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CASE REPORT

Neonatal neuroblastoma

Anna Bogaczyk [1A,D-E], *Kamil Gierek* [2,D], *Marta Kluz-Barłowska* [3,E], *Małgorzata Stefańska* [2,E], *Ewa Kaznowska* [3,E], *Tomasz Kluz* [1,4,A,F]

1 Department of Gynecology, Gynecology Oncology and Obstetrics, Fryderyk Chopin University Hospital, Rzeszow, Poland
2 Neonatal Clinic with Intensive Care, Fryderyk Chopin University Hospital, Rzeszow, Poland
3 Department of Pathology, Fryderyk Chopin University Hospital, Rzeszow, Poland
4 Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: Neuroblastoma is the most common malignant tumor occurring in early childhood. Most of them are located in the adrenal glands. Extra-adrenal localization is rare.
Case description: In this paper, we present a case of congenital neuroblastoma, which was identified in the neonatal period. The tumor was located in the posterior mediastinum in the paravertebral region.
Discussion and evaluation: It was not identified in the prenatal period and did not cause displacement of the thoracic organs. In this article, we provide obstetric, neonatal and pathomorphological descriptions from the autopsy.
Conclusions: We emphasize the need for screening ultrasound examinations in newborns.
Keywords: NB, congenital neuroblastoma, neonatal neuroblastoma, extra-adrenal neuroblastoma

Introduction

In this article we present a congenital neuroblastoma in an unusual, extra-adrenal location. The tumour was detected by chance in the first week of life. The newborn suffered from respiratory failure. The condition of the newborn prevented early diagnosis and treatment of the tumour. We describe atypical symptoms that are not commonly seen in neuroblastoma (e.g., atypical changes in vital signs, atypical test results) and which occurred in the patient.

✉ Anna Bogaczyk, email: annabogaczyk@interia.pl

Obstetric case description, interview

The patient was 26 years old, healthy, and had no systemic diseases. Pregnancy was confirmed in the seventh week of gestation. The course of pregnancy was uncomplicated. The patient underwent ultrasound diagnostics in the first trimester of pregnancy. The examination showed a low risk of genetic defects. 20-week ultrasound examination confirmed a healthy male foetus with normal growth. The patient made nine gynaecological visits during the entire pregnancy. At each of them, the patient's blood pressure was measured (without deviations from the norm), the body weight was measured (normal growth), the patient was examined transvaginally and an ultrasound was performed. A physiological increase in foetal weight was observed; the umbilical cord and middle cerebral artery flows were within the norm, no abnormal or suspicious changes were visualized, and the image of the abdominal and thoracic organs did not deviate from the norm, with no displacements. The laboratory tests were as follows. Virological tests: HbsAg negative; VDRL: negative; AntiHCV: negative; tests for toxoplasmosis and cytomegalovirus infection: negative, and the result of a TSH performed at the beginning of pregnancy was 1.875. Gestational diabetes was also excluded. The last visit to the gynaecologist's office took place in the 37th week of pregnancy. On the day of the visit the patient weighed 89 kg and her RR was 142/94 mmHg, in laboratory tests: Hb 12.3 g/dl, PLT 155 thousand/mm3. A microscopic examination of the urine revealed numerous bacteria and leukocytes: 10–20 in the FOV. A bacteriological culture of urine was ordered and the result was negative (no growth of bacteria). Foetal movements were strongly felt by the patient. The ultrasound examination revealed a single live male foetus in the cephalic position, the EFW was 3290 g, AFI 10 cm, the placenta was located on the posterior wall, and the umbilical artery flows were as follows: PI=0.79, RI=0.56, S/D=2.26. Four days later the patient was admitted to hospital due to decreased foetal movements. RR during admission to the hospital was 122/82 mmHg and her temperature 36.8 degrees C. The CTG performed revealed foetal tachycardia and the patient was qualified for a caesarean section. The male newborn weighed 3640 g and was 55 cm long.

