Ecthyma gangrenosum as a serious complication of *Pseudomonas aeruginosa* infection in departments of paediatric oncology

Przemysław Gałązka[1], Patryk Kaczor[2], Krystian Kałużny[3], Kamil Leis[2]

[1]Department of General and Oncological Surgery for Children and Adolescents, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
[2]Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland
[3]Chair and Clinic of Rehabilitation, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Faculty of Health Sciences, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

Abstract

In most cases *ecthyma gangrenosum* is a consequence of *Pseudomonas aeruginosa* bloodstream infection in immunodeficient patients. This bacterium is characterized by multi-drug resistance and has a number of mechanisms that allow it to survive even in extreme conditions. The disease is characterized by an aggressive course involving the skin and mucous membranes, leading to ulceration with signs of necrosis within 12 to 24 h. Treatment includes targeted antibiotic therapy and surgical cleansing of the wound. If the perianal area is occupied, a colostomy may be performed. Prevention of bacterial infections involves taking special precautions when handling a patient with immunodeficiency.

Key words: ecthyma gangrenosum, *Pseudomonas aeruginosa*, paediatric oncology departments.

Introduction

Ecthyma is one of the forms of lichen which involves dermis [1], whereas *ecthyma gangrenosum* is a pathognomonic disease that, in most cases, develops as a complication of *Pseudomonas aeruginosa* sepsis. It can also occur in previously healthy patients as a result of direct skin infection or secondary to bacteraemia caused by infection with other pathogens [2, 3]. It was first described in 1897 as bacterial vasculitis [3]. Speirs *et al.* in an article published in 1963 were the first to describe the correlations between agammaglobulinemia, sepsis, *Pseudomonas aeruginosa* and *ecthyma gangrenosum* [4, 5]. Most cases of this disease occur in South Asia [6].

Characteristics of *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative bacterium, whose genome is clearly larger compared to the other 25 most commonly sequenced bacteria. Knowledge of the genetic information of this microorganism, which consists of almost 6.3 million base pairs, gives a broader look at its role as a pathogen. Compared to other genomes, it contains much more regulatory sequences, which allows it to adapt efficiently to environmental changes and survive under various conditions. About 150 genes are responsible for membrane proteins that are involved in the export of virulent agents outside the cell and the transport of antibiotics. In addition, they attach the structures responsible for mobility and adhesion. The active efflux system and low outer membrane permeability explain the resistance of the bacterium to first-line antibiotics [7].

This microorganism prefers aerobic conditions, but is also able to survive in an environment with limited oxygen or anaerobic conditions – in which case it breathes with nitrate or nitrite. *Pseudomonas aeruginosa* has a series of oxidases, which allow to lowering O_2 levels, and thus create reduced-oxygen conditions, that are optimal for its growth. This microorganism is a saprophyte in high humidity environment and in the human intestine, it feeds by dead organic matter [8, 9]. *Pseudomonas aeruginosa* is able to survive at extreme temperatures and shows weakened sensitivity to antiseptics [10]. Virulent agents secreted by the bacterium include alkaline

proteases, lipases, elastases and toxins [7]. They lead to disruption of host tissue integrity by destroying specific proteins – elastin, transferrins and collagen. This microorganism is able to synthesize and secrete pyocyanin – a blue dye with oxidation–reduction potential, which is a toxin with harmful effects on host cell mechanisms [11, 12]. It is suggested that this bacterium, through the production of toxins, is able to cause transient neutropenia due to the reduction of neutrocyte quantity and inhibition of their migration to the site of infection [1, 13].

Of all bacteria, it is *Pseudomonas aeruginosa* that contains one of the most advanced chemoreceptor systems. It shows negative chemotaxis towards isothiocyanate and thiocyanate esters and positive chemotaxis to amino acids, sugars and inorganic phosphates. So far 26 DNA segments have been identified to be responsible of encoding proteins involved in these processes [7].

