

## Metastatic congenital neuroblastoma associated with in situ neuroblastoma: case report and review of literature

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### ABSTRACT

Although neonatal tumors are rare, neuroblastoma is the most common neoplasia among them. These tumors, which usually involve children in early infancy, are derived from neural crest cells of adrenal gland medulla or sympathetic ganglia. Even though congenital metastatic neuroblastoma presents a favorable prognosis, it may lead to death if not recognized and treated early on. The authors report the case of a 2-month-old child who was born from in vitro fertilization, and whose diagnosis was made after birth. The form of presentation of this case as a metastatic disease concerning this age group is noteworthy.

### Keywords

Neuroblastoma; Infant; Neoplasm Metastasis; Autopsy.

### CASE REPORT

A 2-month-old female, Caucasian infant was born from in vitro fertilization with 36 weeks and 6 days of gestational age. This was the first pregnancy of her mother, who was 40 years old. The prenatal period and cesarean section were uneventful. After the birth, the mother noticed that the child presented an impairment of sensibility on the left lower limb, the imaging workup of which, by MRI, depicted a tumoral mass extending from T7 to L2 compressing the spinal cord. The child underwent decompression neurosurgery, and the pathological diagnosis resulted in neuroblastoma without specification. Initial imaging staging showed multiple small nodules scattered in the liver parenchyma. Chemotherapy was started with cyclophosphamide plus doxorubicin. In the meantime, the child was admitted to the emergency room with

a history of vomiting followed by acute respiratory failure. During the advanced cardiac and life support, a huge amount of milk was drained from the oral cavity and the child died soon after.

### AUTOPSY

The ectoscopic examination revealed a child weighing 4,175 g and measuring 50 cm; no signs of malformation was observed. The abdomen was distended. Abdominal findings were represented by the presence of a paravertebral pinky-colored mass with an irregular surface, measuring 7.0 × 6.0 × 5.0 cm extending from T5 to L2 levels (Figure 1).

