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Case Report

An Unusual Cause of Vomiting in a Pediatric Patient..! Atypical Teratoid/Rhabdoid Tumor: A Case Report and Literature Review

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Abstract

Introduction: A typical teratoid/rhabdoid tumor is a rare embryonal tumor of the central nervous system. It is usually reported in children below 3 years of age. Spinal canal involvement is extremely rare.

Case Description: A 6 years old girl presented for vomiting of 2 weeks duration, refractory to supportive treatment. Brain MRI showed a posterior fossa tumor. A craniotomy was done for tumor removal, and histologic findings were consistent with an atypical teratoid/rhabdoid tumor. Spinal lesions were found on MRI.

Discussion: Atypical teratoid/rhabdoid tumors are extremely aggressive. They can present with several symptoms. Imaging and histopathologic examinations are necessary to confirm the diagnosis. The treatment of these tumors is largely dependent on the patient's age, the location of the tumor in the central nervous system, and the stage of the disease at time of diagnosis. Surgical excision remains the mainstay of treatment; although a role is reserved for chemotherapy and radiotherapy. Despite this multimodal therapy, the prognosis of these patients remains extremely poor.

Conclusion: Atypical teratoid/rhabdoid tumors can present with symptoms that are common in pediatric population; a high index of suspicion is necessary to diagnose and treat them without delay. This case report also showed several atypical presentations of these tumors.

Keywords: Vomiting; Pediatrics; Atypical Teratoid/Rhabdoid Tumor; Metastase

Introduction

Vomiting is a very common symptom reported in early infancy, to the point that Shakespeare described this age as "mewling and puking in the nurse's arms". It is also a frequent complaint during childhood, and may be caused by several etiologies (infectious, gastrointestinal, metabolic,…).

Rarely, vomiting can be caused by an intracranial pathology (either by increased intracranial pressure, or by direct stimulation of the vomiting center in the brainstem) [1]. In fact, brain tumors often lack specific neurological signs in children; alternatively, an intractable or chronic vomiting (without nausea or deregulation of the water and electrolyte balance) can indicate thepresence of an intracranial process [1]. Vomiting and headache are two nonspecific symptoms that can be present in central nervous system (CNS) tumor of any location. More specific symptoms can point to the particular site of the tumor [2].

In the US, CNS tumors are the most common solid tumors in children and a leading cause of cancer mortality [3]. Malignant CNS tumors account for 15 to 20% of all childhood malignancies [4], with the posterior fossa being the most common site of involvement. Extremely rarepresentations can be as primary isolated extracranial tumor or primary spinal involvement [5].

Atypical teratoid/rhabdoid tumor (AT/RT) is a rare tumor of the CNS, usually affecting children below 3 years of age [4]. Primary CNS AT/RT was added in 1993 to WHO classification as a separate entity and recognized as grade IV embryonal tumor [6,7]. Its diagnosis is established by the presence of rhabdoid cells on histopathology and polyphenotypic immunopositivity for epithelial, mesenchymal, and neuroectodermal markers along with loss of expression of SMARCB1/INI1 or SMARCA4/BRG1 [8]. Despite the recent multimodal therapy, the prognosis remains dismal [9].

Here we present the case of a girl who had an atypical clinical presentation and radiographic features of AT/RT.

Case Report

History and presentation

A 6 years old girl, born by NVD at term with ICN admission at DOL 15 for bronchiolitis,presented for 2 weeks history of nonbilious nonbloody nonprojectile vomiting. During this period, she was not tolerating food; no other associated symptoms were reported (neither abdominal pain, nor nausea, nor change in bowel movements…); she was afebrile. Oral antiemetics and proton pump inhibitors were tried without improvement.

Upon presentation to the Emergency Department, vital signs were within normal range. The girlwas pale. Physical exam was otherwise normal (the abdomen was soft nontender and nondistended; neurological exam was normal).

Diagnostic focus and assessment

The girl was admitted to the pediatric floor for IV hydration and supportive treatment. Blood was drawn for laboratory tests, results are showed in table 1.

Laboratory test	Unit	Result
Hemoglobin	g/dL	14.1
Hematocrit	%	42.1
Platelets	$x10^3/\mu L$	343 000
WBCs	$x10^3/\mu L$	5.40
Neutophils	%	43.1
Lymphocytes	%	52.0
Sodium	mmol/L	140
Potassium	mmol/L	3.9
Chloride	mmol/L	103
CO_2	mmol/L	19
Calcium	mg/dL	9.9
Phosphorus	mg/dL	5.1
Magnesium	mg/dL	2
Creatinine	mg/dL	0.4
SGPT	U/L	14
Alkaline phosphatase	U/L	164
Lipase	U/L	228
CRP	mg/dL	<0.5

Table 1: Laboratory tests results upon presentation.

