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Case Report Open Access

Thymic Atypical Carcinoid with Cyclical Cushing's Syndrome in A 7-Year-Old Boy: a Case Report and Review of the Literature

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Abstract

Thymic carcinoid tumors very rarely occur during childhood and are often associated with the production of adrenocorticotropic hormone (ACTH), which leads to Cushing's syndrome. We describe a 7-year-old male patient with a thymic atypical carcinoid tumor who presented with cyclical Cushing's syndrome. His tumor was initially overlooked on computed tomography scanning in the anterior mediastinum, and was later identified by magnetic resonance imaging scanning. There was an interval of 154 days observed between periods of cyclic hormone production. In addition, we discuss the findings of our literature search of the PubMed database. This report emphasizes the importance of considering thymic carcinoid in the differential diagnosis of ectopic ACTH production in children.

Keywords: Tumors; Cushing's syndrome; Adolescence

Background

Carcinoid tumors of the thymus are separate neoplasms from conventional thymomas. These tumors are thought to arise from the foregut and generally are not associated with carcinoid syndrome [1]. Thymic carcinoid, for which the term well differentiated neuroendocrine carcinoma (NEC) of the thymus has been proposed, accounts for less than 5% of all carcinoid tumors [2]. Thymic carcinoid tumors very rarely occur during childhood and are often associated with the production of ACTH, which leads to Cushing's syndrome [3]. Here, we described the clinical features and outcomes of a pediatric patient with a thymic atypical carcinoid tumor, who presented with cyclical Cushing's syndrome, treated in our hospital. In addition, we discuss the findings of our literature search of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) from 1970 to April 10th, 2014 to identify reported pediatric cases (≤ 10 years of age) of thymic carcinoids with Cushing's syndrome. We excluded journal articles that did not provide the patient's age at diagnosis as well as non-English articles. Our aim of this report is to emphasize the importance of considering thymic carcinoid in the differential diagnosis of ectopic ACTH production in children.

Case Presentation

A 7-year-old boy was referred for further evaluation of rapid weight gain and generalized edema in May 2012. At presentation, he was noted to have facial puffiness, and he rapidly developed pitting edema in his lower limbs. He experienced a 5-kg weight gain within several weeks. He had also developed increased body hair and acne and became tired easily. His past medical history was not contributory. There was no history of endocrine disease on either side of the family.

On physical examination, his blood pressure was 120/70 mmHg, and he had a pulse rate of 88 beats per minute. His height was 120 cm and weight was 27 kg. He had a cushingoid appearance: moon face, "buffalo" obesity, acne, hirsutism, and hyperpigmented macules on his back. Purple striae and ecchymoses were not present. He was in the Tanner stage I of development. Initial laboratory tests revealed an elevated cortisol level (>60 μg/mL; normal range, 8.7-22.4 μg/mL), low potassium level (2.57 mmol/L; normal range, 3.5-5.5 mmol/L), elevated ACTH level (208.79 pg/ml; normal range, 8-80 pg/ml), and elevated lactate dehydrogenase level (820 U/L; normal range, 313-618 U/L). The thyroid-stimulating hormone, free T3 and T4, serum angiotensin II and renin, and blood glucose levels were normal. Computed tomography (CT) scans with contrast of the abdomen and pelvis showed bilateral adrenal cortical hyperplasia (Figure 1E and insert). Magnetic resonance imaging (MRI) of the pituitary was negative (Figure 1D). A CT scan of the chest was judged as normal. The ultrasonographic appearance of the thyroid was normal. The patient was diagnosed with ectopic ACTH syndrome on the basis of these findings. Since imaging studies failed to identify the source of ACTH, symptomatic treatment for edema and hypokalemia was initiated (diuretic therapy and potassium supplement).

