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Case Report

Congenital Neuroblastoma with a Progressive Course in a Neonate

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Abstract

Background: Neuroblastoma can arise throughout the sympathoadrenal axis. It is one of the most common extracranial solid tumors in children, which accounts for about 6-10 % of all childhood cancers. Congenital neuroblastoma accounts for 5% of total neuroblastoma cases and is mostly diagnosed in the neonatal period. Treatment is individualized, and prognosis depends on many factors, including the grade of tumor. In the neonatal period, most cases of this condition regress spontaneously, with a good prognosis.

Case Presentation: A male infant born at 37 weeks of gestation with a birth weight of 3580 grams was admitted to our emergency service on the 19th day of his life. He had abdominal distention that started when the baby was 11 days old, which increased for the next five days. The case was considered to have infantile colic in another clinic and was followed until he was admitted to our hospital. Then, imaging techniques were used, and he was diagnosed with congenital neuroblastoma with massive hepatic involvement. The diagnosis was confirmed by pathologic evaluation in our Neonatal Intensive Care Unit (NICU). He was intubated until he died on the 38th day of his life due to disseminated intravascular coagulation and shock without responding to chemotherapy.

Conclusion: We want to emphasize that abdominal distention in the neonatal period should be evaluated carefully to diagnose and treat such life-threatening diseases as neuroblastoma.

Keywords: Abdomen, Anaplastic Lymphoma Kinase, MYCN Proto-Oncogene Protein, Neuroblastoma

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Introduction

Neuroblastoma arising from sympathetic nervous system, is an embryonal childhood malignancy with an incidence of 6 to 10 percent of childhood cancers (1).

Initial imaging tool is ultrasonography. Computed tomography can show calcification in 50% of tumors. Magnetic resonance imaging (MRI) without radiation exposure is the preferred tool for diagnosis and follow-up (2).

Urinary catecholamines are increased but may be negative in two-thirds of cases.

According to our country's national cancer registry data, 15.713 cases were recorded between 2009 and 2018. The median age of onset is 19 months and 90% of patients are diagnosed within the first five years. Due to heterogeneous clinical conditions, treatment is selected according to risk group. In tumors with a high rate of spontaneous regression, 'wait and see' or only surgery is applied, in tumors where a high response to chemotherapy is expected, surgery and moderate dose chemotherapy are applied, and in tumors resistant to chemotherapy, aggressive multimodal treatment is applied (3). According to the international neuroblastoma risk group staging system, in patients younger than 18 months (547 days) with disease limited to the skin, liver and/or bone marrow (<10%), it is considered stage MS. To be considered stage MS, bone/bone marrow MIBG must be negative and the primary tumor must be localized. In patients who are considered to have stage MS, if there is no MYCN amplification and 11q aberration in tumor samples, the patient is monitored in very low risk arm (4).

In neuroblastoma cases MYCN amplification, PHOX2B and ALK mutations should be analyzed for hereditary neuroblastoma. MYCN oncogene amplification at 2p24 seen in about 20% of all neuroblastoma cases was first described by Schwab et al. (5) which usually shows advance stage of progressive tumor with poor prognosis.

In this paper, we report a patient diagnosed with neuroblastoma in the newborn period, did not have N-myc amplification or, 11q23 deletion, had a progressive course and died on the 38th day of life.

Case Presentation

Our patient was a male, the fourth-born child of a non-consanguineous Turkish couple, born at 37 weeks of gestation with a birth weight of 3580 grams via caesarean section. There was no resuscitation history, and he was not diagnosed with any disease antenatally. The 30-year-old mother, without any pregnancy problems, gave birth due to uterine contractions. The baby was hospitalized in another hospital for indirect hyperbilirubinemia on the fifth day of life for phototherapy, which lasted for 2 days. Until than till 11th day of life parents reported no problem.

