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CASE REPORT

Perinatal neuroblastoma: a case report of Pepper syndrome

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Abstract

Introduction: Perinatal neuroblastoma is the most common malignant tumor in the neonatal period. Stage MS occurs in children under the age of 12 months and is a subgroup of localized primary tumors, with metastases limited to the liver, skin or bone marrow. It is also characterized by a high incidence of spontaneous regression and an excellent survival rate. Pepper syndrome is extremely rare in the neonatal period and results from massive hepatic infiltration by neuroblastoma in advanced stages (M and MS), conditioning respiratory compromise, liver failure and coagulopathy. **Case report:** This case presents this rare form of neonatal neuroblastoma, with rapid metastatic growth and a guarded prognosis due to mechanical complications characteristic of Pepper syndrome. **Discussion:** Despite the adoption of chemotherapy and intensive support therapy, rapid metastatic growth resulted in progressive worsening with liver failure, peri-ventricular hemorrhage and death.

Keywords: Newborn. Neuroblastoma. Pepper syndrome. Case report.

Neuroblastoma perinatal: um relato de caso da síndrome de Pepper

Resumo

Introdução: O neuroblastoma perinatal é o tumor maligno mais frequente no período neonatal. O estádio MS ocorre em crianças com menos de 12 meses e é um subgrupo de tumores primários localizados, com metástases limitadas ao fígado, pele ou medula óssea. Também se caracteriza por uma elevada incidência de regressão espontânea e uma excelente taxa de sobrevivência. A síndroma de Pepper é extremamente rara no período neonatal e resulta da infiltração maciça do fígado pelo neuroblastoma em estádios avançados (M e MS), condicionando comprometimento respiratório, insuficiência hepática e coagulopatia. **Relato de caso:** Este caso representa esta rara apresentação de neuroblastoma neonatal, com crescimento metastático rápido e prognóstico reservado devido a complicações mecânicas, características da síndroma de Pepper. **Discussão:** Apesar da instituição de quimioterapia e terapia de suporte intensiva, o crescimento metastático rápido resultou em agravamento progressivo com insuficiência hepática, hemorragia periventricular e morte.

Palavras-chave: Recém-nascido. Neuroblastoma. Síndroma de pepper. Caso clínico.

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Keypoints

What is known
- Perinatal neuroblastoma is the most common malignant tumor in the neonatal period.
- Pepper syndrome, resulting from massive hepatic infiltration by neuroblastoma in advanced stages (M/MS) is extremely rare in the neonatal period.
- Clinical presentation of Pepper syndrome includes progressive abdominal distension and respiratory compromise.

What is added
- The progressive clinical deterioration described serves as a reminder of a possible atypical evolution of neonatal neuroblastoma.
- This case emphasizes the guarded prognosis associated with Pepper syndrome and the need for the consideration of palliative care when appropriate.

Introduction

Neonatal tumors represent 2% of pediatric malignant tumors. The most common is neonatal neuroblastoma, with an incidence of 0.6/100,000 live births[1-7]. It is the most undifferentiated form of neuroblastic tumors. Perinatal neuroblastoma typically develops between the prenatal period and the first three months of life and is usually diagnosed during the third trimester of pregnancy[1-6].

The incidence is higher in Caucasian males and family cases are extremely rare[8-11]. An association between certain variables and subsequent neuroblastoma development has been identified, including neonatal hemolytic disease, a low Apgar score at the first minute and neonatal respiratory distress[8,9]. Maternal characteristics include young age, anemia, exposure to nitrosatable compounds and wood dust and the consumption of toxins during pregnancy[8-15].

