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A Study of Nineteen Immunocompromised Patients with Extensive Skin Lesions caused by *Pseudomonas aeruginosa* with and without Bacteremia

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Nineteen immunocompromised patients with extensive skin lesions caused by *Pseudomonas aeruginosa* with or without *P. aeruginosa* bacteremia were analysed. Patients whose lesions originated in the skin were in the majority (14 patients). Skin lesions were located at the site of entry of bacteria (apocrine areas in 12 patients). Cutaneous lesions were pleomorphic but the typical picture of ecthyma gangrenosum was common in this group of patients. Only 2 of them developed *P. aeruginosa* septicemia and the prognosis was relatively good (7.5% mortality rate). These observations confirm that ecthyma gangrenosum may be a primary cutaneous disorder not systematically associated with bacteremia. *Key words: Ecthyma gangrenosum; Infection; Agranulocytosis.*

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Ecthyma gangrenosum (EG) is a necrotic and bullous skin disorder almost invariably caused by *Pseudomonas aeruginosa* and frequently located in apocrine areas. This lesion is frequently claimed to be pathognomonic of *Pseudomonas* septicemia (1–4). However, Van den Broek et al. (5) suggested that EG can occur without systemic involvement, on the basis that 2 out of 8 EG patients had negative hemocultures. In 1985, we described 6 immunocompromised patients in whom a folliculitis caused by *P. aeruginosa serotype* O: 11 progressed to a severe EG without *P. aeruginosa* septicemia (6). Recently, Huminer et al. (7) reported 6 cases of EG without bacteremia and also reviewed 8 other cases described in the literature, including 4 of our patients, which support the assumption that EG can be localized to the skin. These lesions were associated with a better prognosis than skin lesions occurring in conjunction with a septicemia (7). Here, we report the observation of 19 immunocompromised patients with skin lesions caused by *P. aeruginosa* with or without septicemia. Our observations show that a majority or these lesions originated from the skin itself.

CASE REPORTS

The findings for the 19 patients are summarized in Tables I and II. The patients were hospitalized in four different hospitals, named for convenience A, B, C or D, and were observed over a period of 8 years by the same physician. The findings in patients believed to have a primary skin lesion are summarized in Table I, and those believed to have skin lesions secondary to bacteremia are included in Table II. The lesions are considered to be primary when at least one of the following criteria is present: absence of bacteremia at the onset of the cutaneous lesions, (patients 1–4, 9–13), observation of a previous wound (patients 7 and 14) or a *P. aeruginosa* 'folliculitis' at the onset of the lesion (patients 5, 6 and 13) or presence of *P. aeruginosa* in a liquid (antiseptic) that was applied to the skin before the lesion started (patient 14). Patient 6 was considered without doubt to have a primary skin lesion, because the bacteria present in the blood had a different serotype and a folliculitis-like lesion was seen before the extensive skin lesion. Patient 8 probably had a primary skin lesion, as the skin lesion preceded the bacteremia. The lesions may have been secondary to a bacteremia when these criteria were absent and when bacteremia caused by *P. aeruginosa* of the same serotype was present before the onset of the lesions (patients 15–19). Only patient 16 had without doubt skin lesions secondary to bacteremia. The septicemic origin of the skin lesions is considered to be only probable for the other patients. However, the origin of the bacteria was believed to be the intestinal tract for patients 15, 18 and 19, and the mouth for patient 17.

The skin lesions caused by *P. aeruginosa* in the immunocompromised patients were pleomorphic = typical EG (vesicular of bullous lesions leaving when ruptured a necrotic ulceration with a concentric annular configuration without cellulitis), cellulitis frequently complicated by bullae or necrosis, nodules, necrosis of the extremities or folliculitis-like eruption evolving as bulla or EG. Most primary skin lesions were granulocytopenic, occurring soon (during the first 2 days) after the onset of granulocytopenia. Patient 12 suffered from AIDS, this is to our knowledge the first case of EG in AIDS reported in the literature. Cutaneous bacte-

Table I. Patients with *P. aeruginosa* skin lesions considered to be primary

Patient No./sex/ age, yr Hospital	Diagnosis	Chemo-therapy	Nature of skin lesion	Localization of lesions	No. of neutro-phils mm^3	Results of bacteriological cultures			Outcome
						Skin	Blood	Other	
1/M/28 A	Malignant histiocytosis	DXR VM BLM CPM	Ecthyma gangrenosum	Axilla, balano-prepuptial fold	<100	PA	Negative		Alive
2/F/38 A	Hodgkin's disease	ADM VLB BLM CPM	Ecthyma gangrenosum	Labia majora	2,925	PA	Negative	Feces, PA; Vagina, PA	Alive
3/F/63 A	Acute mye-loblastic leukemia	DRB ARA-C VCR	Extensive pustules and bullae	Labia majora, perineum	<500	PA	Negative		Alive
4/F/75 A	Breast cancer	ADM VDS 5FU CPM	Ecthyma gangreno-sum; extensive vesicles and bullae	Inguinal folds	<500	PA 011	*Kleb-siella oxytoca*	Vagina PA 011	Death related to *K. oxytoca* septice-mia
5/F/31 A	Acute mye-loblastic leukemia	DRB ARA-C VCR	Folliculitis evolving as ecthyma gangrenosum	Labia majora	<100	PA 011	Negative	Urine PA 011	Alive
6/F/54 A	Breast cancer	ADM VDS 5FU CPM	Folliculitis evolving as ecthyma gangrenosum	Inguinal folds	<100	PA 011	PA 06	Vagina, PA 011; tongue, PA 06; sink and faucet of patient room po-sitive for PA 011	Alive
7/F/46 B	Toxic granulocy-topenia	None	Localized necrosis	Right little finger (at the site of a ring)	<100	PA	PA		Alive
8/M/55 B	Toxic granulocy-topenia	None	Ecthyma gangrenosum	Right inguinal fold	<100	PA	PA		Alive

