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Coexistence of *bla*$_{TEM}$, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ e *bla*$_{OXA-48}$ in polymicrobial bloodstream isolates from a patient with acute myeloid leukemia

Coexistência de of *bla*$_{TEM}$, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ e *bla*$_{OXA-48}$ em isolados polimicrobianos da corrente sanguínea de um paciente com leucemia mieloide aguda

Coexistencia de *bla*$_{TEM}$, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ y *bla*$_{OXA-48}$ en aislados polimicrobianos del torrente sanguíneo de un paciente con leucemia mieloide aguda

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Abstract
Background: Bloodstream infections are among the most frequent and serious complications in patients with haematological malignancies. Case presentation: A patient diagnosed with acute myeloid leukemia was admitted to the hospital for chemotherapy induction, developed several episodes of febrile neutropenia. Had bloodstream infection with at least four strains of Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumanii*. The majority showed resistance to ampicillin, cefepime, ceftriaxone, ciprofloxacin and sulfamethoxazole/trimethoprim. *bla*$_{TEM}$ and *bla*$_{SIM}$ were detected in *P. aeruginosa*, *bla*$_{TEM}$, *bla*$_{CTX}$ and *bla*$_{OXA-48}$ in *E. coli*, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ and *bla*$_{OXA-48}$ in *K. pneumoniae* and *bla*$_{OXA-48}$ in *A. baumannii*. Conclusions: The patient was treated with meropenem for 10 days, without progressing from fever episodes, evolved to death.
Keywords: Polymicrobial infection; Carbapenemases; β-Lactamase; Hematological malignancy; Bloodstream infection.

Resumo
Introdução: As infecções da corrente sanguínea estão entre as complicações mais frequentes e graves em pacientes com doenças hematológicas malignas. Apresentação do caso: Um paciente com diagnóstico de leucemia mielóide aguda foi admitido no hospital para indução de quimioterapia, desenvolveu vários episódios de neutropenia febril. Teve infecção da corrente sanguínea com pelo menos quatro cepas de bactérias Gram-negativas, incluindo *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumoniae* e *Acinetobacter baumanii*. A maioria mostrou resistência a ampicilina, cefepima, ceftriaxona, ciprofloxacina e sulfametoxazol/trimetoprima. *bla*$_{TEM}$ e *bla*$_{SIM}$ foram detectados em *P. aeruginosa*, *bla*$_{TEM}$, *bla*$_{CTX}$ e *bla*$_{OXA-48}$ em *E. coli*, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ e *bla*$_{OXA-48}$ em *K. pneumoniae* e *bla*$_{OXA-48}$ em *A. baumannii*. Conclusões: O paciente foi tratado com meropenem por 10 dias, sem evolução de episódios febris, evoluindo a óbito.
Palavras-chave: Infecção polimicrobiana; Carbapenemases; β-lactamase; Malignidade hematológica; Infecção da corrente sanguínea.

Resumen
Antecedentes: las infecciones del torrente sanguíneo se encuentran entre las complicaciones más frecuentes y graves en pacientes con neoplasias hematológicas. Presentación del caso: Un paciente diagnosticado con leucemia mieloide aguda fue ingresado en el hospital para inducción de quimioterapia, desarrolló varios episodios de neutropenia febril. Tenía una infección del torrente sanguíneo con al menos cuatro cepas de bacterias gramnegativas, incluidas *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumoniae* y *Acinetobacter baumanii*. La mayoría mostró resistencia a ampicilina, cefepima, ceftriaxona, ciprofloxacina y sulfametoxazol / trimetoprima. *bla*$_{TEM}$ y *bla*$_{SIM}$ se detectaron en *P. aeruginosa*, *bla*$_{TEM}$, *bla*$_{CTX}$ y *bla*$_{OXA-48}$ en *E. coli*, *bla*$_{CTX}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{SIM}$ y *bla*$_{OXA-48}$ en *K.*

pneumoniae y bla_{OXA-48} en *A. baumannii*. Conclusiones: El paciente fue tratado con meropenem durante 10 días, sin progresar de episodios febriles, evolucionó hasta la muerte.
Palabras clave: Infección polimicrobiana; Carbapenemasas; β-lactamasa; Malignidad hematológica; Infección del torrente sanguíneo.

