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Case Report

Neonatology Section

Pichia anomala, A Rare Cause of Nosocomial Fungal Sepsis in Newborn. Is Empirical Use of Third Generation Cephalosporin to Blame?

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ABSTRACT

Traditionally, *Candida albicans* is known to be the major cause of nosocomial fungal sepsis in neonates. However, there has been increased detection of various other emerging pathogenic yeasts like *Pichia anomala* (also referred as *Wickerhamomyces anomalous/Hansenula anomala* in the literature). Here, authors report a case of a full-term male neonate born with severe birth asphyxia and respiratory distress empirically treated with third generation cephalosporins, who later developed fungemia and meningitis due to yeast (*Pichia anomala*) has been documented. The possible risk factors could be severe birth asphyxia and empirical use of third generation cephalosporin (cefotaxime) initially.

Keywords: Candida albicans, Fungemia, Neonatal sepsis

CASE REPORT

A case report of full-term 38 weeks, 2.8 kg male baby born through vaginal delivery at private hospital. Patient had a history of birth asphyxia (APGAR score at 1, 5 minute: 3, 5) and had respiratory distress at birth for which he was initially managed at that hospital with oxygen inhalation by nasal prongs, Intravenous (I.V.) fluids, nil by mouth and empirical I.V. cefotaxime, amikacin. Patient had negative sepsis screen initially with Total Leukocyte Count (TLC) of 11,000/mm^3 (60% Neutrophils), Platelet count of 1.9 Lac/mm^3, C-Reactive Protein (CRP) was negative and blood culture showed no growth. Respiratory distress, for which no specific cause was found and probably was due to Transient Tachypnea of New Born (TTNB) or raised pulmonary vascular resistance due to birth asphyxia, settled gradually and on 4th day of life, baby was started on orogastric feeds with expressed breast milk following which baby developed abdominal distension, vomiting and lethargy. On repeat investigations, in view of progressive deterioration patient was found to have leukocyte count of 4500/mm^3 (30% Neutrophils), platelet count of 75,000/mm^3, and CRP titre was 18 mg/dL (normal value <0.5 mg/dL). Baby was referred to our hospital on 5th day of life.

At the time of admission in the present hospital patient had mildly impaired perfusion with Capillary Refill Time (CRT) of 3 seconds but otherwise stable hemodynamically, mild respiratory distress with abdominal distension and altered colour/hemorrhagic aspirate from orogastric tube. The baby was diagnosed as having birth asphyxia, sepsis and suspected Necrotizing Enterocolitis (NEC). Patient was stabilised with IV fluids, oxygen, sugar and temperature maintenance. After taking sample for blood culture I.V. meropenem (40 mg/kg/dose 12 hourly) and I.V. fluconazole (6 mg/kg/day) were started empirically (in view of prior use of third generation cephalosporin (cefotaxime) and clinical markers of sepsis thereby suspecting either gram negative or fungal sepsis). Sepsis screen including complete haemogram and CRP was sent. An amount of 2.5 mL of blood was collected with all aseptic precautions after skin being treated with alcohol and sent for culture and antimicrobial sensitivity. Lumbar puncture was done after initial stabilisation and Cerebrospinal Fluid (CSF) was sent for microscopy, biochemistry and culture sensitivity. X-ray abdomen showed pneumatosis intestinalis suggesting NEC Bell Stage-II. Paediatric surgeon consultation suggested continuing conservative management for NEC. Investigations revealed a positive sepsis screen (CRP-28 mg/dL, leukocyte count 4200/mm^3, absolute neutrophil count of 1200/mm^3 and thrombocytopenia with platelet count of 58,000/mm^3). CSF study revealed 37 leukocytes/HPF (70% neutrophil), 105 mg/dL proteins, 36 mg/dL sugar (RBS-83 mg/dL) which was suggestive of neonatal meningitis. CSF and Blood grew *Pichia anomala* sensitive to fluconazole and amphotericin B, which confirmed the clinical suspicion of fungal sepsis. Contact screening of other newborns in the NICU did not reveal any other case of fungemia. Fluconazole was continued as patient responded well to it and it was given for a total of 21 days. Cranial ultrasound was normal. Baby responded well to treatment and was discharged in a fair condition on breastfeed. On follow-up, the baby remained healthy, hearing screening and neurological examination were done which was normal on follow-up at 1 and 3 months.

