CASE REPORT

Chryseobacterium Indologenes as a Novel Cause of Bacteremia in a Neonate

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ABSTRACT

Chryseobacterium indologenes is a rare human pathogen. It is an emerging species, least frequently reported from pediatric age group and known to cause pneumonia, bacteremia, and meningitis. The inherent resistant of one of the species to commonly prescribed broad-spectrum antibiotics makes it formidable challenge in the hospital settings. We report the first case of *C. indologenes* bacteremia from Pakistan, diagnosed in a preterm newborn in an intensive care setting.

Key Words: *Chryseobacterium indologenes, Bacteremia, Sepsis, Neonatal intensive care, Nosocomial infections.*

INTRODUCTION

Chryseobacterium species (formerly named *Flavobacterium*) are widely distributed in nature, rarely causing human disease.[1,2] They are mostly agents of opportunistic and nosocomial infections like pneumonia, meningitis and septicemia.[3,4] Being susceptible to a narrow spectrum of antibiotics, this genus is an emerging threat, withstanding the usual empirical therapies employed in intensive care settings.[6] We report for the first time, a case of *Chryseobacterium indologenes* bacteremia from Pakistan, diagnosed in a premature infant admitted in Neonatal Intensive Care Unit (NICU).

CASE REPORT

A pregnant lady presented to our hospital at 32 weeks of gestation with 8 days' history of premature rupture of membranes. A premature male infant was delivered following an emergency cesarean section, weighing 1.4 kgs, having sluggish reflexes, nasal flaring, intercostal recession, and increased chest diameter. The baby was immediately shifted to NICU and put on continuous positive airway pressure (CPAP) ventilation. Ultrasound abdomen and chest X-ray carried out with the suspicion of diaphragmatic hernia, but were normal. Blood culture and other routine investigations were sent to the laboratory and injection cefotaxime and injection amikacin were started empirically. The total leucocyte count (TLC) was 9.6 x 10^9/L (normal range: 4.5 - 11.0 x 10^9/L) with 70% lymphocytes and 25% neutrophils. C-reactive protein concentration (CRP) was 0.6 (normal value <6) with deranged blood gases. Patient's oxygen saturation dropped the following day; he was intubated, put on ventilator, and was found to have developed pneumothorax. Chest intubation was done and endotracheal tube had to be changed twice on the 2nd and 3rd day due to blockage. On 3rd day of admission, repeat CRP was found to be raised to 6.9. The blood culture yielded the growth of oxidase positive, non-motile, gram negative rods. Based upon the information, cefotaxime was substituted with injection piperacillin- tazobactam by the neonatologist. On 4th day of admission, the patient went into severe respiratory distress with drop in oxygen saturation and could not be revived after resuscitation.

Simultaneously, the isolate was identified in the microbiology laboratory as "*Sphingobacterium multivorum*" based on API 20 NE (Biomerieux) results. The isolate formed yellow colored round convex colonies on blood agar (Figure 1) with hemolysis and a distinct fruity odor, while it grew as a non-lactose fermenter on MacConkey agar. The isolate was further sent to a reference laboratory (Armed Force Institute of Pathology, Rawalpindi, Pakistan), where it was identified by the Vitek-2 system (Biomerieux-France) as "*Chryseobacterium indologenes*", a different species of the same family, with a probability of 99%. Minimal Inhibitory Concentration (MIC) values (measured by an automated MIC system) showed susceptibility to fluoroquinolones (ciprofloxacin, levofloxacin), co-trimoxazole, piperacillin-tazobactam, and cefoperazone-sulbactam following CLSI breakpoints for non-enterobacteriaceae and pseudomonas.[1] However, the MIC values of ampicillin, ceftriaxone, cefotaxime, ceftazidime, imipenem, meropenem, amikacin, gentamycin, tetracycline, doxycycline, minocycline, tigecycline and colistin were in the resistant range.