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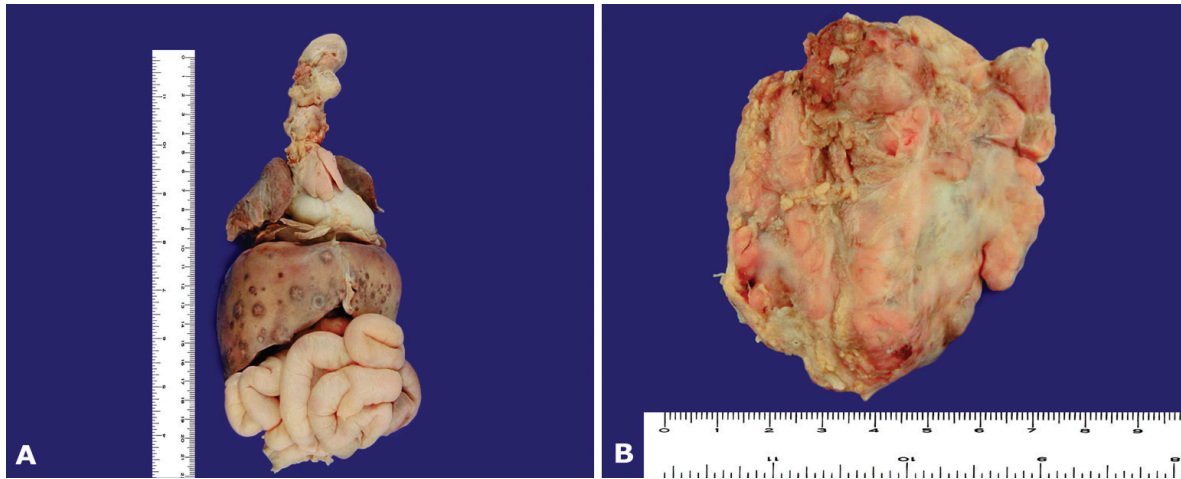
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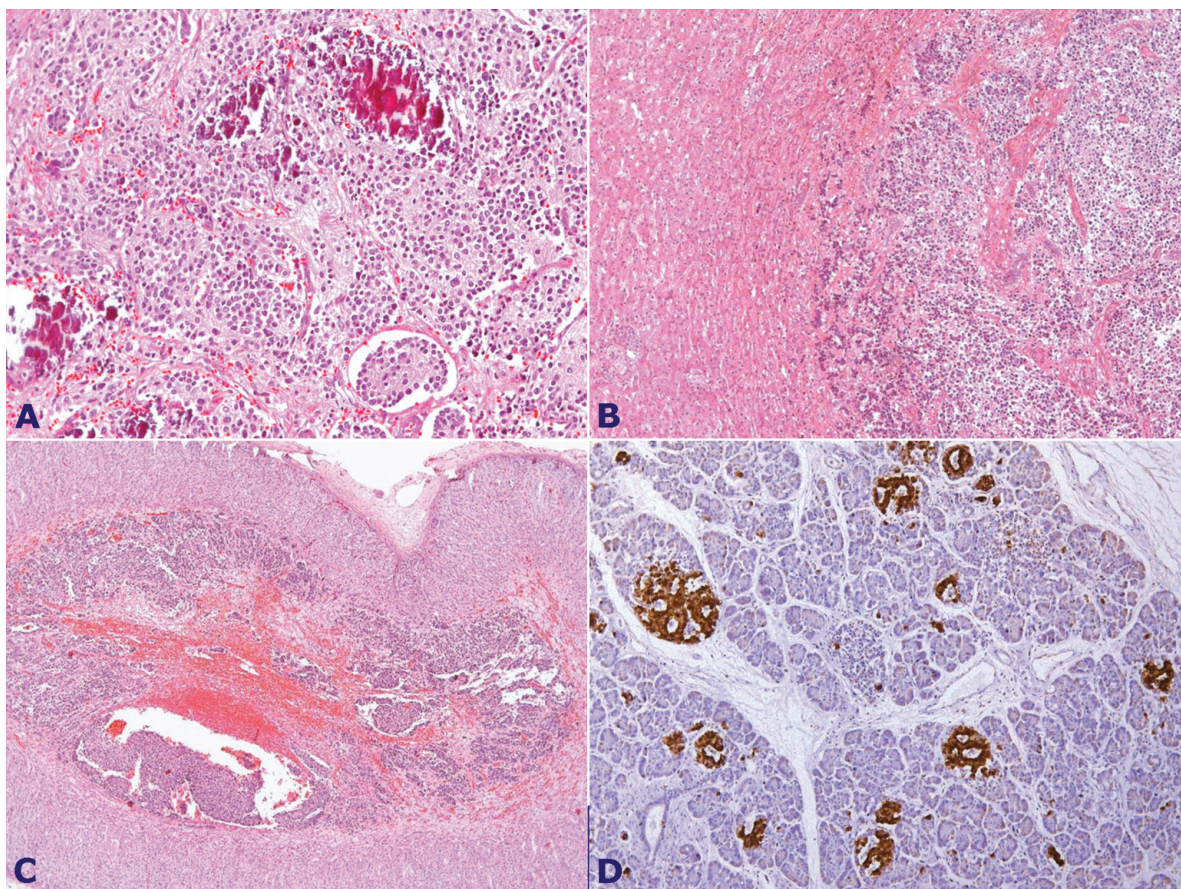


At the cut surface, the mass was pinky and exhibited some necrotic areas. The microscopic examination showed a small-blue-round-cell tumor, with multiple vascular tumoral emboli, perineural infiltration, and dystrophic calcifications consistent with the diagnosis of poorly differentiated neuroblastoma (Figure 2A). The

liver was enlarged and exhibited multiple superficial and parenchymatous well-circumscribed yellowish nodules measuring up to 1.0 cm. At microscopy these nodules represented metastatic neuroblastoma (Figure 2B). A thorough examination of the liver parenchyma also depicted sinusoidal dilation, ductular



**Figure 1.** **A** - Anterior vision of the visceral block showing multiple hepatic metastases; **B** - Gross features of the paravertebral tumoral mass.



