A survival case of premature infant with hepatoblastoma (fetal Pattern) along with other serious co-morbidities and surgical interventions- A Case Report.

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Abstract

An extreme preterm baby was presented in neonatal care unit with respiratory distress. The most disturbing stage here was the appearance of liver mass sizing 5.8cm×1.3cm with necrosis, diagnosed as hepatoblastoma which was evident with the aid of Ultrasound. Hence, chemotherapy was commenced which was in accordance with SIOPEL 3.

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Corresponding author: Dr. Mohammed Fardan Pharm.D., Clinical Pharmacist, Department of Clinical Pharmacology; Apollo Children's Hospital, Greams Road; Chennai- 600006, Tamil Nadu, India. Email id: mohammedfardan4@gmail.com**Abstract**An estimated ratio (i.e. 1 in 10) babies are born too early every year. Roughly 1 million children die each year due to impediments raised pertaining to preterm birth. One such extreme preterm male baby was presented in neonatal care unit with respiratory distress and grunting. He required High flow nasal cannula support till day 103 of his life, his condition begin to deteriorate day after day. Repeat X-rays showed migrating consolidation in both the lungs. Baby also was confirmed to have Ventricular septal defect along with Patent ductus arteriosus and craniosynostosis which was treated with medications and surgical managements. Patient was also on various empirical and prophylactic antibiotics in order to cover microbial growth. The most disturbing stage here was the appearance of liver mass sizing 5.8cm×1.3cm with area of necrosis, diagnosed as hepatoblastoma which was evident with the aid of Ultrasound. Hence, chemotherapy was commenced which was in accordance with Societe Internationale d Oncologie Pediatrique Epithelial Liver Tumor Study Group (SIOPEL 3). Even after the existing comorbidities, the baby made it successfully to get into track by fighting all the hurdles bravely, which was a sheer miracle. Along with the Clinicians/Surgeons, we Clinical Pharmacists worked hand in hand to ensure the baby to be receiving optimized drug regimen keeping in mind the risk-benefit ratio.

Introduction

Hepatoblastoma is one of the common malignancy in early childhood stage, almost accounting for 2/3 rd of primary malignant liver tumours especially seen under 4 years of age and more frequently in premature babies with very low birth weights. Alphafetoprotein (AFP) level in the blood is the important clinical biomarker for Hepatoblastoma. Other diagnostic approaches include CT scan, MRI, Biopsy and series of blood tests. Craniosynostosis, a birth defect where the bones in a baby's skull fuse together in an early stage before the brain is fully developed, this can however limit the growth of brain if not repaired at an initial stage. In India the incidence report of its occurrence is estimated to be 1 in 2500 live births. Treatment usually involves a surgical procedure- craniosynostosis correction, where excision of fused sagittal suture takes place. High prevalence of ventricular septal defect in preterm neonates has been recorded widely in studies done across worldwide. VSD is a defect, which involves a defect in the wall between the heart's lowers chambers. Treatment depends upon the severity of the case. Surgical procedure is accompanied in order to close the defect. Drugs such as Diuretics, antihypertensive medications, inotropes are required to treat the post surgical symptoms. This case report discusses a complex case wherein a preterm baby along with recurrent lung consolidation and ventricular septal defect was diagnosed with hepatoblastoma. Baby was also confirmed to have asymmetrical craniosynostosis.