The site is variable, but in about 90% of cases it has an adrenal origin[1,7]. About half of patients present metastatic disease at the time of diagnosis[5]. The typical clinical presentation is the finding of a mass (cystic, solid or mixed) in a routine fetal ultrasound, usually on the right abdomen, which does not usually cause symptoms in the perinatal period[1,2,7]. However, large or widely-spread metastatic tumors may lead to fetal hydrops, polyhydramnios, maternal preeclampsia, placental insufficiency or progression dystocia with possible fetal or maternal injury[1,7]. The main differential diagnosis of a fetal adrenal mass is adrenal hemorrhage, since it is the most common etiology in this period. Other differential diagnoses should be considered, such as an adrenal cyst or abscess, a bronchogenic cyst or splenic cyst, a liver tumor, retroperitoneal teratoma, extra-lobar pulmonary sequestration and renal anomalies[1-3,7,16]. Fetal magnetic resonance imaging (MRI) is an important complement to prenatal ultrasound in the etiologic investigation[7,16].

A newborn's clinical presentation of neuroblastoma can be asymptomatic, but it can also lead to respiratory distress or complications of anemia or thrombocytopenia, secondary to bone marrow involvement[17]. The likelihood that a palpable abdominal mass in the early neonatal period corresponds to a neuroblastoma is greater than 80%[1]. Occasionally, massive abdominal distension may be present due to the existence of liver metastases (Pepper syndrome)[1,18]. Pepper syndrome is rare in the neonatal period[18] and results from massive hepatic infiltration by neuroblastoma, conditioning progressive abdominal growth and respiratory compromise in its advanced stages (M and MS). About 30% of newborns die with a severe presentation[18].

Urinary catecholamines are useful in diagnosing a neuroblastoma, but an elevation of these is absent in two thirds of patients diagnosed in the prenatal period[1,16]. Scintigraphy with 123I-methyliodobenzylguanidine (123I-MIBG), computed tomography (CT) and abdominal MRI enable an initial characterization of the tumor and an assessment of its response to treatment and evolution over time[1,17]. Bone marrow aspiration and biopsy is recommended to assess its metastatic involvement.

Age at diagnosis, disease stage and genomic amplification of the MYCN oncogene are the three main determinants of prognosis[19]. Combined with the degree of tumor differentiation, changes in the 11q chromosomal region, tumor DNA content and histological category enables risk stratification of the neuroblastoma[19-21]. The most common genetic anomaly, present in about 20% of cases, is MYCN amplification, associated with a more advanced stage and an unfavorable prognosis[9,19]. However, a high expression of TrkA, a neurotrophin receptor, is associated with favorable clinical and biological characteristics[22]. More recently, the CHD5 protein, expressed in low-risk neuroblastic tumors, has been identified as a marker of prognosis and a potential marker of treatment response[20].

The International Neuroblastoma Staging System (INSS) provided the initial neuroblastoma classification system, with most patients with perinatal neuroblastoma

being in stages 1 or 2[1,2]. Recently, the International Neuroblastoma Risk Group Staging System (INRGSS) incorporated pre-surgical risk factors, determined prior to any treatment, which allowed more consistent staging worldwide[17,21]. Disease extension is inversely correlated with prognosis[9], with the exception of the MS stage, which represents about 7-10% of all neuroblastomas and occurs in children under 12 months of age[4,5]. Stage MS neuroblastoma is a subgroup of localized primary tumors, histologically undifferentiated, with metastases limited to the liver, skin and/or bone marrow, with no radiologically detected bone lesion and with no MYCN amplification[5,17]. It has a high incidence of spontaneous regression and an excellent survival rate[4,5,20]. The poor clinical outcome is related to the systemic effects of the disease, namely the respiratory compromise caused by massive abdominal distention[4], despite an aggressive multimodal therapeutic approach[17,18].

Consequently, the treatment of neuroblastoma generally encompasses a wide spectrum of options, from pregnancy with ultrasound monitoring or isolated surgical resection to, in the most advanced stages, a multimodal approach with chemotherapy, surgery, radiotherapy and stem cell transplantation in high-risk neuroblastoma. Advances in immunotherapy have been improving the prognosis in high-risk neuroblastomas[19,23,24]. Strategies designed to reach biologically relevant targets and pathways represent the future of treatment in neuroblastoma[17,25,26].

Case report

We present the case of a female neonate, born in a hospital in the metropolitan area of Lisbon, from a healthy 27-year-old mother, with adequate pregnancy surveillance.

