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CASE REPORT

Successful Treatment of Fournier's Gangrene in Child with Relapsed Acute Lymphoblastic Leukemia: Case Report and Review of the Literature

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Abstract: Neutropenia associated with onco-hematological treatment may contribute to high-mortality infections, especially caused by multidrug-resistant pathogens. In a 4-year-old girl treated due to early isolated central nervous system (CNS) relapse of B-cell acute lymphoblastic leukemia, skin lesions with traits of Fournier's gangrene caused by Klebsiella pneumoniae carbapenemase (KPC)-producing *Pseudomonas aeruginosa* (PsA). The patient was treated with broad-spectrum antibiotic therapy and the wound was debrided and treated with VAC (vacuum-assisted closure) successfully. Despite further intensive anticancer treatment complicated by reactivation of PsA infection, there was no other episode of invasive infection anymore and, nowadays, the patient has been in complete remission for 13 months. The aim of this report is to mention that Fournier's gangrene is a rapid and potentially fatal infectious complication of chemotherapy in onco-hematological pediatric patients, especially if caused by MDR (multidrug-resistant) pathogens. Successful treatment of this necrotizing fasciitis saves a patient's life and allows to continue an effective anticancer therapy.

Keywords: Fournier's gangrene, *Pseudomonas aeruginosa*, multidrug resistance, therapy, child, acute lymphoblastic leukemia

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of the pediatric neoplasm characterized by clonal proliferation of B-cell or T-cell progenitors.[1] Neutropenia associated with anticancer treatment may contribute to high-mortality infections, especially those caused by multidrug-resistant (MDR) pathogens.[2] Bacterial infections indicate the highest mortality rate in onco-hematological patients (68%), followed by fungal (20%) and viral (12%) infections.[3,4] *Pseudomonas aeruginosa* (PsA) is a Gram-negative pathogen in the ESKAPE group of highly virulent and antibiotic-resistant pathogens. As their MDR rate increases, they can evade commonly used antibiotics and become the major cause of life-threatening infections in immunocompromised patients.[5,6]

Fournier's gangrene (FG) is a rare, rapid, progressively necrotizing, and potentially fatal perineum inflammation developed as an infectious complication of chemotherapy or neoplasm itself in cancer patients.[7] It is classified as type 1 necrotizing fasciitis of polymicrobial etiology.[8] The underlying cause is a mixed oxygen-anaerobic bacterial flora with different bacterial species.[9] Mortality rates related to the Fournier's gangrene vary from 4% to 88%, usually range from

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20% to 40%.[10] Despite its rarity, the disease is well-known from an unfavorable prognosis, but its course depends mostly on the timing. It is known that the latency of the first dose of antibiotics is a main risk factor of serious complications in neutropenic fever treated in an ICU. Treatment delay is usually accompanied by a high lethality (reaching 90%), not only because of the septic shock but also associated complications.[11]

Here, we present a case of Fournier's gangrene disease in a child with relapsed ALL during intensive chemotherapy.

Case Report

Twenty-seven months after the primary diagnosis of common preB-ALL, the 4-year-old girl was diagnosed with an isolated CNS (central nervous system) relapse of leukemia and started therapy according to the IntReALL SR 2010 protocol (Table 1). Two days after the 4th course of intensive chemotherapy, the CRP (C-reactive protein) level suddenly elevated and other inflammation parameters were increasing, including white blood cells rising from neutropenic to the level of 3.76×10^9/L. The empirical antibacterial treatment of piperacillin-tazobactam was administered and within the next few days inflammation parameters decreased, just to increase again a week later. Then, subsequent antibiotic therapy, including meropenem and linezolid was administered. One day later fever appeared (39°C), and the patient's condition started deteriorating rapidly. She experienced increasing respiratory failure with such symptoms as tachypnoea

Table 1 Chemotherapy Regimen with Drug Names and Doses

Drug	*Dosage*	*Day of Therapy*
PRIMARY THERAPY		
Induction Phase		
Prednisone	60 mg/m^2/day P.O. divided into 3 doses per day	Days 1–28 (from day 29, tapering over 9 days with halving the dose on every third day)
Vincristine	1,5 mg/m^2/dose i.v.	Days 8, 15, 22, 29
Daunorubicin	30 mg/m^2/dose p.i. (1 h)	Days 8, 15, 22 and 29
PEG-L-Asparaginase	2500 IU/m^2/dose p.i. (2 h)	Days 12 and 26
Methotrexate	10 mg i.th.	Day 1, 12, 33
Consolidation A		
6-Mercaptopurine	60 mg/m^2/day P.O.	Days 36–49
Cytarabine	75 mg/m^2/dose i.v., 2 blocks of 4 days each	Days 38–41, 45–48
Methotrexate	10 mg i.th.	Day 45
Consolidation B$_{short}$		
Cyclophosphamide	1000 mg/m^2/dose p.i. (1 h)	Days 50 and 64
Cytarabine	75 mg/m^2/dose i.v., 2 blocks of 4 days each	Days 52–55 and 59–62
6-Mercaptopurine	60 mg/m^2/day P.O.	Days 50–63
Methotrexate	10 mg i.th.	Day 59
Protocol M		
6-Mercaptopurine	25 mg/m^2/day P.O.	Day 1–56
Methotrexate	5000 mg/m^2/dose p.i. (24 h)	Days 8, 22, 36 and 50
Methotrexate	10 mg i.th.	Days 8, 22, 36 and 50 (during high-dose-MTX infusion)