DISCUSSION

Invasive fungal infections are the common cause of late onset sepsis especially in very low birth weight neonates [1]. Majority of these infections have been reported due to *Candida albicans*. In the recent past, however, there has been an increased identification of non-candida fungal species like *Trichosporon, Malassezia* and *Pichia anomala* [2].

Wickerhamomyces anomalous (*Pichia anomala, Candida pelliculosa, Hansenula anomala*) was initially described by Hansen in 1891 as a free-living Ascomycetes yeast in plants, soil and other organic material [3]. It can grow under extreme environmental conditions like extreme pH, low water activity, high osmotic pressure and anaerobic conditions which enables it to propagate in varied environmental conditions [4]. Though *Candida albicans* has been accounted for majority of invasive fungal infections in past, modern medical therapy and improved laboratory detection methods had shown emergence of other pathogens like *Wickerhamomyces* [2]. Fungal infections due to unusual organisms such as *Pichia anomala* are an emerging cause of opportunistic mycoses in immunocompromised patients and fungemia in NICU [2,5]. Predisposing risk factors include prematurity, low birth weight, long duration of hospital stay, prior use of I.V. antibiotics, lymphoblastic leukaemia and neoplasm [6,7]. Cross-contamination through the hands of caregivers had also been incriminated as an important cause in the past. In the present case, risk factors like prolonged hospital stay prior to broad spectrum antibiotic use (cefotaxime) and cross-contamination via hands of caregivers at private hospital could have been possible contributory risk factors.

Pichia anomala can have varied presentations including apnoea, thrombocytopenia and rarely multi-organ failure and death. Though

in vitro sensitivity to most of the antifungals like fluconazole, amphotericin B has been documented, in vivo resistance i.e., clinical non-response despite in vitro sensitivity can sometimes lead to therapeutic failure [3]. Hence, therapeutic decision making should be guided by clinical response to drugs. Outbreaks control measures for Neonatal Intensive Care Unit (NICU) are strict surveillance including routine culture of babies and hands of medical personnel, strict compliance of hand washing protocols and prophylactic antifungal in high risk case [8].

On comparison with literature reported from India and abroad, it was found that this infection is usually found in low birth weight babies [2,8]. Reporting this unusual infection in an unusual host i.e., a full-term, normal birth weight baby further underlines the hazards associated with empirical use of third generation cephalosporin in neonates.

Non-judicious use of antibacterial therapy increases the density of fungal colonisation in the recipient by reducing competitive pressure exerted by commensal bacteria. Receipt of empirical broad spectrum antibiotics such as 3rd generation cephalosporin is among the most consistently identified risk factor for the neonatal candidiasis [9]. Studies suggest that exposure to 3rd generation cephalosporin is associated with an approximate doubling of risk of invasive candidiasis among Extremely Low Birth Weight (ELBW) babies. Situation is further complicated by delayed initiation of feeds, use of H_2 Blockers, and invasive procedures which may aggravate risk of fungal colonisation and invasive infections [10]. Both the number of antibiotics and days of antibiotic administered correlates with risk of fungemia [11]. Apart from increasing risk fungal sepsis, 3rd generation cephalosporin exert a selection pressure on microorganism resistant to them and also promote the growth of Multidrug Resistant (MDR) bacteria like Coagulase Negative Staphylococci (CONS), Extended Spectrum Beta Lactamase (ESBL), Methicillin resistant *Staphylococcus aureus* (MRSA) and Vancomycin Resistant Enterococci (VRE) [12].

In view of the above mentioned hazards instead of using third generation cephalosporins, aminoglycoside (e.g., amikacin) monotherapy can be a good option. Currently, at our centre amikacin monotherapy for empirical therapy in cases of suspected sepsis in neonates is proven to be safe and effective are used [13]. Therefore, clear antibiotic policies and use of blood culture for making therapeutic decision along with strict asepsis protocol, especially hand-washing are vital steps for prevention of emergence of *candida* and other unusual fungal pathogens like *Pichia anomala* and multi drug resistant bacterial infections [14,15].

CONCLUSION

The judicious use of antibiotics other than 3rd generation cephalosporin for empirical treatment in neonatal settings is suggested and further the antibiotic stewardship based on blood culture surveillance should be done.

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