Vomiting persisted despite hydration, antiemetics and omeprazole. Upper GI series with po contrast and abdominal ultrasound were done and were normal. The girl was planned for endoscopy (gastroscopy).

At day 3 of hospitalization, vomiting was still profuse. High anion gap metabolic acidosis was still present (AG = 18). Metabolic abnormality was suspected as the cause of vomiting. Ammonia and lactate levels were taken and found to be normal.

A central origin of the vomiting should then be ruled out (as part of the continuous vomiting differential diagnosis), and brain MRI with gadolinium was ordered. Left cranial nerve VI paresis started to be noted, without any other neurological abnormality. An enhancing heterogeneous posterior fossa tumor was found on MRI, occupying almost all the fourth ventricle, with surrounding edema, suggesting of an ependymoma (Figure 1).

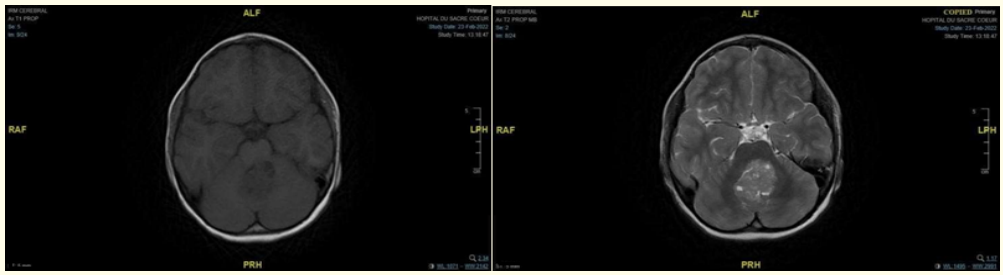

Figure 1: Brain MRI showing the cerebral tumor. A: T1-weighted image. B: T2-weighted image.

Total spine MRI was done, and showed multiple tumors in lumbar spine. We must consider the cranial lesion as the primary one and the spinal ones as secondary (metastatic)(Figure 2). They were adherent to the anterior and posterior sides of cauda equina.

A neurosurgeon and pediatric oncologist were consulted. Dexamethasone was started, and the girl was planned for craniotomy for tumor removal. During the surgery, the tumor was progressively resected from all angles of the fourth ventricle; so a seemingly

Figure 2: Spine MRI showing the spinal lesions. A: T1-weighted image. B: T2-weighted image.

gross-total tumor resection was performed. After the surgery, the girl developed. The facial weakness is of incomplete paresis as the girl could have an ipsilateral eye closure (due to the edema resulting from the manipulation of the tumor), in addition to the cranial nerve VI one. She reported binocular diplopia.

Surprisingly, the histologic examination of the resected tumor showed an atypical teratoid rhabdoid tumor (AT/RT), WHO grade IV. The tumor is poorly differentiated, heterogeneous with primitive neoplastic cells many with rhabdoid features. Immunostains showed focal expression of GFAP, cytokeratin, synaptophysin. There was diffuse loss of nuclear expression of INI indicating loss of SMARCB1.

The girl was referred to another institution for chemotherapy/radiotherapy sessions.

Discussion

Overview

The initial description of a rhabdoid tumor localized within the CNS was given in 1985 [10]. Later, Rorke., *et al*. characterized this tumor as "atypical teratoid/rhabdoid tumor" in 1996, based on the disparate combination of rhabdoid, primitive neuroepithelial, epithelial and mesenchymal components [11].

AT/RT is an extremely rare (1-2% among all pediatric CNS tumors [12]) and highly aggressive CNS tumor, usually presenting in children below 3 years of age (median age 2 years) [13-15]. Males have a higher incidence rate than females, with the reported ratio being 3:2 to 2:1 [15]. This epidemiology makes our case to be reported as it is a 6 years old girl, not in the common age range, nor the more common gender prevalence. The prognosis of this tumor is extremely poor, with the historic median overall survival (OS) ranging from 6 to 18 months [16].

The variety of clinical manifestations (vomiting, lethargy, or cranial nerve palsies) is predominantly related to the location of the tumor [17]. The distribution of AT/RT is as follows: 52% in the posterior fossa (the cerebellum being the predominant site); 39% supratentorial; 5% in the pineal region; 2% in the spine; and 2% are multifocal [18]. To note that in our case the location of the tumor was quiet the second most common site, but what should be reported is the new spinal lesions, with a limitation noted if they are either primary by themselves as the one in the brain, or metastatic lesions to the latter.

