly those with underlying malignant disease [3, 4]. P. aeruginosa is a Gram-negative, aerobic, coccobacillus bacterium that was previously known as Bacterium aeruginosum, Bacillus pyocyaneus, and Bacterium pyocyaneum. The name P. aeruginosa became generally accepted since the 1940s. The importance of this bacterium in dermatology was well described [5].

Since the 1980s, more and more data have been accumulated that various bacteria like Escherichia coli, Citrobacter freundii, Klebsiella pneumonia, various other Pseudomonas species, and Morganella morganii can be etiologic agents for EG, as well as some fungi (Candida albicans, Fusarium, and others) [6–8]. It was also reported that EG can manifest in immunocompetent patients as well [9]. Finally, it was reported that EG can affect an otherwise healthy person and the whole concept that EG is a skin manifestation of severe systemic Pseudomonas infection was questioned [10]. Cases of EG diagnosed in healthy newborn infants added more to this unclear situation [11, 12].
The clinical picture of EG is well described as hemorrhagic pustules evolving into necrotic ulcers. The evolved EG gangrenous ulcer has a black scab and can be surrounded by a red halo. While generally accepted, the exact clinical manifestations also have their own unanswered questions. For example, most of the researches agree that the skin lesions usually occur in the gluteal and perineal regions (57 %) or extremities (30 %) [13, 14]. The lesions, however, may appear on the face, chest, arms, neck, and other parts of the body [10, 15]. At present, the knowledge about EG is still incomplete. In the emerging literature, authors have tried to overcome this confusion, suggesting two definitions: EG and EG-like lesions [12, 16, 17] or “mimicking eczema gangrenosum” lesions [18]. The current review analyzes the above-described controversies.

Search strategy and selection criteria

An extensive search for relevant data was performed through the PubMed, MEDLINE, and ScienceDirect search tools. The articles on the subject published from 1975 till 2014 were analyzed. The search started from the 1940s, when the first relevant articles appeared, but the selection of relevant articles started from 1975, when the diagnosis of P. aeruginosa infection was completely developed. Current microbiologic analysis includes the usage of blood agar or eosin-methylene blue agar, Gram morphology, ability/ inability to ferment lactose, a positive/negative oxidase reaction, odor, ability/ inability to grow at 42 °C, and fluorescence under ultraviolet light. Fluorescence is also used to detect the presence of P. aeruginosa in wounds. The articles that appeared before the 1970s frequently lack this complete set of tests.

Inclusion criterion: all articles on EG cases with EG-specific tissue defect that had signs of general and/or local infection and skin necrosis were included and analyzed, whatever the etiology detected. Exclusion criteria: articles on the subject dealing with EG-like tissue defects that appeared after burns were excluded from the analysis. Articles with incomplete description of differential diagnosis were excluded from the analysis, as well as articles with an unclear description of the microbiologic laboratory diagnostics.

In addition to the location of the lesion, clinical picture, and treatment, three main variables were analyzed: etiology, presence or absence of septicemia, and the immune status of the patients.

Results

From 1975 to 2014, 85 articles on EG were published that met the requirements of the inclusion criteria. These articles described 167 cases of EG of various etiology. Most of the articles described 1–3 cases as case reports. Few articles described several cases, i.e., eight [19, 20], six [21, 22], and seven cases [23]. The most recent article of Chuang et al. in 2014 described 17 cases of EG that were found among 27 cases of Shanghai fever of P. aeruginosa etiology [24].

Etiology

Of the 167 published cases, P. aeruginosa was detected in 123 cases (73.65 %) (Table 1). Various other bacterial etiology was detected in 29 cases (17.35 %), fungi were detected in 15 cases (9 %). Pseudomonas cepacia, Pseudomonas maltophilia, Pseudomonas stutzeri, Aeromonas hydrophila, Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Staphylococcus aureus, Staphylococcus epidermidis, and Stenotrophomonas maltophilia were described as etiology of non-P. aeruginosa cases, as well as disseminated nontuberculous mycobacterial infection and streptococcal infection. The most frequent agents were A. hydrophila (seven cases), P. maltophilia (Xanthomonas maltophilia) (four cases), and E. coli (four cases). Among fungal infections, the authors indicated Mucor pusillus [25], Candida tropicalis [26], Fusarium solani [27], Scytalidium dimidiatum [28], Metarhizium anisopliae [29], and Candida albicans as the EG etiology [8, 12].