Pathogenesis

Pseudomonas aeruginosa is one of the most important opportunistic pathogens responsible for human infections. This bacterium naturally lives in animal and plant tissues, as well as in swamps, soil and marine coastal areas. It is characterized by unusual multi-drug resistance and insensitivity to disinfectants. It mainly causes respiratory pneumonia, sepsis in burn victims and urinary tract infections in catheterized patients. Due to the high resistance to antibiotics, these diseases are difficult to treat [7].

Biofilm formation by *Pseudomonas aeruginosa* is another reason for the severity of infections caused by that pathogen, especially in interventional wards. This process occurs by attachment of the bacterium to the host's body using flagella and fimbria and by producing special exopolysaccharide – alginate [14]. It is an important component of extracellular mucus, which can probably lead to attenuation of phagocytosis by neutrophils and host macrophages, and thus to reduction of bacterial biofilm exposure to destruction by leukocytes [15]. *Pseudomonas aeruginosa* produces specific elastases that allow bacteria to reach the subcutaneous tissues as a result of the destruction of the wall of blood vessels, and thus are responsible for skin necrosis. The ulceration is caused by the release of proteases and exotoxin A by the bacteria [16].

This microorganism is a particularly big difficulty in paediatric patients with leukaemia. The multi-drug resistance *Pseudomonas aeruginosa* significantly limits therapeutic options, making infections one of the main causes of death in paediatric oncology wards [17].

Ecthyma gangrenosum

Ecthyma gangrenosum is an aggressive, infectious disease of the skin and mucous membranes, which in rare cases can take the form of vasculitis. Its development most often occurs as a result of direct infection of the skin of patients with chronic or immunodeficiency diseases and in patients with sepsis, most often with the aetiology of Pseudomonas aeruginosa (EG develops in up to 30% of people with bacteraemia [16]), however, there are cases of *ecthyma gangrenosum* in patients with a properly functioning immune system [18–20].

Paediatric patients with axillary and perianal skin fissures predispose to infection by this bacterium. They are often a side effect of chemotherapy or can arise directly as a result of malnutrition in the process of cancer in children [21]. Patients hospitalized for a longer period of time have more *Pseudomonas aeruginosa* colonies on their skin. This microorganism in patients with impaired immunity enters the body through microfissures in the skin, resulting mainly from thermal damage, vascular and urinary catheters, and bedsores [16]. Ear canal or gastrointestinal tract can also be the entrance for the bacteria [6].

Pseudomonas aeruginosa infection is the most frequent predisposition to *ecthyma gangrenosum*. Cases of infections by other pathogens are also reported, including *Staphylococcus aureus, Streptococcus pyogenes, Serratia marcescens, Neisseria meningitidis, Neisseria gonorrhoeae, Klebsiella pneumoniae, Chromobacterium violaceum, Escherichia coli, Citrobacter freundii* and *Aeromonas hydrophila*. There are single cases of infections caused by fungi, including *Candida albicans, Aspergillus fumigatus, Fusarium* spp., *Curvularia* spp., *Exserohilum* spp., *Rhizopus* spp. *or Mucor* spp. *Herpes simplex virus* may be responsible for *ecthyma gangrenosum*-like lesions. Viral infections can lead to a temporary impairment of the host's immune system or directly weaken the gastrointestinal defence barrier, which increases the risk of secondary infection with *Pseudomonas aeruginosa* [1, 9, 10, 19, 22, 23].

Symptoms

The lesions initially appear as red, painless macules, most often in the lumbar region, perineum and buttocks (57%), limbs (30%), face (6%), neck and torso (6%), which may be accompanied by non-specific symptoms, including abdominal pain, diarrhoea, fever and flu-like symptoms [4, 6, 9, 18, 24]. *Ecthyma gangrenosum* can present as single or multiple lesions [19]. The skin lesions then gradually increase and become papulae. The next stage is the stage of the hemorrhagic blister, which over time breaks and transforms into a black eschar surrounded by erythema – the transformation from a papula into an eschar takes 12 to 24 h. At the site of skin disruption, necrotic penetrating ulcers eventually appear [4, 18, 23].