(*Continued*)

Table 1 (Continued).

Drug	*Dosage*	*Day of Therapy*
Protocol II		
Dexamethasone	10 mg/m^2/day P.O. divided into 3 doses per day	Days 1–21 (from day 22 tapering over 9 days, with halving the dose on every third day)
Vincristine	1,5 mg/m^2/dose i.v.	Days 8, 15, 22 and 29
Doxorubicin	30 mg/m^2/dose p.i. (1 h)	
PEG-L-Asparaginase	2500 IU/m^2/dose p.i. (2 h)	Day 8
Cyclophosphamide	1000 mg/m^2/dose p.i. (1 h)	Day 36
Cytarabine	75 mg/m^2/dose i.v., 2 blocks of 4 days each	Days 38–41, 45–48
Thioguanine	60 mg/m^2/day P.O.	Days 36–49
Methotrexate	10 mg i.th.	Days 38 and 45
Maintenance therapy		
6-Mercaptopurine	50 mg/m^2/day P.O.	Daily
Methotrexate	20 mg/m^2/dose P.O.	Once a week
RELAPSE THERAPY		
Induction phase		
Dexamethasone	20 mg/m^2 P.O. divided in 2 daily doses	Day 1–5 of week 1 and 3
Vincristine	1,5 mg/m^2/dose	Day 1 and 6 of week 1, day 1 of week 3
Methotrexate	1 g/m^2 i.v.	Day 1 of week 1 (over 36 hours)
PEG-L-Asparaginase	1000 IU/m^2 i.v.	Day 4 of week 1, day 4 of week 3
Cytarabine	3 g/m^2 i.v. every 12 hours	Day 1 and 2 of week 3
Methotrexate	12 mg i.th.	Day 1 and 6 of week 1, day 5 of week 3 (directly before or until 1 hour after start of the methotrexate infusion)
Cytarabine	30 mg i.th.	
Prednisolone	10 mg i.th.	
Post-induction phase (relapse)		
1st chemotherapy block		
Dexamethasone	6 mg/m^2 P.O. divided in 2 daily doses on day 1–7 of week 5 and 6 (tapering the dose to 3 mg/m² on day 1–3 of week 7, 1.5 mg/m^2 on day 4–6 of week 7 and 0.75 mg/m² on day 7 of week 7 and day 1–2 of week 8)	
Vincristine	1,5 mg/m^2/dose i.v.	Day 1 of week 5–8
Idarubicin	6 mg/m^2 i.v.	
PEG-L-Asparaginase	1000 IU/m^2 i.v.	Day 1 of week 5, day 4 of week 6
Methotrexate	12 mg i.th.	Day 1 of week 5–7
Cytarabine	30 mg i.th.	
Prednisolone	10 mg i.th.	

(*Continued*)

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Table 1 (Continued).

Drug	*Dosage*	*Day of Therapy*
2nd chemotherapy block		
Cytarabine	75 mg/m^2 i.v.	Day 3–6 of week 9 and 10
Thioguanine	60 mg/m^2 P.O.	Day 1–7 of week 9 and 10
Methotrexate	12 mg i.th.	Day 3 of week 9–10
Cytarabine	30 mg i.th.	
Prednisolone	10 mg i.th.	
3rd chemotherapy block		
Dexamethasone	20 mg/m^2 P.O., divided in 2 daily doses – day 1–5, and 10 mg/m^2 on day 6 of week 13, 19 and 25	
6-Mercaptopurine	100 mg/m^2 P.O.	Day 1–5 of week 13, 19 and 25
Vincristine	1,5 mg/m^2/dose	Day 1 and 6 of week 13, 19 and 25
Methotrexate	1 g/m^2 i.v. over 36 hours starting	Day 1 of week 13, 19 and 25
Cytarabine	2 g/m^2 i.v. every 12 hours	Day 5 of week 13, 19, and 25
PEG-L-Asparaginase	1000 IU/m^2 i.v.	Day 6 of week 13, 19 and 25
Methotrexate	12 mg i.th.	Day 1 of week 13, 19 and 25 (directly before or until 1 hour after start of the methotrexate infusion)
Cytarabine	30 mg i.th.	
Prednisolone	10 mg i.th.	