He was admitted to our emergency service on the 19th day of life due to abdominal distention, which started on the 11th day of life and had been increased for the past five days. It had initially been evaluated as infantile colic in another hospital, but the distention worsened over the last two days. On the physical examination, his weight was 3590 gr (75th percentile), length was 52 cm (75-90th percentile), and head circumference was 36 cm (75-90th percentile). The heart rate was 154/min., respiratory rate was 62/min without fever. Abdomen was distended with mild respiratory distress, the liver was palpable 5 cm below the right costal margin (Figure 1). He had no dysmorphic features. Initial laboratory findings; liver and kidney function tests were normal with slight increase in AST:70 IU/l, Hemoglobin:9,7gr/dl, platelet:263.000/microliter, He was treated with oxygen on admission due to respiratory distress. On the second day of follow up his hemoglobin was 7.6 gr/dl due to hemorrhage from upper gastrointestinal tract that is due to compromise of liver function and required erythrocyte transfusion. Abdominal ultrasonography revealed massive hepatomegaly with diffuse parenchymal micro-cysts and a solid lesion with a heterogeneous appearance, hypoechoic and hyperechoic, measuring 50x47 mm, in the right adrenal gland area near the right kidney. Abdominal magnetic resonance imaging supporting neuroblastoma originating from right adrenal gland with a size of 43x53x56 cm complicated by hemorrhage and liver metastasis with diffuse involvement (Figure 2 a-f). Alfa-fetoprotein: 5316 ng/ml (N:0-100000),

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BetaHCG:0,35 IU/l (N:0-2). Serum neuron-specific enolase was 67.7ng/ml (N:<25) increased. AST level was increased to 595 IU/l on the follow. On the 28th day of life, he needed nasal positive pressure because of increased respiratory effort, and the next day his respiratory distress increased, requiring endotracheal intubation. In the same day, biopsy was taken from the mass. As a result of the biopsy, a diagnosis of poorly differentiated neuroblastoma was made. Diffuse sheets of neuroblasts and Homer-Wright rosettes were seen in Figure 3. Tumor cells were positive for Tyrosine Hydroxylase, Synaptophysin and Chromogranin staining (Figure 4,5,6). In the molecular examination performed on the tissue, both N-myc amplification and 11q23 deletion were negative; DNA was detected as near diploid.

A life-threatening event occurred in this patient, who could be closely monitored without treatment, the A7 (Vincristine, Carboplatin, Etoposide) course was given in accordance with the Turkish Pediatric Oncology Group Neuroblastoma-protocol (6). During chemotherapy, he required dialysis due to renal failure. He was followed intubated until he died due to disseminated intravascular coagulation and shock on the 38th day of life without any response to chemotherapy.

Table I shows hematologic and biochemical investigations.

Table I: Hematologic and Biochemical Investigations

Alfafetoprotein(serum) (ng/L)	5316 (N:0-100000)
BetaHCG (serum) (IU/l)	0.35 (N:0-2)
Serum neuron-specific enolase (ng/L)	67.7 (N:<25)
Homovanillic acid (urine) (mg/dl)	1170 (N:0-20.7)
Vanilmandelic acid (urine) (mg/dl)	718.36 (N:0-14)
Haptoglobin(g/L)	<0,1 (N:0.3-2)
Ceruloplasmin(g/L)	0.268 (N:0.2-0.6)
Ferritin (µg/L)	520 (N:30-400)
Hemoglobin (gr/dl)	9.7
Hemotocrit (%)	31
WBC (103u/L)	25.05
Platelet (103u/L)	263
BUN(mg/dl)	2 (N:6-20)
Creatinin(mg/dl)	0.3 (N:0.24-0.85)
Calcium(mg/dl)	12.4 (N:9-11)
Uric Acid(mg/dl)	3.2 (N:3.7-7)
Total protein(gr/dl)	3.6 (N:46-70)
Albumin(gr/dl)	2.9 (N:3.8-5.4)
AST (U/L)	70 (N:0-40)
ALT(U/L)	9 (N:0-41)
GGT(U/L)	416 (N:0-60)
LDH (U/L)	756 (N:135-225)
Total/Direct Bilirubin (mg/dl)	8.31 (N:0-1.2)/0.96 (N:0-0.3)
aPTTminute	26.9 (N:24.8-35)
PTminute	17.4 (N:10.5-16.2)
INR	1.37 (N:0.8-1.2)
N-myc amplification	Negative
11q23 deletion	Negative
Histological examination	Poorly differentiated neuroblastoma
Immunohistochemical staining	Positive expression of Chromogranin A, Synaptophysin, and Tyrosine Hydroxylase

Note: ALT: Alanine Aminotransferase, aPTT: Activated Partial Thromboplastin Time, AST: Aspartate Aminotransferase, BetaHCG: Beta-Human Chorionic Gonadotrophin. BUN: Blood Urea Nitrogen, GGT: Gamma-Glutamyl Transferase, INR:

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International Normalized Ratio, LDH: Lactate Dehydrogenase, N: Normal range, PT: Prothrombin Time, WBC: White Blood Cell Count.

