Case Report

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Neonatal neuroblastoma with adrenal primary and metastasis to the liver: A case report and a review of literature

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ABSTRACT

We report the case of a 23-day-old neonate with neuroblastoma (NBL) in the right adrenal gland and widespread metastases to the liver. This raises the possibility of foetal NBL, which was missed during periodic ultrasonography done during the mother's pregnancy. We hope that this report would increase the awareness of physicians about foetal, congenital and neonatal NBL; and of sonographers about space-occupying lesions in the foetus. The clinicopathologic features and the management of neonatal NBL are discussed.

Key words: Antenatal/foetal ultrasonography, neonatal neuroblastoma

INTRODUCTION

This is the report of a female neonate with Stage 4S neuroblastoma (NBL), who presented with an abdominal mass lesion. The fact that the abdominal mass was first noticed at birth raises the possibility of congenital NBL and of a cancer predisposition syndrome.[1]

If NBL had been present in this patient in utero, it was missed by ultrasonography (US), and she was deprived the opportunity to have appropriate monitoring and or management before delivery.[2-4] In general, neonatal NBLs are rare,[2] and many clinicians have limited experience in its management.[2]

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CASE REPORT

The patient was a 23-day-old female neonate who was referred to our centre on account of progressive abdominal distension starting from birth, 11 days' history of bilateral pedal oedema, and 2 days' history of high-grade fever. The abdominal distension was not associated with vomiting, constipation or delay in passage of meconium. The pedal oedema progressed to involve the legs and then the thighs. She was delivered at term by spontaneous vaginal delivery. Pregnancy was uneventful and antenatal obstetric scans done revealed no abnormality. Birth weight was 2.6 kg and there was no history of birth asphyxia. On examination, she was in respiratory distress, febrile (38.8°C) and irritable with bilateral pitting pedal oedema extending up to the thighs. Abdominal examination revealed abdominal distension (abdominal girth of 52 cm, measured at the level of the umbilicus, mean abdominal girth for patient's weight is 16.3–21.5 cm (18.9 ± patient's weight in kg).[5]

There was hepatosplenomegaly (the liver was palpated 13 cm below the right coastal margin and the spleen 7 cm below the left coastal margin). She had tachypnoea (respiratory rate of 64 breaths/min), hypoxaemia (oxygen saturation of 89%) and tachycardia (heart rate of 176 beats/min). Abdominal ultrasound scan showed

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gross hepatomegaly with areas of increased echogenicity that were diffusely distributed throughout the liver. Abdominopelvic computerised tomography (CT) scan revealed an enlarged right adrenal gland, solid, nodular, with a central area of calcification; it measured 32 cm × 25 cm × 24 cm. A diagnosis of an adrenal NBL was made. Full blood count showed features suggestive of sepsis, with anaemia and leucocytosis. She was managed with intranasal oxygen, intravenous fluids and intravenous antibiotics. Packed cell volume (PCV) done on the 20th day of life was 39%, and 2 days later, 34%. The patient was transfused with 40 ml of whole blood a few hours before her demise. Urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) assays were requested but not done. She was being worked up for surgery but had multiple apnoeic attacks and bouts of hypoglycaemia. On the 3rd day of admission, she developed another apnoeic attack and attempts at resuscitation were unsuccessful. She was certified dead shortly thereafter.

At autopsy, the body is that of a female neonate weighing 2.7 kg with head circumference of 37 cm (normal range, 32–34 cm), crown-heel length of 54 cm (normal range 45.6–47.8), crown-rump length of 36 cm, chest circumference of 35 cm and abdominal circumference of 52 cm measured at the level of the umbilicus. She was severely pale. There was bilateral pitting pedal oedema. No dysmorphic features or congenital abnormalities are seen. There is generalised pallor of the organs. The right adrenal gland is enlarged [Figure 1]; it weighs 10 g (normal range, 2.0–2.45 g). Cut sections reveal homogenous tan-coloured surfaces with multiple petechial haemorrhages. The left adrenal gland appears unremarkable. The liver is enlarged, it weighs 750 g (normal range, 123–127 g) and shows multiple dark brown nodules on its surface and within its substance which vary in size from 1 cm × 1 cm to 3 cm × 2 cm [Figure 2]. Multifocal areas of haemorrhage are seen on the cut surfaces of the liver. The spleen is enlarged; it weighs 50 g (normal range, 10–12 g). Cut sections show no tumour nodules but a sharp cutting edge. The right and left lungs are heavy and weigh 35 g (normal range, 29–31 g) and 30 g (normal range, 26–27 g), respectively. Cut sections show moderate pulmonary oedema. The kidneys show evidence of shock and the brain shows moderate cerebral oedema. Histology of the right adrenal gland shows sheets of small round blue cells within delicate fibrovascular stroma with a few Homer Wright rosettes being seen [Figure 3]. Areas of necrosis and haemorrhage are also seen. Similar cells are also seen infiltrating the substance of the liver [Figure 4]. The patient's disease was complicated by severe anaemia which resulted in congestive cardiac failure and ultimately, in her death.