Case description of a newborn

The newborn was male and born at 37 weeks of gestation by caesarean section due to impending asphyxia. He had foetal tachycardia and on the day of delivery he had weakly detectable foetal movements, assessed on the Apgar scale at 9, 10 and 10 points respectively at 1, 5 and 10 minutes, with a body weight of 3640 g (LGA 90–97 percentile). The mother had HBs(-);

GBS(-); HIV(-). After birth, the child was crying, with a normal heart rate and pale pink skin. The results of cord blood gasometry were pH: 7.31; pCO2: 47.3 mmHg; BE: -2.48 mmol/l; Lactate: 4.1 mmol/l. Prophylactic procedures were performed (Vit K was administered and Crede's procedure was performed). From the 12th minute of life, the heart rate increased to 190–210/min., the ECG showed sinus tachycardia and respiratory difficulties appeared – CPAP breathing support was used with FiO2 0.21. The results of the control gasometric test were pH: 6.96; pCO2: 53.9 mmHg; BE: -19.8 mmol/l; Lactate 12.7 mmol/l. The boy was transferred to the neonatal intensive care unit. Monitoring of brain activity using aEEG was initiated. Central catheters (UVC, UAC) were inserted under ultrasound control. Direct measurement of blood pressure was started (mean pressure oscillated at 50–55 mmHg). Additional tests showed signs of anemization and a four-fold increased level of ammonia. In the CNS ultrasound examination, a blurred image of brain tissue was accompanied by an abnormal aEEG recording (extended, without sleep/wake rhythm). Due to the suspicion of intrauterine hypoxia, therapeutic whole-body hypothermia was initiated. Red blood cell concentrate was urgently transfused, blood culture was secured, and empirical antibiotic therapy, morphine analgesia sedation and parenteral nutrition were initiated. Functional echocardiography revealed signs of increased pulmonary resistance, and lung ultrasound (assessed through anterior and lateral access to the chest) showed a dominance of A-line artifacts. The newborn was intubated – mechanical ventilation was initiated in SIMV mode with FiO2 0.21. Despite the initially small improvement (reduction of base deficit, increase in peripheral perfusion, normalization of ammonia level), organ function disorders were still observed and the newborn required multidirectional measures: the circulatory system was supported with an infusion of pressor amines, blood products were transfused (red blood cell concentrate five times, fresh frozen plasma four times and platelet concentrate twice), electrolyte levels were supplemented (ion disorders), and due to weakening diuresis and then anuria, diuretics were administered.

On the second day, due to increasing circulatory failure (increasing pulmonary resistance, renal failure and increasing edema), oscillatory ventilation mode was used and inhaled nitric oxide (iNO) therapy was started, hydrocortisone was introduced into the treatment and diuretic therapy was intensified. After obtaining information about the colonization of the mother's genital tract by *Klebsiella pneumoniae* bacteria, antibiotic therapy was modified; according to the antibiogram, Meropenem was added.

On the second day, a lung ultrasound performed revealed a solid structure measuring 2 × 2.4 × 3.9 cm on the left paravertebral side. The lesion

was richly vascularized on the periphery. Pleura sliding was observed over the tumour (Figure 1 A and B). This was likely a proliferative lesion, warranting further imaging diagnostics. An CNS ultrasound showed signs of reperfusion. Blood gasometry showed persistent and worsening metabolic acidosis despite therapy, as well as progressive multiorgan failure and severe oedema. Despite multidirectional actions, the patient's condition did not stabilize. Death occurred after less than 6 days of treatment.

The autopsy examination supplemented the diagnosis of the lesion visible in ultrasound at the base of the left lung with neuroblastoma.

