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CASE REPORT OPEN ACCESS

Chryseobacterium Bloodstream Infection in a Case of Non-Hodgkins Lymphoma: An Emerging Pathogen Complicating Clinical Management in Cancer Patients

Ashima Jain Vidyarthi[1], Salman Khan[1], Babita Kataria[2], Mukesh Nandal[3], Vishal Phogat[4], Arghya Das[1]* and Rama Chaudhry[5]

[1]Department of Microbiology, National Cancer Institute (Jhajjar campus) of AIIMS, New Delhi, India.
[2]Department of Medical Oncology, National Cancer Institute (Jhajjar campus) of AIIMS, New Delhi, India.
[3]Department of Emergency Medicine, National Cancer Institute (Jhajjar campus) of AIIMS, New Delhi, India.
[4]Department of Hospital Administration, AIIMS, New Delhi, India.
[5]Department of Microbiology, AIIMS, New Delhi, India.

Abstract

Over the past decade, novel pathogens causing infections in patients have been identified. *Chryseobacterium* is one such emerging pathogen that is frequently reported in hospitalized patients. Case reports of bloodstream infections, and pneumonia due to *Chryseobacterium* spp in cancer patients from different parts of the world are drawing the attention of the clinical community to this bacterium as an emerging threat in patients with malignancies. Besides its propensity to cause serious infection to the immune-compromised patients, the antibiotic-resistant trait is posing a serious challenge, further complicating the clinical management of malignancies. We report a similar experience with the bacterium causing bloodstream infection in a patient with Non-Hodgkin lymphoma. The new automated identification systems have enabled us to identify these relatively uncommon pathogens in our clinical setting and also recognize their role in causing infection in hospitalized patients. Besides the difficulties in the treatment of these antibiotic-resistant pathogens, detecting their source within the healthcare setup remains a challenge for medical professionals.

Keywords: *Chryseobacterium indologenes,* Multi-drug Resistant, Malignancy

***Correspondence:** arghyadas2401@gmail.com

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INTRODUCTION

Chryseobacterium spp. (formerly known as *Flavobacterium*) is an emerging Gram-negative microbe belonging to the CDC group IIb. It has been isolated earlier from various environmental samples like soil as well as from hospital surfaces.[1,2] Although the clinical significance of this organism is still under research, it has been reported from cases of septicemia, pneumonia, pyelonephritis, peritonitis, pyomyositis, meningitis, cellulitis, wound sepsis, etc.[3-6] The most commonly isolated species from clinical specimens are *C. indologenes*, and *C. meningosepticum*. Four more species namely *C. multivorum, C. gleum, C. breve,* and *C. odoratum* have also been implicated to cause clinical infections.[7] Among all of these species, *C. meningosepticum,* also known as *Elizabethkingia meningoseptica,* is considered to be the most pathogenic species.[8,9]

Being a ubiquitous organism, *Chryseobacterium* sustain well on the environmental surfaces and also may be resistant to chlorination used for water supplies.[8] It finds its way to colonize hospitalized patients via both invasive (prosthetic valves and intravascular catheters) and non-invasive (humidifiers, respirators, endotracheal tubes, etc.) medical devices and equipment as well as hands of the healthcare personnel.[8,10,11] The predisposing factors are diabetes mellitus, immuno-compromised state including neutropenia, malignancy, and prolonged use of antibiotics like colistin, and tigecycline.[12-15]

C. indologenes in particular is intrinsically resistant to multiple antibiotics viz. aminopenicillins, first generation cephalosporins, aztreonam, and aminoglycosides.[3] The resistance rates against other antibiotics like cefepime, imipenem, meropenem, piperacillin-tazobactam, fluoroquinolones were also found to be extremely high (≥70%) in different studies.[16-17] Besides, the multi-drug resistance trait, its inextricable virulent nature posed by the biofilm forming ability and production of protease enzyme made it a formidable pathogen in the clinical set up.[18,19] Furthermore, the laboratory confirmation of the bacterium remains a challenge owing to its fastidious nature and inability to grow on routinely used culture medium like MacConkey agar.[20,21]

Since the beginning of the 21st century, the application of automated systems with some cutting edge technologies has revolutionized the microbial detection of pathogens in Microbiology laboratories. Relatively unknown microbes are being identified more frequently which were earlier overlooked or missed. This privilege has brought the opportunity of further research and assessment on the spectrum of infection and pathogenicity of rarely reported bacterial isolates like *C. indologenes*. Albeit, the reports on this particular bacterial infection among cancer patients, specially from India, are still very limited in the literature.[22,23] The occurrence of infection with *C. indologenes* among cancer patients are primarily attributed to the immunosuppression caused due to administration of chemotherapeutic agents, prolonged hospitalization and requirement for indwelling devices, and invasive procedures.[14] The putative oncogenic potential of the bacterium has also been suggested in a micro-array based genetic assessment in ovarian cancer patients. In the study by Banerjee et al., it was listed among the top four bacterial signatures with the highest hybridization signal detected in the ovarian cancer patients.[24] Here, in this report we present a case of bacteremia with *Chryseobacterium indologenes* in a patient with B-cell Non-Hodgkin Lymphoma (NHL).