Final anatomical diagnosis

Cause of death

Neuroblastoma with primary in the right adrenal gland and metastasis to the liver.

Mechanism of death

Congestive cardiac failure secondary to severe anaemia.

DISCUSSION

The patient presented with a palpable abdominal mass. This is the most common presentation among neonates with NBL.[1-3] As seen in the index patient, the abdominal mass may occur secondary to hepatomegaly and be indicative of metastatic disease.[2,3]

Masses in the neck, chest and head can also occur, from primary tumours or from metastases. Skin lesions, described as blueberry muffin spots, are suggestive of disseminated disease.[2] Almost 60% of infants with NBL have metastatic disease at presentation.[3] Metastasis is via blood vessels and lymphatics,[3] with common sites including the liver, the skeleton, bone marrow and skin.[3]

The finding of a tumour in this patient in the perinatal period raises the possibility of a cancer predisposition syndrome.[1] Even though <10% of childhood cancers are associated with a known cancer predisposition syndrome, the frequency is likely to increase as we advance in the knowledge and skills for cancer genetics.[1] Aside of the finding of a tumour in the perinatal period, the index patient had no other features to suggest a cancer predisposition syndrome

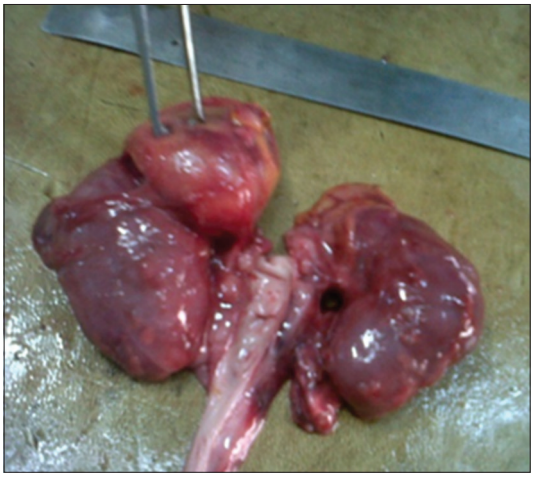

Figure 1: Gross picture of the enlarged right adrenal gland

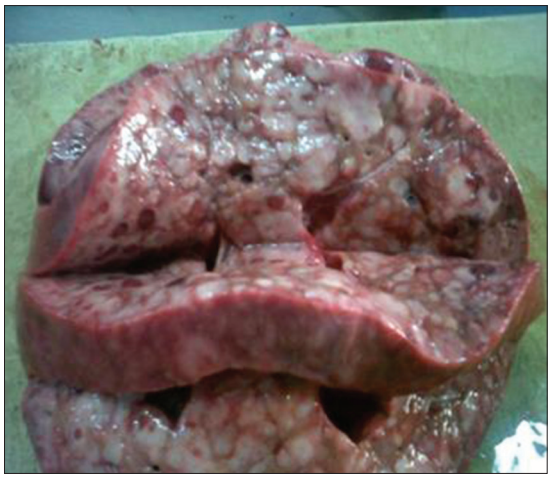

Figure 2: Cut-sections through the liver showing multiple diffusely distributed nodules

