ECTHYMA GANGRENOSUM IN CHILDREN WITH CANCER: DIAGNOSIS AT A GLANCE. A retrospective study form the Infection Working Group of Italian Pediatric Hematology Oncology Association.

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Abstract

Purpose. To describe ecthyma gangrenosum (EG) characteristics and complications in a large multicenter pediatric retrospective collection of children with malignancies or bone marrow failure syndromes. Methods. EG episodes diagnosed in the period 2009-2019 were identified by a retrospective review of clinical charts at centers belonging to the Italian Pediatric Hematology Oncology Association. Results. EG occurred in 38 children (male/female 16/22; median age 5.2 years) with hematological malignancy (33), allogeneic stem cell transplantation (2) or relapsed/refractory solid tumor (3). The involved sites were: perineal region (19), limbs (10), trunk (6), head and the iliac crest (3). Bacteremia was present in 22 patients. Overall, the germs isolated were Pseudomonas aeruginosa (34), Stenotrophomonas maltophilia (3) and Escherichia Coli (1); 31% of them were MDR. All patients received antibacterial treatment while surgery was performed in 24 patients (63.1%). Predisposing underlying conditions for EG were: severe neutropenia (97.3%), corticosteroid treatment (71%), iatrogenic diabetes (23.7%). All patients recovered, but EG recurred in 5 patients. Nine patients (24%) showed sequelae (deep scars, with muscle atrophy

in 2). Four patients (10.5%) died, 1 due to relapse of EG with KPC co-infection, 3 due to the underlying disease. Conclusions. EG requires early recognition and a proper and timely treatment to obtain the recovery and to avoid larger necrotic evolution. The occurrence of scarring sequelae might affect the quality of life of patients.

INTRODUCTION

Ecthyma gangrenosum (EG) is a relatively uncommon cutaneous infection that mostly occurs in individuals with immunosuppression due to different underlying diseases including hematologic disorders, malignancies, lymphoproliferative disorders and autoimmune diseases. However, it has also been reported among previously healthy individuals[1-4], both adults and children. *Pseudomonas aeruginosa* is the most common cause of EG, with or without bacteremia, although it is also known to be caused by a variety of pathogens, including different bacteria, fungi and viruses[1]. Lesions first appear as painless papules which rapidly evolve in gangrenous ulcers. The macroscopic appearance corresponds to the microvascular thrombosis and subsequent dermal ischemic necrosis[5]. Single or multiple lesions might involve one or more sites in the body, mainly the axillary and perineal regions. Prompt recognition and timely adequate treatment are crucial for the prognosis[1].

In patients with hematological malignancies and cancer, many factors (immunosuppression, mucositis and epithelial damage, microbiome dysbiosis and prolonged use of central venous devices) predispose to bacterial infections, usually affecting integumental surfaces such as respiratory tract, gastrointestinal tract and skin. The frequently atypical clinical presentation of these infections makes the prompt recognition often challenging[6].

There are scant reports describing the occurrence of EG in onco-hematological patients, mainly as case reports or small case series[7-16]. We report the results of a large multicenter pediatric retrospective collection of 38 cases of proven EG diagnosed between 2009 and 2019 in children with hematological disease and cancer. The aim is to describe the clinical picture and characteristics of EG, to early recognize and diagnose it, since timely treatment influences the outcome of this infection. In fact, particularly in this setting of patients, prompt interventions may change the course of both this serious infection and the underlying disease. The wide spectrum of clinical pictures at different levels of severity in our sample allowed a more complete evaluation of EG infection at different stages, considering that cases reported in the literature have mainly a devastating clinical presentation.

PATIENTS AND METHODS

This retrospective study was conducted in 14 Pediatric Oncology and Hematology centers belonging to the Italian Association of Pediatric Hematology and Oncology (AIEOP) over 11-year period from 01/01/2009 to 31/12/2019.

