The pathogenesis of ecthyma gangrenosum

P. J. van den Broek, J. W. M. van der Meer
and M. W. Kunst

University Hospital, Leiden, The Netherlands,
Department of Infectious Diseases

Summary
Eight patients with ecthyma gangrenosum were studied. In two the ecthyma gangrenosum was secondary to Pseudomonas bacteraemia, and two showed no evidence of bacteraemia. In two of the other four patients with Pseudomonas bacteraemia, the blood stream invasion was probably secondary to the skin lesions. In view of these findings it is concluded that ecthyma gangrenosum can arise in two ways: as a primary skin lesion that may or may not be followed by bacteraemia, or as a lesion secondary to Pseudomonas bacteraemia.

Introduction
Ecthyma gangrenosum is a characteristic skin lesion caused by Pseudomonas spp., as shown by Hitschman and Kreibich in 1897. Their observations in two young children, one with tuberculosis and the other with enteritis, led them to conclude that ecthyma gangrenosum was a primary infection of the skin. At present, however, the lesion is said to be pathognomonic for Pseudomonas septicaemia (Dorff, Geimer, Rosenthal and Rytel, 1971; Hall, Callaway, Tindall and Smith, 1968; Stanley, 1947).

During the last four years we have had eight patients with ecthyma gangrenosum. The findings in our patients justify reconsideration of the ideas of Hitschman and Kreibich (1897) providing an alternative hypothesis concerning the genesis of ecthyma gangrenosum.

Patients
The relevant data of the patients are given in Table I. All of these patients had fewer than $0.3 \times 10^9/\text{l}$ granulocytes at the onset of the ecthyma gangrenosum. Patient 1, who was treated with partial antibiotic decontamination (Guiot and van Furth, 1977) and whose bacteriological cultures (faeces, urine, mouth and various skin sites) showed no Pseudomonas spp., developed fever, after which Pseudomonas aeruginosa was cultured from the blood and the tip of an intravenous catheter. A day later, several ecthyma gangrenosum lesions appeared. In patient 2, multiple lesions arose simultaneously on one arm. Blood cultures taken on the same day were positive for
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis*</th>
<th>Localization of skin lesions</th>
<th><em>Pseudomonas cultures</em></th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>aa</td>
<td>Back, elbow</td>
<td>Local: positive</td>
<td>Tobramycin, Carbenicillin</td>
<td>Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>41</td>
<td>amml</td>
<td>Arm (multiple)</td>
<td>Local: not done</td>
<td>Gentamicin, Carbenicillin</td>
<td>Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>34</td>
<td>aa</td>
<td>Axilla</td>
<td>Local: positive</td>
<td>Gentamicin, Cephaloridine</td>
<td>Fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>19</td>
<td>aa</td>
<td>Scrotum</td>
<td>Local: positive</td>
<td>Tobramycin, Amikacin, Carbenicillin, Granulocyte Transfusions</td>
<td>Fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>30</td>
<td>aml</td>
<td>Foot</td>
<td>Local: positive</td>
<td>Amikacin, Tobramycin, Carbenicillin, Granulocyte Transfusions</td>
<td>Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>47</td>
<td>aml</td>
<td>Scrotum, perineum</td>
<td>Local: positive</td>
<td>Amikacin, Carbenicillin, Granulocyte Transfusions</td>
<td>Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>22</td>
<td>cml, blastcrises</td>
<td>Scrotum, groin</td>
<td>Local: positive</td>
<td>Tobramycin, Carbenicillin</td>
<td>Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>21</td>
<td>aa</td>
<td>Scrotum, groin</td>
<td>Local: positive</td>
<td>Amikacin, Carbenicillin, Granulocyte Transfusions</td>
<td>Fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood: positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aa = aplastic anemia; amml = acute myelo-monoblastic leukemia; aml = acute myeloid leukemia; cml = chronic myeloid leukemia.
Plate 1: Ecthyma gangrenosum in patient 5: haemorrhagic bullous stage.
Plate 2. Ecthyma gangrenosum in patient 6: final stage, necrotic lesions.
**Ecthyma gangrenosum**

*Pseudomonas aeruginosa.* Patients 3 and 4 also produced positive blood cultures and skin lesions simultaneously. In patients 5 and 6, all blood cultures were negative. Patient 5 was not febrile on the day on which the ecthyma gangrenosum was diagnosed (Plate 1). Two blood cultures taken on that day, prior to antibiotic therapy, and nine subsequent blood cultures displayed no growth, but *Pseudomonas aeruginosa* was cultured from the skin lesion. In patient 6, four blood cultures drawn on the day on which the skin lesions were first noticed (Plate 2) and before antibiotic therapy was started, were negative. Ten blood cultures taken on the following days were also negative. In patient 7, *Pseudomonas aeruginosa* was cultured from the groins during routine bacteriological assessment. Four days later, he developed fever and ecthyma gangrenosum in the groin. Blood cultures taken on that day were positive for *Pseudomonas aeruginosa*. Patient 8 initially had fever and a necrotic lesion in the groin from which *Pseudomonas aeruginosa* was cultured. At that time, the blood cultures were negative. Despite appropriate antibiotic therapy and granulocyte transfusions, the lesion did not improve and the temperature remained elevated. On admission to our hospital four weeks after the first manifestation of the lesion in the groin, the first blood cultures positive for *Pseudomonas aeruginosa* were obtained and new ecthyma gangrenosum lesions developed, after which the disease ran a rapid and fatal course.

