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Case Report

Spontaneous regression of stage 4S bilateral neuroblastoma in an infant: a case report

Rani Ahmad

Radiology Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

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Abstract: Bilateral neuroblastoma requires treatment according to the development of lesion. Objective: A two-month-old female infant presented with bilateral adrenal masses and marked hepatomegaly owing to diffuse hepatic metastatic lesions. A provisional diagnosis of bilateral adrenal neuroblastoma was made with computed tomography (CT), followed by metaiodobenzylguanidine scintigraphy, and thereafter was confirmed histopathologically. A follow-up ultrasound examination performed 1.5 years after diagnosis showed stage 4S behavior of the disease, which involved spontaneous resolution of the adrenal masses. Conclusion: This finding supports the idea that bilateral disease must be staged separately in order to select the best treatment plan and to explore any possible associated prognostic factors.

Keywords: Bilateral adrenal neuroblastoma, neuroblastoma in infants, stage 4S neuroblast

Introduction

Neuroblastoma is a rare kind of cancer that commonly develops in the adrenal glands and is typically diagnosed as a tumor in children and newborns. It accounts for around 7.8% of paediatric malignancies. Neuroblastoma is one of the most often diagnosed tumors in babies, with 40% of patients diagnosed during the first three months of life [1]. When neuroblastoma is detected in children less than one year, the 5-year survival rate is much greater than when it is diagnosed in individuals older than one year [2].

Neuroblastic tumors are suspected based on specific imaging patterns and patient age. Imaging of neuroblastoma commonly reveals lesions with cystic components and enhancement on post-contrast magnetic resonance imaging (MRI) [3-5]. Tumors can arise in the neck, posterior mediastinum, para-spinal sympathetic chains, and Zuckerkandl organ. Mostly, these tumors are located in the unilateral adrenal medulla and emerge in the form of solid masses, some of which may present as hemorrhagic cysts [6]. The bilateral adrenal glands are rarely involved, but when they are the condition is often difficult to describe accurately, whether just contralateral metastasis or unilateral tumors that have another synchronous lesion [7, 8]. In such cases, the process of cancer staging can be confusing, and therapeutic interventions have to be independently integrated.

While pathological findings and tumor markers remain the mainstay of diagnosis for most cancers, the biggest challenge in diagnosing neuroblastoma is the differentiation between renal and extrarenal retroperitoneal tumors, since, for example, Wilms' tumor (nephroblastoma), a rare kidney cancer, and neuroblastoma often present in a similar age group [9]. Multiplanar imaging can be helpful in making the distinction in this situation. There are, however, cases where a neuroblastoma extends into the kidney, and so it can be incorrectly diagnosed as Wilms' tumor, or vice versa, a Wilms' tumor can occasionally be misdiagnosed as neuroblastoma [10, 11].

For staging purposes, Brodeur et al. [11] recommend the International Neuroblastoma Staging

System (INSS) to classify neuroblastoma, which is as follows:

Stage 1

● Cancer is localized with gross total excision (± microscopic residual disease).

● Microscopically negative findings in the ipsilateral lymph nodes for tumor.

Stage 2A

● Unilateral localized tumor comprising incomplete gross excision.

● Ipsilateral non-adherent lymph nodes and contralateral nodes showed negative tumor in microscopic findings.

Stage 2B

● Tumor has either complete or incomplete gross excision but is localized to one side.

● Positive results for tumor in non-adherent ipsilateral lymph nodes.

● Contralateral lymph nodes remain negative microscopically.

Stage 3

Tumor can present in any of these three variants:

● Unresectable unilateral tumor crossing midline (± integration of regional lymph node).

● Tumor confined to one side (+ integration of the regional lymph node involvement on the opposite side).

● Lymph nodes extension of tumor (on both sides).

Stage 4

● Any tumor with dissemination to another organ, including the liver, skin, bone marrow, distant lymph nodes, or any other organ. This stage excludes the criteria of the 4S stage.

Stage 4S (also called “special” neuroblastoma):

● Age < 1 year.

● Localized unilateral primary tumor.

● The disease is restricted to the liver, bone marrow (involvement of marrow less than 10 percent on biopsy and MIBG-negative marrow), and skin [12, 13].

Another important staging criterion is the International Neuroblastoma Risk Group Staging System (INRGSS), published in Monclair et al. [14]. It is designed for tumor staging before any treatment modality, including surgery. Image-defined risk factors (IDRFs) are surgical risk factors that are incorporated within the system that help in choosing the best treatment plan. At the time of diagnosis, IDRFs can be used to determine whether tumor excision is difficult or risky. **Table 1** provides a description of IDRFs according to anatomical region [15].