**Figure 2.** Photomicrography of: **A** - Neuroblastoma with areas of calcification and lymphatic neoplastic embolization (HE, 200x); **B** - Hepatic infiltration by neuroblastoma (HE, 100x); **C** - In situ adrenal neuroblastoma (HE, 50x); **D** - Nesidioblastosis (immunohistochemistry for insulin, 400x).

reaction at the portal triad, besides tumoral emboli within portal branches. Metastases were also found in a peripancreatic lymph node and bone marrow. An in situ neuroblastoma was also found in the adrenal gland (Figure 2C). Nesidioblastosis was evidenced in the pancreas (Figure 2D).

Histological findings associated with the immunohistochemical profile (Synaptophysin/CD56/ NB84 positive) yielded the diagnosis of stage IV congenital neuroblastoma, undifferentiated (unfavorable histology; see Table 1). Respiratory insufficiency by bronchoaspiration was the immediate cause of death.

## DISCUSSION

In 1863, Virchow<sup>1</sup> first described neuroblastoma – a tumor derived from the neural crest – as representing the most common malignant neoplasm (30-50%) of the neonatal period.<sup>2,3</sup> Approximately 80% of the cases occur before the fourth year of life; the mean age at diagnosis is 21 months.<sup>4</sup> Neuroblastoma represents the most common extra-cranial solid tumor of infancy.<sup>5</sup>

This neoplasm may arise in any site of the sympathetic nervous system. The majority of the primary tumors occur in the abdominal cavity arising from the adrenal gland medulla in up to 50% of cases. Other common sites include the neck, thorax, and

pelvis.<sup>6</sup> Unusual primary sites have been described, and involve the thymus, lungs, kidney, mediastinum, stomach, and cauda equina.<sup>7</sup>

The diagnosis of neuroblastoma is established by tumoral mass biopsy, bone marrow biopsy, or smear with tumoral cells in the presence of enhanced urinary catecholamines levels. The typical histological features permit a precise diagnosis in the vast majority of cases. However, when the fibrillar neuronal stroma and the Homer Wright pseudorosettes are not evident, the immunohistochemical panel, including vimentin, synaptophysin, chromogranin, protein S100, CD56, NB84, CD99, desmin, myogenin, and hematopoietic markers, are helpful in defining the differential diagnosis with the other small-blue-round-cell tumors.

In 1984, Shimada et al.<sup>8</sup> proposed the most useful stratifying neuroblastic tumors histological system, correlating prognosis with histologic presentation. In 1999, this system was replaced by the “International Neuroblastic Pathology Classification” (INPC) that remain validated until recently.<sup>9-12</sup> This classification stratifies the patients in two groups: (1) favorable histology; and (2) unfavorable histology—taking into account the patient’s age, the presence of tumor cell nodules, nodules into the tumor mass, the differentiation grade of the tumoral cells, and the proportion of cells exhibiting mitosis and karyorrhexis (Table 1).

**Table 1.** Favorable vs. unfavorable histology in neuroblastic tumors

Tumor	Differentiation	MKI	Age (yrs)	Histologic classification
NB	Undifferentiated	Any	Any	Unfavorable
	Poorly differentiated	High	Any	Unfavorable
		Low or intermediate	> 1.5	Unfavorable
	Differentiating	High	Any	Unfavorable
		Intermediate	> 1.5	Unfavorable
			< 1.5	Favorable
Low		> 5	Unfavorable	
< 5	Favorable			
GNB	Nodular	*	*	Unfavorable or favorable*
	Intermixed	NA	Any	Favorable
GN	Mature or maturing	NA	Any	Favorable

\* = the determination of favorable or unfavorable histology in nodular GNB is based on the nodular NB component; GN = ganglioneuroma; GNB = ganglioneuroblastoma; MKI: mitosis/karyorrhexis index; NA = not applicable; NB = neuroblastoma.

The clinical presentation of neuroblastoma is widely variable and depends on the primary site as well as the presence of metastatic disease and paraneoplastic syndrome. Up to 40% of patients present a confined or localized disease, but the range of presentation is represented by incidental pre-natal ultrasonographic findings of an adrenal mass, locally invasive tumors, and huge masses along the sympathetic chain. Paraspinal tumors of the thoracic, abdominal, and pelvic regions are present in 5-15% of patients and may present symptoms related to nervous roots compression.