Figure 1:

Figure 2:

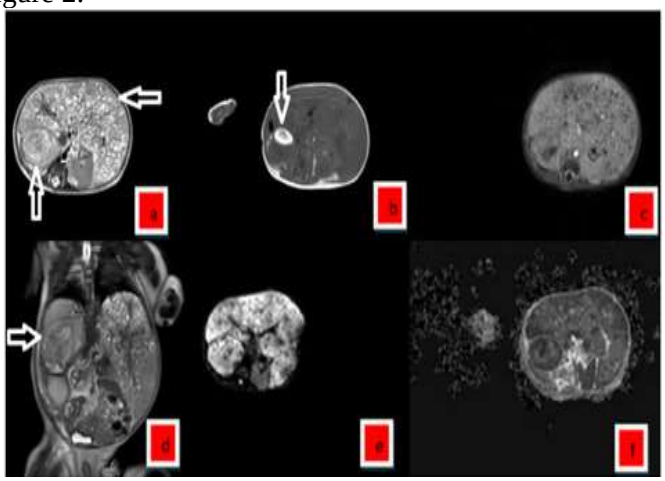


Figure 3:

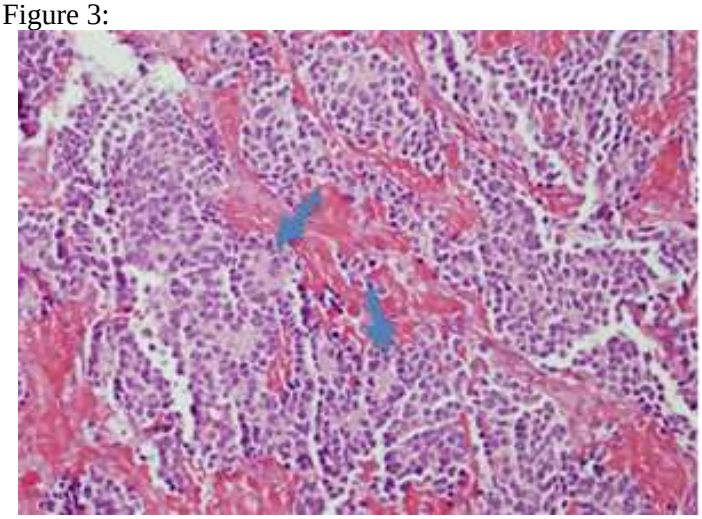
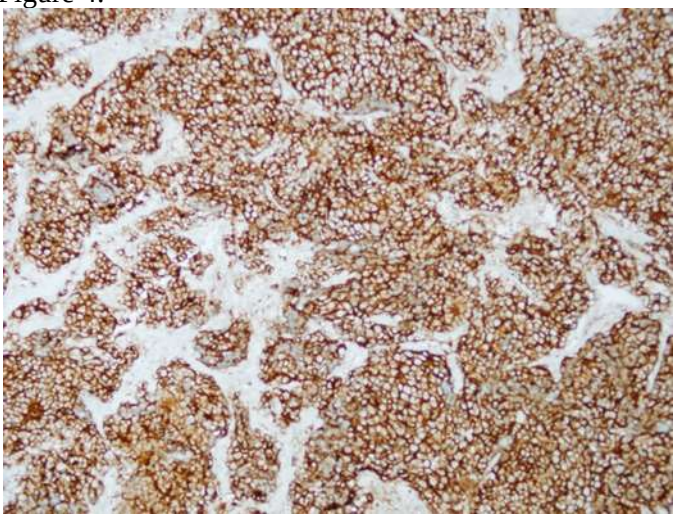


Figure 4:



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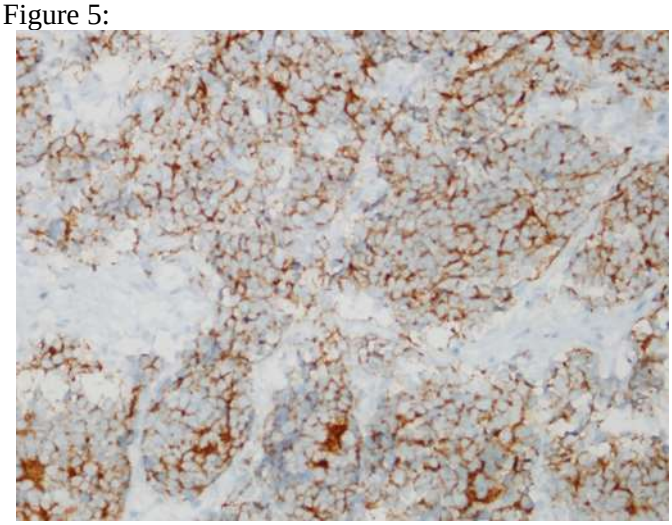

