

Persistent Carbapenem-resistant *Klebsiella pneumoniae* Bacteremia in a Patient with Acute Lymphoblastic Leukemia

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Infections are highly prevalent in patients with hematological malignancies due to the underlying malignancy and/or chemotherapy, and their prevention and treatment are a critical part of patient management. A substantial proportion of bacteria-causing infections among these patients are resistant to conventional, and sometimes also to, broad-spectrum antimicrobial agents. The treatment of such infectious episodes might be complex in face of both the patient's underlying immunosuppression on the one hand and the pathogen's virulence and the availability of effective antibacterial agents on the other.

We present a case illustrating the dilemma of managing infections caused by multidrug-resistant bacteria in a severely immune-compromised patient.

PATIENT DESCRIPTION

A 64 year old previously healthy woman was diagnosed in September 2010 with pro-B acute lymphoblastic leukemia. Poor prognostic factors of her disease included advanced age, hyperleukocytosis and the pro-B ALL immunophenotype.

ALL = acute lymphoblastic leukemia

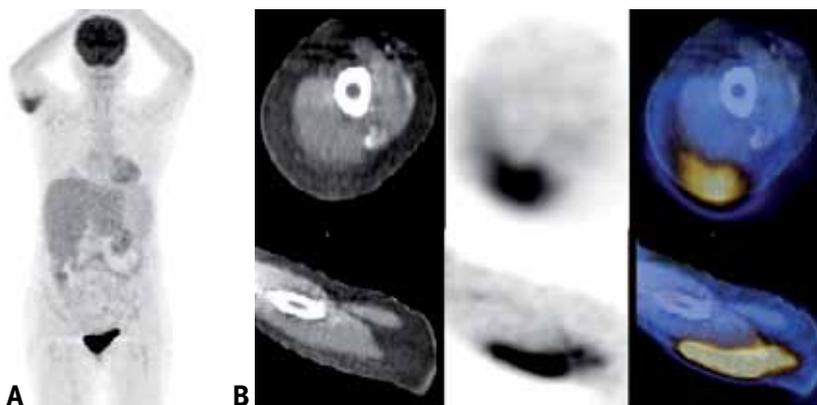
A peripherally inserted central catheter line was inserted and the patient received the first part of induction chemotherapy according to the GMALL 06/1999 protocol. The treatment course was uneventful and bone marrow aspirate at the end of the course was compatible with complete remission. On day 3 after the initiation of the second part of the induction course, the patient became febrile (38.6°C) and antibiotic treatment with piperacillin-tazobactam was initiated according to the policy of our department, with defervescence. Two days later she became neutropenic. On day 10, breakthrough fever of 40°C occurred with the patient complaining of pain at the back of her right arm. The antimicrobial regimen was changed to meropenem and vancomycin and chemotherapy was withheld.

Results of blood cultures obtained on day 10 were reported 3 days later and

were positive for carbapenem-resistant *Klebsiella pneumoniae*. The isolate was sensitive to colistin and amikacin only, thus colistin was added to the regimen. A positron emission tomography/computed tomography scan done on the same day showed extensive inflammation of the subcutaneous tissues of the dorsal aspect of the right arm without muscle involvement or axillary vein thrombophlebitis [Figure]. The PICC line was removed although there were no signs of line infection, and cultures obtained from the tip of the catheter were negative. During the following days the patient's arm and forearm became edematous with local tenderness without crepitus, and superficial bulous lesions appeared, which grew CRKP. Repeated sonographic evaluation

PICC = peripherally inserted central catheter
CRKP = carbapenem-resistant *Klebsiella pneumoniae*

PET/CT scan of the patient showing increased pathological uptake in the dorsum of the right arm [A] Whole body view, [B] View of the right arm



of the right arm showed generalized subcutaneous edema without abscess formation. No gas was observed on plain X-ray. A bedside subcutaneous tissue biopsy showed inflamed tissue with no evidence of fascial necrosis.

During the ensuing days the blood cultures remained persistently positive for CRKP. Tigecycline, a novel tetracycline antibiotic, was added to the regimen on day 16 following susceptibility testing. Due to the persistence of bacteremia, administration of granulocyte transfusions, given on a daily basis, was initiated on day 17. A mild increment in the absolute neutrophil count from nil to 100 cells/ml was noted.

Laboratory tests during that period showed progressive isolated direct hyperbilirubinemia (up to 22 mg/dl). Abdominal ultrasound was normal. The patient later developed progressive non-oliguric renal failure. During the following days, multi-organ failure requiring invasive mechanical ventilation ensued. On day 18, due to persistent bacteremia and the deteriorating clinical status of the patient, amikacin and rifampicin were added to the regimen. Despite intensive care the patient died on day 22. Blood cultures obtained between day 18 and day 22 were negative.