The International Neuroblastoma Staging System (INSS) universally accepted, is based on the clinical pattern of the tumoral dissemination evidenced by imaging studies (radiologic and scintigraphic), surgical resectability, and involvement of lymph nodes and bone marrow.<sup>7</sup> This staging score ranges from 1 to 4S and correlates with prognosis and treatment evaluation.<sup>13</sup>

Confined or localized tumors, considered a low-stage disease, are divided into stage 1 and stage 2 depending on the local lymph nodes involvement. In contrast to other neoplasia, microscopic residual disease does not interfere with the staging, although the information of surgical margins should be included in the anatomopathological report. Stage 3 tumors, considered high-stage disease, are unresectable and extend beyond the middle line. Stage 4 includes all patients over 12 months of age who present metastatic disease (lymph nodes, bone marrow, liver, and other sites). Neuroblastoma stage 4S represents the metastatic disease in infancy.<sup>14</sup> Originally described in 1971, stage 4S characterizes children under 12 months of age with metastases confined to the liver, skin, and bone marrow (with less than 10% of tumoral cells). Patients with the disease in the 4S stage (7-10% of cases)<sup>15</sup> usually present a favorable outcome compared

with other patients with metastatic neuroblastoma, showing spontaneous maturation and regression. More recently, the International Neuroblastoma risk Group (INRG) proposed a modified staging system (Table 2).<sup>16</sup>

Up to half of the patients present evidence of hematogenous metastasis at the time of diagnosis. In this setting, it is important to distinguish distant metastases from locoregional lymph nodes involvement close to the primary tumor site. The liver is the most common site for distant metastasis followed by the placenta, retroperitoneal lymph nodes, bone, skin, and umbilical cord. The lungs and the brain are rarely involved.<sup>14</sup>

The most common genetic aberration associated with the worst prognosis among neuroblastomas is represented by the genomic amplification of *MYCN* (more than 10 copies by Southern blot or FISH). The gene *MYCN* is located in the short arm of chromosome 2, and responds with excessive production of protein N-Myc when amplified. The protein complex Myc-Max within the tumoral cell nucleus inhibits the cellular differentiation, but promotes cellular proliferation and apoptosis. This amplification is observed in undifferentiated or poorly differentiated neuroblastomas. It occurs in up to 20% of the primary tumors and is strongly associated with advanced diseases and therapeutic failures.<sup>5</sup> Other molecular alterations, including loss of heterozygosity of 1p and 11q (both associated with poor prognosis) and increased expression of TrkA (high-affinity nerve growth factor receptor—associated with better prognosis), have been identified and their inclusion in the risk stratification system have been proposed.<sup>17</sup>

According to the above data (namely, patient age, histology [favorable or unfavorable], clinical stage, and amplification of *MYCN*), the patients are stratified in groups of risk: low, intermediate, and high. Solely for

**Table 2.** International Neuroblastoma Risk Group staging system<sup>16</sup>

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with the presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Note. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table

stage 4S patients, the stratification will benefit by the determination of the DNA ploidy (DNA index = 1 or DNA index > 1) defined throughout flow cytometry (Table 3).

In 1983, Fénart et al.<sup>18</sup> first described the pre-natal diagnosis of congenital neuroblastoma. Diagnosis may be feasible intra-uterus through fetal ultrasonography or antenatal magnetic resonance imaging (MRI), from 19 weeks of gestational age, but the mean age for better diagnosing ranges around 36 weeks. This tumor has its origin in the adrenal glands in 90% of cases, usually presenting in the stages 1, 2, or 4S. However, some findings may jeopardize the early diagnosis, as the normal development of the adrenal glands may be indistinguishable from an in situ neuroblastoma. The ultrasonographic features may be varied and the differential diagnosis includes mesoblastic nephroma,

extra lobar pulmonary sequestration, and adrenal hemorrhage.<sup>7</sup>

Due to the routine gestational ultrasonographic examination, there is an increasing number of diagnoses of congenital neuroblastoma. It is noteworthy to remember that congenital neuroblastomas exhibit a high index of spontaneous regression and good prognosis. Granata et al.<sup>19</sup> studied 17 cases of prenatally diagnosed neuroblastoma between 1993 and 1998 taken from the Italian Neuroblastoma Registry. They observed that all cases showed a favorable histology and a good prognosis during follow-up. Surgical treatment should be destined for those tumors with unfavorable biological behavior.