Pulido *et al.* in an article published in 2012 describe the case of an 11-month-old girl, whose first symptoms appeared 3 days before admission to the hospital in the form of discomfort during diaper change, caused by

swelling and slight redness of the right labia. The patient was feverish and had previously been diagnosed with acute lymphoblastic leukaemia along with neutropenia associated with chemotherapy. After admission to the ward, no other skin symptoms were found, and thus the decision to administer cefepime and gentamicin was made. On the second day of hospitalization, a round spot with a diameter of 8 mm with associated erythema and central necrosis was noticed on the inner surface of the right labia major. After consultation, due to the inability to collect a skin point biopsy, a surgical biopsy was decided. During the operation, the lesion was removed completely and the samples were sent for microbiological tests, which confirmed *Pseudomonas aeruginosa* infection. The tissue around the wound was hardened, but according to previous suspicions, there were no purulent foci due to the patient's neutropenia [19, 25].

Differentiation

Pathologically changed areas of the skin have a characteristic morphology, therefore they should be quickly diagnosed in order to avoid serious complications [18]. In most cases, *ecthyma gangrenosum* in the form of necrotic ulcers surrounded by erythema is a pathognomonic symptom of *Pseudomonas aeruginosa* sepsis, most of the time in patients with impaired immunity and neutropenia. However, cases of infection with this pathogen without direct development of bacteraemia have been reported [26]. The increased risk of death in the event of incorrect identification of *ecthyma gangrenosum* may be due to the lack of sufficiently fast administration of appropriate antibiotics. Skin changes should be differentiated primarily from fungal infections, which often occur in patients with immunodeficiency [19]. The initial stage of the disease in the form of small papulae may be similar to chickenpox, but in the case of *ecthyma gangrenosum* they are rapidly increasing in size. Necrotic skin, in order to avoid administration of steroid drugs, should be differentiated from *pyoderma gangrenosum*, which is characterized by the absence of bacteria in the histopathological preparation and the presence of purulent lesions. *Ecthyma gangrenosum*, compared to usual *cellulitis*, has a faster course occurring with the characteristic evolution of the affected skin areas [2, 6].

Ishikawa *et al.* in their scientific work published in 2005 describe the case of a 4-year-old boy who, after antibiotic therapy (cefaclor, piperacillin, ampicillin + sulbactam), developed changes in the form of widespread necrotizing ulcers that showed similarity to *ecthyma gangrenosum*. Despite the lack of a positive result of microbiological examination, based on clinical symptoms, the patient was diagnosed with *Streptococcus* spp. group A infection. Histopathological examination should be performed in order to differentiate *Pseudomonas aeruginosa* infection from *Staphylococcus* spp. and *Streptococcus* spp. ones. In *Pseudomonas aeruginosa* case it is possible to observe a small inflammatory reaction, hemorrhagic necrosis with numerous eosinophilic bacteria in the surrounding of and directly in the adventitia and middle layer of blood vessels resulting in occlusive inflammation [23, 26], as well as the formation of a fibrin clot. On the other hand, in case of *Staphylococcus* spp. and *Streptococcus* spp. infections, a diffuse inflammatory reaction is observed, most of the time without the presence of bacterial cultures. However, the exact mechanism of *ecthyma gangrenosum*-like changes after antibiotic therapy remains unknown; the potential cause is the destruction of pathogens and follow-up release of toxins or the post-antibiotic change in the intestinal microflora [27].

Treatment

In the case of *ecthyma gangrenosum* caused by *Pseudomonas aeruginosa* in patients with immunodeficiency, it is particularly important to make a rapid diagnosis of the causative agent and implement appropriate targeted antibiotic therapy [10, 21]. Neutropenia in children may result in the rapid progression of the disease, and thus lead to necrosis of new tissues [18].

