Neonatal candida guilliermondii sepsis-An unusual bug in neonatal intensive care unit

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Abstract

Fungemia particularly due to candida species is a well-recognized entity in Neonatal Intensive Care Units(NICU). A cause of concern is the increasing occurrence of sepsis due to non-albicans candida species. These are associated with increasing morbidity and drug resistance.

We report a rare case of neonatal sepsis due to Candida Guilliermondii, a yeast which was considered to rarely cause infection in humans. The neonate, born in an outreach facility, was admitted in NICU with features of systemic, CNS and dermatological manifestations. The initial investigation revealed thrombocytopenia with positive CRP and CSF suggestive of infection for which empirical antibiotic therapy**(Vancomycin+Meropenem)** in meningitic doses was started. Initial blood culture was sterile. Thrombocytopenia progressively worsened and patient manifested dermatological lesions in the form of hyperpigmented macular lesions over face which progressed caudally. In view of clinical sepsis, persistent thrombocytopenia and dermatological manifestations, a fungal etiology of sepsis was suspected. Blood and urine culture for fungus was sent and patient was started on IV Fluconazole along with topical antifungal ointment (Clotrimazole). Blood culture grew Candida Guilliermondii which was sensitive to Caspofungin, Micafungin, Flucytosine and resistant to Fluconazole and Amphotericin B. As the patient had already been on fluconazole therapy for 4 days on which she had shown clinical improvement in the form of improved activity, some regression of hyperpigmented patches and thrombocytopenia, IV fluconazole along with topical clotrimazole was continued for 3 weeks. After three weeks of antifungal therapy, there was normalising of haematological parameters in the form of resolving of thrombocytopenia, negative CRP and CSF studies within normal limits.

The neonate was treated successfully with intravenous Fluconazole, in spite of antibiotic sensitivity pattern suggesting its resistance in-vitro. This demonstrates a difference in in-vivo and in-vitro efficacy of drugs and the necessity of exercising clinical judgement before rapidly changing antibiotic therapy which could in the long run stem development of drug resistance.

Keywords: Candida Guilliermondi, Neonatal non-albican candida sepsis, Antifungals

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Introduction

Fungemia particularly due to candida species is a well-recognized entity in Neonatal Intensive Care Unit(NICU). A cause of concern is the occurrence of non-albicans Candida species which were hitherto considered as contaminants and are now increasingly recognized to be associated with disease and increasing morbidity particularly in the immunocompromised patients. These are associated with drug resistance and increasing disease burden.

We report a rare case of Candida Guilliermondii sepsis in a neonate admitted in NICU with features of systemic as well as dermatological manifestation of infection. The infant was treated successfully with intravenous Fluconazole, in spite of antibiotic sensitivity pattern suggesting resistance to it. This demonstrates a difference in in-vivo and in-vitro efficacy of drugs. It also amply demonstrates the necessity of clinical judgement taking precedence and the need to exercise restraint of frequent change of antibiotics which could lead to development of increasing drug resistance.

Case Report

A term male baby was born to a 25yrs old G3P2L2 mother by elective LSCS with no history of maternal illness at a rural birthing centre. Baby was roomed in with mother. On day 7 of life the baby was admitted in NICU with features of sepsis in the form of fever, lethargy and poor feeding, multiple seizures with respiratory distress of two days duration.

Clinical examination at admission revealed a lethargic term neonate with respiratory distress(Downe's score-5) and suffering repeated subtle seizures .Baby was euthermic, normotensive and SPO_2 was 80% in room air. There was no organomegaly detected, anterior fontanelle was flushed and there was no focal neurological deficit.

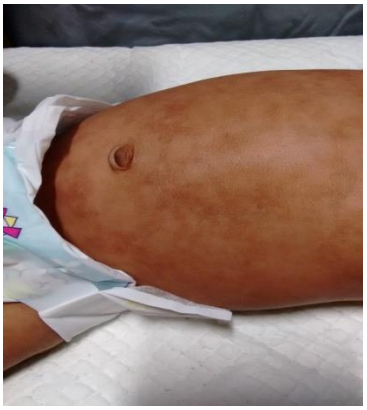
Baby was euglycemic. Haematological parameters revealed normal haemoglobin, total and differential white blood counts, thrombocytopenia (62,000/cumm) was present with no shift to left in peripheral smear. CRP was 34 mg/l. Serum Electrolytes, Calcium, magnesium and blood sugar levels were normal. CSF

examination revealed Sugar-30mgm% (Blood sugar-108mg/dl), protein-115mgm% Cell count-58(neutrophils-50%, lymphocytes-50%) which was suggestive of meningitis. Blood & CSF culture were sterile.