Our patient presented a huge paravertebral mass with neurologic symptoms compatible with spinal cord compression, metastases to the liver, bone marrow, and periaortic lymph node, which is an example of

**Table 3.** International Neuroblastoma Risk Group (INRG) consensus pretreatment classification schema<sup>17</sup>

INRG stage	Age (months)	Histologic category	Grade of tumor differentiation	MYCN	11q aberration	Ploidy	Pretreatment risk group
L1/L2		GN maturing GNB intermixed					A: very low
L1		Any except GN maturing or GNB intermixed		NA			B: very Low
L2	< 18	Any except GN maturing or GNB intermixed		NA	No		D: low
					Yes		G: intermediate
	≥ 18	GNB nodular; Neuroblastoma	Differentiating	NA	No		E: low
			Poorly differentiating or undifferentiating	NA	Yes		H: intermediate
				Amp			N: high
M	< 18			NA		Hyperdiploid	F: low
	< 12			NA		Diploid	I: intermediate
	12-18			NA		Diploid	J: intermediate
	< 18			Amp			O: high
	≥ 18						P: high
MS	< 18			NA	No		C: very low
					Yes		Q: high
					Amp		

Amp = amplified; GN = ganglioneuroma; GNB = ganglioneuroblastoma; L1 = localized, L2 = locoregional tumor; M = distant metastatic disease (except MS); MS = metastatic disease confined to skin; ; MKI: mitosis/karyorrhexis index; NA = non amplified; NB = neuroblastoma.

stage 4 congenital neuroblastoma. The presence of a concomitant adrenal in situ neuroblastoma was an interesting finding. In 1963, Beckwith and Perrin<sup>20</sup> proposed the concept of in situ neuroblastoma for foci confined to the newborn adrenals. The incidence varies between 0.4% and 2.5% in different series of autopsies. This rate, compared with the rarity of clinically evident neuroblastomas, suggests that a substantial number of these lesions may present spontaneous regression, degeneration, or maturation.<sup>20,21</sup>

In this case, we also observed the presence of nesidioblastosis, which could be interpreted as a mere coincidence, but we dare to remind readers that this coexistence may be related to the same histogenesis of both cells. Some cells derived from the neural crest may differentiate in peculiar neuroendocrine structures, which are generally named as chromaffin bodies. Nesidioblastosis develops from these cells, which will give origin to Langerhans islets.<sup>22</sup> The association of congenital neuroblastoma and nesidioblastosis has been recently described as a new complex neurocristopathy, with very few case reports.<sup>22,23</sup>

The current oncologic therapeutic strategies are based on the predicted biologic behavior of the neoplasia. This concept is highly valuable for patients with neuroblastoma, since some of these tumors may present spontaneous regression, while others will present maturation, and a further group will rapidly progress in spite of the therapeutic regimen. Thus the therapeutic protocols are designed according to the patient's stratification risk, as described above.<sup>17</sup>

During the last two decades, the tumoral histology, *MYNC* oncogene status, and the ploidy of the tumoral cells were considered as independent predictive prognostic factors. Recently, the aberration of 11q (allelic status of 11q23) was included in the pre-treatment risk classification.<sup>9,17</sup>

Specifically concerning congenital neuroblastomas, the first therapeutic approach is still debatable. Controversies do exist if patients deserve being treated with aggressive therapeutic strategies soon after birth, or if, due to the potential good prognosis of these tumors, patients should be kept under surveillance in an attempt to give time to spontaneous regression. It is worth remembering that, as with all the oncologic therapeutic proposals, side effects may be more harmful than the tumor. The compressive spinal cord

symptoms presented by this child contributed to the decision of chemotherapy treatment.

It is true that much has been achieved in the treatment of this neoplasia. However, despite recent discoveries on the molecular biology field and its use to guide new therapeutic regimens, many studies are still needed in an attempt to uncover and treat this disease more effectively.

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