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MENINGITIS AND BACTEREMIA BY CHRYSEOBACTERIUM INDOLOGENES IN AN IMMUNODEFICIENT PATIENT: CASE REPORT

Luiz Custódio Moreira Junior
Resident doctor at the Medical Clinic of ``Hospital Geral Dr César Cals de Oliveira`` (HGCC) Fortaleza – CE
http://lattes.cnpq.br/335607419605360

Germison Silva Lopes
Hematologist and preceptor of the Medical Clinic residency at ``Hospital Geral Dr César Cals de Oliveira `` (HGCC) Fortaleza – CE
http://lattes.cnpq.br/5503059490213145

Henrique Girão Martins
Hematologist and preceptor of the Medical Clinic residency at ``Hospital Geral Dr César Cals de Oliveira`` (HGCC) Fortaleza – CE
http://lattes.cnpq.br/7334325431636233

Paulo Henrique Silva Rodrigues
Hematologist and preceptor of the Medical Clinic residency at ``Hospital Geral Dr César Cals de Oliveira``(HGCC) Fortaleza – CE
http://lattes.cnpq.br/3224735044428211

Emanoel Lucas Pinheiro Xavier
Medical student at ``Universidade Federal do Ceará`` (UFC)
http://lattes.cnpq.br/3582562744836821

Layrianne de Sá Barbosa Matias
Resident doctor at the Medical Clinic at ``Hospital Geral Dr César Cals de Oliveira`` (HGCC) Fortaleza – CE
http://lattes.cnpq.br/6682691508403662

Abstract: INTRODUCTION: Chryseobacterium indologenes (CI) is an aerobic gram-negative bacillus present in nature, but is rarely present in human microflora. This pathogen can be aggressive, causing significant morbidity and mortality among patients with predisposing conditions, such as extremes of age, prolonged antibiotic therapy, recent surgery, immunodeficiency, malignancies, presence of invasive devices and prolonged use of catheters. Thus, it is considered a multidrug-resistant nosocomial bacterium, but it is rarely found as a cause/pain of bacteremia or meningitis. **CASE REPORT**: Patient, 58 years old, admitted to the HGCC in January 2023 to undergo chemotherapy for Type B Acute Lymphoid Leukemia. Initially, she developed severe mucositis and profound febrile neutropenia, with empirical antibiotic therapy being instituted initially and, subsequently, guided by urine and blood cultures. The multidrug-resistant spectrum CI was isolated in blood culture, and, through discussions with the Hospital Infection Control Committee (CCIH), therapies were instituted. The patient presented with a seizure, which led to a cerebrospinal fluid culture, in which Chryseobacterium indologenes was identified. Furthermore, she presented a reduced level of consciousness and respiratory instability, being taken to the intensive care unit, but later progressing to brain death. **DISCUSSION:** Although *Chryseobacterium spp* is less prevalent than other pathogens and has lower virulence, it gains notoriety as it becomes an organism that causes serious and multidrug-resistant infections. C. indologenes is a species intrinsically resistant to aminoglycosides, first-generation cephalosporins, aminopenicillins and aztreonam, which limits therapeutic options. The emergence of carbapenem-resistant strains of C. indologenes has further restricted antibiotic therapy. Studies have shown that quinolones have the greatest activity against C. indologenes. **CONCLUSION:** The treatment of critical patients involves great concern on the part of the healthcare team, especially in shortening the length of stay, preventing the transmission of hospital pathogens and avoiding the use of extended-spectrum antibiotics. The literature demonstrates that multiresistant strains of C. indologenes are becoming a threat in hospital environments. Furthermore, new studies on the multidrug-resistant pathogen need to be developed mainly in the context of care for complex patients.
Keywords: Meningitis; Bacteremia; Chryseobacterium indologenes; Immunodeficiency.

INTRODUCTION

Chryseobacterium indologenes is an aerobic gram-negative bacillus present in nature, but is rarely present in human microflora. Although rare, it can cause different types of infections, including bacteremia, meningitis, pneumonia and infections associated with internal devices.[1]

These species have been isolated not only from soil, saltwater and freshwater, but also from dry and moist surfaces in the clinical environment and hospital equipment. Due to their good ability to adapt to hostile environments, they contribute greatly to the extensive contamination of healthcare environments.[2]

Although C. *indologenes* has low virulence, it can be an aggressive pathogen, causing significant morbidity and mortality among patients with predisposing conditions, such as extremes of age, prolonged antibiotic therapy, recent surgery, immunodeficiency, malignancies, presence of invasive devices, and prolonged use of catheters. [3] It is important to recognize this, as part of the population assisted in tertiary services presents great complexity with multiple comorbidities and frequently needs to use medical devices (accesses, probes, among others), which

increases the risk of increasingly rare opportunistic infections, mainly considering a context of overuse of invasive devices and abuse of broad-spectrum antibiotic therapy.