- Cranial USG was normal.
- EEG showed bihemispherical epileptogenic foci.

A clinical diagnosis of sepsis with CNS involvement was made. Broad spectrum antibiotics (Vancomycin+Meropenem**)** were commenced in meningitic doses. Supportive care in the form of parenteral nutrition, trophic feeds and temperature management was instituted. Anticonvulsant therapy was started with Phenobarbitone which was stepped up to maximum dosages. In view of repeated seizures, Levitiracetam and Phenytoin needed to be provided to control seizures over a period of 36 hours.

Repeat haematological parameters monitoring showed a worsening of thrombocytopenia to 10,300/cumm with associated ecchymosis and GI bleeding. Therefore SDP transfusions were provided. By the 3rd day of hospitalization, baby developed hyperpigmented macular eruptions over face which progressed caudally.[Fig. 1] In view of continuing downhill course worsening thrombocytopenia and dermatological manifestation, a suspicion of fungal sepsis was considered and antifungal therapy (IV Fluconazole and Topical Clotrimazole) commenced after obtaining blood and urine for fungal culture. Patient showed gradual improvement over the next few days.[Fig. 2]



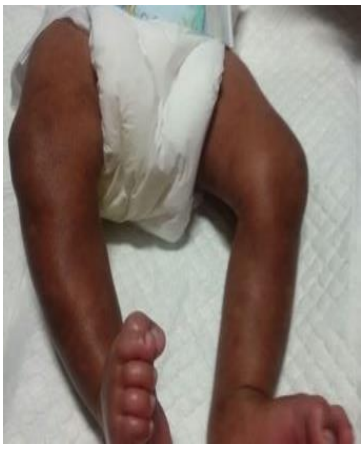
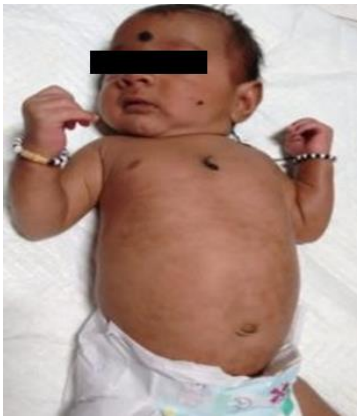


Fig. 1: Clinical photograph demonstrating dermatological manifestations of Candida Guilliermondii sepsis viz macular, hyperpigmented patches over face, trunk and extremities



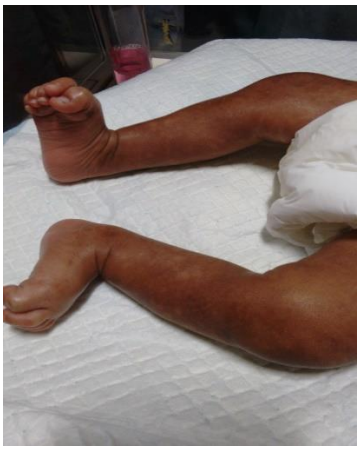


Fig. 2: Clinical Post Treatment Photograph of Patient showing Regression of Skin Lesions

Blood culture report which came in four days later revealed growth of Candida Guilliermondii sensitive to Caspofungin, Micafungin, Flucytosine and resistance to Fluconazole and Amphotericin B.

The patient meanwhile showed a clinical improvement in the form of improved activity, feed tolerance, reducing skin lesions and seizure control.

Haematological parameters too showed an improvement in the form of increased platelet count and normalising WBC counts. Hence the same antibiotics and antifungal therapy was continued with biweekly monitoring of haematological parameters. Antimicrobial therapy was continued for 3 weeks duration. Repeat CSF examination showed normalization. The patient was discharged on one anticonvulsant (Phenobarbitone). Follow up at 6 weeks and 3 months showed a neuro-developmentally normal infant with normal haematological parameters and complete regression of skin lesion.