1. Introduction

The epidemiology of bloodstream infection in patients with haematological cancer has been changing over time. Gram-negative bacteria infections are increasingly prominent in patients with hematological malignancies associated with antimicrobial resistance (Pagano et al., 2014).

Multidrug-resistant gram-negative bacterial infections are an increasing cause of mortality in acute myeloid leukemia (AML), compromising the success of antineoplastic therapy (Castañón et al., 2019). Patients with bloodstream infection (BSI), particularly those with multidrug-resistant bacteria (MDR), have a higher risk of mortality (Islas-Muñoz et al., 2018). As a result, the mortality rate in patients with hematological neoplasms increases with bloodstream infections. Bloodstream infections in carbapenem-resistant Enterobacteriaceae are appearing in patients with hematological malignancies and are associated with ineffective initial empirical therapy, long delays in the administration of active antimicrobials and high mortality rates (Satlin et al., 2013).

Bacteremia due to polymicrobial infections is uncommon, however, it has already been reported to be caused by *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* multiresistant (Khan et al., 2020; Dumont et al., 2020), especially in cancer patients (Royo-Cebrecos et al., 2017; Agrawal et al., 2019).

Escherichia coli and *Klebsiella pneumoniae* are more frequent (58.0% and 22.9%) respectively in patients with hematological malignancies (Mert et al, 2019). The incidence of bloodstream infections has been documented in patients colonized by MDR (25.7%) in patients with hematological malignancies, showing a propensity to develop BSIs by *Klebsiella* and *Enterobacter* (Cattaneo et al., 2018). Exposição prévia a antibioticos tem sido fator de risco para bacteremia por *Klebsiella pneumoniae* produtora de beta-lactamase de espectro estendido (ESBL-KP) em pacientes com câncer (Nham et al., 2020). In Brazil, the incidence of BSI by Gram-negative bacteria (BGN) reaches 24.1%, of BSI by multidrug-resistant BGN or polymicrobial infection drops to 3.9% (Rosa; Goldani, 2014).

2. Methodology

We conducted a case report at a referral center for people with cancer in Pernambuco, Brazil. We analyzed all consecutive episodes of bloodstream infection in a cancer patient. Information on baseline characteristics, clinical characteristics, were prospectively collected from medical records. And the etiology, antimicrobial susceptibility, empirical antibiotic therapy and resistance genes were determined through phenotypic and molecular tests. The study was approved by the Research Ethics Committee of the Hospital do Câncer de Pernambuco.

3. Case Presentation

A 24-year-old woman with acute myeloid leukemia M3 subtype - LMA-M3 (promyelocytic leukemia) was admitted to the hematology department of the Pernambuco Cancer Hospital on 01/20/20 to start the first cycle of chemotherapy with daunorubicin and cytarabine, without any comorbidity, and used prophylactic sulfamethoxazole + trimethoprim and acyclovir. The patient presented dyspnea associated with fever and productive cough, requiring supplemental oxygenation. Ceftriaxone 2g / day (D7) and azithromycin 500mg / day (D5) were started. During hospitalization, the patient had several peaks of febrile neutropenia, the first episode of fever was 02/05/20 with 38.2°C. The second episode was 02/14/20 with 38.4°C and the third

episode on 02/17/20 with 38.4ºC. More than three episodes of NF were recorded during hospitalization. Made use of 300 mcg (30 UM / mL) of granulokine during hospitalization.

The complete blood count exams showed intense leukopenia, thrombocytopenia according to hemoglobin values 7.9 g/dL, leukocyte count of 220/mm³, neutrophils 201/mm³ and platelets of 23,000/mm³. Presenting a decrease in the values of red blood cells 2.59, hemoglobin 7.5 g/dL, leukocytes 150/mm³, neutrophils 38/mm³, and platelets 12,000/mm³. Biochemical laboratory tests showed serum levels of 143 mEq/L sodium (Na^+), 3.7 mEq/L potassium (K^+), 100 mEq/L chloride (Cl^-), 2.1 mEq/L magnesium (Mg^{++}) and 31.6 mg/dL of C-reactive protein. Other tests were ordered, such as ferritin, 1650ng/mL, iron 63µg/dL, transferitin 103mg/dL, fibrinogen 412mg/dL. Serology for HBV, HCV, CMV, EBV, HIV, Herpes I and II, VDRL, were all negative. Computed tomography of the chest showed a small bilateral pleural effusion to a greater degree on the right, compressive atelectasis of the pulmonary segments adjacent to the effusion. There was no evidence of ground-glass opacity or consolidations between the parenchyma that would allow the detection of a disease of pulmonary infectious nature detectable by the method. In transitional sections with the upper abdomen, homogeneous hepatomegaly was observed, with no detectable lesions between the parenchyma.