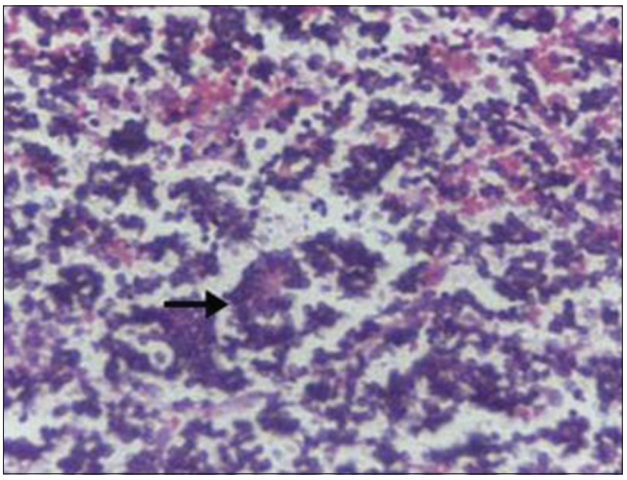

Figure 3: Photomicrograph showing sheets of small round blue cells withHomer Wright rosettes (arrow) (H and E, × 400)

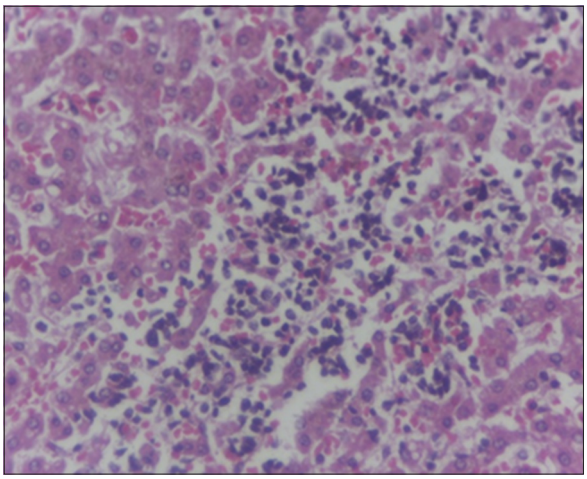

Figure 4: Photomicrograph showing small round blue cells infiltrating through the parenchyma of the liver (H and E, ×400)

such as multicentric, bilateral or multifocal disease, associated congenital malformations, and cancer in close relatives.[1]

The patient's disease was complicated by severe anaemia with possible contributions from the malignancy and from sepsis. It is not uncommon for malignant disease in Africa to be complicated by co-morbidities such as sepsis and malaria with consequences for management.[6]

The prevalence of anaemia in patients with solid tumours is close to 40%. Possible causes of the anaemia of cancer include the direct effects of the malignancy, chemotherapy and blood loss from haemorrhage[7] such as from phlebotomy, bleeding oesophageal varies or from coagulopathies resulting from the compromise of liver function.[3,8] Chemotherapy was not commenced before the patient's demise and there was no evidence of haemorrhage at autopsy.

Cancer is known to increase inflammatory cytokine production which suppresses erythroid progenitor cell proliferation, erythropoietin production and impaired iron utilisation.[7] The cancer can also cause increased haemophagocytosis and increased red cell haemolysis thus reducing the life span of the existing red cells.[7] In neonates, other causes of anaemia include inadequate nutrient intake and cardiorespiratory disease.[9]

The patient subsequently developed congestive heart failure (CCF), likely from the anaemia. Aside of the abdominal mass and distension, the patient presented with features of CCF including pallor, tachycardia, increased pulse rate, hepatomegaly and bilateral pedal oedema with progression to anasarca. Regardless of the aetiology, the first manifestation of CCF is usually tachycardia.[10] Secretion of catecholamine metabolites may also cause flushing, sweating, tachycardia and hypertension.[10] Hypertension may also occur from the stimulation of the renin-angiotensin system following stretching of the renal artery by the tumour.[9] Uncompensated CCF is one associated with low cardiac output and in an infant, primarily manifests as failure to thrive.[10] In severe cases, failure to thrive may be followed by signs of renal and hepatic failure.[10] After 23 days of life, the patient had only recorded a gain in weight of 0.1 kg.

She had respiratory distress and tachypnoea at presentation and at autopsy, she was found to have pulmonary oedema. Aside of the splinting of the diaphragm by the enlarged liver, other possible contributory factors include the pulmonary venous congestion and left-sided heart failure. She had hepatosplenomegaly, likely from systemic venous congestion and right-sided heart failure. Less frequently, right-sided heart failure may also result in oedema or ascites.

CCF occurs when the heart fails to meet the metabolic demands of the body at normal venous pressures, and the compensatory mechanisms become overwhelmed.[10] Typically, the heart responds to increased demands by increasing the heart rate, increasing the contractility of the ventricles and augmenting the pre-load.[10]

The patient subsequently went into circulatory shock, with increased corticomedullary differentiation in the kidneys at autopsy. Possibilities include cardiogenic shock from the congestive cardiac failure and or arrhythmias (tachycardia) or septic shock from the bacterial infection/sepsis she had. The hypoxaemia and apnoeic attacks that she had terminally were likely due to shock.