DISCUSSION

The genus *Chryseobacterium*, a rare human pathogen, was first described in 1994 by Vandamme and colleagues

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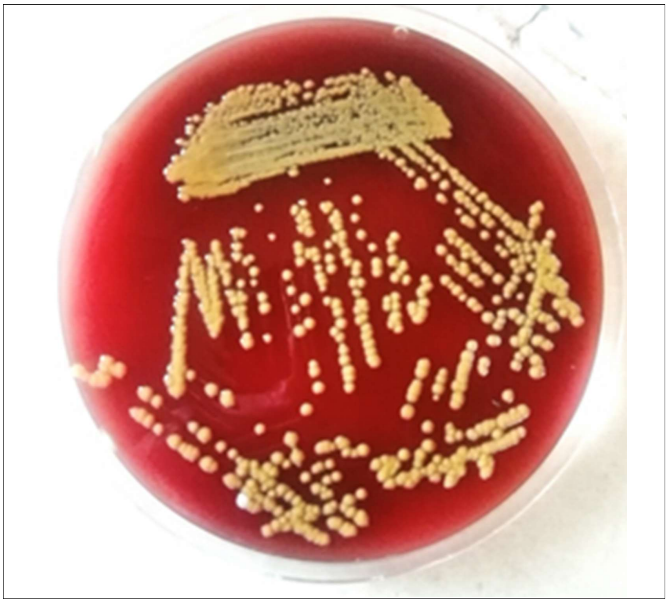

Figure 1: Yellow pigmented colonies of *C.indologenes* on blood agar.

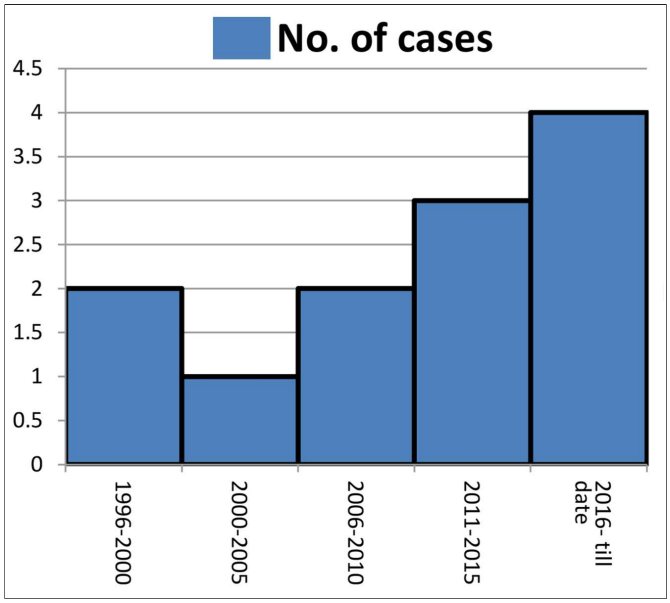

Figure 2: *C.indologenes* bacteremia cases reported in pediatric patients (1996-till date).

as non-motile, oxidase and catalase positive, non-glucose fermenter gram-negative bacilli. It has wide distribution in nature including water systems and is frequently found in hospital environments.[2] It comprises of many species formerly grouped under the genus *Flavobacterium*.[3,4] The most common species causing human disease are *C.meningosepticum* followed by C.indologenes, with others like *C.odoratum, C.multivorum, C.breve* and *C.gleum*, are rarely isolated.[3]

C.indologenes was first reported as a cause of human infections in 1996 by Hsueh *et al*.[5] Clinical manifestations caused by the species include nosocomial pneumonia, primary bacteremia, meningitis, peritonitis, surgical wound infection, intravascular catheter related bacteremia and artificial shunt infections.[5,6] Bacteremia caused by the species is frequently linked to hospital stay with underlying disease, immunocompromised state and indwelling devices.[2]