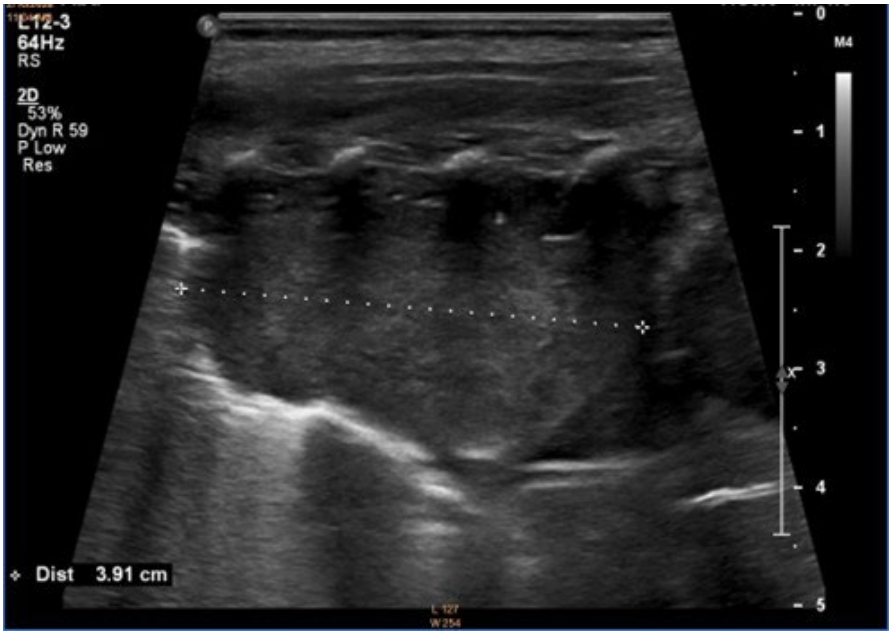

Figure 1A. The solid structure revealed in lung ultrasound

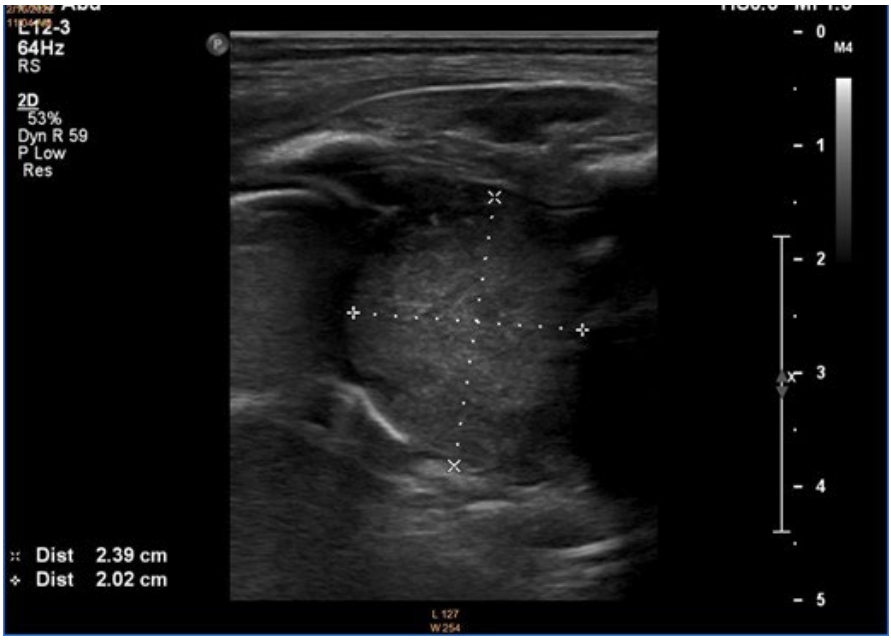

Figure 1B. The solid structure revealed in lung ultrasound

Pathomorphological case description

The autopsy was performed 68 hours after death. A tumour measuring 50 × 30 × 20 mm was found. It was located in the posterior mediastinum, in a paravertebral position. A histopathological examination confirmed neuroblastoma, a malignant small round cell tumour, of an undifferentiated type and encapsulated. In addition, the following were found: infant respiratory distress syndrome, massive pulmonary oedema and congestion, massive fibrin deposits in the lumen of the bronchioles closing their lumen, congestion of the myocardium and epicardium, congestion of the brain and cerebellum, congestion of the meninges, microthromboses in the cerebral vessels and in the vessels of the brain stem, a focus of foetal erythropoiesis in the liver, hepatic congestion, congestion of the thyroid gland, thymus, haemorrhagic necrosis of the renal medulla and ischemia of the renal cortex, congestion of the adrenal medulla with a focus of necrosis, a fibrinous thrombus in the umbilical arterial vessel closing the lumen, inflammatory infiltrates of lymphoblasts and neutrophils present in the lumen of the umbilical vessels, congestion of the wall of the small and large intestine, massive congestion and signs of incipient autolysis of the spleen, and congestion of the pancreas.