Case Report

A moderate preterm baby of 32 weeks gestation was received in NICU after emergency LSCS due to the indicated concern of pregnancy induced hypertension with hypertensive dilative cardiomyopathy. The birth weight was recorded to be 1 kg. Baby was intubated in view of respiratory distress and grunting. Baby was extubated to oxygen via high flow nasal cannula (HFNC) within 24 hours of birth, despite baby continued to have respiratory distress with retractions. Hence, serious chest X- rays were taken at various intervals which showed migrating consolidation in both the lungs. Nebulization with N-Acetylcysteine (NAC) was given along with a short course of Inj. Furosemide to relieve the distress. Baby responded well to treatment but however required HFNC support till day 103 of life. On clinical examination of cardiovascular system, baby was having a systolic murmur. ECHO confirmed ventricular septal defect of 5mm and patent ductus arteriosus (PDA). Since, PDA was persistent in subsequent ECHO's; a 5 day course of IV Acetaminophen was ordered. ECHO on 2nd month of baby's life showed VSD ->4.3mm size along with increased pulmonary vascular resistance. Baby underwent ventricular septal defect closure + patent ductus arteriosus ligation successfully, post surgery he required inotropes for initial period of 48hrs which was slowly tapered prior to stopping, and he also required inodilators cycling (milrinone+ levosimendan) for 10 days. The blood samples for sepsis screened were sent on day 1 itself, initial WBCs and platelet counts were low with negative CRP, subsequent CRP result showed higher numbers, hence 7 days of piperacillin+ tazobactum course was started. Another blood screen on 3rd week of life showed highly positive CRP and procalcitonin levels with methicillin sensitive Staphylococcus aureus (MSSA) septicaemia., followed by which he was started with IV antibiotics cefazolin and meropenem, since then, CRP showed decreasing trend and the repeat blood culture was sterile. Post VSD surgery, bronchial wash specimen showed growth of ESBL, E. coli and Ralstonia picketti for which further antibiotics were given. Ambiguous genitalia were noted at birth, for which karyotyping and Fluorescence in situ hybridisation (FISH) performed depicted normal karyotyping- 46 XY. On follow up, both the testes were descended in the 7th month of his life. Hypospadias surgery was advised to be done after 1 year of age. On 3rd week of life, liver was palpable during clinical examination which was initially attributed to the abscess. Ultrasound abdomen showed a liver mass measuring 5.8 cm×1.3 cm with areas of necrosis; CT abdomen was suggestive to hepatic neoplasm. Alphafoetoprotein was markedly elevated (1,36,402 ng/ml). Finally, Ultrasound guided liver biopsy done was consistent with hepatoblastoma (fetal pattern). Baby was commenced on chemotherapy which was in accordance with SIOPEL 3 Protocol (Societe Internationale d Oncologie Pediatrique- Epithelial Liver Tumor Study Group), underwent two cycles of two drug therapy (Carboplatin/Doxorubicin). Baby received one dose of granulocyte stimulating factor after each cycle in