The third-trimester routine ultrasound at 33 weeks of gestation identified a para-renal solid mass measuring 42 × 37 mm. At the 36th week, the mass showed an increase in size (53 × 41 × 40 mm) and was localized near the upper edge of the right kidney, with a normal cleavage plane. The liver was enlarged, a varicosed umbilical vein was identified and the amniotic fluid index was reduced. Fetal magnetic resonance was not performed in time due to hospitalization because of decreased fetal movements and a biophysical profile score of 2/8 with fetal Doppler compromise. A cesarean delivery was performed at 37 weeks of gestation. The newborn, weighing 2720 g, with an Apgar score of 8/9, was admitted to the neonatal unit. Physical examination revealed abdominal distension (abdominal perimeter of 35 cm) with a visible venous plexus (Fig. 1), stable vital signs and no feeding intolerance or respiratory distress. Abdominal CT: solid heterogeneous adrenal mass measuring 50 × 40 mm and significant hepatomegaly reaching the pelvic cavity, multiple liver nodules of varying sizes and significant deformation of the inferior vena cava and normal configuration of the renal vessels (Fig. 2). Blood tests showed an elevation of

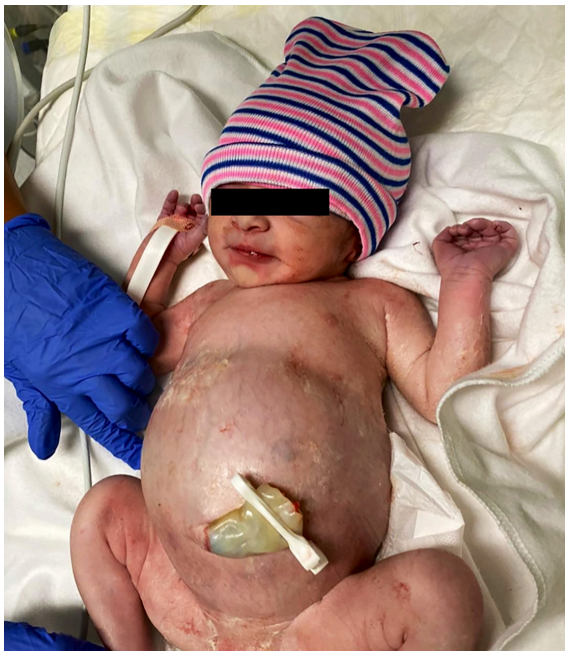

Figure 1. Picture taken immediately after birth, with abdominal distension and visible venous plexus.

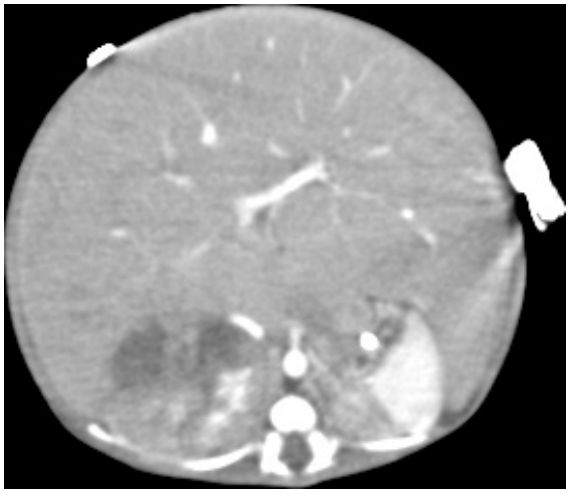

Figure 2. Abdominal CT with contrast performed on the fifth day of life, showing liver metastasis.

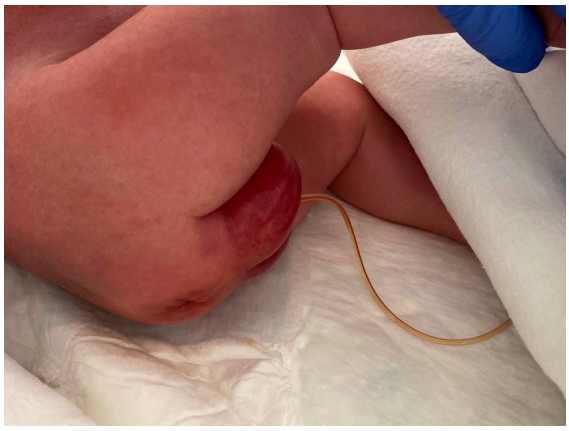

Figure 3. Rectal prolapse due to increased intra-abdominal pressure.