On the basis of clinical data in combination with autopsy data, supported by histopathological examination of the collected samples, the main cause of death of the newborn was determined to be the presence of a neuroblastoma tumour located in the posterior mediastinum. Tumours located in the chest in a paravertebral position may cause respiratory disorders or superior vena cava syndrome. These tumours are a source of catecholamines and may therefore cause tachycardia or hypertension and heart rate disorders, which could contribute to terminal respiratory and circulatory failure.

Discussion

Neuroblastoma (NB) is a childhood cancer. It is diagnosed in 10.5/1 million children per year [1]. It originates from neural crest cells (NCC), which are a transient population of multipotent cells. NCCs migrate from the neural plate border to target sites where they differentiate into different tissue types. Neuroblastoma occurs when NCC cells undergo defective differentiation due to, for example, genomic or epigenetic disorders. This mechanism explains why NB can arise in various locations, but the most common locations are the adrenal glands and paraspinal ganglia. NB is characterized by an early age of disease onset, a high rate of metastasis at diagnosis, and a tendency for spontaneous regression of tumours in infancy [2]. NB accounts for approximately 10% of all childhood cancers [3]. It is the most common malignant tumour in infants and most of them are small tumours located in the adrenal glands [4]. In the case of our patient, the tumour was located in the paraspinal region in the chest. This is an unusual location and is rarely seen. Giglioti et al. report that only 7.5% of neonatal NBs were located in the thoracic cavity [5]. Evans also describes two neonates with prevertebral NB. The neonates described died of respiratory failure [6]. The literature also describes cases of prevertebral NB in foetuses that died during pregnancy [7]. A similar localization is described by Moppett et al. in two patients out of all 33 cases of NB detected between 1986 and 1994. In these patients, the tumour was located, as in our patient, in a paravertebral position. In both patients, the tumours were detected in the neonatal period after the onset of respiratory failure symptoms. The patients were treated surgically. The patients also had comorbidities with complications such as abnormal sweating and flaccid paralysis of the lower limbs [8]. Our patient did not experience other accompanying symptoms that may occur in patients with neuroblastoma, such as excessive sweating and flaccid paralysis of the lower limbs. There was no pleural effusion [9]. Other visible symptoms accompanying NB may include a berry rash and subcutaneous skin nodules [10]. Our patient did not experience any of the above. Symptoms

of NB depend on the location of the primary tumour and the presence of paraneoplastic or metastatic syndromes. The most frequently described symptoms of NB in newborns and small children are lethargy, irritability, eating problems (lack of appetite), swallowing problems, vomiting, defaecation problems (constipation), abdominal enlargement, and abdominal pain. NB are often incidentally detected tumours. Our patient did not demonstrate any of these symptoms. The patient's main complaint was respiratory failure. Evans, in his description of five cases of posthumously diagnosed NB, writes about respiratory failure. He also describes the occurrence of anaemia in one of the children, similarly to our patient [6].

In the cases described, a case of acute shock in a newborn child was found, which occurred in the first hour of the child's life. In this case, shock was diagnosed and the child received treatment (chemotherapy) [11]. Neuroblastoma can also occur in utero. Harvey and Grey describe a paravertebral NB in a macerated foetus [12].

90% of NB tumours produce catecholamines and therefore the diagnosis is made on the basis of the results of biochemical tests (determination of catecholamines and their metabolites in a 24-hour urine collection or in a single test) in combination with imaging studies and histological analysis. The most commonly used tests are VMA (vanillylmandelic acid) and HVA (homovanillic acid), which have a sensitivity of 81.6% and 80.5%, respectively. Better results are obtained in the presence of metastatic disease (sensitivity 100%, specificity 99.7%). There is evidence that the combination of NMN (normatenephrine) with VMA or HVA improves diagnostic efficiency, while the inclusion of 3-methoxytyramine increases diagnostic sensitivity to 95%. In the case of our patient and his serious general condition, it was not possible to perform a quick diagnosis [13–15].