Diagnosis: Imaging, histology and genetics

With regard to imaging studies, AT/RTs appear as lesions with increased density on unenhancedComputerized Tomography (CT) images, and heterogeneous enhancement with the administration of contrast material [19]. On MRI, decreased density on T1-weighted images andenhancement with gadolinium are usually detected [20], as it was the case in our patient.

Histopathologically, AT/RTs are characterized by the presence of rhabdoid cells, with or withoutfields resembling a typical embryonal tumor, epithelial tissue, and neoplastic mesenchyme [18,21,22]. The rhabdoid cell has an eccentric round nucleus in an abundant eosinophilic cytoplasm and a prominent nucleolus [23]. Necrosis and brisk mitotic activity are common in the rhabdoid cell [23,24]. ATRTs are polyphenotypic tumors which characteristically show expression of EMA, vimentin and SMA, as well as various other markers, on immunohistochemical staining [20]. Additionally, expression of GFAP, neurofilaments, S-100, Synaptophysin, NSE, CD68, α1-antitrypsin, α1-antichymotrypsin and keratin may be detected, depending on the abovementioned different cellular composition of the neoplasm [11,20]. However, it should be pointed out that ATRTs typically do not express desmin or any of the markers for germ cell tumors [11,25]. In our case immunostains showed focal expression of GFAP, cytokeratin, synaptophysin.

Genetically, the cellular origin of AT/RTs is unknown, but inactivating mutations of the hSNF5/INI1 gene in chromosomal region 22q11.2 are regarded as a critical step in its molecular pathogenesis [26]. AT/RTs are characterized by a loss of the long arm of the chromosome 22, which results in a loss of the hSNF5/INI1 gene, causing the INI1 protein expression to be negative [27]. In our case, there was diffuse loss of nuclear expression of INI indicating loss of SMARCB1. Though the INI1 nuclear protein (the product of hSNF5/INI1 gene) is typically expressed in normal brain tissue and in the majority of other neoplasms, loss of its expression has been observed in most ATRTs [25,28]. The hSNF5/INI1 gene is considered as a tumor suppressor gene in peripheral AT/RTs of the CNS [29,30]. Previous studies have suggested that INI1 suppresses tumor formation by regulating cell proliferation via the Rb cell cycle checkpoint [31]. But it is important to note that the loss of INI1 expression is not a certainty, so we cannot diagnose AT/RT merely on the basis of a loss of nuclear INI1 expression; and a minor subset may have retained INI1 expression and should be evaluated for the loss of nuclear BGR1 (SMARCA4) expression from a side and the loss of INI1 that may occur in other rare neoplasms, including poorly differentiated chordomas, and schwannomatosis-associated schwannomas (in a mosaic pattern), from another side. Therefore, correlations with morphological and clinicopathological features should be noted as well [32].

So, the essential diagnostic criteria for AT/RT include: a CNS embryonal tumor with a polyimmunophenotype AND a loss of nuclear SMARCB1 (INI1) or SMARCA4 (BRG1) expression in tumor cells OR a DNA methylation profile aligned with AT/RT, as in our case.

Management

Therapies of AT/RT are largely dependent on the age of the patient, the location of the tumor inthe CNS, and the stage of the disease at the time of diagnosis [33]. In general, surgical resection

of AT/RT is the principal treatment. Surgical treatment generally guarantees most of the removal of the tumor according to the relationship between the location of the tumor and the blood vessels in the surrounding tissues. Taking into account the blood vessels around the tumor, especially the tumor in difficult location, angiography and preoperative embolization may yield some effects on surgery [34]. Adjuvant therapy includes radiotherapy, high-dose chemotherapy, and autologous stem cell transplantation [14,35]. In addition, it has been demonstrated that anti-sense mediated downregulation of insulin-like growth factor I receptor (IGF-IR) results in sensitization to doxorubicin and cisplatin [22]. The use of high-dose chemotherapy and autologous stem cell transplantation (HDCT/auto-SCT) has shown clinical benefits in children with brain tumors [36]. Moreover, literature has shown that a tumor vaccination strategy using lysate-loaded autologous dendritic cells is feasible and safe even in small children with AT/RT [37].

Prognosis

Finally, the prognosis of patients with ATRTs is extremely poor [25,38]. It is generally believed that most of the patients die within approximately 1 year after the initial diagnosis, probably as a result of metastatic lesions through the cerebrospinal pathway, which are common in this aggressive neoplasm [20,25,38,39].

Conclusion

To summarize, this case report showed the clinical presentation, diagnostic tools and management of AT/RT. It is important for clinicians to recognize that AT/RT can present with several clinical manifestations. Some of these symptoms are routinely encountered in pediatric population, such as vomiting. A high index of suspicion is necessary to diagnose and treat these aggressive CNS malignancies without delay.

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