The viral etiology remains unclear and poorly described. Two articles described non-bacteremic EG in patients with acquired immune deficiency syndrome (AIDS; three cases), but the connection between EG and human immunodeficiency virus (HIV) remains very unclear [30, 31]. Herpes simplex was indicated among the possible viral etiological agents, but its connection with EG is also unclear [32]. The infection is not necessarily a monoculture and, for example, Fusarium spp. can coexist with P. aeruginosa in the same patient [16].

General clinical picture

As a rule, P. aeruginosa or other etiological agents invade the venules, resulting in secondary thrombosis of the arterioles, tissue edema, and separation of the epidermis that leads to a specific clinical picture of EG. Almost all of the analyzed reports and articles describe the same clinical manifestation of EG, with very slight variations. The skin lesions begin as an erythematous nodule or hemorrhagic vesicle, usually macule first and then papule, which evolves into a necrotic ulcer with eschar [4–15]. The skin lesions can be single or widespread over the body. In the analyzed literature, we detected no difference in the descriptions of the clinical picture, time from nodule to ulcer, lesion location, and number of lesions per person between Pseudomonas and non-Pseudomonas cases.
EG with and without septicemia

Of the 123 EG cases of *P. aeruginosa* etiology, sepsis/septicemia/bacteremia were described in 72 cases (58.5 % of *Pseudomonas* cases or 43.1 % of all cases) and an absence of septicemia was detected in 51 cases (41.5 % of *Pseudomonas* cases). Any age can be affected, starting from neonatal *P. aeruginosa* sepsis [33]. In older patients (72 years), *Pseudomonas* bacteremia can coexist with disseminated fusariosis in wounds [16]. Up to the 1980s, it was generally accepted that EG complicating *Pseudomonas* bacteremia/sepsis is fatal to most patients, especially infants [3, 34]. Further development of antibiotic therapy helped to reduce the number of fatalities. At present, even a newborn with EG and neonatal sepsis associated with significant leukopenia, thrombocytopenia, and alteration of the coagulation profile can be saved by intravenous antibiotic treatment [33].

When EG was caused by other bacteria species, bacteremia was detected in a much lower number of cases. Of the 29 EG cases with various bacterial etiology, only two cases (6.9 % of bacterial etiology or 1.2 % of all cases) had positive blood cultures. Blood cultures were positive for *Pseudomonas stutzeri* [35] and *Escherichia coli* [36, 37]. Fungal flora can also be cultured from the blood of patients with EG, as well as from the lesions. Two case reports described that blood culture grew *Scytalidium dimidiatum* and *Candida albicans* [8, 28]. These two cases represent 13.33 % of 15 cases with fungal etiology.

EG and the immune status of the patients

The immunocompromised status is not obligatory for the patients with EG. Among 123 patients with *P. aeruginosa* EG, only 73 (59 % of *Pseudomonas* cases) were immunocompromised and the remaining 50 (41 %) were immunocompetent. EG cases of various other bacterial etiology present approximately the same picture: 17 immunocompromised vs. 12 immunocompetent out of the total of 29 cases (58.62 vs. 41.38 %). In contrast, fungal EG can be found in immunocompromised patients almost always (13 cases out of 15, 86.66 %).

Diagnosis and differential diagnosis

During the period from 1975 to 2014, the basics of EG diagnostics remained generally the same. Blood cultures and skin biopsy are optimal for precise diagnosis. A skin biopsy should be sent for tissue culture for bacteria, fungi, yeasts, and mycobacteria. Sensitivity tests should be performed on any isolated organisms. Specimen processing includes the detection of bacteria by culturing, biochemical identification, and susceptibility testing.

The majority of case reports do not describe microbiological procedures in detail, indicating only the microorganism that the wound cultures grew. The present protocol indicates that the specimens should be inoculated into MacConkey agar and blood agar. Cultured plates should be examined after overnight incubation at 37 °C. If no growth was obtained in the plates, they should be reincubated for another 24 h. The identification of *Pseudomonas aeruginosa* and antibiotics susceptibility tests are performed by using a VITEK 2 (bioMérieux) or similar instrument, according to the interpretive standards of the Clinical and Laboratory Standards Institute (CLSI) [38–40].

While in the majority of cases the clinical picture is specific and convincing, the differential diagnosis should be performed between EG and warfarin-induced skin necrosis, cocaine-induced skin necrosis, calciphylaxis, septic emboli, loxoscelism, diabetic microangiopathy, disseminated intravascular coagulation, paraneoplastic extensive necrotizing vasculitis, pyoderma gangrenosum, livedoid vasculopathy, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, cutaneous necrotizing vasculitis as a manifestation of familial Mediterranean fever, and necrosis secondary to the use of vasoactive drugs [41, 42].