COMMENT

This patient's clinical course demonstrates the challenge of infection management in patients with hematological malignancies. In the case presented here the clinical course was characterized by persistent bacteremia caused by CRKP. This case highlights two infectious aspects in hematological patients, namely, the optimal antibiotic regimen for CRKP infections and the dilemma of surgical intervention for suspected necrotizing fasciitis in a neutropenic patient.

The CRKP isolated was susceptible to colistin, amikacin and tigecycline only. Our patient did not receive empirical treatment with colistin from the outset since the last and single case of carbapenem-resistant

bacteria in our unit was reported in 2007. Furthermore, the experience in our institute shows a non-significantly increased risk for mortality with colistin as compared to beta-lactams in the treatment of MDR gram-negative infections [1]. Amikacin administration was postponed since it was shown that aminoglycosides are significantly inferior to beta-lactams in the treatment of gram-negative bacteremia, and beta-lactam aminoglycoside combinations offer no advantage over beta-lactam monotherapy in the management of febrile neutropenia [2]. Tigecycline is a novel bacteriostatic tetracycline antimicrobial agent with broad-spectrum coverage against MDR gram-negative bacteria. In 2010 the U.S. Food and Drug Administration issued a warning regarding the possibility of increased risk for death in patients with serious infections treated with tigecycline as compared to other antibiotics, probably due to progression of the infection. Therefore, tigecycline was added as a last resort treatment. Finally, rifampin was added based on in vitro studies showing synergism against MDR gram-negative bacteria [3]. Overall, we lack effective antibiotics for the treatment of infections caused by CRKP and we have no data on which to base the optimal antibiotic regimen for these infections.

Alternatively, an uncontrolled extravascular focus of infection might have caused persistent bacteremia in our patient. Soft tissue abscess was ruled out by imaging, but necrotizing fasciitis was seriously considered. This severe condition is characterized by the rapid spread of infection in the subcutaneous tissue with fascial necrosis. While *K. pneumoniae* has been described as a causative pathogen, CRKP has not been reported.

Although necrotizing fasciitis is a rare infection in hematological patients, it might occur either during the course of the disease or, more commonly, as a complication of treatment. The pathogen most commonly reported among hematological patients is *Pseudomonas aerugi-*

nosa. Since an explorative procedure with extensive debridement is the only way to diagnose and treat necrotizing fasciitis, it is a major challenge for physicians dealing with hematological patients. The present patient was treated conservatively and an explorative procedure was not carried out due to severe pancytopenia and lack of supportive evidence for necrotizing fasciitis according to the diagnostic procedure employed, i.e., CT scan and bedside soft tissue biopsy.

An important aspect in the management of this case was the need to track down the source of acquisition of the resistant bacterium, especially in an effort to prevent further spread of this strain in the hemato-oncology ward. The patient underwent rectal surveillance for carbapenem-resistant Enterobacteriaceae upon her first admission to our ward in September 2010 as part of routine surveillance for resistant bacteria. The patient was negative at that time for CRE. No further cases of active infection or carrier state were encountered in our ward and despite our best efforts the source of acquisition of the described infection remains unknown.

Recently, Zuckerman et al. [4] reported a pilot study evaluating eradication of CRKP carrier state among 15 patients undergoing intensive chemotherapy or stem cell transplantation [4]. Patients who were positive for CRKP on rectal swab culture were given oral gentamicin until eradication. Eradication was accomplished in 10 of the 15 patients and all patients in whom eradication failed died, usually as a direct consequence of the active infection caused by CRKP. These figures highlight how unacceptable it is that hematological cancer patients acquire carbapenem-resistant bacteria. Substantial efforts to prevent transmission of MDR bacteria in such patients should be made, namely the prevention of cross-transmission from another carrier.

Another unusual aspect in the management of this patient was the use of

MDR = multi-drug resistant

CRE = carbapenem-resistant Enterobacteriaceae

granulocyte transfusions. This serves as bridging treatment until resolution of neutropenia. The use of such a measure is limited due to the short half-life of neutrophils, severe transfusion reactions, and the use of growth factors in recent years. As their efficacy has been controversial and the number of randomized trials published is small, Stanworth and co-authors [5] recently conducted a meta-analysis in which they showed a survival advantage for patients treated with granulocyte transfusions at high doses. Although there was a minor increase in the neutrophil count of our patients with the administration of granulocyte transfusions, it failed to achieve its designated purpose in our patient.

In conclusion, the present report highlights the dismal prognosis of such patients and the importance of preventing carbapenem-resistant bacteria acquisition in hematological cancer patients. Infection control and the prevention of nosocomial infections with hospital-acquired resistant pathogens should be a main target in the management of these patients.

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