At each episode of febrile neutropenia, blood was collected for blood culture. After blood collection for culture tests and antimicrobial susceptibility, empirical therapy of meropenem and vancomycin was administered for 10 days, in addition anidulafungin was administered for the same period. The febrile neutropenic patient with major impairment of general condition underwent transfusion of blood components. The result of blood culture revealed polymicrobial infection with the presence of *Pseudomonas aeruginosa* and *Escherichia coli* on the first day of collection 02/05/20. Only the antimicrobial meropenem was maintained with the result of the culture. On 02/14/20, the patient presented the second peak of NF at 38.4°C, whose blood culture result revealed the presence of *Klebsiella pneumoniae* and *Escherichia coli* in the bloodstream. At the third peak of NF (38.4°C) on 02/17/20, *Acinetobacter baumanii* was observed.

Species identification was carried out by automated testing and biochemical tests. The resistance genes were detected by the molecular technique (Table 1). And the antimicrobial profile was performed using the minimum inhibitory concentration (MIC) (Table 1).

After the diagnosis, the therapy was adjusted according to the antimicrobial profile, with this, the use of meropenem was maintained, however the patient evolved to death due to the severity of her health status due to septic shock, febrile neutropenia, pneumonia and acute myeloid leukemia.

Antimicrobial susceptibility profile

The antimicrobial susceptibility test was tested using a disc fusion method and microdilution using the lowest inhibitory concentration. Most isolates were resistant to ampicillin, azithromycin, ceftazidime, ciprofloxacin, ceftriaxone and tetracycline. All showed resistance to sulfamethoxazole / trimethoprim by the disk diffusion method (table 1). Resistance to ampicillin, cefepime, ceftriaxone, ciprofloxacin and piperacillin / tazobactam was detected by the minimum inhibitory concentration in most isolates (Table 1).

Detection of the extended-spectrum beta-lactamase resistance genes (ESBL) and metallo-β-lactamase (MβL)

The bacterial isolates were identified and by automated tests and biochemical tests, then they were subcultured in Brain Heart Infusion (BHI) broth for 37ºC at 24 hours, to perform DNA extraction and amplification by Polymerase Chain Reaction (PCR) to detect the resistance genes. DNA extraction was performed using the boiling lysis method. The cell suspension of a culture overnight was boiled at 100 ° C for 10 min and immediately maintained at -20 ° C for at least 6 h. The supernatant was used as a model for PCR amplification and was stored at -20°C.

The presence of ESBL encoding genes was detected by monoplex PCR using primers specific for *bla*$_{SHV}$, *bla*$_{TEM}$, *bla*$_{CTX}$ was performed using the following protocol for amplification; initial denaturation 95ºC at 5 min, followed by 30 cycles of denaturation 95ºC at 1 min, annealing 60ºC at 1 min and extension 72ºC at 1 min. Foi realizada uma etapa de extensão final a 72ºC a 10 min, para cada um dos genes estudado. The presence of genes encoding MβL was detected by PCR using specific primers for *bla*$_{SPM}$, *bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{NDM}$, *bla*$_{KPC}$, *bla*$_{GIM}$ and *bla*$_{SIM}$, using the following protocol for amplification; initial denaturation 95ºC at 5 min, followed by 25 cycles of denaturation 95ºC at 1 min, annealing 60ºC at 1 min and extension 72ºC at 1 min.

The strains were also subjected to PCR to detect class D carbapenemases, such as oxacillinase (*bla*$_{OXA-48}$, *bla*$_{OXA-58}$), using the following protocol for amplification; initial denaturation 94ºC at 5 min, followed by 30 cycles of denaturation 94ºC at 45 sec, annealing 52ºC at 45 sec and extension 72ºC at 1 min. A final extension step was performed at 72ºC at 6 min.