view of significant neutropenia. Alphafoetoprotein count after therapy was (1350ng/ml), marking a good response. Right Hepatectomy was performed on 5th month of his life. Serum AFP was monitored frequently and the value showed a decreasing trend. He was given phosphate and albumin correction following Hepatectomy. Post Hepatectomy his blood cultures grew ESBL, Klebsiella Pneumonia; Endotracheal secretions grew Acinetobacter and Klebsiella Pneumoniae and abdominal Drain fluid grew Pseudomonas aeruginosa for which he received broad spectrum antibiotic for duration of 14 days further. ECHO at this time done showed normal cardiac function. Calcium correction was given intravenously. Renal function tests and electrolytes done periodically were within normal limits. Meanwhile, amidst the treatment phase, baby's head continued to grow in an abnormal shape and sagittal suture appeared to be partially fused on clinical examination. A CT brain was done which confirmed the presence of asymmetrical craniosynostosis. Finally, craniosynostosis correction and excision of fused sagittal suture was done prior to 3rd and 4th cycle of chemotherapy. He was started on prophylactic anti-epileptic (levetiracetam) post surgery and advised to continue for 3 months. 3 weeks post craniosynostosis he had been given with 2 more remaining cycles of chemotherapy which according to guideline was single drug therapy (cisplatin). Final AFP done after completion of chemotherapy showed value of 38ng/ml. Baby responded well to treatment, he was stable and successfully discharged after serving 8 months of his life in hospital.**Discussion**The clinical course of this patient was way too complicated; it indicated us three main clinical manifestations in treatment approach pertaining to the diagnosis. First of all, one must be cautious of hepatoblastoma occurrence, especially in neonates with extremely low birth weight. The incidence of Hepatoblastoma in Extremely Low Birth Weight (ELBW) neonates is on a surge according to reports, it might be the reason for an increase in the count of more immature infants with a more sensitive liver.[1] AFP has been shown to correlate with tumour size and volume at time of diagnosis.[2]Since, the level of AFP is high in preterm infants, serial measurements and vigilance in the transition of AFP levels is indispensable.[3] Studies shows that incidence of Hepatoblastoma is infrequent in black population when compared to white.[4] In this case, as discussed, connecting the dots in view of infection, baby was believed to be having liver abscess, since the baby was septic from day 1 of life. It was only after performing the essential diagnosing tests; baby was confirmed to have hepatoblastoma. SIOPEL protocol was followed for the treatment of hepatoblastoma. Societe Internationale d'oncologie Pediatrique- Epithelial Liver Tumor Study Group (SIOPEL) is a result of an international collaborative effort of a multidisciplinary team originally found in Jerusalem to study these sort of diseases internationally.[5] In this case, two cycles of two drug chemotherapy (Carboplatin/ Doxorubicin) was ordered before resective surgery and post surgery 2 more cycles of single drug chemotherapy (Cisplatin) was introduced, this chemotherapeutic approach was in accordance with SIOPEL 3 protocol. For infants <5 kg, Carboplatin and doxorubicin dosage is 11.5 mg/kg and 1.34 mg/kg accordingly. The latter must be given in 48hrs continuous infusion. The dose of cisplatin is 80mg/m^2continuous infusion for 24 hrs which is to be run concurrently with 120ml/m^2 /hour/ day of solution containing Glucose/NaCl + Mannitol, KCl, $MgSO_4$ and Calcium Gluconate. Since, infants are at a higher risk of Cisplatin-induced electrolyte imbalance than older children, the need for regular electrolyte monitoring is particularly important. Prior to individual chemotherapy, pre-medications like antihistamines, anti-emetics must be given to cope up with untoward symptoms. Second of all, one should be well aware of various neurological ill-effects that craniosynostosis holds along with skull deformity. It is often evident that proper neurosurgical management at appropriate time would ensure excellent outcomes for craniosynostosis patients.[6] The aim of surgery is to warrant normal growth of brain, to prevent increase in intracranial tension and to improve facial and skull appearance without compromising visual and auditory function. The incidence of seizures in patients treated with levetiracetam is relatively less after neurosurgeries.[7] In this case, post craniosynostosis; levetiracetam was ordered for 2 months as a prophylaxis measure to avoid the risk of developing seizure later on. It was advised to taper slowly after two months prior to stopping completely. Third of all, is to consider cardiovascular examination in preterm neonates predominantly. VSD along with patent ductus arteriosus is not something uncommon and accounts for higher percentages in neonates.[8] Repeat ECHO must be done post surgery to ensure no traces of residual VSD. The septicemia condition even after 3 major surgeries (Right Hepatectomy, craniosynostosis correction and VSD closure + Patent ductus arteriosus ligation) was well treated with definitive antibiotic therapy approach. The baby mentioned herein, fought all the odds well, survived tedious treatments and it's nothing short of miracle. He

was finally discharged after spending first 8 months of his life in the hospital with regular follow-up strategic plan.**Ethics Approval and consent to participate**Not Applicable**Consent for publication**We have obtained appropriate consent from the baby's father to publish this case report.**Availability of date and material**Not Applicable**Competing Interests**The authors declare that they have no competing interests.**Funding**No funding sources**Author's Contributions**Mohammed Fardan, Priya Shiva & Aswathy M Shaji have contributed equally in writing the paper. K.Arun Chander Yadav played his part in reviewing and proofreading the final case report.**Acknowledgements**We would like to express our immense gratitude to the clinician's and surgeon's team of neonatal care unit for their highly obliged manner by helping us with all the clinical data's and cardinal information's. Also we would like to thank the nursing team to be supportive throughout.

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8. Seon Young Cho et al. 2012. Recent Incidence of congenital heart disease in neonatal care unit of secondary medical centre: a single center study. Korean J Pediatr 55(7):232-237.**Figure LegendsFigure 1. Image showing the abnormal mass which is situated very adherent to the liver.** This image was taken during the Hepatectomy procedure.

Figure 2. Image showing dissected tumour. The abnormal mass (tumor) has been removed by performing hepatectomy and the image here displays the dissected part.

Figure 3. Sagittal synostosis correction- before and after images. The picture here shows the before (in the left) and after Craniosynostosis correction (in the right) images; surgery was performed successfully and the outcome was remarkable.**Figure 4. Fluorescence in-situ hybridization (FISH) – Report.**This test was performed in order to analyze sex chromosomal anomalies.