Thus, it can be considered a multidrug-resistant nosocomial bacterium, but it is rarely found as a cause of bacteremia. In this context, the absence of guidelines and/or expert consensus makes treatment for this germ even more challenging given the severity of the most affected groups.[4]

Within the scope of the study, importance is given to the chemotherapy environment of onco-hematological patients, where chemotherapies are traditionally associated with a greater risk of infections, secondary neoplasms and autoimmune diseases.[5]

CASE REPORT

Female patient, 58 years old, hypertensive and diabetic, admitted to the Dr. César Cals de Oliveira General Hospital (HGCC), in January 2023, for chemotherapy treatment for high-risk Type B Acute Lymphoid Leukemia (B-ALL), with positive BCR-ABL and history of platelet refractoriness. The established protocol consisted of an intravenous infusion of methotrexate and cytarabine, associated with an intrathecal dose of methotrexate, cytarabine and dexamethasone.

Upon admission, as she was hemodynamically stable, a central venous catheter (CVC) was inserted into the right jugular vein (RJV) for chemotherapy follow-up. Despite complications and adversities from previous hospitalizations, imaging changes were recorded on chest tomography due to invasive fungal infection, as well as profound febrile neutropenia.

After starting the proposed treatment, during the first fortnight of hospitalization, the patient developed diarrhea, severe mucositis and profound febrile neutropenia, and empirical antibiotics were started, but without growth of any germ in urine cultures and/or blood cultures, until then. In this context, measures were initiated for deep aplasia, requiring blood transfusion of platelets and red blood cells in different situations, according to the service protocol.

Due to infectious screening, despite febrile events, a multidrug-resistant *Pseudomonas aeruginosa* was isolated in urine culture in the antibiogram, which guided treatment with intravenous polymyxin B and amikacin. At that time, the patient had already completed empirical regimens such as ampicillin + tazobactam, meropenem and vancomycin.

After 20 days of hospitalization and treatment for a previous urinary tract infection (UTI), new febrile events were triggered and, in a new blood culture, this time by polymerase chain reaction (PCR), the germ *Chryseobacterium indologes*, with a multidrug-resistant spectrum, was isolated.

The case was discussed with the Hospital Infection Control Commission (CCIH), as it was an unprecedented germ in the local microflora, as well as in all hospitals in the state of Ceará, and it was decided in a joint evaluation, initiation of Ciprofloxacin at a dose of 1200mg/day. During follow-up, due to the instability of the condition, polymyxin B was added to the regimen after the third uninterrupted day of fever.

Two days after the second proposed regimen, the patient developed a short-lasting, generalized tonic-clonic convulsive event, progressing to drowsiness and disorientation in a post-ictal state. At the time, in addition to airway support and protection measures, a skull tomography was requested urgently, but no structural injuries were found to justify the condition. Faced with an unprecedented convulsive crisis in a patient with hematological malignancy and a picture suggestive of possible encephalopathy of undefined etiology, acyclovir was empirically

started due to the possibility of herpetic encephalitis and, due to the worsening of the general condition, the decision was made to expand the antimicrobial spectrum to vancomycin and maintenance therapeutic regimen with ciprofloxacin and polymyxin b. In table 1, all cultures performed by the patient during hospitalization were recorded.

The patient subsequently developed a reduced level of consciousness, noisy breathing, bilateral pinpoint pupils, no anisocoria and no presence of gaze scanning or stereotypical movements. The hypothesis of morphine intoxication was raised, with naloxone being administered immediately and, thus, partial improvement of the neurological condition (ECG= 12). However, due to respiratory instability and dyspnea, the patient was referred to a bed in an intensive care unit (ICU), with measures for severe chronic critical illness.

Due to the continued hemodynamic instability, with a lower level of consciousness that made it impossible to protect the airway, orotracheal intubation was instituted in rapid sequence, however, due to the difficult airway, the procedure was not successful after a few attempts and the patient progressed to cardiorespiratory arrest (CRA) in pulseless electrical activity (PEA), returning spontaneous circulation after 03 cycles of cardiopulmonary resuscitation (CPR) according to the ACLS protocol.