In the first episode of febrile neutropenia, blood culture showed two bacterial isolates in the same sample carrying the *bla*$_{TEM}$ genes in both isolates of *P. aeruginosa* and *E. coli*. The *bla*$_{SIM}$ and *bla*$_{OXA-48}$ genes were also detected in the species, respectively.

In the second episode of NF, two microorganisms were detected the presence of *bla*$_{KPC}$ e *bla*$_{NDM}$, *bla*$_{SIM,}$ *bla*$_{OXA-48}$ e *bla*$_{CTX}$ cohabiting *K. penumoniae* and the presence of the *bla*$_{TEM}$, *bla*$_{CTX}$ in *E. coli*. Genotypic detection of the isolates revealed the presence of at least two resistance genes for the bacterial isolates.

Resistant *Acinetobacter baumanii* oxacillinase (*bla*$_{OXA-48}$) was isolated in the third episode of NF. None of the isolates contained *bla*$_{SHV}$, *bla*$_{SPM}$, *bla*$_{GIM}$, *bla*$_{GES}$, *bla*$_{IMP}$ and *bla*$_{VIM}$. The distribution of the genes encoding ESBL and MβL is given in Table 2.

Table 1 - Minimum Inhibitory Concentration (MIC) of bacterial isolates from infection in the bloodstream of a patient with acute myeloid lymphoma.

	NAL	AMI	AMP	ASB	CFL	CPM	CRO	CFO	CAZ	CRX	CIP	GEN	ERTAP	MER	IPM	NOR	PPT
1220		S (≤2,00)				S (2,00)					S (≤0,25)	S (≤1,00)		S (≤0,25)		S (≤0,50)	S (8,00)
1398	R (≥32,00)	S (≤2,00)	R (≥32,00)		R (≥64,00)	R (8,00)	R (≥64,00)			R (≥64,00)	R (≥4,00)	R (≥16,00)	S (≤0,50)	S (≤0,25)		R (≥16,00)	S (≤4,00)
49	R (≥32,00)	S (≤2,00)	R (≥32,00)		R (≥64,00)	R (8,00)	R (≥64,00)			R (≥64,00),	R (≥4,00)	S (≤1,00)	S (≤0,50)	S (≤0,25)		R (≥16,00)	I (64)
263		S (≤2,00)	R (≥32,00)	R (≥32,00)		R (≥64,00)	R (≥64,00)	R (≥64,00)	R (≥64,00)		R (≥4,00)	S (≤1,00)	R (≥8,00)	R (≥16,00)	R (8,00)		R (≥128,00)
419		I (32,00)				R (32,00)					R (≥4,00)	S (≤1,00)		R (≥16,00)			R (≥128,00)

Subtitle: (S) sensitive, standard dosage, (I) sensitive increasing exposure, (R) resistant. Numerical values express the minimum inhibitory concentration (MIC) NAL- Nalidixic Acid, AMI - Amikacin, AMP - Ampicillin, ASB - Ampicillin + Sulbactam, CFL - Cephalothin, CPM - Cefepime, CRO - Ceftriaxone, CFO - Cefoxitin, CAZ - Ceftazidime, CRX - Cefuroxine, Cynuroxine, Cynuroxine, Cynuroxine, Cynuroxine, Cynuroxine, Cynuroxine, Cynuroxine and Coxin. , ERT - Ertapenem, MER - Meropenem, IPM - Imipenem, NOR - Norfloxacin, PPT - Piperacillin + Tazobactam.
Source: Authors.

Table 2 - Bacterial identification and distribution of resistance genes isolated from a patient with acute myeloid lymphoma.