Underlying diseases

The analysis of 85 selected articles indicates that a broad spectrum of diseases might be associated with EG. Malignancy, specific infectious diseases, connective tissue diseases, diabetes, AIDS, and other immunocompromising pathologies are common for the patients with EG, irrespective of the

<p>| Table 1 | Distribution of 167 ecthyma gangrenosum (EG) cases described in the literature since 1975 |
|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Septicemia</th>
<th><em>P. aeruginosa</em></th>
<th>Other bacteria</th>
<th>Fungal</th>
<th>Immune status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32</td>
<td>2</td>
<td>2</td>
<td></td>
<td>Immunocompromised</td>
</tr>
<tr>
<td>No</td>
<td>41</td>
<td>15</td>
<td>11</td>
<td></td>
<td>Immunocompromised</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Immunocompetent</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td></td>
<td>Immunocompetent</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Healthy</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Healthy</td>
</tr>
<tr>
<td>Total</td>
<td>123 (73.65 %)</td>
<td>29 (17.35 %)</td>
<td>15 (9 %)</td>
<td></td>
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</tr>
</tbody>
</table>
etiological agent. Species other than *P. aeruginosa* can easily infect an immunocompromised patient. For example, a patient with acute myelocytic leukemia developed EG caused by *Citrobacter freundii* [43]. In another case, disseminated invasive infection due to *Metarhizium anisopliae* in an immunocompromised child (acute lymphoblastic leukemia) also produced EG [29]. The majority of immunocompromised patients usually suffer from leukemia, lymphoma, other malignant diseases, severe burns or organ transplant [44], or might be receiving immunosuppressive therapy.

In the 1980s, it was generally accepted that *P. aeruginosa* can cause green nail syndrome, toe web infections, hot tub folliculitis, infectious eczematoid dermatitis, and other mild cutaneous infections in healthy individuals, while *Pseudomonas* septicemia causes EG [45]. At present, we detect a growing number of reports describing EG in healthy individuals [10, 46–52].

An underlying disease does not necessarily affect the immune status of a patient. For example, *P. aeruginosa* EG was described in a woman with recurrent Graves’ disease who had normal white blood cell count, immunoglobulins, and lymphocyte subsets [53].

Location of the lesions

Of the 167 described cases, the buttocks and/or lower extremities were affected in 110 cases (65.8 %), but the remaining 57 cases (34.2 %) presented lesions in various parts of the body, including the face. The face and the whole head and neck region are affected much more often than is usually thought. At least 14 cases of EG lesions were described as being located within the head and neck region [11, 33–35, 53–61]. The last two references are case reports describing EG of the nasal cavity. Several more similar case reports were published, but the differential diagnosis between EG and noma remained unclear, and we do include these data in the present review. An EG lesion of the genital area was also described [62].

Severe perineal ecthyma gangrenosum can result in a cloaca-like deformity [63]. Cases with affected buttocks, anogenital area, and/or lower extremities are numerous and blood cultures can be both positive and negative for *P. aeruginosa* or other bacteria [64]. The route of infection is generally difficult to establish and analysis of the topographic anatomy of the muscles, nerves, and arteries of the perineum does not present any clear solution. Both physically active and immobile patients with severe diseases that can cause inadequate blood supply to the buttocks and perineum may have EG of these areas. Further studies are needed in order to clarify the picture.

Treatment

There are three stages of the treatment of EG: (1) empiric antibiotic therapy is administered initially, (2) when the etiology is established, aggressive antibiotic or antifungal treatment is prescribed, but because EG manifests as a necrotizing soft-tissue lesion, (3) surgical excision is often necessary.

During the period from 1975 to 2014, empiric antibiotic therapy experienced significant changes that do not permit precise evaluation. In general, ceftazidime, ampicillin, amoxicillin–clavulanate, and conventional amphotericin B were used more often. Specific therapy should be administered upon the availability of results from the microbiological department. As can be seen from the 167 analyzed cases, there is no uniformity in these results. For example, 28 isolates in *P. aeruginosa* cases were resistant to cefazolin, and another 21 isolates were resistant to ampicillin but susceptible to cefazolin. Following bacteriological results, the administered antibiotic treatment in *P. aeruginosa* EG cases (n=123) included gentamicin (22 cases), ampicillin (39 cases), carbenicillin (five cases), ceftazidime (11 cases), ciprofloxacin (17 cases), doxorubicin+vinristine (seven cases), cefazolin (11 cases), and clindamycin+ciprofloxacin (seven cases) that were administered as standard protocols require. In four cases, the specific therapy was not administered because the patients died before the culture results were received from the laboratory.