Eligibility criteria were a diagnosis of EG in patients affected by hematologic/oncologic malignancies or bone marrow failure syndromes, aged 0-18 years, microbiologically documented by demonstration of the microorganism in positive culture from wound swab or skin biopsy and/or in positive blood culture. The date of diagnosis corresponded to the first microbiological evidence of infection. Disseminated infection was defined when two or more noncontiguous sites were involved; associated bacteremia was defined when blood culture was positive.

The following information were extracted from the clinical records of the patients: demographic characteristics, type of malignancy, adjunctive risk factors occurring until 7 days before the diagnosis of infection (corticosteroid treatment, iatrogenic diabetes) clinical symptoms and signs of infection, radiological findings, site of infection, laboratory findings (e.g. neutrophil count, microbiological isolates), treatments received and duration of treatment, outcome, clinical status at last follow-up. Severe and prolonged neutropenia was defined by an absolute neutrophil count $<0.5 \times 10^9$/L for >10 days. Prolonged use of corticosteroids was defined by a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks[17].

Multi-drug resistance was defined in the presence of isolates with non-susceptibility to at least 3 different drug classes, in accordance with EUCAST international standards and breakpoints.

A descriptive analysis of the data was performed. Univariate analysis of variables regarding clinical presentation between multi drug resistant (MDR) e non-MDR infections was estimated by Fisher exact test. In all analyses a probability value less than 0.05 was considered statistically significant. Data were analyzed using the "R" language statistical software (version 3.6.2).

Patients or parent informed consent was obtained. Data processing was in accordance with Italian law for patient confidentiality and good clinical practice. The study was conducted according to Italian policy for retrospective studies and in accordance with local Ethical Committee judgment.

RESULTS

During the study period 38 cases of EG (male 16, female 22) were recorded. Demographic and clinical characteristics of the patients are presented in table 1.

Figure 1 shows the age distribution of patients, according to gender. Sexteen out of 38 (42.1%) patients were in the age 0-3 years, 13 of them (13/16, 81.2%) were females, 5 were infant, 17/38 patients (44.7%) were above the age of 10.

Hematological disease was present in 35/38 (92.1%) patients (table 1). Five out of 38 (13.1%) patients were under treatment for relapsed disease (4/29 for acute leukemia, 1 for Ewing sarcoma).

The infection occurred after an average time of 5.4 months (median 4.8 months, range 0.07-21.8 months) from the diagnosis of the underlying disease or the relapse. Sixteen out of 38 (42.1%) patients were in the induction phase of treatment, 8 in the consolidation phase, 8 in the re-induction phase, 1 patient in the maintenance phase, 2 in the salvage treatment, 2 patients had received allogeneic stem cell transplantation, 1 patient had underwent surgery for treatment of relapsed Ewing sarcoma.

Thirty-seven out of 38 (97.3%) patients had severe neutropenia lasting more than 7 days, with neutrophil count < 0.1 x 10^9/L in 35 patients (92.1%), 27/38 (71%) patients had received prolonged corticosteroid treatment at the moment of EG. Nine out of 38 (23.7%) patients had iatrogenic diabetes.

Diagnosis. The diagnosis of EG was documented by positive culture of wound swab in 34/38 patients, associated with positive blood culture in 18 patients; by positive blood culture in 4. In total 22/38 (57.9%) patients had bacteremia.

The isolated bacteria was *Pseudomonas aeruginosa* in 34 cases,*Stenotrophomonas maltophilia* in 3 and *Escherichia coli* in 1. In 10 patients a co-infection, with presence of more than one bacteria in the same culture, was documented: 3 *Staphylococcus epidermidis,* 1 *Staphylococcus haemoliticus,* 1*Corynebacterium striatum,* 1 *Enterococcus faecalis,* 1*Enterococcus faecium,* 1 *Enterococcus faecium* +*Bacteroides fragilis,* 1 *Enterobacter cloacae,* 1 multidrug resistant *Klebsiella pneumoniae.*

The EG involved the perineal region in 19/38 (50%) patients, other sites of EG are presented in table 2.

