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CASE REPORT

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Congenital neuroblastoma with in-utero metastases: A report of a rare case

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Abstract: Congenital Neuroblastoma is rare and the prenatal metastatic form even rarer. We describe a neonate, a product of non-consanguineous marriage, a booked and term uneventful pregnancy till the 38th week of gestation when mother had preeclampsia and abruptio placenta and was delivered via emergency caesarean section. He was but critically ill at birth with clinical evidence of metastases to the skin, bone marrow and liver (Stage 4S). Our case, the first to be documented from our center, is the prenatal form of congenital neuroblastoma with intrauterine metastases which has a uniformly poor prognosis. Abdominal ultrasound and CT scan were suggestive with masses and intralesional calcifications and the diagnosis of congenital neuroblastoma was confirmed histologically postmortem He died seven days after admission. Our case buttresses the need for improved resources to enhance early diagnosis, a high index of suspicion and optimal care in order to improve and modify outcomes.

Key words: Congenital, neuroblastoma, metastases, calcifications, post-mortem biopsy, histology.

Résumé: Le neuroblastome congénital est rare, et sa forme métastatique prénatale l'est encore plus. Nous décrivons le cas d'un nouveau-né, issu d'un mariage non consanguin, dont la grossesse s'est déroulée sans incident jusqu'à la 38e semaine. La mère a ensuite présenté une prééclampsie compliquée d'un décollement placentaire, ayant nécessité un accouchement d'urgence par césarienne. À la naissance, le nouveau-né était dans un état critique. Il a présenté des signes cliniques de métastases cutanées, médullaires et hépatiques (stade 4S). Il s'agit du premier cas documenté dans notre centre, d'un neuroblastome congénital à présentation prénatale avec métastases intra-utérines, une forme associée à un pronostic particulièrement défavorable. L'échographie abdominale et le scanner ont révélé des masses et des calcifications intralésionnelles. Le diagnostic de neuroblastome congénital a été confirmé histologiquement en post mortem. Il est décédé sept jours après son admission en raison de l'évolution des métastases multisystémiques. Ce cas souligne la nécessité d'améliorer les ressources pour favoriser le diagnostic précoce, d'élever le niveau de suspicion clinique, et d'optimiser la prise en charge afin d'améliorer le pronostic de ces formes néonatales graves.

Mots clés: Congénital, neuroblastome, métastases, calcifications, biopsie post mortem

Introduction

Neuroblastoma is the most frequent extracranial solid tumor of childhood and accounts for 7% of all paediatric tumours.[1] Neonatal malignant tumours are rare and comprise only 2% of all childhood malignancies with neuroblastoma accounting for 20-50% of all malignant neonatal tumours[2]. It originates in the neural crest cells and can be located anywhere along the neuroectodermal sympathetic nervous chain[3].

Congenital neuroblastoma is defined as neuroblastoma detected during the prenatal period or within the immediate 28 days after birth[3]. It accounts for 5% of all cases of neuroblastoma. In prenatal neuroblastoma (NBL),>90% originate in the adrenal medulla, hence a solid adrenal mass on prenatal ultrasound Scan (USS) is suggestive of congenital neuroblastoma[3.] It metastasizes to the liver, lymph nodes, bone marrow and skin[4].

Case report

Z A was a term baby boy who was delivered to a 24-year-old P^{0+1} via emergency lower segment caesarean section (EMLCS) on account of maternal abruptio placentae and severe pre-eclampsia. Birth weight was 3.1kg, APGAR scores of 9, 10 and 10 at 1,5 and 10 minutes respectively. He was brought to the neonatology unit for assessment at the 35th minute of life.

Pregnancy was booked at a comprehensive health center at 28 weeks gestational age with normal booking investigations and examinations. No history of exposure to teratogens, or family history of congenital malformations. Serology for syphilis, HIV and Hepatitis B and C were nonreactive with ultrasound scans at the 24th and 28th week of gestation showing normal findings. She was referred from the booking facility on the day of delivery at 38 weeks due to symptoms of pre-eclampsia and ultrasound (USS) ascities done at this point showed a single viable foetus with ascites and mild placental abruption. The fetal heart rate was reactive. She was counseled for an emergency abdominal delivery and placed on magnesium sulfate ($MgSo_4$), and anti-hypertensives (labetalol and nifedipine). The fetus was monitored with a cardiotocograph.