Case Report

A 32-year-old Indian male of lower-middle socio-economic class from an urban area in the national capital region of Delhi was referred to our hospital outpatient department from a private clinic. He presented with painless lumps under the skin in the bilateral axilla and on the sides of the neck for three weeks. The swelling was insidious in onset and gradually progressed in size. He also complained of diffuse abdominal swelling of the abdomen, multiple episodes of vomiting (4-5 times per day), and low-grade fever. There was a history of easy fatigability but no loss of appetite and loss of body weight. There was no history of cough, chest pain, shortness of breath, and night sweats. The patient neither suffered any similar complaints in the past nor had a history of diabetes, hypertension, tuberculosis, or any other chronic diseases. He was a non-smoker and non-alcoholic. There was no family history of malignancy.

The patient's vitals were stable. On general examination, he had icterus and generalized lymphadenopathy. There were enlarged lymph nodes in the cervical region at level II, III, IV, V (largest at level III on the right side; 3 x 2 cm), axillary regions (16 x14 cm on the right side and 20 x 12 cm on the left side) with tenderness and skin discoloration noted on the right side, and inguinal regions (2 x 1 cm on the right side and 1 x 1 cm on the left side). Palpation of the abdomen revealed enlarged liver, tender, and firm in consistency, palpable up to 4 cm below the right costal margin. Findings of other systemic examinations were unremarkable.

A decision was made to admit the patient for detailed diagnostic workup and management.

His initial blood investigation at admission revealed decreased haemoglobin (11.1 g/dL), red blood cell count (3.9 X 10 6 / mm 3), platelet count (25 x 10 3 / mm 3) and increased white blood cell count (17.3 X 10 3 / mm 3), bilirubin (9.1 mg/dL), SGPT (282 U/L), SGOT (1112 U/L), alkaline phosphatase (651 U/L), serum urea (85.6 mg/dL), uric acid (16.9 mg/dL), and lactate dehydrogenase (8273 U/L) values. The patient was seronegative for HIV 1&2 Ab, HBsAg, and anti-HCV Ab. Prothrombin time was markedly increased (18.8 seconds). Contrast-enhanced CT (CECT) scan of neck, thorax, abdomen, and pelvic region revealed generalized lymphadenopathy, hepatosplenomegaly, and multiple lung nodules suggestive of lymphoma. Peripheral smear examination of the bone-marrow

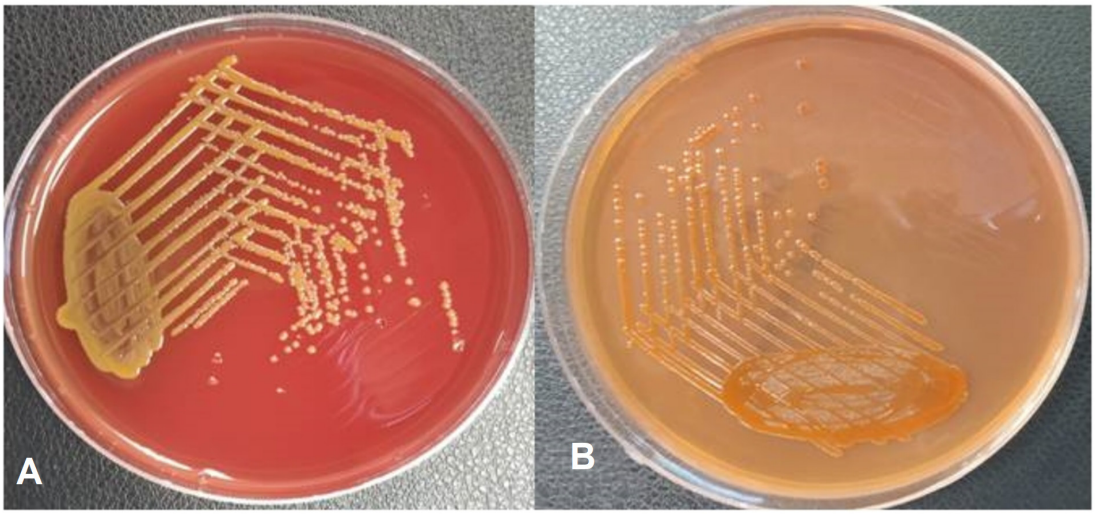

Figure 1. Growth of *Chryseobacterium indologenes* on Blood Agar (Figure 1A) and MacConkey Agar (Figure 1B)