In 22/38 (57.9%) patients of our series the EG was associated with bacteremia, in 14 cases as single lesion, in 8 cases involving multiple sites in the body. Among the 16 patients without bacteremia, the infection was disseminated in 3/16 (18.7%), localized in 13/16 (81.3%).

In total, in 13/38 (34.2%) cases the EG presented as no-bacteriemic single cutaneous lesion.

The different age of presentation as regard to bacteriemic and non bacteriemic forms are presented in table 3. No different age distribution appeared between the bacteriemic and no-bacteriemic group (average age 8.5 years vs 6.8 yrs respectively, *ns*); however the group of children with bacteriemic EG and disseminated presentation were apparently older (11.4 yrs) compared to the other groups (table 3).

Sixteen out of 38 (42.1%) patients were receiving antimicrobial prophylaxis or empiric antibacterial treatment, according to local practices, based on amoxicillin/clavulanate in 5 patients, cotrimoxazole in 2,

meropenem in 2, ciprofloxacin in 2, ceftriaxone in 2, ceftazidime in 1, clindamicin in 1, ampicillin in 1.

Treatment and outcome. Treatment was based on antibacterial drugs in all children, started after a median of 1.1 days, with a latency of 0 days in 21 patients, 1-3 days in 13 patients, $>$ 3 days in 3. The therapy was delivered for a median time of 20.5 days (range 9-270 days). Eleven patients received monotherapy with anti-Gram negative agent (piperacillin/tazobactam in 5, meropenem in 4, ciprofloxacin and ceftazidime in 1 each), 27 children received combined antimicrobal treatment, with 2 drugs in 22 patients (ceftazidime or cefepime and amikacin in 13, meropenem or imipenem and amikacin in 4, meropenem and ciprofloxacin in 2), [?]3 drugs in 5 cases. Second line antibiotic treatment was needed in 6/11 patients in which a monotherapy approach had been attempted, and in 5/22 children treated with two drug-combined therapy. In 12/37 (32.4%) tested patients the antimicrobal susceptibility revealed MDR bacteria (table 4), 9 of them had received antimicrobal prophylaxis. Ten out of 12 (83.3%) patients with MDR infection presented a bacteremic form of EG (83.3% in the MDR group vs 46.1% in the non-MDR group, *p=0.0403*). The lenght of treatment did not differ between cases with MDR bacteria and non-MDR (average 30.6 days vs 27.2 days, *ns*).

Surgical treatment, namely debridement of the necrotic tissue, was performed in 24/38 (63.1%) patients, 18/24 (75%) of these patients had the EG involving more sites in the body and/or bacteriemic disease. In addition five patients underwent Vacuum therapy and 4 patients were treated with hyperbaric chamber. In 5 patients the intervention of plastic surgery with skin graft was needed.

In all patients the recovery from the infection was documented, unfortunately in 5 patients the EG recurred. Nine out of 38 patients, after healing of the lesions, showed deep scars, with muscle atrophy in 2 cases.

The median follow up time was 38.3 months (range 2.9-121.9 months).

Four out of 38 (10.5% mortality rate) patients died, one due to relapse of the EG with KPC co-infection, two due to progression of the underlying disease, the last one died later on due to transplant related mortality after allogeneic stem cell transplantation (SCT). Death occurred after 4, 4.5, 13 and 10 months, respectively. Three out of 4 deaths occurred in the bacteremic infections, with a mortality rate of 13.6% (3/22) in this group. The mortality rate in the non-bacteremic EG was 6.2% (1/16).