riologic samples were obtained by needle aspiration of cellulitis, abscesses, or of a non-disrupted bulla. The bacteria were cultured on chocolate agar, Drigalski agar and tryptic soy agar with 5.0% sheep blood for aerobic growth and Columbia blood agar for anaerobic growth (Diagnostics Pasteur, Paris, France). *P. aeruginosa* was isolated in all the lesions in pure culture except in the case of patient 14 who also had *Enterobacter sakazaki* in her skin lesions. *P. aeruginosa* was invariably seen in the Gram stain of the bacteriological samples and the bacteria were serotyped in 12 patients. Anaerobic cultures always remained negative. Numerous hemocultures were taken in all patients on the appearance of lesions and during the course of the disease (more than six hemocultures were done for each patient,

Table I (continued)

9/F/60 B	Myelodysplatic syndrome	None	Ecthyma gangrenosum	Labia majora	<500	PA	*K. oxytoca*		Death related to *K. oxytoca* septicemia
10/F/54 B	Acute myeloid leukemia	ADM ARA-A BCNU	Ecthyma gangrenosum	Left eye lid, axilla, sternum, labia majora	<500	PA 04	Negative	Vagina PA 04	Alive
11/M/63 B	Acute myeloid leukemia	DRB ARA-C VCR	Ecthyma gangrenosum	Sternum, balanopreputial fold	<500	PA 08	Negative		Alive
12/F/28 C	AIDS	None	Ecthyma gangrenosum	Labia majora, chest, face	3000	PA 011	Negative	Sputum, PA 011; urine, PA 011;	Death probably not related to PA infection
13/F/5 D	Acute lymphoblastic leukemia	DRB ASP VCR PDN	Folliculitis of the thighs evolving as an ecthyma gangrenosum, abscesses of the thighs	Right and left thighs	800	PA 06	Negative		Alive
14/F/2 D	Acute megakaryoblastic leukemia	ARA-C VCR	Superinfection of erosions of the vulva, evolution as an extensive and necrotic cellulitis	Perineum, abdomen, thighs	<100	PA 010 *Enterobacter sakazaki*	*Negative*	E. sakazaki and PA 010 in an antiseptic use to treat the vulva	Death related to PA infection

Key to abbreviations: P. A. = *P. aeruginosa*; DXR = Doxorubicin; VM = VM 26; BLM = Bléomycin; CPM = Cyclophosphamide; ADM = Adriblastine; VLB = Vinblastine; CPM = Cyclophosphamide;DRB = Daunorubicin; ARA-C = Cytosine Arabinoside; VCR = Vincristine; VDS = Vindésine; 5FU = 5 Flourouracil; BCNU = Carmustine; ASP = Asparaginase; PDN = Prednisone; See main text for definition of A, B, C, D.

except patient 14 who had only four hemocultures). Hemocultures were made in Castaneda and Anaer "S" blood culture bottles respectively for aerobic and anaerobic growth (Diagnostics Pasteur, Paris). Aerobic blood cultures were carefully aerated to promote the growth of *P. aeruginosa*. Cultures from stool, urine, and throat were performed for some patients. Patients 4 and 9 had *Klebsiella* septicemia at the same time, though the skin cultures identified *P. aeruginosa* and no *Klebsiella*.

All patients were treated parenterally with a combination of two antibiotics active against *P. aeruginosa*. A local treatment (antibiotic ointment or antiseptic) was applied upon the superficial lesions. The abscesses of patient 13 were drained successfully a few weeks after his granulocytopenia resolved. Patient 14 who had perineal cellulitis underwent operative drainage, but experienced subsequent progression of the local infection. Skin lesions healed rapidly in all granulocytopenic patients when the number of granulocytes returned to normal. Death attributed directly to *P. aeruginosa* infection was relatively rare (7.5% in the primary group, 20% in the secondary group). Irrespective of the absence or presence of bacteremia, necrotic and

Table II Patients with *P. aeruginosa* skin lesions considered to be secondary to bacteremia