Two months later (July 2012), the patient discontinued all treatment because his parents wanted him to pursue a "natural" way of life without taking any medication. The patient reported resolution of the signs and symptoms of hypercortisolism (eg. the weight of this patient spontaneously decreased to 24 kg, blood pressure was 120/80 mmHg; potassium level was 3.52 mmol/L, with normal cortisol and ACTH level) except for the full face. This remission persisted for 5 months and was followed by recurrent hypercortisolemia. The patient underwent an MRI scan of the chest in March 2013. The MRI scan showed an anterior homogeneous enhancing mediastinal mass (2.96 × 2.08 cm) (Figure 1A, B, and C). Hence, the CT scans of the chest performed in May 2012 were reviewed and revised. On CT, a small

tumor of 2 × 2 cm appeared to be present in the anterior mediastinum, which had been overlooked initially (Figure 1F).

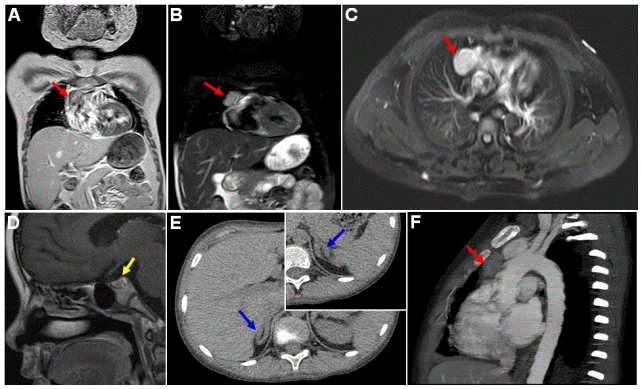

Figure 1: Images from a 7-year old boy with Cushing's syndrome due to a thymic atypical carcinoid tumor. A,B,C: MRI of the mediastinal mass (red arrows). **D:** MRI of the normal pituitary in the parasellar region (yellow arrow). **E** and insert: CT imaging of the bilateral adrenal cortical hyperplasia (blue arrows). **F:** CT imaging of the mediastinal mass which was overlooked initially (red arrow).

A neuroendocrine tumor, most likely a thymic carcinoid, was suspected after careful discussion between the endocrine and pediatric hematology/oncology services. The patient experienced a median sternotomy with resection of the right anterior mediastinal tumor. Microscopically, the thymic carcinoid tumor exhibited a growth pattern with solid nests, which were separated by delicate capillaries with focal calcification and blood vessel invasion, necrosis, and a tumor thrombus was visible in vessels. In addition, mitosis was observed (Figure 2A and insert). These features were compatible with atypical thymic carcinoid. Immunohistochemically, the tumor cells were positive for chromogranin A, synaptophysin, neuron-specific enolase, CD56, and ACTH (Figure 2B).

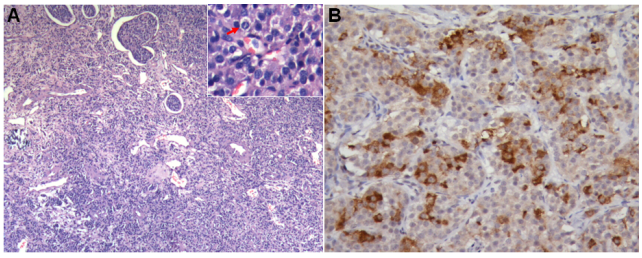

Figure 2: Histological appearance of the atypical thymic carcinoid. A: Hematoxylin-eosin staining of the atypical thymic carcinoid, solid nests formation with focal calcification, necrosis and blood vessel invasion (original magnification×50) Insert: Mitotic cells in the tumor (red arrow, ×200). B: The carcinoid cells show immunoreactivity for ACTH (×200).

Discussion

Carcinoid tumors of the thymus were first described as a specific entity in 1972 by Rosai and Higa [4]. About 25% of patients with thymic carcinoid present with Cushing's syndrome due to ectopic ACTH production. Thymic carcinomas with Cushing's syndrome can occur at any age, but the peak prevalence is between the second and the fourth decades of a patient's life. Confirmed thymic carcinoids have been described in children. McCaughey et al described a child with Cushing's syndrome at 2 years of age who had a bilateral adrenalectomy. The thymic carcinoid tumor was not diagnosed until she was 10 years and 11 months of age [5]. There are 5 reports of pediatric patients (≤ 10 years old) with Cushing's syndrome due to a thymic carcinoid tumor (Table1) [6-9].