The definition of congenital NBL is neuroblastoma detected prenatally or within 28 days of birth. Since our patient's tumour was diagnosed in the first week of life, we can speak of congenital NB. Congenital tumours constitute 5% of all NB cases diagnosed annually and most cases are diagnosed in the first month after birth [14].

In the Italian registry, Gigliotti et al. report that only 20% of NB cases, regardless of location, were detected prenatally [5]. NB detected prenatally at 30 weeks of pregnancy is described by Park et al. The tumour was located on the right side of the chest and was accompanied by a pleural effusion in the right pleura, which made diagnostics easier [9].

The incidence is slightly increased in males (1.2:1) [16]. This was also the case with our patient.

A high rate of spontaneous regression has been observed in infants with NB. Investigators such as Holgersen et al., Acharya et al., Sauvat et al. and

Oue et al. have observed spontaneous regression of adrenal tumours that were diagnosed prenatally. There is also evidence of spontaneous regression of tumours detected in population-based NB screening programs [17–20]. In our patient, due to the rapidly progressing deterioration of his general condition, no tumour regression was observed; on the contrary, on the second day of life the dimensions of the tumour in the ultrasound examination were 2 × 2.4 × 3.9 cm, while in the autopsy examination they were already: 2 × 3 × 5 cm.

Kerbl et al. did not observe spontaneous tumour regression in his patients. He described cases of congenital NB in four patients; one patient's tumor was detected prenatally and the other three in the first weeks of life. In all four cases, the tumours were located in the adrenal glands. Kerbl reports that neither noninvasive nor invasive tests were able to predict tumour behaviour. Kerbl et al. conclude that a general "wait and see" strategy cannot be recommended for patients with early and incidentally detected NB [21].

In our patient, due to his poor general condition, the need to stabilize the vital parameters came to the fore. It was not possible to perform imaging tests such as computed tomography or magnetic resonance imaging. The only imaging diagnostics was ultrasonography and it was adjusted to the child's condition. The images presented in Figures 1 and 2 were taken in the sagittal and transverse planes, showing the paravertebral region on the left side in the thoracic section. Histopathological diagnosis was not possible during his lifetime, thus implementation of a treatment plan was also unlikely. Due to the patient's death on the 6th day of life, diagnosis was provided posthumously.

In children with good performance status, Maris et al. report that approximately half of all cases are now classified as high-risk tumours, and overall survival rates are less than 40%, despite intensive multimodal therapy [3].

In the International Neuroblastoma Risk Group (INRG), an analytical cohort of 8800 patients, the proportion was fairly evenly distributed between North America (48%) and Europe (47%), as well as patients from Japan (5%). According to INRG, the overall 5-year EFS (event-free survival) and OS (overall survival) rates were 63% ± 1% and 70% ± 1%, respectively, with a median follow-up of 5.2 years in 5819 patients alive without disease relapse [22].

The standard treatment is surgical resection, which gives excellent overall results, or chemotherapy [11,23].

Conclusions

The increasing quality of ultrasound diagnostics during prenatal examinations does not reduce the need for postnatal ultrasound diagnostics.

It is important to remember that NB may be extra-adrenal.

Analysis of catecholamine metabolites in 24-hour urine samples is helpful in making a diagnosis in paediatric patients. In such young patients as ours with multi-organ failure, it is difficult to obtain a sufficient amount of urine. However, using an indicator calculated on the basis of creatinine clearance, for which we can use a single urine collection, is associated with a measurement error dependent on muscle mass.

We cannot conclude that NB was the cause of the poor condition of the newborn, because due to his rapidly deteriorating condition and unstable situation, it was not possible to undertake diagnostic and therapeutic procedures for the mediastinal tumour. It is also possible that the tumour contributed to the general condition and eventual death of the newborn.

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