The INRGSS classify tumors into four categories [14]:

● L1: Tumor is isolated to one body compartment, and no vital structures are involved.

● L2: Tumor is restricted to one region, and there are one or more IDRFs.

● M: Spreading of tumor to distant sites (except when defined in stage MS).

● MS: Spreading of tumor to distant sites, but is restricted to liver, skin, and ± bone marrow among children aged less than 18 months.

When the above illustrated staging criteria is applied, a bilateral adrenal neuroblastoma can be considered with a poor prognostic factor. However, this presentation in infants is rare, and further research is required to enable accurate outcome estimation and better selection of treatment options.

Case examination

A two-month-old girl was brought to the emergency department with lethargy and massive abdominal distension. She appeared cachectic, although with stable vital signs. On examination, a large mass was found occupying the abdominal cavity. Screening ultrasound showed a severely enlarged liver with apparent adrenal masses on both sides.

Table 1. Description of IDRFS

Anatomical Region	Description
Tumor extension on same side in either of two body compartments	Chest and neck Chest and abdomen Pelvis and abdomen
Neck	Cancer near internal jugular vein and carotid or vertebral artery Tumor extension to the skull base Trachea compression by tumor
Junction of cervico-thoracic	Tumor surrounding brachial plexus roots Tumor close to subclavian vessels and vertebral or carotid artery Compression of trachea by tumor
Thorax	Tumor near aorta or its major branches Tumor led compression of principal bronchi or trachea Tumor with lower mediastinal following infiltration of costovertebral junction from T9 to T12
Junction of thoracoabdominal	Tumor surrounding vena cave or aorta
Pelvis and abdomen	Tumor infiltration to hepatoduodenal ligament or porta hepatis At mesenteric root, tumor surrounding superior mesenteric artery branches Tumor around coeliac axis origin or superior mesenteric artery origin Tumor invasion to renal pedicles, either one or both Tumor surrounding vena cava or aorta Tumor surrounding iliac vessels Pelvic cancer at the sciatic notch crossing
Extension of intraspinal tumor	Spinal canal involvement of > 1/3rd in axial plane or perimedullary leptomeningeal spaces nonvisibility and abnormal spinal signals
Infiltration of adjacent organs and structures	Any organ involvement, such as kidney, pericardium, duodenopancreatic block, diaphragm, or liver

Diagnosis, investigation, and treatment

A computed tomography (CT) scan of the abdomen and pelvis was carried out, with sagittal and coronal reformations. The imaging showed that both adrenal glands had two heterogeneously enhancing lesions and internal areas of hypodensities consistent with necrosis. The mass was present in the right adrenal gland measured 4 × 2 × 4 cms, while the left adrenal gland measured 4.5 × 4 × 6 cms. Both lesions were separable from the kidneys, pancreas, and vascular structures by a clear flat plane (**Figure 1**). There were no calcifications observed in the lesions or any crossing of the midline or para-spinal extension. The liver was enlarged, measuring approximately 14 cm in craniocaudal dimension, and was almost completely replaced with large solid hypervascular nodular metastatic lesions. Portal and hepatic veins were narrowed but remained patent. The inferior vena cava was compressed by the liver, which may have been the cause of the observed mild free fluid and subcutaneous edema (**Figure 2**).

Despite these findings, no enlargements were observed in the lymph nodes on imaging. The patient's spleen, pancreas, and bowel loops were unremarkable, and no aggressive lesions were noted in the osseous structures. Small bilateral pleural effusions in the lower thorax were found. A preliminary bilateral neuroblastoma diagnosis was made based on the CT findings.

A metaiodobenzylguanidine (MIBG) scintigraphy scan was performed at 24 and 48 hours after the intravenous injection of MIBG. Anterior and posterior projection images of the chest, head, and abdomen were obtained. These confirmed the metastasis diagnosis of the liver, and showed ill-defined intense heterogeneous uptake occupying most of the abdomen (**Figure 3**). Normal bio-distribution was observed in the rest of the scan, revealing no other metastatic deposits.