Patient No/ sex/age, yr Hospital	Diagnosis	Chemo-therapy	Nature of skin lesion	Localization	N° of neutrophils mm^3	Results of bacteriological cultures			Outcome
						Skin	Blood	Other	
15/F/65 A	Breast cancer	CPM MTX 5FU	Cellulitis with bullae	Abdomen, thigh	<100	PA 012	PA 012		Death related to *P. aeruginosa* infection
16/M/44 C	Kidney transplant recipient	PDN AZT	Necrosis of finger tips, abscesses	Bilateral (fingers and thighs)	3000	PA	PA	Catheter PA	Alive
17/F/4 D	Acute lympho-blastic leukemia	DRB ASP VCR PDN	Necrotic and bullous cellulitis	Cheeks, chest, right thigh	<500	PA 06	PA 06	Mouth PA 06	Alive (with large scars)
18/M/4 D	Acute myeloid leukemia	ARA-C VP 16	Cellulitis	Neck	<500	PA 011	PA 011	Feces, sputum PA 011	Alive
19/F/5 D	Acute myeloid leukemia	ARA-C VP 16	Cellulitis	Abdomen	<500	PA 06	PA 06	Feces PA 06	Alive

Key to abbreviations: PA = *P. aeruginosa;* CPM = Cyclophosphamide; MTX = Méthotrexate; 5FU = 5 Fluorouracil; PDN = Prednisone; AZT = Azathioprine; DRB = Daunorubicin; ASP = Asparaginase; VCR = Vincristine, ARA-C = Cytosine Arabinoside; VP 16 = Etoposide. See text for definition of A, C, D.

bullous cellulitis seemed to be associated with a poor prognosis (two deaths in 3 cases and a bad scare for the patient who survives).

DISCUSSION

During the course of *P. aeruginosa* septicemia, cutaneous manifestations are observed in some 3–6% of patients (8–11). EG is a well known lesion generally said to be pathognomonic for *Pseudomonas* septicemia (1–3), though it has also been described in rare cases of *Aeromonas hydrophila, Serratia marcescens, Pseudomonas maltophilia, Candida albicans or Aspergillus* infections (12). Moreover, it is now clear that some of these skin lesions in immunocompromised hosts represent the site of entry of the bacteria (5–7).

Our observations shows that a majority of extensive skin lesions caused by *P. aeruginosa* in immunodepressed patients originated from the skin itself. There appeared to be different clinical presentations in the two groups of patients:

– The group of patients with skin lesions probably secondary to bacteremia comprised 5 patients. The skin lesions included cellulitis with bullae, abscesses, and necrotic lesions and were located anywhere on the body.

– The group of patients with skin originating from the skin was presominant in our study (14 patients). The lesions were due to superinfection of a previous wound in 2 patients and appeared spontaneously in apocrine areas without preceding trauma or wound in the remaining 12 individuals. In a few cases (patients 5, 6 and 13) we observed very small lesions similar to a folliculitis at the inception of or just before the onset of agranulocytosis. These lesions remained small (1 cm diameter) or became extensive and numerous, evolving rapidly like EG.

The typical EG in our study were observed specifically in the group of patients with skin lesions orig-

inating from the skin. The cutaneous origin of these lesions probably explains the peculiar location of EG in apocrine areas. It was difficult to attribute to this localization a metastatic localization of bacteremia. The frequent localization of this lesion in apocrine areas is probably due to the humidity of these areas which promotes the proliferation of *P. aeruginosa* and to the proximity of a *P. aeruginosa* reservoir (feces). Moreover, previous broad parenteral antibiotic therapy, as performed in nearly all of our patients, may predispose to the superinfection of the hair follicles by *P. aeruginosa*. After *P. aeruginosa* colonization of the apocrine areas, agranulocytosis observed in nearly all of the patients of this group promotes the extensive and necrotic evolution of lesions.

Huminer et al. insist that the prognosis of EG is better without bacteremia, and consider it to be an additional indirect proof that their cases were not secondary to internal sepsis (7). We found similar results in our patients with 'primary' lesions. However, necrotic and bullous cellulitis with or without bacteremia seems to have a poor prognosis. The relatively good prognosis for our patients with 'primary' lesions is convincingly explained by the absence of internal abscesses, the rarity of bacteremia (only 2 *P. aeruginosa* septicemia cases in this group of patients) and rapid healing of the lesions when the granulocyte count returned to normal. One other feature we share with the Huminer report is the high incidence of women in the group of patients with skin lesions considered to be primary (11 women; 3 men), this finding might be attributable to a reservoir of *P. aeruginosa* in the vagina.

In an initial report, we suggested that the serotypes frequently found in 'swimming pool folliculitis' (serotype 0: 11 and 0: 4) (14–16) were characteristic of the 'primary' EG secondary to folliculitis (6). In fact various serotypes may cause the skin lesions (Table I). We now believe that the incidence of serotype 0: 11 in our initial report may be explained in part by the epidemic nature of many of our cases which appeared in the same hospital (hospital A). However, it is important to be aware that the frequent recovery of the same serotype even over a long period may indicate the presence of this bacteria in a liquid use for the cleansing or the disinfection of the patients or a colonization of the patients of the hematology-oncology service needing contact isolation precautions (17).

Our observations confirm that EG may be a primary skin lesion not always accompanied by bacteremia. This may influence the degree of thoroughness in the treatment of and search for an internal portal of entry.

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