**Blood culture technique**

Blood cultures were performed as follows: 5 ml of blood were put into separate bottles one with liquid the other containing tryptone soya broth (TSB) with kanamycin. In the laboratory the contents of the liquid bottle was distributed in equal amounts into a tube with TSB, a tube with TSB plus serum and two tubes with thioglycolate. These tubes and the bottles with TSB with kanamycin were incubated at 37°C for five days. Subcultures on blood agar and heated blood agar were made on day two and day five.

**Discussion**

Ecthyma gangrenosum is a skin lesion which is caused by *Pseudomonas* species and has a characteristic appearance and course. The onset is characterized by localized oedema and an initially slight, but rapidly increasing, erythema. This is followed by the development of a hemorrhagic, blueish-violet bulla with a hyperemic zone (Plate 1). This bulla ruptures, leaving a necrotic lesion with a concentric-rings configuration (Plate 2). The development from the first manifestation to the final stage takes about 12 to 24 hours.

Microscopically, the fully developed lesion shows oedema, haemorrhagic necrosis, sparse neutrophilic infiltrate, and bacilli on the medial and adventitial layers of the arteries and veins (Teplitz, 1965). The sparse neutrophilic infiltrate is not due to the granulocytopenia which is often present in patients...
with ecthyma gangrenosum. Teplitz (1965) observed the same sparse neutrophilic infiltrate in ecthyma gangrenosum induced by the intradermal injection of *Pseudomonas* spp. into rabbits with normal granulocyte counts.

Another remarkable feature is the presence of bacilli in the media and adventitia of the vascular wall but not in the intima. Therefore, the infiltration of the vascular wall by these organisms seems to arise not from the vascular lumen, but from outside the blood vessels. The lesions are probably caused by proteases, produced by *Pseudomonas aeruginosa* (Meinke, Barum, Rosenberg and Berk, 1970).

Once the diagnosis is suggested by the appearance of the skin lesions, Gram staining and culture of material from the lesion should be performed. Therapy should be instituted immediately in view of the severity and frequently fatal outcome of these *Pseudomonas* infections. The most effective antibiotic therapy is a combination of carbenicillin and an aminoglycoside (gentamicin, tobramycin or amikacin) (Schimpff, 1977). If severe granulocytopenia is present, granulocyte transfusions may enhance the effect of antibiotic treatment in a *Pseudomonas* infection (Dale, Reynolds, Penson, Elin and Herzig, 1976).

Ecthyma gangrenosum is said to be pathognomonic for *Pseudomonas* septicaemia (Dorff, Geimer, Rosenthal and Rytel, 1971; Hall, Callaway, Tindall and Smith, 1968; Stanley, 1947), although Hitschman and Kreibich (1897), who gave the first detailed description of the lesion, considered it to be a primary infection of the skin. The frequency of ecthyma gangrenosum in patients with known *Pseudomonas* bacteraemia varies in several series from 0.7 to 28 per cent (Baltch and Griffin, 1977; Flick and Cluff, 1976; Whitecar, Luna and Bodey, 1970).

In two of our patients (nos. 5 and 6), blood cultures taken when the first manifestation of the ecthyma gangrenosum was seen were negative, and subsequent cultures were also negative. In the other six patients the blood cultures were all positive. However, in one of these patients (no. 8) the first skin lesion preceded the first positive blood culture by four weeks and in another patient (no. 7) *Pseudomonas* was cultured from the groins four days before the development of ecthyma gangrenosum in that site. In these patients the ecthyma gangrenosum was probably the source of the bacteraemia. In one patient (no. 1) the ecthyma gangrenosum lesions were certainly secondary to a *Pseudomonas* bacteraemia, and in another patient (no. 2) the simultaneously appearance of multiple skin lesions on one arm makes it likely that in this patient, too, the lesions were secondary to a bacteraemia. In two patients (nos. 3 and 4) the sequence of the events could not be established with any certainty. Thus, two of the patients showed no bacteraemia at all and in two other patients the skin lesions were probably the source of the bacteraemia.

With respect to the possible origin of ecthyma gangrenosum, the experimental findings of Teplitz (1965) are of interest. Within hours after the intradermal inoculation into rabbits of old cultures of *Pseudomonas aeruginosa*...
Ecthyma gangrenosum

osa, the animals developed skin lesions showing pseudomonas vasculitis and haemorrhagic necrosis, which are characteristic of ecthyma gangrenosum in man. Apparently, bacteraemia is not a prerequisite for the genesis of ecthyma gangrenosum.

In man, ecthyma gangrenosum occurs preferentially in humid parts of the skin (groin, scrotum, perineum, and axilla), which are commonly colonised by Pseudomonas spp. in severely ill patients. This preference can only be understood if the lesions arise through local penetration and infection of the skin by Pseudomonas. The two patients in our series with ecthyma gangrenosum that was certainly or very probably secondary to bacteraemia were the only patients with multiple lesions outside these regions.

On the basis of our observations, ecthyma gangrenosum can arise in two ways: as a primary infection of the skin, which may or may be not followed by bacteraemia, and as a lesion secondary to Pseudomonas bacteraemia.

References