According to the SENTRY antimicrobial surveillance program (1997-2001), *C.indologenes* infections are least frequently reported from pediatric age group (≤5 years of age) as compared to their higher frequency reported amongst adults (≥65years of age).[7] A thorough literature review was performed *via* search on database MEDLINE (PubMed) and Google Scholar. A total number of 22 patients in pediatric age group (newborn to 18 years) were found to be reported with *C.indologenes* infections (1996-2016). Out of these, 12 (54.5%) had bacteremia while the remaining suffered from meningitis (n=6), ventilator associated pneumonia (n=3) and iumboperitoneal shunt infection (n=1).[3] Figure 2 shows the increasing trend of *C.indologenes* bacteremia cases reported over the last two decades (1996-2016). All the patients with bacteremia belonged to the age group of 5 years and below, while more than 50% were less than 1 year of age including one preterm newborn. Our case, hence, is the second one to be reported in a preterm newborn. Most of the *C.indologenes* infections have been reported from the region of Taiwan in literature, however, the pediatric bacteremia cases in our search were reported mostly from Turkey (Table I).[4]

Risk factors associated with *C.indologenes* bacteremia include underlying medical illness, immunocompromised condition, presence of indwelling devices and prolonged exposure to broad spectrum antibiotics. In our literature review, all except one case of bacteremia were linked to co-morbid conditions like neoplasms, diabetes, congenital heart diseases, metabolic diseases, immunosuppressive therapy and preterm birth.[8] Amongst the cases, 3 were documented as catheter related blood stream infections (CRBSI), whereas others (n=9) were reported as primary bacteremias.[3] Out of these, 6 were linked to intravascular catheter devices and 3 were associated with mechanical ventilation. Our case carried the risk factors of preterm birth, vertical transmission due to colonized birth canal and instrumentation during C-section. Removal of indwelling catheters in catheter related cases was not recommended initially by Hsueh *et al.* but newer studies suggest that the catheters be removed from bacteremia patients as soon as possible.[3] The portal of bacteremia was not clearly defined in most of the cases due to insufficient microbiological study and retrospective nature of most of the studies. In one study by Bayraktar *et al.,* reporting a case of *C.indologenes* CRBSI, same species was isolated from hospital water source, commercial distilled water and patient's feeding bottle.[3] In our study, extensive environmental screening of NICU was performed. Swabs from various areas

Table I: Summary of literature review of *chryseobacterium indologenes* bacteremia in pediatric patients (1996-2016).

Case No.	Reference (Reporting year)	Region	Age / Gender	Underlying conditions	Indwelling devices	Hospital stay before infection	Antibiotics before c.indologenes isolation	Antibiotics after c.indologenes isolation	Outcome
1	Hsueh *et al. (*1996)	Taiwan	5y / F	Neuroblastoma, chemotherapy	Hickman catheter	7-10 days	Not reported	Not reported	Recoverd
2	Hsueh *et al.* (1996)	Taiwan	1y / F	Hepatoblastoma, chemotherapy	Port-A- catheter	7-10 days	Not reported	Not reported	Recoverd
3	Cascio *et al.* (2005)	Italy	2y / M	Type1 diabetes mellitus	Perephral catheter	10 days	Ceftriaxone	Ceftriaxone (10 days)	Recoverd
4	Bayraktar *et al.* (2007)	Turkey	5mo / M	Down syndrome, atrial septal defect operated	MV	7 days	Ceftriaxone, amphotericin B	Vancomycin, ofloxacin	Expired
5	Douvoyiannis *et al.* (2010)	USA	33d/ F	None	None	None	Cefotaxime, ampicillin	Cefepime (10 days)	Recoverd
6	Sudharani *et al.* (2011)	India	36w /NB	Preterm neonate	MV	None	Cefotaxime amikacin	Cefoperazone sulbactam	Recoverd
7	Kodama et al. (2013)	Japan	3y / F	AML, cord blood stem cell transplantation	CVC	Not reported	Ciprofloxacin,	Recovery minocycline	
8	Teke *et al.* (2014)	Turkey	3mo / F	Congenital heart disease	CVC		meropenem	trimethoprim sulfamethoxazole (21 days)	Recoved
9	Aykac *et al.* (2016)	Turkey	3mo / M	Metabolic disease	MV/CVC	67 days	Ciprofloxacin, imipenem, colimycin, linezolid	Ciprofloxacin, imipenem, colimycin, linezolid	Expired
10	Aykac *et al.* (2016)	Turkey	8mo / M	Ileus	CVC	14 days	Not reported	Ciprofloxacin, meropenem, vancomycin	Recoverd
11	Aykac *et al.* (2016)	Turkey	1y / F	ITP, immunosuppressive therapy	None	14 days	Not reported	Ceftriaxone (7days)	Recoverd
12	Aykac *et al.* (2016)	Turkey	3y / F	Cerebral palsy	CVC	14 days	Not reported	Meropenem, amikacin	Recoverd
13	Our case (2017)	Pakistan	32w NB/M	Preterm neonate	MV	3 days	Cefotaxime, amikacin	trimethoprim sulfamethoxazole	Expired