shallow breathing with a great respiratory effort and oxygen saturation below 90%, circulatory failure (tachycardia, decreased left ventricular contractility and positive fluid balance despite administered diuretics). Moreover, the liver was enlarged and laboratory findings indicated abnormalities in the coagulation panel. Capillary blood gas analysis conjointly with lactate blood level depicted lactic acidosis. Immediately, metronidazole and micafungin were added. Nevertheless, fever persisted and skin lesions with traits of Fournier's gangrene appeared in the left groin. It was swollen and painful. The bacteriological blood cultures and wound swab confirmed Klebsiella pneumoniae carbapenemase (KPC)-producing PsA, which the girl had not hosted earlier. Despite the antibacterial treatment, the patient developed multiple-organ dysfunction syndrome (MODS) and was transferred to the pediatric intensive care unit, where additionally to intensive antimicrobial treatment, mechanical ventilation and hemodiafiltration were administered. After the final microbiological result, due to resistance of PsA to meropenem, antibacterial therapy was replaced with ceftazidime-avibactam. The targeted antibiotic therapy lasted for 33 days. Due to concurrent probable invasive pulmonary aspergillosis, empirical antifungal treatment of micafungin was replaced by preemptive therapy with voriconazole. The wound was surgically debrided and treated with vacuum-assisted closure (VAC) (Figure 1). After clinical and hematological recovery, the girl continued anticancer treatment held due to the infection for 4 weeks. Unfortunately, in another episode of neutropenia, the subsequent wound on the girl's neck appeared after wearing a necklace. Microbiological wound swab confirmed KPC-producing *PsA*, but this time resistant to both meropenem and also ceftazidime-avibactam. Luckily, PsA strain was sensitive to ceftolozane-tazobactam, which was administered subsequently, and the generalized infection did not occur. Due to the fact of constant immunosuppression and further therapy in front of the patient, anti-PsA vaccine was applied successfully. Neither *PsA* colonization nor infection has been observed since then. After CAR-T cell-based consolidation of ALL relapse treatment, the patient has been in complete remission for 13 months.

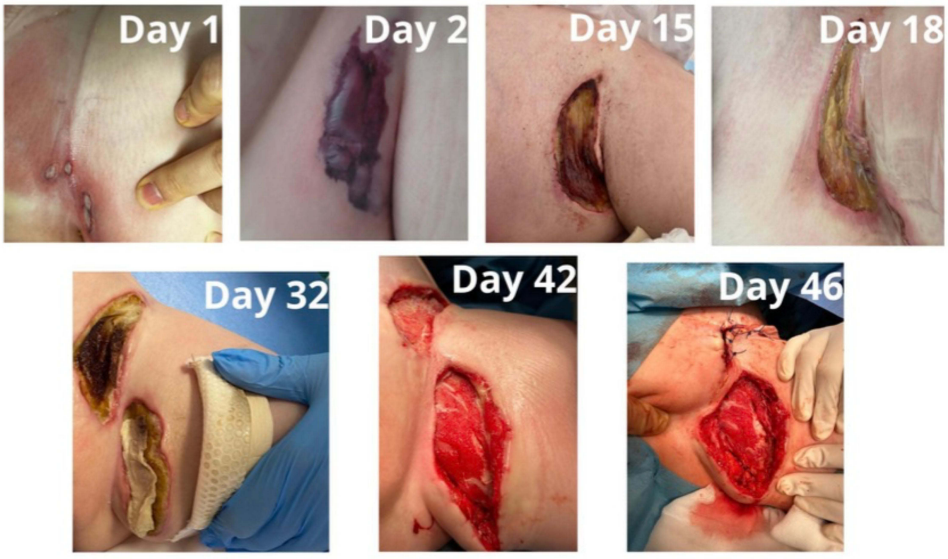

Figure 1 The evolution of skin lesions with features of Fournier's gangrene (photos are used with parental informed consent). Day 1: The appearance of skin lesions with traits of FG in the patient's left groin. Day 2: Skin lesions with traits of FG the following day. Day 15: Skin lesions with traits of FG after 2 weeks (15 days) of conservative treatment. Day 18: Skin lesions with traits of FG after 18 days of conservative treatment. Day 32: Surgical debridement of the wound and implementation of vacuum-assisted closure (VAC). Day 42: Surgical debridement of the wound and reimplementation of VAC. Day 46: VAC removal and stitches placement.