At delivery, he was pale but vigorous, and required no immediate resuscitation. However, he was noticed to have widespread non-tender hard nodular masses on the scalp, face, neck, trunk, and limbs sparing the palms and soles, the largest measuring 3cm x 4cm on the trunk posteriorly (Fig 1).There was a distended abdomen with visible anterior abdominal wall veins draining upwards (Fig 2) and multiple ballotable intra-abdominal masses spanning from the right hypochondrial region and extended diagonally to the left iliac fossa. The masses were hard, irregular, non-tender with the largest in the left lumbar region measuring 10cm by 9cm, clinically distinct from the spleen. He had massive ascites. The heart rate was 142b/m, blood pressure was 82/54 mmHg and the 1^{st} and 2^{nd} heart sounds were heard and distinct. He was tachypneic but not dyspneic with versicular breath sound and good air entry bilaterally, with an oxygen saturation of 98% in room air. He had a good tone and optimal primitive reflexes. Random blood sugar at presentation was 4.9mmol/.

He was managed for presumed sepsis (Fever, temperature instability and leucopenia) Congenital infection to rule out (R/O) congenital neuroblastoma. He had the relevant investigations, commenced on intravenous broad spectrum antibiotics and had fresh whole blood transfusion. Judicious fluid and calories were provided via partial parenteral nutrition and other supportive management as per the unit protocol.

Results

Full blood count and differentials done at presentation showed pancytopenia (leucopenia 1.7 x10^9/L, severe anemia HCT- 32.9% and mild thrombocytopenia platelet 123x10^9/L, differential cell count (Granulocytes % - 69.4%, lymphocytes 26.7%). No blast cells were seen.
Ultrasound sound scan of the abdomen showed multiple solid intra abdominal masses with the largest encircling the aorta with some areas of calcification and bilateral hydronephrosis.

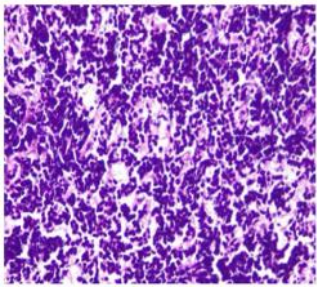
Abdominal CT scan showed a huge mass in the para-aortic region, abutting the medial borders of both kidneys (Suprarenal) with resultant hydroureteronephrosis, worse on the right. The mass was bordered superiorly by the liver and gastrium and and inferiorly by the bladder inferiorly. It measured 8.1cm x 8.9cm x 10cm in dimension with displacement and encasement of the aorta and its branches. There was intralesional calcifications. Urea and electrolytes were essentially normal.

Histology of biopsied subcutaneous nodule showed small round blue cells forming roselte pattern These are within a moderate neutrophil fibrillary stroma with areas of necrosis (Fig 3)

Fig 1

Fig 2

Fig 3: Small round blue cells in diffuse sheets and forming rosettes x 400



H &E x 400

Discussion

This case illustrates a rare case of congenital neuroblastoma with metastases to the liver, bone marrow and skin at birth (4S). Congenital neuroblastoma is the leading malignant neoplasm in the perinatal period[1]. There is sparsity of literature on it with <100 cases documented globally[2]. Olutekunbi et al from Lagos, Nigeria described a case whose symptoms were noted around the 16th month after birth[5], however in this case, there was no intrauterine metastases. Diagnosis of neuroblastoma is established by catecholamines and their urinary metabolites, imaging studies and histopathological analysis[3]. Unfortunately, we couldn't measure maternal levels of catecholamines viz- vanillyl mandelic acid, (VMA) and homovanillic acid (HMA) which have sensitivity of 100% and specificity of 99.7% in the presence of metastases. Could the maternal severe pre-eclampsia and abruption placenta have been secondry to elevated catecholamine level?