After confirming the diagnosis, targeted antibiotic therapy with the option of surgically resecting necrotic areas is currently preferred [18, 19]. In addition, skin incision and tissue cleansing from necrosis are practiced, and in some cases skin transplantation is also considered [21, 28]. It is suggested to use chlorhexidine and polymyxin B to wash the wound and its subsequent protection using paraffin dressings [10]. Due to the location of deep lesions in the dermis and high mortality, systemic treatment is preferred over surface therapy [1]. Until the results of microbiological tests are received, in patients with immunodeficiency and neutropenia with suspicion of *ecthyma gangrenosum*, empirical treatment with broad-spectrum β-lactam antibiotics is being implemented, including imipenem, aminoglycosides (gentamicin), cefepime and fluoroquinolones [19, 29]. Two of them should have proven effectiveness against *Pseudomonas aeruginosa* before. When the test results are obtained, the antibiotics should be changed to those with the narrowest spectrum, according to the antibiogram [19]. In oncological patients with *Pseudomonas aeruginosa* sepsis, the use of only one antibiotic is preferred; the effectiveness of combination therapy has not been proved. Prolonged infusion of antibiotics lasting several hours is in consideration; it has been proven in animal models that this strategy allows the minimum inhibitory concentration (MIC) to be maintained for a longer period of time, thus increasing the efficacy of therapy against *Pseudomonas aeruginosa* [29]. In 2002–2004, in Albany Medical Center in New York, USA, and in 2010–2011 in the Ohio State University Medical Center in Ohio, USA, single-centre observational studies were conducted on patients infected with *Pseudomonas aeruginosa*, which

showed a reduction in mortality when using prolonged infusions of antibiotics [29–31].

Aitken *et al.* in a paper published in 2016 described the case of a 9-year-old boy with acute myeloid leukaemia relapse and neutropenic fever. They proved that the best therapeutic option for blood infection with the multi-resistant *Pseudomonas aeruginosa*, after colistin (which in patients with neutropenia has limited efficacy and the optimal dose is not known), is the ceftolozane/tazobactam combination. The combination of ceftazidime/avibactam, which was effective in the treatment of multi-resistant *Klebsiella pneumoniae* sepsis, was also considered, but bacterial resistance and lack of efficacy were found in *Pseudomonas aeruginosa* infections. The final dose of the ceftolozane/tazobactam combination should, based on pharmacokinetic and pharmacodynamic analyses, be selected so that blood levels of a minimum of double MIC for ceftolozane are obtained throughout the whole treatment period. The antibiotic should be administered as a prolonged intravenous infusion lasting 3 h, given every 6 h. Such strategy allows maintaining a concentration of ceftolozane unbound to plasma proteins of a minimum of twice the MIC throughout the entire cycle of administration of one dose [17].

In paediatric patients who have had necrosis involving the anal sphincter in the perianal area, a temporary protective colostomy may be performed. This procedure allows to isolate locally altered, infected skin from the stool, and thus start the wound healing process. There are three types of colostomy: loop colostomy (most often performed for paediatric patients); end colostomy/single–barrel (Hartmann's operation – preferred in adults); and double barrel colostomy. A few months after completing the treatment of the perianal area, patients may undergo reversal colostomy and reconnection of intestinal loops to restore physiological intestinal continuity [21, 28].

Lau *et al.* in an article published in 2014 suggest that reducing the concentration of pyocyanin – a toxin produced by *Pseudomonas aeruginosa* – by neutralizing it as a result of antioxidant therapy or by completely inhibiting its synthesis may be an alternative, supporting method of treating infection caused by this pathogen [12]. If a fungal infection is suspected, systemic antifungal therapy should be implemented. In patients with immune disorders, including agammaglobulinemia, hypoglobulinemia or neutropenia, administration of immunoglobulins or granulocyte stimulating factors may be considered in order to increase the chances of recovery [4, 23]. It is also necessary to provide adequate nutrition to the patient [16].