Histopathological sections of two cores of liver tissue revealed invasive sheets and groups of malignant undifferentiated blue round cell tumors with indistinct cell borders and occa-

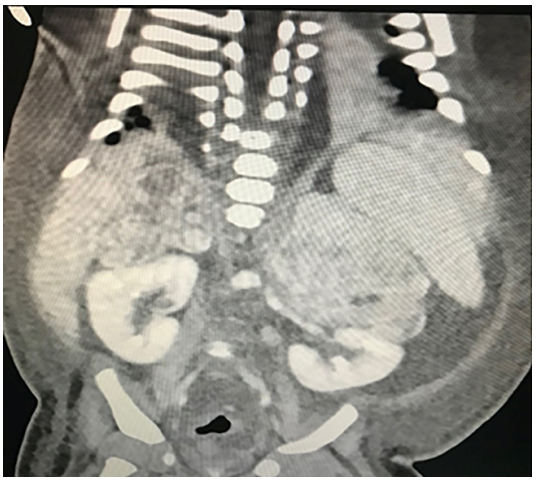

Figure 1. Computed tomography (CT) scan of the abdomen and pelvis showing bilateral adrenal large masses.

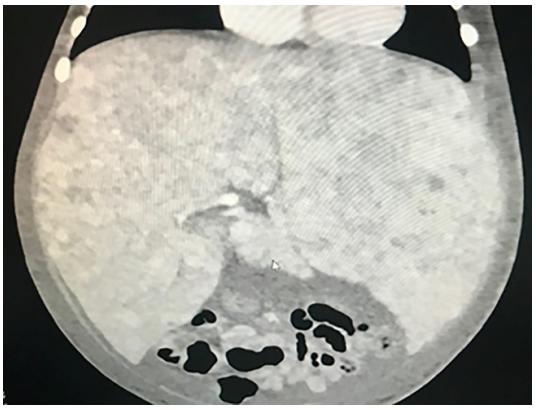

Figure 2. Coronal CT reconstruction showing enlarged liver with hypervascular nodular metastatic solid lesions.

sional pseudorossettes. Granular, salt-and-pepper chromatin cells were observed. The immunohistochemistry was positive for synaptophysin, vimentin, CD56, CD57, ALK, and NSE (weak and focal), and negative for CK Pan, S100, GFAP, and CD99 (**Figure 4**).

Outcome and follow-up

The INSS and INRGSS criteria were applied and it was found that the patient's disease did not fit either stage 4S or MS satisfactorily, owing to the bilateral nature of her condition and its poor clinical presentation. The patient was assumed to have INSS stage 4 with at least one IDRF in the abdomen, which prevented surgical intervention. A trial dose of chemotherapy

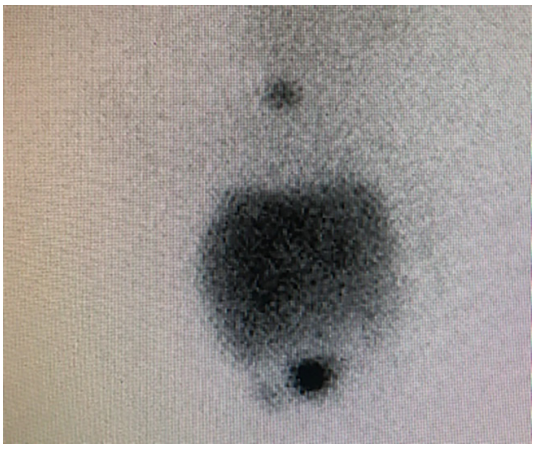

Figure 3. Metaiodobenzylguanidine (MIBG) scintiscan showing abdominal trace uptake and no distal metastases.

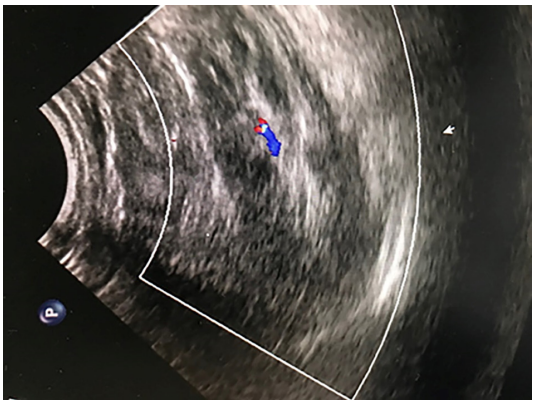

Figure 4. Follow-up ultrasound study after 1.5 years showing resolution of the adrenal masses.

was administered which was then ceased because the follow-up ultrasound showed an increase in the size of the lesions. The patient was eventually classified with a do-not-resuscitate (DNR) status. She was discharged and had regular follow-up visits as an outpatient. However, a further follow-up ultrasound performed 1.5 years later revealed the resolution of the adrenal masses, without interventional treatment.