Intra-uterine ultrasound scan (USS) and Magnetic Resonance Imaging (MRI) especially in the mid and late trimesters are essential for prenatal diagnosis[4]. Though USS was done in this case at 24th and 28th week of gestation it was reported as normal. This buttresses the fact that USS is an operator dependent investigation requiring expertise honed with experience so there was no prenatal diagnosis. Intrapartum USS done at our centre at 38 weeks showed foetal ascites and other features of hydrops foetalis . Literature[6] has documented foetal hydrops in prenatal neuroblastoma attributable to the mechanisms described viz-hepatomegaly with mechanical obstruction of the umbilical vein and inferior vena cava, hypoalbuminemia, bone marrow infiltration with anaemia, leading to cardiac failure, arrythmia from excessive catecholamine release or hypersecretion of foetal aldosterone[6].

It arises from the adrenal gland in 90% percent of cases[3], this could pose a diagnostic dilemma as the normal development of the adrenal gland may be indistinguishable from an in -situ neuroblastoma[1]. Clinical presentation is variable depending on the primary tumour site, presence of metastases and occurrence of paraneoplastic syndromes[3].

Our case presented with intrauterine multiorgan metastases and was critically ill at birth which is stage 4S. The International Neuroblastoma Staging System (INSS)[7] stages from 1- 4S ('S' for special). Stage 4S was first described in 1971[7] usually found in children below twelve months of age with metastases to the liver, bone marrow and skin. Traditionally, stage 4S is associated with a favourable prognosis with spontaneous regression[8], this however only applies when symptoms present in later infancy or where the liver is the only site of metastases as it has been documented to have normal myelocytomatosis (MYCN) oncogene and hyperdiploid DNA which confers a favourable prognosis[8].

The MYCN gene is located on the short arm of chromosome 2 and when amplified, responds with excessive production of the protein complex N-myc which inhibits cellular differentiation, promotes cellular proliferation and apoptosis thus conferring poor prognostic characteristics[8]. Congenital neuroblastoma with in utero metastases has a poor prognosis and is uniformly fatal.[9,10.] Qilan[11] et all in 2015 documented a 10-year survival rate of 91% for stages 1-3 and 38% for stage 4 (S) cases >18 months of age. Similarly, Norman and Kara[12] reported a 3-year survival for patients with high-risk neuroblastoma (inclusive of congenital neuroblastoma with dissemination at birth) treated with conventional chemotherapy, radiation and surgery of 20%.

Treatment modalities are chemotherapy, radiotherapy and surgery. Reports from Saudi[13]Arabia and Nigeria [5]have shown good response to chemotherapy (Vincristine, Adriamycin and Cyclophosphamide) and long-term survival. However, in this instances metastasis was localized only to the liver and skin respectively unlike in the reported case with multi organ infiltration including the bone marrow.

Diagnosis of congenital neuroblastoma requires prompt specific investigations. These are usually not readily available and cost prohibitive and so are the treatment modalities ranging from surgery chemotherapy to radiotherapy inclusive of supportive care. All of these remain unachievable in a context of limited resources and financial constraints. The reported case was characterized by extreme neonatal resource limitation and financial constraints with lack of health insurance being the major constraint. This inevitably led to avoidable delays arriving at a definitive diagnosis, in managing complications efficiently and non- commencement of specific chemotherapy.

Another highlight of the case was the parental acceptance of postmortem biopsy which is not readily accepted in this locale for cultural and religious reasons. The biopsy and history though postmortem confirmed the diagnosis.

Metastatic and compressive sequalae ultimately led to the demise of the patient which is in consonance with documentation from literature[9,10,13].

Conclusion

We have described a rare case with none documented from literature in the sub-region of congenital neuroblastoma with in-utero metastases (stage 4S). Lack of prenatal or antenatal diagnosis further worsened the outcome. It is recommended that improved sonographic skills, focused antenatal care, universal health coverage with emphasis on neonatal health insurance will prevent delays, aid prompt definitive diagnosis, and management.

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