After this event, a study of the CSF was carried out, which showed a cloudy appearance, xanthochromic color, with a global count (red blood cells: 56; cells: 111), differential count (lymphocytes 15%; neutrophils 80%), negative AFB testing, direct testing for *Crhyptococcus neoformans* negative, LDH (1223), glucose (54), proteins (370), as well as *Chryseobacterium indologenes* was cultivated in culture with the hypothesis of severe meningitis due to a multidrug-resistant germ, with sensitivity to *Ciprofloxacin*, but increasing exposure.

The patient progressed, despite culture-guided antibiotic therapy, using ciprofloxacin and ceftazidime + avibactam, both with relative sensitivity, and increased MIC, with worsening of the hemodynamic condition and absence of brainstem reflexes, in addition to a head tomography showing indistinction between white and gray matter and diffuse effacement of the cerebral grooves, fissures and cisterns, suggestive of brain death. The brain death protocol was opened, and an electroencephalogram was then performed with the absence of spontaneous electrical activity and evidence of brain electrical silence. After completing the protocol steps and in view of the evidence, death was certified due to brain death.

DISCUSSION

Chryseobacterium indologenes is a gram-negative bacterium commonly found in nature, especially in soil, plants, water and food products.[6] In the hospital environment, it is often recovered from wet surfaces and water sources, which contributes, given the bacteria's good adaptability, to contamination in healthcare. Previous studies have reported that *Chryseobacterium* spp can grow in chlorine-treated water sources and colonize sinks, saline solutions and taps. Additionally, isolation of the bacteria from other medical devices such as feeding tubes, respirators, syringes, arterial catheters, and implanted surgical devices has also been documented.[3,7,8]

Although *Chryseobacterium spp* is less prevalent than other pathogens and presents less virulence, it gains notoriety as it becomes an organism that causes serious and multidrug-resistant infections, including pneumonia, bacteremia, meningitis and sepsis in nosocomial environments, mainly in hospitalized individuals with medical devices.

long stay and prolonged exposure to broad-spectrum antibiotics.6 Some authors believe that the introduction of antibiotic therapy with colistin and tigecycline may have contributed to the increased prevalence of C. indologenes infections.[9,10]

C. indologenes is a species intrinsically resistant to aminoglycosides, first-generation cephalosporins, aminopenicillins and aztreonam, which limits therapeutic options.[11] The emergence of carbapenem-resistant strains of C. indologenes has further restricted antibiotic therapy, with strains producing metallo-β-lactamases (MBL) enzymes representing the greatest threat.[12] MBL-producing bacteria are resistant to all penicillins, cephalosporins and carbapenems, in addition to being unaffected by available β-lactamase inhibitor antibiotics, including the most advanced ones, such as Avibactam or Vaborbactam. Monobactams, such as Aztreonam, are not inactivated by MBL, however, most bacteria that express MBL also express other resistance mechanisms, such as the production of ESBL, which neutralize Aztreonam. Several studies have shown that seven variants of the blaIND genes (IND-1 to IND-6 and 2a) are the main MBL genes harbored by C. indologenes. However, in Khajuria's work[13] there was the report of the first case of a strain of C. indologenes carrying the blaNDM-1 gene, this being the gene that expresses the predominant MBL found in strains of Gram-negative bacilli resistant to carbapenems.[14] The isolation of C. indologenes strains harboring the blaNDM-1 gene is of great concern as it may lead to widespread resistance to carbapenems through horizontal gene transfer.[11]

Reports from the SENTRY Antimicrobial Surveillance program demonstrated that the group of drugs that have the greatest activity against C. indologenes are the quinolones (85–100%). Among β-lactams, piperacillin-tazobactam showed the highest sensitivity (90%), while carbapenems had a poor sensitivity profile (10–15%).10 In more recent studies in India, the highest sensitivity was for the quinolone group (100%), which agreed with the SENTRY Surveillance findings. However, among β-lactams, sensitivity to carbapenems was much higher (42.9% for meropenem and 47.6% for imipenem). Furthermore, the MIC values of strains with the blaNDM-1 gene were ≥32 and ≥16 in the antibiogram with meropenem and imipenem, respectively. In strains harboring blaIND genes, a higher MIC value (≥64) was observed for imipenem and meropenem. The highest sensitivity was ciprofloxacin (100%) followed by co-trimoxazole (81%).[11]