Discussion

It is difficult to predict which neuroblastoma will regress merely on the basis of age and stage. As a result, research concentrated on stage 4S tumors as a surrogate for regressing neuroblastoma [16]. While the patient presented with signs more closely matching INSS stage 4 crite-

Table 2. Image studies for neuroblastoma

Author	Year	Title
Oebisu et al.	2014	Contrast-enhanced color Doppler ultrasonography increases diagnostic accuracy for soft tissue tumors
Zhou, Xuan and Wang	2019	Diagnostic value of ultrasound score, color Doppler ultrasound RI and spiral CT for ovarian tumors
Chu et al.	2011	Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm
Chandraprakash, Abhijeet and Shamim	2001	Bilateral adrenal neuroblastoma; stage IV-a case report
Tas et al.	2020	Neuroblastoma stage 4S: Tumor regression rate and risk factors of progressive disease
Gupta et al.	2014	Stage 4S Bilateral Adrenal Neuroblastoma in a Newborn
Brodeur	2018	Spontaneous regression of neuroblastoma

ria, the actual clinical course revealed a pattern more consistent with stage 4S, which holds an excellent survival rate (70-90%) and is broadly considered a self-limiting disease. This case supports an approach of considering each lesion in isolation for staging purposes, and determining prognostic information and treatment plans accordingly, especially in infants [17-19]. Clinical behavior of neuroblastoma can range from extremely malignant and aggressive (low response to treatment) to spontaneous remission, resulting in a histologically benign mass. For instance, in newborns like in the patient in this case, and even in people with extensive neuroblastomas throughout the body, the condition might be very benign [20]. Another study reported a case that revealed patients with neuroblastoma stage 4S who are 4 weeks old are at danger of dying due to the development of liver metastases. In other cases, tumor regression is marked by fast biochemical normalization before radiological regression [21]. Gupta et al. also defined the good prognostic outcome and revealed that the liver metastasis had completely regressed, and the bilateral adrenal tumors were calcified. A three-year follow-up revealed no recurrences or persistent tumors [22]. However, this is not the case in patients with MYCN gene amplification or other chromosomal aberrations, which show very poor prognosis in bilateral disease [23, 24]. Also, previous studies have reported the association of bilateral neuroblastoma with Fanconi's anemia, total colonic aganglionosis, microcephaly, and VACTERAL syndrome, all of which affect the prognosis and treatment protocols for patients [25, 26].

Imaging studies are an extremely important component of diagnosis, staging, and decisions regarding the preferred treatment protocols of neuroblastoma (**Table 2**). Ultrasonography studies are usually initially requested to demonstrate the adrenal gland neuroblastoma as a suprarenal heterogeneous echogenic mass, and to screen for tumor extension, vascular displacement or compression, liver metastasis, and lymph node enlargement. However, when neuroblastomas are larger, ultrasound might not be able to define their precise organ of origin, particularly when they have disseminated into the chest or abdomen. Moreover, ultrasound has limited efficacy in detecting metastases in retrocrural and retroperitoneal lymph nodes. Neuroblastomas, like many other tumors, generally have increased blood flow that can be detected by ultrasonic color Doppler imaging [27, 28].

Using CT imaging, neuroblastomas emerge as homogenous or heterogeneous soft tissue masses that may have a lobulated surface. Indeed, CT scanning is very effective in identifying affected lymph nodes and another organ metastasis. It also helps in the identification of paravertebral and retrocrural tumor extensions in the chest and can be used to detect necrosis, calcification, and hemorrhage, which are common associations with this type of tumor [19, 29].

MRI is generally more effective with respect to tumor intraspinal extension and bone marrow infiltration than CT imaging [30]. MRI, owing to its excellent tissue characterization, shows superior local staging capability over CT imag-

ing because of its greater facility in detecting invasion to adjacent structures. A further option in the detection and treatment of neuroblastoma is MIBG scanning. The combination of most or all of these radiological methods is crucial in the staging of the disease, and must be considered in light of additional clinical findings and associated disorders.

Conclusion

This case report demonstrates that despite the initial manifestation of severe symptoms, bilateral neuroblastoma can spontaneously regress. In general, stage 4S bilateral neuroblastoma in infants has the highest chance of self-regression of all the variations. While this study investigated a case that met the general criteria for stage 4 according to the INSS, the patient actually experienced a clinical course more consistent with 4S. These findings reinforce the notion that in situations of bilateral illness, the clinical expert must carefully stage each lesion independently and then determine treatment approaches. This case report lays the path for future research aimed at elucidating disease's course, staging criteria, and treatment choices in greater detail.

Disclosure of conflict of interest

None.

Address correspondence to: Rani Ahmad, Radiology Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. Tel: 00966555520327; Fax: 00966126408341; E-mail: rahmad@kau.edu.sa

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