Date	Códe	Isolated species	Genes	Disc diffusion antimicrobial resistance
02/05/20	1220	*Pseudomonas aeruginosa*	bla_{TEM}, bla_{SIM}	SUT
02/05/20	1398	*Escherichia coli*	bla_{TEM}, bla_{OXA-48}	ATM, CFL, CRO, AMC, SUT, TET
02/14/20	49	*Escherichia coli*	bla_{TEM}, bla_{CTX}	AMP, CPM, CFL, CAZ, CIP, AMC, PPT, SUT
02/14/20	263	*Klebsiella pneumoniae*	bla_{CTX}, bla_{KPC}, bla_{NDM}, bla_{SIM} and bla_{OXA-48}	AMP, ATM, CPM, CAZ, CIP, SUT, TET
02/17/20	419	*Acinetobacter baumanii*	bla_{OXA-48}	AMI,CAZ, CRO, CIP, IPM, MER, SUT

Source: Authors.

4. Discussion

Although polymicrobial infection is less frequent in patients with hematological malignancies (Rosa; Goldani, 2014), the risk of mortality is high in these patients. Chemotherapy treatment can induce neutropenia and fever, thereby temporarily decreasing the levels of leukocytes, neutrophils and platelets in the blood, increasing the risk of infection (Lubwama et al., 2019).

Infections in the bloodstream of patients with haematological neoplasia have often been caused by *Klebsiella pneumoniae* Carbapenemase (KPC) (Pagano et al., 2014), *Pseudomonas aeruginosa* (Tofas et al., 2017) and *Acinetobacter baumannii* (Shargian-Alon et al., 2019), as described in our study. Resistance to β-lactams and carbapenemases has been reported in these patients (Mimura et al., 2020).

Adequate and early empirical therapy is a crucial factor in increasing the survival of these patients. In a study in Hunan, China (Tang et al., 2020), the rate of inadequate initial antimicrobial therapy was classified as a risk factor for early mortality in patients with hematological malignancies associated with febrile neutropenia caused by BGN-BSI.

The prophylaxis with sulfamethoxazole / trimethoprim did not reduce the incidence of infection by gram-negative bacteria. In contrast, the study by Castañón et al., (2019) fluoroquinolone significantly reduced the incidence of carbapenemase and GNB-producing species of *Klebisella pneumoniae*, resulting in a reduction in mortality in patients with acute myeloid leukemia.

Resistance to cefepime was widely detected in the patient's blood culture isolates, a similar result was observed by Chong et al. (2010). Although the utility of cefepime and piperacillin-tazobactam as an empirical therapy for Enterobactericeae bacteremia in patients with hematological malignancy is widely known in our region, most isolates showed resistance to these, making therapeutic options difficult. Empirical therapy with cefepime or piperacillin-tazobactam adjusted for carbapenems at the beginning of treatment was not linked to increased mortality, as documented in another study (Benanti et al., 2019).

Meropenem was used for the empirical treatment of infections. The effectiveness of meropenem was assessed in a study in Japan (Wakisaka et al., 2015) with febrile neutropenics (81.8%), patients with hematological malignancy (79.2%) and with solid tumor (91.8%). The increase in the use of 4th generation cephalosporins has led to increased resistance, which is often expressed with resistance to other classes of antibiotics needed in the treatment of febrile patients with hematological malignancies such as extended-spectrum cephalosporins and carbapenems.

5. Conclusion

In conclusion, we present a case of persistent polymicrobial bloodstream infection in a patient with acute myeloid leukemia caused by gram-negative bacteria resistant to β-lactams and carbapenemases. Empirical treatment with cefepime or meropenem has been routinely used in these cases. In the last cultures collected for diagnosis, resistance to meropenem has been observed. The extensive use of antibiotics active against carbapenemases-resistant Enterobactericeae should be avoided, and combinations of empirical antibiotics active against carbapenemases may be suggested as treatment in patients with hematological malignancies in febrile neutropenia. New antibiotics must be produced, as well as the combination of pharmaceuticals can be used to minimize antimicrobial resistance.

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Ethics approval and consent to participate

Written informed consent for the publication of their clinical details was obtained from the patient's parents. A copy of the consent form is available for review by the Editor of this magazine. Written informed consent was given and maintained by the authors. This work was approved by the Research Ethics Committee of the Pernambuco Cancer Hospital (HCP) in which the work was carried out (CAAE: 16285219.5.0000.5205).

Consent for publication

Consent for publication was obtained by the patient, signing the Free and Informed Consent Term (ICF) approved by the CEP of the Pernambuco Cancer Hospital, following resolution 466/12 of the National Health Council.

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