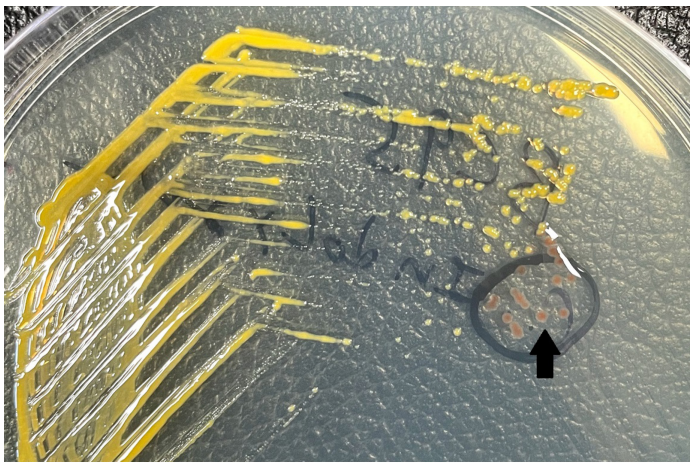

Figure 2. Demonstration of flexirubin pigment production by *Chryseobacterium indologenes*

Table. Minimum inhibitory concentrations of different antibiotics and their susceptibility profile against the *Chryseobacterium indologenes* isolate

Antibiotic	Minimum Inhibitory Concen. (MIC)	Interpretation*
Ampicillin	>32µg/ml	Resistant
Amoxicillin-clavulanate	32/16µg/ml	Resistant
Cefixime	>4µg/ml	Resistant
Ceftriaxone	>4µg/ml	Resistant
Ceftazidime	>32µg/ml	Resistant
Cefepime	>16µg/ml	Resistant
Cefoperazone-sulbactam	>32/8µg/ml	Resistant
Piperacillin-tazobactam	>64/4µg/ml	Resistant
Ertapenem	>2µg/ml	Resistant
Imipenem	>4µg/ml	Resistant
Meropenem	>4µg/ml	Resistant
Colistin	>4µg/ml	Resistant
Gentamicin	>16µg/ml	Resistant
Amikacin	64µg/ml	Resistant
Levofloxacin	≤1µg/ml	Susceptible
Cotrimoxazole	≤2/38µg/ml	Susceptible

* Breakpoints for this emerging pathogen is not yet available. Hence, the breakpoints of *Pseudomonas aeruginosa* has been used for interpretation of the susceptibility against different antibiotics.[30]

showed erythroid hyperplasia and megaloblastic change (M: E= 1:1) with thrombocytopenia, dimorphic anemia, and 5% atypical cells. Finally, bone marrow biopsy examination with immune-histochemistry confirmed the diagnosis of B-cell non-Hodgkin lymphoma (NHL), immune-positive for CD20.

He was started on injection cyclophosphamide, steroids (pre-phase) along with supportive care for tumor lysis syndrome and liver dysfunction. During this course of inpatient management, the patient remained afebrile and his vitals were stable. He initially responded to cytoreductive pre-phase with improvement in liver dysfunction. However, on the 12th day of admission, the patient developed a fever of 102.2°F. His WBC count was reduced to 6.62 X 10^3/ mm^3 from the initial count. Multiple blood samples were received consequently, for culture and susceptibility testing on two separate occasions (2 bottles on each occasion with a gap of 2 days). He was started on injection cefoperazone-sulbactam empirically. However, the therapy was escalated to meropenem and teicoplanin when the patient continued to deteriorate. The blood cultures were processed on an automated blood culture system (BACTEC, Becton Dickinson, USA). All samples flashed positive within 10 hours. The Gram stain made from the positive bottles showed Gram-negative bacilli. The samples were subcultured on Blood and MacConkey agar as per the laboratory protocols. After 24 hours of incubation at 37°C, the blood agar grew 0.5-1 mm, non-hemolytic, yellow-colored moist colonies with smooth surface and entire edges (Figure 1). The MacConkey agar grew non-lactose fermenting colonies (Figure 1). They were oxidase and catalase positive. The colonies were further processed for identification and susceptibility testing on the automated system (Phoenix M50, Becton Dickinson, USA). All four blood samples were identified as *Chryseobacterium indologenes* which were resistant to ampicillin, amoxicillin-clavulanate, cefixime, ceftriaxone, ceftazidime, cefepime, cefoperazone-sulbactam, piperacillin-tazobactam, colistin, gentamicin, amikacin, and susceptible to levofloxacin and cotrimoxazole. The minimum inhibitory concentrations (MIC) values of different antibiotics against the isolate have been mentioned in Table. A subculture was also made to nutrient agar to check for the flexirubin pigment. The yellow colonies on nutrient agar turned red (Figure 2) on the addition of 10% potassium hydroxide (KOH) solution.[6] Injection levofloxacin was started, and the patient became afebrile. Subsequent two blood cultures yielded no growth. However, despite the intense effort in management, the patient's liver dysfunction and DIC worsened. The patient succumbed on the 26th day of admission due to refractory status epilepticus with massive pulmonary bleeding and recurrent ventricular fibrillation resulting from subacute liver failure.