As for non-*Pseudomonas* cases, various specific treatments were administered. *Aeromonas hydrophila* (six cases) had different antibiotic sensitivities and was treated mainly with cephalosporin. The case caused by *Pseudomonas stutzeri* was successfully treated with chlorhexidine. *Escherichia coli* can be successfully treated with ampicillin. 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. If treatment is successful, the ulcer diminishes and disappears (Fig. 1a, b).

The surgeries vary from aggressive surgical debridement and skin grafting to relatively mild plastic surgeries. Irrespective of the etiological agent, surgical procedures were needed in 128 cases out of 167 (76.6 %), but in most of the cases (n=99; 59.3 %), surgical debridement was enough. Minor plastic surgery and/or skin grafting was performed in 29 cases (17.4 %). Standard wound care included wet to dry dressing changes. Among these 29 surgical cases, acute inflammatory cell infiltration and vascular proliferation were seen in the dermis in 20 cases, but in nine cases, the process involved the subcutaneous tissue as well. The surgical approach to *Pseudomonas* and non-*Pseudomonas* cases was similar.

Discussion

Descriptions of EG cases of various etiology, in immunocompetent and even healthy individuals, started from the 1960s
and 1970s. As stated in the introduction to this review, the present definition of EG as a bacterial skin infection caused by *P. aeruginosa* that appears with *P. aeruginosa* sepsis in immunocompromised patients cannot be applied to all EG cases. In fact, as can be seen from Table 1, the complete triad *P. aeruginosa* in the lesion+*P. aeruginosa* sepsis+immunocompromised status was indicated only in 32 cases out of the 167 described cases (19.2 %). This percentage, however, does not reflect the real picture. With rare exceptions, the analyzed 1975–2014 publications were case reports. A case report is designed to present some rare or even unique case. Therefore, we believe that the majority of the “normative” EG cases were not reported.

With new case reports being published, the initial reports on EG of non-*Pseudomonas* etiology presented as “unique” are no longer unique. At present, for example, 12 cases were published in which *E. coli* was detected as an etiological agent for EG. EG caused by *E. coli* can occur following spontaneous bacterial peritonitis due to the same organism and Shiga toxin-producing *E. coli* can cooperate with *P. aeruginosa* sepsis in producing EG [65, 66]. Such cases are usually associated with *E. coli* bacteremia [36, 37, 65–67].

As *P. aeruginosa* is not the only etiological agent for EG, attempts were made to separate “real” EG from “EG-like” or “EG-mimicking” lesions. The first definition should be applied to *P. aeruginosa* EG cases and the second definition to all EG cases of different etiology. The term “nonpseudomonal ecthyma gangrenosum” was suggested as well [68].

Scrupulous analysis of the cases that were described in the literature do not indicate any clinical difference between *Pseudomonas* and non-*Pseudomonas* EG cases. As the data of Table 2 show, a more or less strong correlation exists only between EG and the immunocompromised status of a patient if etiology is not taken into account. One report even suggested that *P. aeruginosa* sepsis and EG might be initial manifestations of primary immunodeficiency [69]. Clinically, the authors describe the same disorder whatever the culture obtained.

The authors of the analyzed articles described all possible variations of the disorder: EG due to *P. aeruginosa* in an immunocompromised patient with or without septicemia, EG due to *P. aeruginosa* in an immunocompetent patient, EG due to *P. aeruginosa* in a healthy patient, EG due to various bacterial infections in immunocompromised and immunocompetent patients, fungal EG with and without septicemia, etc. [43].

Any attempt to change the definition is open for further discussion. Analyzing reports in the emerging literature, we suggest to define 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.

**Conclusion**

Necrotic lesions of the skin diagnosed as ecthyma gangrenosum (EG) have various microbiological etiology, such as *P. aeruginosa*, *E. coli*, and even fungal infections. Understanding the different etiological agents and their interactions with the host’s immune system is crucial for accurate diagnosis and effective treatment. Further research is needed to elucidate the complex interplay between bacterial infection and immunocompromised status in the development of EG.
can occur in immunocompetent or even healthy persons, and are not necessarily connected with septicemia. While the clinical picture of the disease and the treatment strategy remain the same, there is no need to invent two separate definitions for *Pseudomonas* and non-*Pseudomonas* cases. We suggest accepting a broader definition of EG.

**Conflict of interest** Disclosure of potential conflicts of interest: the authors state no potential conflict of interest.

**Compliance with ethical standards** Research involving human participants and/or animals: N/A.

Informed consent: N/A.

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