Figure 6:

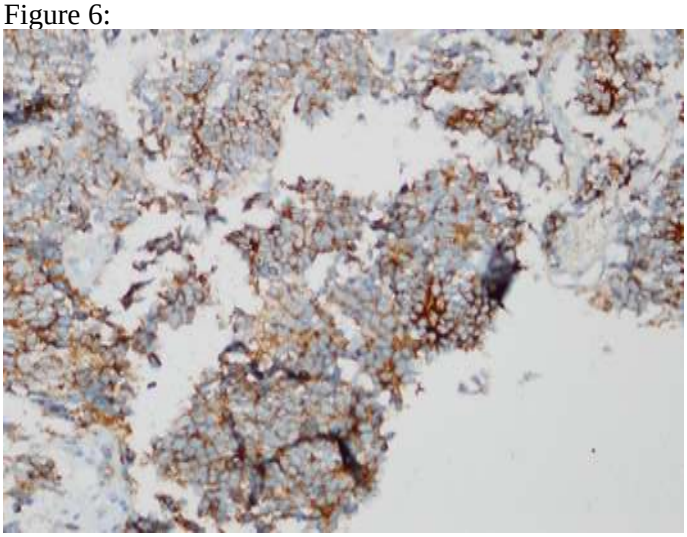

Figure legends

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Figure 1: Abdominal distention and mild respiratory distress were noted. The liver was palpated 5 cm below the right costal margin.
Figure 2. The left lobe of the liver extends to the left of the midline and inferiorly, and massive hepatomegaly is observed (horizontal arrow in Figure a). Millimetric cystic changes are observed in all segments of the parenchyma (horizontal arrow in Figure a). Heterogeneous hyperintense mass lesion is observed in the right adrenal gland area adjacent to the upper pole of the right kidney (vertical arrow in figure a and horizontal arrow in d). The lesion in the right adrenal gland shows T1 hyperintense hemorrhagic signal changes seen in Figure b (vertical arrow), heterogeneous contrast enhancement with cystic changes were seen in Figure c, diffusion restriction in the liver parenchyma is also clearly seen in Figure e and f.
Figure 3: Neuroblastoma, poorly differentiated subtype, diffuse sheets of neuroblasts and Homer-Wright rosettes. (blue arrows) (H&E , 400x)
Figure 4: (x200 IHC) Tumor cells positive for Tyrosine Hydroxylase staining.
Figure 5: (x400 IHC) Tumor cells positive for Synaptophysin staining.
Figure 6: (x400 IHC) Tumor cells positive for Chromogranin staining.

Disscussion

We report the case of a male neonate with neonatal neuroblastoma and massive hepatic involvement. The case presented with abdominal distention on the 19th day of his life and followed a rapidly fatal course. Congenital neuroblastoma with such extensive hepatic involvement is extremely rare. While abdominal distention, often due to factors such as large feedings, gas, or constipation, is a common finding in the neonatal period, it can also indicate more serious gastrointestinal issues, including intussusception, volvulus, malrotation, congenital megacolon, anal atresia, intestinal atresia, intestinal duplication cysts, posterior urethral valves, and sepsis (7). Intra-abdominal masses, such as Wilms tumor, hepatoblastoma, and neuroblastoma, can also be accompanied by abdominal distention. Abdominal X-ray and ultrasonography are valuable tools for differential diagnosis. Considering our patient, abdominal ultrasonography revealed massive hepatomegaly with diffuse parenchymal microcysts and a 50x47 mm heterogeneous solid lesion in the right adrenal gland region. Subsequent abdominal MRI showed a mass originating from the right adrenal gland, 43 x 53 x 56 mm, and complicated by hemorrhage and diffuse liver metastases.

Congenital neuroblastoma typically occurs within the first month of life, and prenatal diagnosis is possible (8, 9). When diagnosed antenatally, a Cesarean section may be considered to minimize the risk of hemorrhage into the tumor during delivery. In this particular case, the neuroblastoma was not diagnosed prenatally, although the infant was delivered via Cesarean section.