At autopsy, she had features of moderate cerebral oedema, possibly secondary to hypoxic-ischemic encephalopathy following the severe anaemia.

At 2.6 kg, the birth weight was lower than the mean birth weight for babies born in Lagos and other regions of Nigeria.[11] In the United States, expected foetal weight at term is 2960–3250 g.[12] At autopsy, the patient weighed 2.7 kg. Physiologic weight loss occurs in the 1st week of life, with the foetus returning to the birth weight by the 15th day of life.[13] A weight gain of 10–20 g/kg/day is expected from that point forward.[13]

NBL is one of the embryonal malignancies of childhood, an immature (blast) tumour of the nervous system derived from primordial neural crest cells which give rise to the sympathetic ganglia and the adrenal medulla.[3,13]

NBL can be identified as early as 23 weeks with meticulous sonography.[13] The finding of polyhydramnios or non-immune hydrops fetalis may suggest the possibility of a lesion in the foetal liver.[3,4] A suprarenal mass may also be found. Other causes of a suprarenal mass include adrenal haemorrhage,[2,13] extrapulmonary sequestration,[2] bronchogenic cyst[2] or uropathy.[2]

Obstetric US, readily available in Nigeria, is an adequate tool for the identification of space-occupying lesions in the foetus.[4] With more proficient use of routine antenatal US,[2] one is more likely to identify these lesions, and also,[1,2] increasingly earlier in the gestation.[2] Management can be offered before birth.[2-4] In addition, it is known that haemorrhage can occur into the tumour during delivery[4] and if diagnosis is made while the foetus is in utero, caesarean section can be offered as a precaution.

When there is suspicion of a malignant tumour, careful follow-up with US done twice weekly to evaluate the foetal biometry, amniotic fluid volume, biophysical profile and tumour measurements is indicated.[4]

By US, NBLs are heterogeneous solid lesions, mostly echogenic.[15] Cystic anechoic areas are much less common in NBLs than in Wilms tumour and usually represent haemorrhage or necrosis within the tumour.[15] Calcification is common, either coarse as focal echogenic areas with usually no distal acoustic shadowing, or fine, resulting in diffusely increased echogenicity of the tumour.[15] The ipsilateral kidney is usually displaced by the large retroperitoneal tumour, and its identification facilitates differentiation from Wilms tumour.[16] The aorta and the inferior vena cava are usually displaced anteriorly and together with the portal vein, the coeliac axis, the mesenteric and the renal vessels, they may be surrounded by the lesion.[16] Their patency can be evaluated with colour Doppler US. Metastatic involvement or invasion of the liver can be detected with US.[16] The typical finding suggesting invasion of the liver by the mass is the absence of differential movement between them.[16]

On CT scan, NBLs present as large, heterogeneous, lobulated soft-tissue masses that show heterogeneous or little enhancement.[15,16] Coarse, finely stippled or curvilinear calcifications are seen in 85% of the abdominal and 50% of the thoracic NBLs on CT.[14,15] Low attenuation areas seen within the tumour represent pseudo-necrosis or haemorrhage. CT scan also demonstrates encasement and compression of the major abdominal vessels.[14,15] Distinguishing between the primary tumour and the adjacent nodal disease is often impossible.[14,15]

Around 50% of newborns have foetal adrenal rests which often degenerate early in the neonatal period, within the adrenal gland or at other sites to match the pathways for migration of neural crest cells in the embryonic period. Persistent adrenal rests may present as congenital NBL.[14]

NBLs are rare, occurring in 1 of every 12,500–27,500 live-births.[1] Even though NBL is the most common malignancy seen in the neonatal age group and accounts for more than 20% of neonatal cancers,[1,14] neonatal neoplasms in general are rare, account for only about 2% of childhood malignancies,[2] and most neonatology units would be consulted on only one case of NBL every 1–2 years.[2] There is a need for increased awareness about this disease.[2]

One study reported that 16% of neonatal NBLs in the 1st year of life are diagnosed during the 1st month of life (i.e., neonatal) and 41% during the first 3 months.[14] The male to female ratio for NBL is 1.2:1.[14]