Reference	Age at diagnosis (years)	Country	Sex	Cushing's syndrome	Cyclical Cushing's syndrome	Imaging studies	Treatment
Salyer [3]	10	USA	Female	Yes	NA	Chest radiograph	Surgical resection
Wick [4]	9	USA	NA	Yes	NA	NA	Surgical resection
McCaughey [1]	10	UK	Female	Yes	Yes	Chest radiograph	Surgical resection
Doppman [5]	10	USA	Female	Yes	NA	CT	Surgical resection
Lin [6]	8	China Taiwan	Female	Yes	NA	Technetium-99mm MIBI scan and MRI	Surgical resection
MIBI: Methoxy Isobutyl Isonitrile; NA: Not Available; UK: United Kingdom; USA: United States of America							

Table 1: Reports of children ≤ 10 years old with Cushing's syndrome due to thymic carcinoid tumor (by date of publication)

The majority of ACTH-secreting neoplasms are either bronchial or thymic carcinoids or other neuroendocrine tumors. However, identifying the source of the ectopic ACTH production may be extremely difficult since as many as 50% of these patients harbor an occult underlying tumor [10]. CT or MRI scans of the neck, chest and abdomen are the most useful diagnostic approaches. MRI is preferable as it may detect bronchial carcinoid tumors overlooked on CT [11]. On CT scans of the anterior mediastinum, thymic tissue and small thymic carcinoid tumors may appear similar, potentially leading to an incorrect diagnosis [12]. In our case, evidence of an anterior mediastinal mass was observed only on retrospective review of the chest CT. In this prepubertal boy, the small thymic carcinoid tumor

was initially treated as normal thymus tissue. Since thymic tissue regresses with age, this confusion will not often arise in patients older than 40 years of age.

To date, it has been described in a few child-patents with thymic carcinoid tumors. The clinical and laboratory features of a cyclical Cushing's syndrome are often misleading; therefore, it may take years before the correct diagnosis is made [13].

Atypical carcinoids consist of small nests or interconnectingn trabeculae of uniform cells separated by a prominent vascular stroma and numerous thin-walled blood vessels. The histopathologic features of atypical carcinoid are as follows: (a) increased mitotic activity, (b) greater cytologic pleomorphism and higher nuclear-to-cytoplasmic ratios, (c) increased cellularity and architectural irregularities, and (d) more areas of tumor necrosis [14]. Immunohistochemical staining for neurosecretory granules is usually diffuse. The expressions of neuron-specific enolase, chromogranin, and synaptophysin, so-called pan-neuroendocrine markers, are valuable in terms of identifying neuroendocrine features [15].

In neuroendocrine carcinoma of the thymus, surgery remains the first-line treatment while chemotherapy and/or radiotherapy are reserved for advanced disease. Yet, the role of radiotherapy, chemotherapy, or both has not been adequately established in the treatment of thymic carcinoid tumors [16]. A poor prognosis is associated with these tumors despite aggressive therapy. Most patients present with local recurrence or metastasis within 5 years after surgery and die within 10 years. The prognosis is directly linked to the degree of tumor differentiation. The 5-year survival rate is approximately 50% for patients with well-differentiated thymic carcinoid tumors, 25% for those with moderately differentiated tumors, and 10% for those with poorly differentiated tumors [17]. Our patient didn't receive any adjuvant chemotherapy or radiotherapy after surgery. Postoperative follow-ups, with serum free cortisol and ACTH testing as well as regular chest CT or MRI scans, are scheduled every 3 months for the first year after surgery.

Conclusion

This report emphasizes the importance of considering thymic carcinoid in the differential diagnosis of ectopic ACTH production in children.

Consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' contributions

QM contributed to data acquisition and wrote the manuscript. YJG conceptualized and designed the study, supervised data collection, reviewed the manuscript critically for intellectual content, and revised the manuscript. MZY, JYT, YMZ and WXD made contributions to data analysis. All authors approved the final manuscript as submitted.

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