While most neonatal neuroblastomas have a favorable prognosis, our case followed a progressive and ultimately fatal course. Similar to our case, Omoseebi et al. (10) reported a 23-day-old female newborn presenting with abdominal distention, fever, and hepatomegaly. The case, with no prenatal diagnosis, was diagnosed with stage 4S neuroblastoma of the right adrenal gland, which was complicated by liver metastasis. The infant died due to shock before the administration of chemotherapy. Urinary VMA and HVA levels were not measured in that case. The researchers confirmed their diagnosis via autopsy, revealing sheets of small round blue cells with delicate fibrovascular stroma and rare Homer Wright rosettes in the right adrenal gland (10). In that case, however, analyses of N-myc amplification, diploidy, 11p23 deletion, and immunohistochemical staining were not performed, and the patient did not receive any chemotherapy (10).

Another reported case of neonatal neuroblastoma in Türkiye involved a newborn presenting with abdominal distention on the 6th day of his life, who was ultimately diagnosed with inferior vena cava (IVC) syndrome and massive hepatomegaly (11). Despite receiving modified VEC between days 20 and 23, the

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tumor failed to respond, and the infant died due to shock (11). Our patient, similarly presenting with a poor clinical condition, was treated with a modified VEC protocol for three courses. Notably, similar to our patient, this case also reported no MYC-N amplification (11).

Stage 4S (or MS) neuroblastoma, a unique category defined by metastatic disease in infants younger than 18 months, typically is presented with a localized primary adrenal tumor and metastases limited to the skin, liver, and/or bone marrow (12). This stage reflects the unique clinical behavior of neonatal neuroblastoma, notably its high rate of spontaneous regression. Despite being diagnosed with Stage MS, our patient had a poor prognosis.

Infants with Stage MS (4s) neuroblastoma presenting with massive liver enlargement and associated respiratory or cardiovascular symptoms may require intervention, which can typically be low-dose chemotherapy or radiation therapy (13).

Our patient, who was younger than 18 months and presented with liver involvement and a life-threatening event, received the A7 chemotherapy protocol. This patient, presenting with an intra-abdominal mass causing respiratory distress, required intubation and subsequently developed intratumoral bleeding. Disseminated intravascular coagulation was also diagnosed, and the patient eventually died due to multi-organ failure.

Neonatal patients with neuroblastoma who present with localized disease or Stage MS tumor, and show no life- or organ-threatening symptoms or adverse genetic features, such as MYCN amplification or segmental chromosomal abnormalities, are considered low-risk, and they often experience spontaneous regression; therefore, they typically require no treatment (14). For the minority requiring treatment, the prognosis is generally good (13). N-myc amplification, diploidy, and 11p23 deletion have been identified as independent predictors of poorer outcomes in numerous large retrospective and prospective studies (13). MYC-N amplification is a strong prognostic marker for neuroblastoma at all ages (15). Although our patient did not have MYC-N amplification, the outcome was still poor.

Nam et al. (15) studied 17 neonatal neuroblastoma patients and considered five of them as having Stage 4S neuroblastoma of the adrenal gland. All these patients presented with abdominal distension, three had only liver metastases, and two had both liver and bone marrow metastases. Considering our study, the infant had liver metastasis, but it was not possible to perform bone marrow biopsy. Two of the patients were N-myc positive and considered high risk, and three were evaluated as intermediate risk. The two high-risk patients had a V/H ratio >1 in the study by Nam et al. (15). Our patient had a V/H ratio <1 and was N-myc negative, and thus he was considered low risk. In the study by Nam et al. (15), all five patients with 4S were given chemotherapy; the two patients in the high-risk group died, and the other three patients recovered. Our patient, despite being in the low-risk group, died.

In general, neonatal cancers, making up only about 2% of childhood malignancies, are not common. This can mean that most neonatology units will likely see only one case of NBL every 1–2 years (13). Therefore, increasing awareness about NBL is essential (13).

We want to emphasize the importance of careful evaluation of abdominal distention in neonates to facilitate prompt diagnosis and treatment of such life-threatening conditions as neuroblastoma. Furthermore, thorough antenatal ultrasonography is crucial to avoid missing congenital tumors like neuroblastoma, as prenatal diagnosis allows for appropriate follow-up of congenital neuroblastoma cases.

Availability of Data

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that they have no competing financial or non-financial interests that are relevant to the content of this article.

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Ethical Considerations

Informed consent was obtained from the patients' parents.

Authors' Contributions

FCC: Designed, wrote and reviewed the initial manuscript draft.

FKN: Contributed to the conception

ATY: Drafted the oncologic section of the manuscript.

EC: Drafted the radiologic section of the manuscript.

YA and CCO:Critically reviewed the draft.

Artificial Intelligence Use Disclosure Statement

The authors declare that no artificial intelligence tools or technologies were used in the manuscript.

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