FINAL CONSIDERATIONS

In view of the above, it is clear that patients with serious underlying comorbidities, such as the case of the patient presented in this case report, often require hospitalization for various reasons (treatment of the underlying cause and treatment of complications). Once these patients acquire nosocomial infections, the period of hospitalization becomes increasingly longer, which increases morbidity and mortality rates. Thus, the treatment of these critically ill patients generally involves great concern on the part of the healthcare team, especially in shortening the length of stay as much as possible, increasing care to prevent the transmission of hospital-acquired pathogens and avoiding the use of extended-spectrum antibiotics.

The literature demonstrates that carbapenem-resistant strains of C. indologenes are becoming a threat, especially in hospital environments. The presence of MBL-producing C. indologenes strains has complicated this problem by severely limiting therapeutic options in patients. The emergence of strains carrying blaNDM-1

genes has become a cause for great concern, as it increases the chance of spreading resistance to carbapenems through horizontal gene transfer. Therefore, rigorous antimicrobial management programs are necessary to combat and prevent the worsening of this problem, which further highlights the importance of the role of the Hospital Infection Control Committee (CCIH) of each health unit.

There is still no solid evidence to define the ideal treatment for Chryseobacterium infections, with the choice of antibiotics being based on the sensitivity profiles of the hospital flora, which must be discussed with the unit's CCIH and, when available, on the results of antimicrobial sensitivity tests. Although some studies, such as the SENTRY Antimicrobial Surveillance Program, have already highlighted the most sensitive/resistant groups of drugs for this bacterium, new studies on the multidrug-resistant pathogen need to be developed mainly in the context of healthcare for complex patients.

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ANNEXES

DATE	04/02	04/02	12/02	13/02	16/02	17/02	26/02	15/03	21/03
SAMPLE MATERIAL	Blood	Urine	Blood	Blood	Pleural Fluid	Urine	Blood	Blood	Liquor
ISOLATED MICROORGANISM	S. epidermidis	P. aeruginosa	SC	Contam.	SC	P. aeruginosa	C. indologenes	C. indologenes	C. indologenes
ANTIBIOGRAM ↓									
CLINDAMICIN	R	NT	NT	NT	NT	NT	NT	NT	NT
DAPTOMICIN	S	NT	NT	NT	NT	NT	NT	NT	NT
GENTAMICIN	R	NT	NT	NT	NT	NT	R	R	R
LEVOFLOXACIN	R	NT	NT	NT	NT	NT	NT	NT	NT
LINEZOLID	S	NT	NT	NT	NT	NT	NT	NT	NT
OXACILLIN	R	NT	NT	NT	NT	NT	NT	NT	NT
RIFAMPICIN	S	NT	NT	NT	NT	NT	NT	NT	NT
TIGECYCLINE	S	NT	NT	NT	NT	NT	NT	NT	NT
TRIMETOPRIM/ SULFAMETOXAZOL	S	NT	NT	NT	NT	NT	NT	NT	NT
VANCOMYCIN	S	NT	NT	NT	NT	NT	NT	NT	NT
AMICACIN	NT	R	NT	NT	NT	R	R	R	R
CEFEPIME	NT	R	NT	NT	NT	R	R	R	R
SHVTZDMA	NT	R	NT	NT	NT	I	R	R	R
CEFTAZIDIMA/ AVIBACTAM	NT	S	NT	NT	NT	S	NT	NT	NT
CEFTAZIDIMA/ TAZOBACTAM	NT	S	NT	NT	NT	S	NT	NT	NT
CIPROFLOXACINA	NT	R	NT	NT	NT	I	R	R	I
MEROPENEM	NT	R	NT	NT	NT	R	R	R	R
PIPERACILINA/ TAZOBACTAM	NT	R	NT	NT	NT	NT	R	R	R
AZTREONAM	NT	NT	NT	NT	NT	NT	R	R	R
CEFTRIAXONE	NT	NT	NT	NT	NT	NT	R	R	R

TABLE 1. RESULT OF CULTURES CARRIED OUT DURING ADMISSION AT HGCC IN 2023

* Subtitle: SC (No Bacterial Growth), Contam. (Contaminated Sample), R (Resistant), S (Sensitive), I (Intermediate), NT (Not Tested by Laboratory).