DISCUSSION

This study reports on a series of 38 cases of EG in children with hematological disease and cancer. EG is reported mainly in immunocompromised and cancer patients, nevertheless, even in patients with malignancies, this complication is described only as case reports or small case series. An extensive review described a total of 162 cases of EG in immunocompromised and immunocompetent patients of any age, among whom there are several case reports and case series, the largest being of 17 patients[1]. Our study represents the most extensive series of EG in the hematology and oncology setting, not only pediatric. Based on the wider number of patients in our study, we aimed at outlining the characteristics of presentation of EG in children with malignancies, in order to point out the clinical profile of patients at risk, to early recognize the EG and to treat it properly.

As expected, children in our population were affected mostly (92.1%) by hematological malignancies, since 34/38 patients had acute leukemia and 1 patient severe aplastic anemia (SAA), confirming the role of the underlying disease as risk factor for the infectious disease. In fact, the treatment of acute leukemia is associated with deep alteration of innate and adoptive immunity. Almost all patients in our series had severe neutropenia (97.3%) and the majority was on corticosteroid treatment (71%) at the moment of infection, while 9/38 (23.7%) children had iatrogenic diabetes.

Neutropenia has been reported as the most frequent risk factor for EG in different reports[1,3,4], while corticosteroid treatment is known to play a role abrogating host defenses against bacterias[18-19]. In addition, hyperglicemia influences the risk of infection in hematologic malignancies[20].

All these risk factors are known to have detrimental effect on the host immune response due to suppression

of phagocyte-mediated killing, humoral immune and T-lymphocyte responses[21]. The skin and gut dysbiosis, the mucositis and epithelial damage, consequence of the disease treatment, represent an open window for the access and spreading of pathogens[4,6]. Moreover the endothelial damage likely due to chemotherapy[22] might be a facilitating risk factor for the development of EG, which starts typically with microvessel lesion and necrotizing vasculitis caused by bacteria, leading to perivascular invasion and ischemic necrosis of the surrounding tissue. EG is a septic vasculitis in which microorganisms may be demonstrated within the vessel wall and may occlude the vessels lumina[23]. The microscopic lesion justify the clinical picture of a cutaneous erithematous papula rapidly evolving into the typical destruent and large necrotic lesion (supplemental figure S1).

EG has been described as localized lesion or as bacteremic form often with septicemic dissemination, involving different sites in the body[5]. In accordance to data reported in the literature[1], the majority of patients (57.9%) in our series presented the EG associated with bacteremia, while about in one third (34.2%) of cases the EG presented as single cutaneous lesion without bacteremia.

According to most case reports, the primary involved site was the perineal region (50% of primary site), and this did not differ among patients with or without bacteremia. However we observed also less typical sites of EG such as central venous catheter (CVC) exit, the site of bone marrow puncture at the posterior iliac crest, the periombelical area, the scapula, providing that any area of the body might be involved. As a result, the occurrence of EG in hidden skin sites hampers the early diagnosis. We therefore suggest an accurate inspection of the skin in patients at risk of EG, in order to recognize the initial lesion as early as possible (supplemental figures S1, S2, S4).

Apparently no prevalent age-distribution could be documented in our series, since almost any age is represented, from very young children to older ones. However, a more accurate analysis of the age of presentation suggests some considerations (figure 1): first we confirmed the susceptibility of older children to infectious complications in the pediatric hematological setting as previously reported[24-27], in fact near half of children were older than 10 years. In addition, our data demonstrated that over 50% of patients were around the age of 5 or younger and, in particular, 42.1% of patients were in the age 0-3 years and five patients were infants. Moreover in the age group 0-3 years over 80% were females. Thus in our sample younger female children might be at higher risk for this peculiar infection. The occurrence of EG in very young children and newborns is also described in some case reports[11-13, 28].

As generally reported for infectious complications in hematological malignancies[29], more than 40% of EG were documented in the induction phase of treatment. This is detrimental for the outcome of the malignancy, considering the subsequent delay in the delivery of chemotherapy due to such a devastating skin lesion.