F = Female, M = Male, NB = Newborn, mo = months, y = year, AML = Acute myeloid leukemia, ITP = Immune thrombocytopenic purpura, CVC = Central venous catheter, MV = Mechanical ventilation

including incubators, suction machines, ventilators, emergency trolleys, counter tops, floors, *etc* were taken as well as air and water sampling was done to establish a source but it was inconclusive.

The choice of appropriate antimicrobials for *C.indologenes* infections is a difficult area due to the species' resistance to a wide range of drugs. No effective empirical therapy is recommended in these cases due to the limited data available. The isolates show consistent resistance towards most β-lactams including carbapenems, aminoglycosides, clindamycin, erythromycin and teicoplanin.[3,6] According to the SENTRY antimicrobial surveillance program (1997-2001), quinolones showed the highest potency against these isolates with garenoxacin being the most effective followed by gatifloxacin, levofloxacin and ciprofloxacin. Amongst β-lactams piperacillin, piperacillin-tazobactam and cefepime were the most active agents found. The species also demonstrated 95% susceptibility to trimethoprim-sulfamethoxazole.[7] Thereafter, a study by Chen *et al*. in 2012 reported that piperacillin-tazobactam and newer quinolones were no longer reliable; whereas, trimethoprim-sulfamethoxazole and cefoperazone-sulbactam were recommended. Minocycline also showed good susceptibility rates of 92-100%.[6] A recent study in pediatric patients recommended combined therapy with ciprofloxacin and trimethoprim sulpha-methoxazole than monotherapy.[3] The MICs in case of our isolate showed susceptibility to quinolones (levo-floxacin, ciprofloxacin), trimethoprim-sulfamethoxazole, piperacillin-tazobactam and cefoperazone-sulbactam.

The outcome of all the pediatric cases reviewed was three deaths out of 13 (including this case) as compared to high mortality rates (up to 64% in bacteremia) reported for adults.[6] All three patients that expired were neonates of less than 6 months of age and had received mechanical ventilation. These patients, despite being started on the appropriate antimicrobials following sensitivity patterns, were all having comorbid conditions of either Down syndrome with atrial septal defects, metabolic disease or decreased immunity due to preterm birth. These observations depict that apart from effective antimicrobial therapy, other factors like age, comorbidity and hospital stay with indwelling devices are also important in determining the patient outcome.

C.indologenes is an emerging threat, mostly causing opportunistic and nosocomial infections. Due to the scarcity of pediatric patients reported with *C.indologenes* bacteremia, limited data is available in defining standard empirical therapy for the species in children. However, susceptibility breakpoints need to be defined for the species. The narrow spectrum of susceptible choices available presents a dilemma to the clinicians in prescribing appropriate antimicrobials. Since the role of maternal colonization in infection by this species is not fully known, strict aseptic techniques and judicious use of antibiotics remain the cornerstone in prevention of *C.indologenes* infections.

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