Intermixed Ganglioneuroblastoma in Children: A Case Report and Review of the Literature

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Abstract
Neuroblastomas are common tumors in children. However, in the same tumor spectrum, intermixed ganglioneuroblastomas are much rarer. In our case report, we present a 10-year-old boy with an asymptomatic adrenal intermixed ganglioneuroblastoma discovered incidentally. He was treated with total adrenalectomy and had no recurrence of the disease.

Introduction
Neuroblastics tumors are the third most common cause of cancer in children [1]. It is the most commonly diagnosed cancer in the first year of life, with a median age of 22 months at diagnosis [1-3]. Ninety percent of cancers are diagnosed before the age of 10 [3]. These tumors result from neural crest cell damage during embryogenesis [2]. They constitute a tumor spectrum that includes neuroblastoma, ganglioneuroma, intermixed ganglioneuroblastoma and nodular ganglioneuroblastoma.

Case Presentation
The patient is a 10-year-old male known for proteinuria and non-nephrotic albuminuria. In 2016, an ultrasound of the abdomen performed in another context discovers a right adrenal incidentaloma for which the patient is asymptomatic. Magnetic resonance imaging confirms the presence of a mass of 5 cm × 4 cm, independent of the kidney, slightly polylobulated with well-defined edges and not infiltrating the neighborhood structures. The lesion has no fat or cystic component but appears to be hypervascularized. There is no locoregional lymphadenopathy (Figure 1, 2).

Blood tests are normal. The urine output shows an increased dopamine at 3'174 nmol/24 h (N: <2'600 nmol/24 h) and a dopamine/creatinine mole fraction at 547.2 10E-6 (N: <360.0 10E-6). The metanephrines and normetanephrines are in the normal range, namely 1026.0 nmol/24 h (N: <2100 nmol/24 h) and 260.0 (N: <1'300.0 nmol/24 h) respectively. Scintigraphy and PET-MRI with Iodine-123 MIBG demonstrate hyperfixation of the right adrenal lesion. The scintigraphy shows no evidence of locoregional or distant lesions (Figure 3 and 4).

A multidisciplinary consultation meeting concludes with a probable localized neuroblastoma, even if a pheochromocytoma is not entirely excluded. Laparoscopic right adrenalectomy and locoregional lymph node dissection are performed, and puncture-biopsy of the marrow is done to complete the staging. Histopathological examination of the right adrenal tumor diagnoses an intermixed ganglioneuroblastoma, with a favorable histopronostic according to Shimada. The amplification of MYCN at the level of the tumor cells is absent. Immunohistochemical analysis of the hematopoietic marrow by the search for GD2 and HLA-I markers is negative. The
pathological analysis confirms the complete excision. Intermixed ganglioneuroblastoma is classified as stage 1 according to The International Neuroblastoma Staging System. The patient does not receive any other treatment. We realize a clinical follow-up at 1 month with abdominal ultrasonography, an Iodine-123 MIBG scintigraphy and a catecholamine dosage. Then, the patient is followed by clinical examination and abdominal ultrasound every 3 months during the first 18 months post-surgery, then every 6 months. Three year after the operation, there is no sign of recurrent disease (Figure 5).

**Discussion**

The spectrum of neuroblastic tumors is classified according to histological criteria defined by The International Neuroblastoma Pathology Classification (INPC). Tumor differentiation plays a prognostic role. Since ganglioneuroma and intermixed ganglioneuroblastomas are well differentiated, they belong to the favorable prognosis group [4]. Several studies have shown an increase in the median age at diagnosis for more differentiated neuroblastic tumors [5,6].

The clinical presentation of these tumors is very heterogeneous. Patients may be totally asymptomatic but may also have non-specific symptoms or related to possible metastases or paraneoplastic syndromes [2]. The extension assessment includes imaging examinations and laboratory tests. Ultrasound is not strictly part of the standard assessment, but this imaging technique is frequently used as first-line imaging modality for abdominal masses in children [7,8]. The evaluation of the primary tumor is done by CT and/or MRI. Iodine 123-MIBG scintigraphy establishes metastatic spread. It is an indispensable examination in the evaluation of neuroblastic tumors, because of its sensitivity of about 90% and its specificity is almost 100% [9]. Ten percent of neuroblastic tumors do not capture MIBG [10]. 18FDG-PET appears to be an additional consideration for patients with negative MIBG scintigraphy, but more evidence is needed [3,10,11]. Two bilateral biopsy-punctures at the posterior iliac crests associated with immunohistochimical analysis are part of the extension assessment and reveal bone marrow invasion [3]. Laboratory tests include a blood and urine measurement of catecholamines and their metabolites, since neuroblastomas are often responsible for an abnormality in the production, secretion or catabolism of catecholamines [3]. In urine, it is recommended to look for certain catecholaminergic metabolites, namely Vanillylmandelate (VMA) and Homovanilate (HVA). Dopamine can be assayed in the blood or in the urine and will help inform about the adrenergic nature of the tumor [12]. The diagnosis of neuroblastoma can be confirmed in two ways: either by histopathological analysis of the primary tumor, or by the presence of both tumor cells on the puncture-biopsy of the bone marrow and an increase in catecholamines or urinary catecholaminergic metabolites [12] (Table 1,2).