Confirming the epidemiology traditionally reported, *P. aeruginosa*was identified in the majority of patients (89.5%). *S. maltophilia* , and *E. Coli,* also described as etiologic agent of EG[1], were cultured in the remaining cases. In 10 patients a co-infection was documented, which influenced negatively the outcome in 1 case.

The distribution of resistance to antibiotics of the gram negative bacteria identified, revealed 31.6% of prevalence of MDR bacteria, comparable to the prevalence of 30% reported in a previous AIEOP survey on *P. aeuginosa* bacteremias in the same setting of patients[30]. These data are also corroborated by the recent report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)[31], in particular as regard to piperacillina-tazobactam, the antibiotic to whom 1/3 of isolates were resistant in our series.

The subset of 12 patients infected by MDR bacteria, as expected, showed characteristics of more aggressive clinical presentation and outcome, with a significantly different distribution of bacteremia.

The start of targeted antibiotic treatment was prompt in the majority of patients. This is an important key in the treatment of EG[32], in keeping with the recommendations of international guidelines[33] to overcome the rapid growth of the lesion. The necrosis of the tissue in the outcome of EG is a problem of utmost importance, since delays the recovery from the infection and might challenge the quality of life of this setting of patients, even after healing of the lesion, due to the occurrence of deep scarring (supplemental figures S2,

S3, S5, S6).

In order to remove the infected necrotic tissue and to ameliorate and the healing of the wound, in our experience a surgical debridement has been considered in most cases, especially for larger lesions with extensive necrosis and more aggressive disease, confirming a described approach[34,35].

The vacuum therapy, reported in some cases to promote faster healing of the wound bed[36], has been also applied in 5 patients, and in 3 cases prevented the occurrence of deep scars. The treatment with hyperbaric chamber has been also attempted in 4 cases, with successful result in 2.

In those patients with extensive tissue loss, different techniques for wound healing, such as negative-pressure therapy, hyperbaric chamber and dermal substitutes implant, might have a role.

The mortality rate for EG reported in the literature ranges from 8-15% in non-bacteremic infections to 20-77% in bacteremic EG[5-6]. In our experience we documented lower fatality rate, probably due to the prompt start of targeted therapy in almost all patients. However in some cases the delay in the delivery of proper anticancer treatment probably hampered the control of the underlying disease.

CONCLUSIONS.

EG is an infectious complication described in pediatric patients under treatment for hematological malignancies and cancers, especially during severe neutropenia. Very young and older children seemed to be at higher risk of EG. Prompt recognition of early lesion is of utmost importance. Timely start of proper treatment approach warrants the recovery, although scarring sequelae might occure.

DISCLOSURES

Conflicts of interest: The authors have no conflicts of interest to disclose. **Ethics approval:** Data processing was in accordance with Italian law for patient confidentiality and good clinical practice. The study was conducted according to Italian policy for retrospective studies and in accordance with local Ethical Committee judgment. All the procedures used were in accordance with the ethical standards of the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards.

Availability of Data: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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LEGEND LIST

Figure 1

Distribution of n= 38 patients with echtyma gangrenosum according to different age groups and gender.

Supplemental Figure S1

A cutaneous erithematous papula (A) rapidly evolving (B) into the typical destruent and large necrotic lesions (C,D)

Supplemental Figure S2

Picture of ecthyma gangrenosum. The early erythematous lesion (A), the papula (B), the resulting scarring skin lesion (C)

Supplemental Figure S3

Localized ecthyma gangrenosum: a small papula (A) evolving in eschar (B), the clean lesion (C), the resulting scar (D)

Supplemental Figure S4

Echtyma gangrenosum: a bluish (A) and a reddish (B) papula

Supplemental Figure S5

The eschar (A) and the scar (B) resulting from the same ecthyma gangrenosum lesion

Supplemental Figure S6

A case of muscle atrophy after healing of large ecthyma gangrenosum localization

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