Stage 4s/Ms ('s' stands for 'special') NBL is defined as metastatic NBL presenting in an infant aged <12 (or <18) months. Classically, there is a localised primary adrenal tumour with metastases limited to skin, liver and/or bone marrow.[3,14] NBL shows unique clinical behaviour in the neonatal period; hence, the need for an additional stage, MS (4s), most cases of which would spontaneously regress.[2]

Most NBLs are suprarenal tumours.[1] Aside of the suprarenal location, NBLs can occur in other sites along the sympathetic chain from the neck to the groin.[3,14] The variety of locations of neuroblastic tumours and the varying degrees of differentiation results in an array of enigmatic tumours demonstrating diverse clinical and biological features.[14]

The treatment depends on the stage as determined by the International NBL Risk Group Staging System (INRGSS).[2] This current system is based on radiological features at diagnosis.[2] The old International NBL Staging System was based on the anatomical features of the tumour.

Three main risk groups are defined on the basis of the degree of resectability of the tumour as determined by its radiological appearance on Magnetic resonance imaging (preferably) or CT.[14] The three groups, the low risk, intermediate risk and high-risk groups are associated with 95–100%, 85–95% and 30–40% for 5 year survival.[14]

Patients with localised disease or Stage MS disease without life- or organ-threatening symptoms or adverse genetic features (MYCN amplification or segmental chromosomal abnormalities) carry low risk, most would spontaneously regress; hence, they do not usually require treatment.[1,2] Seventy percent of neonatal NBLs fall into the low-risk group.[5] In cases where treatment is indicated, they are associated with good clinical outcomes.[2-4]

The INRGSS recommends surgery alone for low-risk accessible tumours, biopsy with adjuvant chemotherapy, and surgery for intermediate risk disease and intensive adjuvant chemotherapy, and surgery for high-risk disease.[2] Unfavourable N-myc status irrespective of stage is treated as a high-risk disease.[2] Around 20% of neonatal NBLs become complicated by spinal cord compression which is an emergency requiring treatment with steroids and chemotherapy.[14]

Stage MS (4s) patients with massive liver enlargement and resultant respiratory and cardiovascular symptoms may require intervention, and low-dose chemotherapy or radiation therapy is the first line of management.[2]

The most important prognostic indicators in NBL are the age and the degree of tumour spread[2] with aggressive disease being associated with an older age at diagnosis and with widespread disease.[2,4]

The degree of amplification of N-myc, diploidy and deletion of 11p23 has been shown to be independently predictive of poorer outcomes in large retrospective and prospective studies.[2]

Grossly, NBLs are lobulated masses with delicate, membranous capsules covering soft, fleshy, greyish-white, often partially haemorrhagic tumours.[14] Microscopically, neuroblastic tumours include NBL, ganglioneuroblastoma and ganglioneuroma.[14] Ganglioneuroblastomas and ganglioneuromas are more mature than NBL and are rare in the 1st year of life.[14] Neuroblastic tumours comprise two main cell populations: neuroblasts and Schwannian cells.[14] The neuroblasts are the tumour cells, whereas the Schwannian cells are reactive stromal cells.[14] The International NBL Pathology Classification (INPC) is widely used to classify neuroblastic tumours into four groups which include NBL, ganglioneuroblastoma, intermixed type; ganglioneuroblastoma, nodular type and ganglioneuromas.[14] A neuroblastic tumour can be categorised as INPC unfavourable histology or INPC favourable histology using this classification, along with the age of the patient, and the mitosis-karyorrhexis index.[14] Germline mutations in Anaplastic lymphoma kinase and PHOX2B account for most cases of hereditary NBL in the neonatal period.[14]

Urinary catecholamine metabolites, namely VMA and HVA are raised in the majority of patients with NBL in the 1st month of life.[14] The values of these metabolites, along with findings on bone marrow aspirate may be enough to arrive at a diagnosis where tissue biopsy is not advisable.[14]

CONCLUSION

The finding of an abdominal mass in this 23-day-old neonate raises the possibility of disease beginning in utero, and of this disease having been missed during antenatal US.[14] The finding of foetal NBL presents

the opportunity to offer treatment while the foetus is in utero, and the observance of necessary precautions during delivery. We hope this article would increase the awareness of neonatologists and obstetricians about neuroblastoma in general, and of sonographers about space-occupying lesions in the foetus.

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Conflicts of interest

There are no conflicts of interest.

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