Epidemiology

Main risk factors for nosocomial infection with the multi-drug resistant *Pseudomonas aeruginosa* include pri-

or administration of antibiotics, intubation and mechanical ventilation. However, up to 90% of blood infections occur through the central venous catheter. Ultimately, the development of bacteraemia significantly increases the mortality rate of nosocomial infections [14]. Cases of non-bacterial *ecthyma gangrenosum* have been reported in healthy individuals, without exposure to risk factors [18].

Pseudomonas aeruginosa is an opportunistic pathogen that is particularly common for skin, mucous membranes and subcutaneous tissue infections in immunocompromised and neutropenic children, most commonly as a result of acute leukaemia or other malignant neoplastic diseases, aplastic anaemia, hypogammaglobulinemia, agammaglobulinemia, steroid therapy or AIDS [10, 21, 23]. Reduced immunity, especially in patients from haematology and oncology departments who have undergone allogenic hematopoietic bone marrow transplantation, predispose to infection with Gram-negative bacteria, including the multi-drug resistant *Pseudomonas aeruginosa* [32]. Wounds in paediatric patients with immunosuppression and neutropenia are often infected by this pathogen [21].

This bacterium has the ability to create a biofilm, especially in environments with high humidity. Good conditions for this process are provided by hospital sanitary and water supply systems, which means that they can be a source of infection with this microorganism [32].

Depending on the source, the mortality of *ecthyma gangrenosum* with bacteraemia, especially caused by *Pseudomonas aeruginosa* infection, is 38–77%, while in the absence of sepsis, this rate drops to 15% [18, 23]. A single skin lesion is associated with a better prognosis than multiple lesions [19]. In addition, septic shock, multi-drug resistant microorganism infection, neutropenia and delayed antibiotic therapy are associated with an increased risk of death [23].

Resistance of *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a multi-drug resistant pathogen against which most antibiotics are not effective [33]. Colistin, as a drug of last resort in case of patients with neutropenia, has limited effectiveness and the optimal dose is unknown [17]. The bacterium is characterized by overproduction of AmpC chromosomal cephalosporinases, which is probably associated with β-lactam resistance [33]. According to the scientific work of Rossi Gonçalves *et al.* published in 2016, carbapenems and β-lactams are the most commonly used antibiotics in Brazilian hospitals. 60% of *Pseudomonas aeruginosa* infections in these medical centres cannot be treated with them because of resistance to these drugs caused by producing specific metal-β-lactamases (MBL – mainly: SPM-1, VIM, IMP-1) by these bacteria. Not all carbapenem-resistant strains produced MBL – another possible explanation for bacterial resistance to this group of antibiotics is reduced expression of OprD porins [14, 33].

A characteristic feature of *Pseudomonas aeruginosa* is the extraordinary ability to develop resistance to further antibiotics. Beta-lactam antibiotics used to treat febrile neutropenia are not effective against many strains of this bacterium. In 2009–2012 in Italy, a total of 66 *Pseudomonas aeruginosa*-positive blood samples were taken from 9 haematological departments, followed by antibiograms; the results of this study are presented in Table 1 [29, 34].

The results of these studies explain the lack of effectiveness of empirical antibiotic therapy with β-lactams in the hospitals involved in the analysis, and thus the increase in the mortality of patients with neutropenia who developed Gram-negative bacteria bloodstream infection [29].

The problem of *Pseudomonas aeruginosa* drug resistance is also becoming significant in other countries. In 2009–2012, studies on 279 blood samples reported to the CDC (Centers for Disease Control and Prevention) and drawn from central venous catheters of oncological patients infected with this pathogen were carried out. Resistance to carbapenems and cephalosporins was found in 20% and in 14% of cases, respectively [29, 35].