In order to evaluate the prognostic value of 13 factors, The INRG Task Force carried out a retrospective cohort study using 5-year Event-Free Survival (EFS) for comparison purposes [13]. The statistically significant prognostic factors found are the tumor stage, age, histological type, tumor differentiation grade, MYCN oncogene amplification status, 11q chromosomal status and ploidy of the tumor cells [13]. With the combination of all these prognostic factors, it is possible to associate each patient with one of the four pre-therapeutic risk groups, which predicts the EFS at 5 years [13]. Our patient is classified in the very low risk group and therefore has very favorable EFS, which is more than 85% (Table 3).

The histological category of the tumor is therefore a determining prognostic factor. Wen-Guang He et al. [5] compared the clinical and biological features between neuroblastomas and ganglioneuroblastomas in a retrospective study involving 279 patients [5]. This study demonstrates, like Decarolis B et al. [6], that intermixed ganglioneuroblastomas occur in older patients compared to neuroblastomas [6]. Normal serum level of ferritin, Lactate Dehydrogenase (LDH) and Neuron-Specific Enolase (NSE) are more commonly found in intermixed ganglioneuroblastomas than in neuroblastomas [5]. Intermixed ganglioneuroblastomas are associated with less metastatic disease and less amplification of the MYCN oncogene [5]. The overall survival of patients with ganglioneuroblastoma is greater (100%) than that of patients with neuroblastoma (50.8 ± 4.5%) or nodular ganglioneuroblastoma (74.5% ± 11.4%) [5,6].

Decarolis B et al. [6] performed a retrospective study of 808 patients with neuroblastic tumors, 7% of whom were intermixed ganglioneuroblastomes [6]. They found that intermixed
Table 1: INSS. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment [12].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision, with ipsilateral non adherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contra lateral lymph nodes must be negative microscopically.</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contra lateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for Stage 4S).</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A or 2B, with dissemination limited to skin, liver, and/or bone marrow &quot;limited to infants &lt;1 year of age).</td>
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NOTE: Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript letter M (e.g., 3M)

† The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

Table 2: Diagnosis of Neuroblastoma. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment [12].

**Definition**

Stage 1

1. Localized tumor with complete gross excision, with or without microscopic residual disease representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive) OR
2. Localized tumor with incomplete gross excision, with ipsilateral non adherent lymph nodes negative for tumor microscopically.

**Diagnosis of Neuroblastoma**

Established if:
1. Unequivocal pathologic diagnosis is made from tumor tissue by light microscopy (with or without immunohistology, electron microscopy, increased urine or serum catecholamines or metabolites †); OR
2. Bone marrow aspirate or trephine biopsy contains unequivocal tumor cells (e.g., syncytia or immunocytologically positive clumps of cells) and increased urine or serum catecholamines or metabolites.

Table 3: Pretreatment risk group. Modified by The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report [13].

<table>
<thead>
<tr>
<th>Pretreatment Risk Group</th>
<th>5-Year Event-Free Survival</th>
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<tr>
<td>Low</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;75% - ≤ 85%</td>
</tr>
<tr>
<td>High</td>
<td>≤50% ≤ 75%</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 50%</td>
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Table 3: Pretreatment risk group. Modified by The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report [13].

The therapeutic management of neuroblastic tumors is based on the division of patients into three groups according to the criteria established by The Children’s Oncology Group. Based on age at diagnosis (≤ 365 days), disease stage according to The International Staging System, MYCN oncogene amplification status, Shimada histological classification and tumor cell ploidy, patients are classified into low, intermediate or high-risk groups [14]. Following to this classification, the treatments can be adapted to each category and could be reduced for the first two groups, without modifying the outcome [15].

The low risk group is treated by surgery with tumor removal. Strother et al. [15] demonstrated that multi-agent chemotherapy in addition to surgery when managing patients with an INSS 2 stage did not change EFS and overall survival rates [15]. Several studies have also shown that surgery, even subtotal, allowed the healing of a majority of patients INSS stage 1 and INSS stage 2a/2b with favorable prognostic factors [15,16]. Decarolis B. et al. [6] found that EFS remains unchanged when surgical management of intermixed ganglioneuroblastomas and ganglioneuromas is incomplete, provided that tumor residues are less than 2 cm [6]. Chemotherapy has confirmed its effectiveness in case of progression or recurrence of the disease [16,17].

In conclusion, we followed the recommendations of the current literature. The extension assessment of the intermixed ganglioneuroblastoma included MRI, blood and urine tests, a scintigraphy and a PET-MRI with 1-123 MIBG fusion. Belonging to the low-risk group, our patient had a total excision of his adrenal tumor, without further treatment. After three years, the patient is free of disease. Histopathological examination confirmed the histological type and classified the tumor as stage 1 according to the INSS. This case report correlates with the scientific literature about this rare histological type of neuroblastic tumor, but with generally favorable prognosis. The case of our patient remains however relevant, given the late age at which intermixed ganglioneuroblastoma was discovered.

References