Discussion

Fungal infection due to candida albican in intensive care units has been a worrisome issue, particularly so in immunocompromised patients. Of concern is the recent emergence of non-albican candida species e.g. *Candida Tropicalis, C. Parapsilosis, C. Glabrata* and *C. Krusei* causing disease, particularly in the intensive care settings. These strains were earlier considered contaminants but are now causing disease and are associated with increasing morbidity and mortality. Emergence of these uncommon species as pathogens in NICU has been a cause of worry.[1,2,3]

C. Guilliermondii is considered an uncommon clinical isolate globally.*C. Guilliermondii* ranks fourth behind *C. Albicans*, *Candida Tropicalis*, and *C. Parapsilosis* and ahead of both *C. Glabrata* and *C. Krusei*.[4]

Candida Guilliermondii is an uncommon species of *Candida* that is most often associated with onychomycosis[5]. It has been associated with poor clinical outcomes and hematologic malignancies[6]. It may be found on human skin and as part of the genitourinary and gastrointestinal tract flora. It has been documented to cause infection in patients undergoing surgical procedures, endocarditis in intravenous drug users and fungemia in immunocompromised patients. C. Guilliermondii has also been isolated in urinary tract infections[7]. Few reports of its isolation from bloodstream is particularly restricted to patients of hematological malignancy.

Only recently there are scant reports of its isolation from NICUs. These include a report of pseudoisolation in NICU. Exhaustive investigation on the blood culture practices revealed that when drawing blood for a culture from small infants, heparin flushes used was contaminated. Culture of a single lot of diluted heparin vials, grew between 10,000 and 15,000 colony-forming units of Candida Guilliermondii/ml[8].

Lately there are trends of its isolation from bloodstream and of CNS infection in adults and immunocompromised patients, particularly those with malignancies. However reports of sepsis in neonates with this fungi are few and far between. When it occurs, there are increasing reports of its resistance to Fluconazole[8]. *C. Guilliermondii* does appear to exhibit decreased susceptibility to fluconazole, and this pattern is seen in all geographic regions [9-12] It may also develop resistance to amphotericin B. The index case too demonstrated an in-vitro resistance to both fluconazole and amphotericin B.[13-14]

Antifungal Surveillance Program [ARTEMIS DISK] showed decreased susceptibility of Candida Guilliermondii to fluconazole, and voriconazole was more active in vitro against *C. Guilliermondii* than fluconazole.[15] It has also been seen that isolates of candida Guilliermondi from South Asian regions were most sensitive to fluconazole {77.4%} then other regions viz (Europe (73%), Latin America (77.0%), North America (67.7%). South Asian strains (7.9%) of Candida Guilliermondii showed least resistance to fluconazole therapy when compared to Europe(13%), Latin America(10.2%) and North America(8.8%). It has also been observed that in vitro resistance to fluconazole was the least in South Asia as compared to other antifungals.

Voriconazole has displayed more efficacy against *C. Guilliermondii* than fluconazole, irrespective of geographic region. However, its in vitro resistance rate has also been higher than fluconazole. Latest 2016 IDSA guidelines recommend Amphotericin B for treatment of disseminated candidiasis and Fluconazole as a reasonable alternative in patients who have not been on fluconazole prophylaxis.[16] Thus in view of these observation, fluconazole appears to be the most effective first line of therapy in South Asian regions.

Many NICUs adopt the policy of fluconazole prophylaxis because of high incidence of candida infection. But since in our unit fungal infections are uncommon, we do not use antifungal prophylaxis as a routine. This patient was provided IV Fluconazole on a clinical suspicion of a fungal septicemia. Our patient showed clinical improvement. Hence the same antifungal therapy was continued in spite of blood culture showing resistance to fluconazole. Also the high cost and side effects associated with use of Amphotericin and voriconazole were considered a limiting factor to its usage in our baby who had showed improvement on fluconazole. Further the use of fluconazole as a first line is in accordance with current recommended practice.[17]

Conclusion

We report a rare case of Candida Guilliermondii sepsis with CNS & dermatological involvement in a term neonate. We treated the baby successfully with IV Fluconazole in spite of blood culture showing resistance to it. This baby showed a progressive improvement. This reiterates a differing in-vivo and in-vitro efficacy of antimicrobials. It highlights the importance of clinical monitoring in deciding antimicrobial therapy and its efficacy in a given case. Furthermore, rapid changing of antimicrobials in a patient who is showing clinical improvement based on

laboratory reports, would encourage development of drug resistance. Thus exercising clinical judgement and restraint from frequent change of antimicrobials would contribute greatly to improving healthcare in the long run.

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