Prevention

In the prevention of bacterial infections, including the multi-drug resistant *Pseudomonas aeruginosa* (MDRP), it is important to take special precautions which, when used simultaneously, significantly contribute to increasing the effectiveness of prevention against infections. These include: careful hygiene and hand disinfection; adherence to the principles of EBM (evidence-based medicine) regarding vascular catheters; placing patients (if possible) in isolated rooms; maintaining a clean hospital environment; implementation of special precautions against patients colonized with multi-drug resistant strains of bacteria. It is difficult to prioritize these activities; it is suggested to follow them simultaneously. In oncology departments, it is suggested to limit the use of broad-spectrum antibiotics when there is no need to ad-

Table 1. Results of *Pseudomonas aeruginosa* resistance to β-lactams in 9 haematology departments in Italy in 2009–2012 [29, 34]

Antibiotic	Resistance number of blood samples: 66
Meropenem	71%
Ceftazidime	55%
Piperacillin + tazobactam	42%

minister them as they are a risk factor for infection with multi-resistant strains [29]. In order to protect healthy children from infection, inflatable garden swimming pools should be regularly chlorinated since they can be a source of *Pseudomonas aeruginosa* infection [3].

In 2011–2014 at the University Children's Hospital in Muenster in Germany, the transplant department was renovated, with the main goal of reducing the environmental risk of infection with the multi-drug resistant strains of *Pseudomonas aeruginosa*. It was supposed to be achieved through creating adverse conditions for biofilm formation by these bacteria. New, specially designed, easy to disinfect shower drains have been implemented. Taps and shower heads were equipped with water filters and disinfecting siphons were installed under the sinks. The toilet bowls were replaced with rimless ones and a disinfectant was added to the flushing water. Patients' rooms were cleaned and disinfected on a daily basis and, at least once-a-month, environmental sampling for microbiological testing was started. In addition, hospital cleaning staff and other employees who have direct or indirect contact with patients have been thoroughly trained in hygiene procedures. All these actions eventually led to positive epidemiological changes presented in Table 2 [32].

Summary

In most cases, *ecthyma gangrenosum* is a complication of *Pseudomonas aeruginosa* sepsis. Most often it de-

Table 2. Epidemiological changes after renovation at the Children's University Hospital in Muenster, Germany in 2011–2014 [32]

Factor	Year	
	2012–2013 (before renovation)	2014 (after renovation)
Number of patients tested	338	179
Number (percentage) of patients colonized and/or infected with MDRP	31 (10.5%)	3 (1.68%)
Number (percentage) of patients infected with MDRP	13 (3.85%)	1 (0.56%)
Number (percentage) of deaths due to MDRP infection	12 (3.55%)	0 (0%)
Number (percentage) of MDRP in toilet samples	125 of 660 (18.94%)	23 of 275 (6.13%)
Number (percentage) of MDRP in shower drain samples	52 of 641 (8.11%)	11 of 372 (2.96%)

MDRP – multi-drug resistant Pseudomonas aeruginosa.

velops in patients with immunodeficiency, but it can also occur in healthy people. Single or multiple lesions mainly involve the perineum, buttocks and lumbar region and progress rapidly; initially they appear as papules, which after 12 to 24 h eventually turn into a black scab with penetrating ulceration and necrosis. Empirical antibiotic therapy should be implemented as soon as possible and be changed to targeted one after obtaining the results of microbiological tests; *Pseudomonas aeruginosa* is an opportunistic multi-drug resistant pathogen, against which most antibiotics are not effective. Surgical cleansing of necrotic tissues and, ultimately, skin transplantation are also practiced. If the perianal area is affected with anal sphincter necrosis, a protective colostomy is performed, which is reversed after a few months. Prevention of infections with this pathogen primarily includes the use of special precautions by medical staff when dealing with a paediatric immunocompromised patient.

Conflict of interest

The authors declare no conflict of interest.

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