Discussion

Hematologic patients belong to a high-risk group for bacterial infections, to which they are particularly predisposed due to complex immune deficiencies resulting from their underlying disease and treatment.[12,13] The following factors qualified our patient to the highest group of infectious complications, including Fournier's gangrene, ie relapse of ALL, neutropenia, recently applied steroid and chemotherapy.[12–14]

Fournier's gangrene belongs to necrotizing fasciitis associated with a high mortality rate, involving both skin and subcutaneous tissue on the external genitalia and in the perianal region.[7] Moreover, the frequency is higher in adults, including 10–40 times higher in males.[11] However, despite its usual infrequency in children, this has been also reported as one of the potential consequences of treatment in pediatric onco-hematological population.[15] Immunosuppression, including this phenomenon arising from hematological malignancies, such as treated relapsed leukemia in our patient, is a recognized risk factor for necrotizing fasciitis.[16,17] However, the diagnosis and therapy of Fournier's gangrene still remain challenging and troublesome.

The etiological factor of a Fournier's gangrene is a mixed oxygen-anaerobic bacterial flora,[9] mostly the physiological flora of the urogenital or anorectal region, such as enteric rods (*Escherichia coli, Klebsiella spp., Proteus spp)*., Gram-positive cocci (*staphylococci, streptococci, enterococci*) and obligate anaerobic bacteria (*Clostridium spp., Bacteroides spp., Fusobacterium*),[8] and in rare cases fungi, including *Candida spp*. or molds.[18,19] However, the cultures of patients with concurrent Fournier's gangrene and hematological malignancies usually contain Gram-negative bacteria, such as *PsA* and *Escherichia coli*. Moreover, in patients with onco-hematological diseases monomicrobial *PsA* infection is more common than in the general population of Fournier's gangrene patients.[7]

The causative microflora is often polymicrobial (aerobic and anaerobic); hence, drugs of choice for Fournier's gangrene treatment are III–IV generation cephalosporins with antibiotics of the group of nitroimidazole, fluoroquinolones, aminoglycosides. Carbapenems should be introduced within the complex antibacterial therapy, providing the refractory forms.[11] In our patient due to rapidly deteriorating general condition, the de-escalation regimen of antibiotic therapy was chosen in the management of Fournier's gangrene.[12,14] Unfortunately, the presence of KPC-*PsA*, the MDR strain predisposed by multiple previous antibiotic treatments, prolonged hospitalization, immunosuppression, underlying disease and damage to the mucosal barrier, led to the development of septic shock.[12,20,21] An appropriate combination of antimicrobial drugs, especially in combination with ceftazidime-avibactam recommended for MDR *PsA* infection,

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followed by V generation cephalosporin + beta-lactamase inhibitor, ie ceftolozane-tazobactam, consolidated with subsequent administration of an anti-*PsA* vaccine enabled therapeutic success and continuation of anticancer treatment without recurrence of invasive *PsA* infection.[21–23]

A significantly relevant issue to consider in the treatment of Fournier's gangrene is an emergency surgical intervention concomitant with antibacterial therapy. It is known that the most effective way to complement systemic treatment of Fournier's gangrene is using negative pressure wound therapy with VAC.[24] It accelerates healing of difficult wounds by accelerating granulation of the wound bed. It is also an effective method of wound debridement, cutting off the fasciitis process.[25,26] This may provide significant treatment benefits, leading to improved clinical outcomes and patient quality of life, as well as shorter hospital stays, less analgesic use, faster wound closure, reduced markers of sepsis, fewer operations and postoperative dressing changes.[27–30] Interestingly, lower percentages of surgical treatments in immunocompromised patients have been reported by some authors compared with non-immunocompromised patients. Albasanz-Puig A. et al observed that only 62.5% of hematological patients underwent surgical treatment of necrotizing fasciitis, compared with 100% of non-hematological patients.[16] The hypothesised reason could be the fear of increased intraoperative bleeding associated with severe pancytopenia, eventually leading to high intraoperative mortality.[16] Fortunately, results from the literature review depict that most hematological patients affected by Fournier's gangrene undergo surgical debridement with long-term benefits.[7]

Conclusions

The presented case is an example of a patient with Fournier's gangrene, which developed due to the burden of intensive oncological treatment of a childhood ALL relapse, especially after chemotherapy followed by the neutropenic phase. Results from the presented case and review of the literature have relevant clinical implications. High index of suspicion followed by early diagnosis, target antimicrobial therapy, and early surgery are the key factors of successful Fournier's gangrene management. Fournier's gangrene is well-known for its aggressiveness, especially in onco-hematological patients, but surprisingly a high recovery rate in pediatric patients has been reported. Therefore, Gram-negative bacteria, mainly PsA, must be included in the spectrum of antibiotics administered in these group of patients.

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Oral and written consent was obtained for publication of this case report and photos from the patient's parents.

Disclosure

The authors report no conflicts of interest in this work.

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