DISCUSSION

Isolation of a rare organism in clinical specimens is a situation that is encountered by microbiology laboratories throughout the world. The establishment of these organisms

as pathogens or contaminants/colonizers is a challenging task. *Chryseobacterium indologenes* is one such organism. It does not belong to the normal human flora but is ubiquitously present in the environment. Taps, sinks within hospitals have been identified as the potential reservoir of the bacterium. Besides immunosuppression due to corticosteroids, diabetes, age-related immune senescence have also been implicated as predisposing factors to chryseobacterial infections.[25] The infection has also been reported in cancer patients with both hematological as well as solid organ malignancies. Most of these reports suggested that the infection primarily acquired in the hospital settings caused pneumonia or bloodstream infections and posed substantial challenges to treatment due to the multi-drug resistant trait of the bacterium.[14,22,23,26,27]

Our patient was a case of NHL, with a central line in place, on cyclophosphamide therapy and antibiotics (cefoperazone-sulbactam) due to the leucocytosis seen at the time of admission. The antibiotic therapy was further escalated to meropenem and teicoplanin due to the persistent deteriorating state of the patient. Meanwhile, multiple blood cultures were received which all grew *Chryseobacterium indologenes*, an organism intrinsically resistant to both the ongoing antibiotics. The first isolation of this organism could easily be disregarded being an environmental contaminant. However, the clinical state of the patient and sudden decrease in leucocyte count indicated a septicemic state. Hence, targeted therapy with levofloxacin was advised which led to an initial improvement in the condition. The blood cultures obtained 5 days after targeted treatment revealed no growth.

This organism is intrinsically resistant (i.e., the innate ability of a type of the bacterium to resist an antibiotic's action by the virtue of its own naturally occurring structural or functional characteristics) against the commonly used antibiotics including amino-penicillins, first generation cephalosporins, aminoglycosides, and aztreonam.[3] Thus choosing appropriate antibiotics for this bacterium is a matter of concern.[2] The resistance to β-lactam drugs including carbapenems has been reported to be due to the constitutive expression of Ambler class B β-lactamases or, metallo-β-lactamases as well as Ambler class A β-lactamases, which hydrolyze the antibiotic molecules rendering them ineffective.[15] On the other hand, resistance to colistin and aminoglycosides is due to the presence of genes coding for efflux pump which causes extrusion of the antibiotic molecules from inside the bacterial cells.[28] The SENTRY Antimicrobial Surveillance Program reported the quinolones (levofloxacin, gatifloxacin, garenoxacin), trimethoprim-sulfamethoxazole, piperacillin-tazobactam to be the most effective drugs against *C. indologenes*. Alternatively, other antimicrobials namely ciprofloxacin, cefepime, ceftazidime, cefoperazone, cefpirome, minocycline, piperacillin, and rifampicin might be used depending on the susceptibility pattern of the respective isolate.[2,8] Even with scarce antibiotic choices, studies have indicated successful outcomes for this infection when specific therapy is provided as guided by the culture report.[2] Interestingly, it has also been suggested that the removal of the implicated indwelling device for source control is also a mandatory requirement.[29] However, further studies with larger sample sizes are required for this organism to be understood well. Although the patient eventually succumbed due to the complications of his primary disease, this case highlighted the significance of the right diagnosis and right therapy for the bug concerned. It also conveys the importance of diagnostic stewardship and timely microbiological diagnosis.

CONCLUSION

The concerted efforts and vigilance of the clinicians and microbiology team are essential for the timely diagnosis and management of such rare pathogens. Clinical correlation with methodical history-taking is of prime importance to discern the status of the isolated organism as a colonizer or pathogen, especially where organisms grown maybe potential contaminants in the hospital environment. Moreover, repeated isolation of the same organism from more than one sample on multiple occasions is also indicative of its pathogenic role. The present case reiterates the clinical importance of chryseobacterial infections mentioned in the previous reports. Targeted therapy initiated early for such multi-drug resistant organisms may help in reducing the associated

morbidity and mortality in many cases. Further, the judicious and ethical use of appropriate antibiotics is indispensable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

AJV and SK conceptualized the manuscript. SK and BK collected the clinical and investigational details. AJV and AD wrote the initial draft. MN and VP critically evaluated and revised the manuscript. RC supervised the entire work and edited the final manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This article does not include any results of experiments conducted on humans or animals. The confidentiality of the patient has been maintained in the article.

INFORMED CONSENT

Written informed consent was obtained from the patient.

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