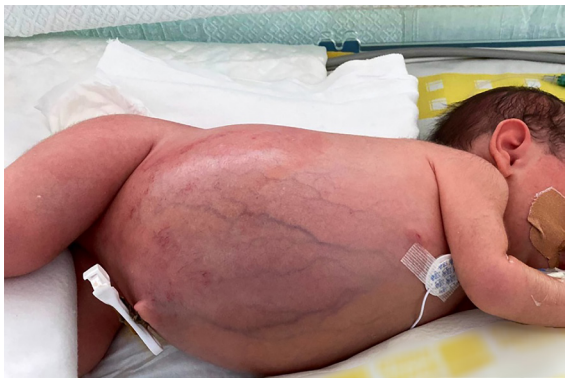

Figure 4. Clinical deterioration with enlargement of abdominal perimeter and anasarca.

vanillylmandelic acid and neuron-specific enolase. Those findings suggested the diagnosis of stage M/MS neuroblastoma (INRGSS), with massive hepatic metastasis – Pepper syndrome.

Progressive massive hepatomegaly and progression to compartment syndrome with respiratory and hepatic failure, progressive anemia, consumption coagulopathy, anuria, ileus and rectal prolapse (Fig. 3). Ascites requiring paracentesis on day seven and spontaneous drainage of ascitic fluid afterwards. A grade 3 periventricular hemorrhage since day three was diagnosed, complicated with periventricular infarction.

Chemotherapy with vincristine and cyclophosphamide was initiated with no response and physical deterioration with enlargement of the abdominal perimeter (Fig. 4) and anasarca was inevitable. Analgesia with opioids from day seven were needed due to significant pain and discomfort.

Despite intensive support therapy (invasive ventilation, furosemide, multiple transfusions of plasma, platelets and red blood cells, fibrinogen and vitamin K) there was progressive clinical deterioration.

In a multidisciplinary team evaluation, it was decided not to proceed with further investigation or more invasive treatments. After a family meeting, palliative care was decided on day 10. Death occurred on the fifteenth day of life.

Discussion

This case represents an extremely rare presentation of neonatal neuroblastoma, with diffuse hepatic metastasis and guarded prognosis due to mechanical complications characteristic of Pepper syndrome[18]. The large size of the tumor caused placental insufficiency, requiring delivery before fetal MRI could be performed as an additional measure to the prenatal ultrasound. In this case, surgical intervention was precluded due to abdominal compartment syndrome, progressive respiratory distress and coagulopathy. Despite the adoption of chemotherapy with vincristine and cyclophosphamide and intensive supportive therapy, rapid metastatic growth resulted in progressive worsening with liver failure, peri-ventricular hemorrhage and death.

This case report is relevant as it shows an atypical evolution of a neonatal neuroblastoma, with poor prognosis and culminating in the death of a newborn, and it opens the spectrum to the differential diagnosis of a neonatal abdominal mass.

Previous presentations

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Author contributions

B. Ribeiro Aguiar: Intellectual contribution to the conception of the article, bibliographical search, drafting of the manuscript, critical reviewing of the content of the article, approval of the final version. J. Ribeiro: Intellectual contribution to the conception of the article, drafting of the manuscript, critical reviewing of the content of the article, approval of the final version. D. Martins: Intellectual contribution to the conception of the article, drafting of the manuscript, critical reviewing of the content of the article, approval of the final version. S.N. Prado: Intellectual contribution to the conception of the article, drafting of the manuscript, critical reviewing of the content of the article, approval of the final version. H. Cavaco: Intellectual

contribution to the conception of the article, drafting of the manuscript, critical reviewing of the content of the article, approval of the final version.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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