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CASE REPORT

Atypical cardiac myxoma in the course of Carney complex in the child

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Abstract

Cardiac tumors in infants and children are rare. Myxomas are the second (after rhabdomyomas) most common primary cardiac tumors in pediatric patients. Cardiac, cutaneous and mucous myxomas are likewise the second most frequent manifestation of the Carney complex, an autosomal dominant multi neoplasia syndrome, which consists of myxomas in different locations, spotty skin pigmentation and endocrine overactivity. We present a case of 13-years-old boy send to our department from a district hospital because of the large tumor in the right atrium discovered in the echo study. On admission he presented discrete signs of Cushing's syndrome and scarse pigmented nevi on the face and trunc. The detailed echo examination showed the large right atrial tumor with features of myxoma, protruding across the tricuspid valve into the right ventricle during diastolic period. Atypical location of cardiac myxoma as well as the signs of Cushing's syndrome suggested Carney's complex. Detailed endocrine studies confirmed the hypothesis. Thus two-step bilateral adrenalectomy was planned. The histopathologic study confirmed primary pigmented nodular adrenocortical disease.

INTRODUCTION

Carney complex is an inherited autosomal-dominant disorder characterized by spotty skin pigmentation, lentigines, blue nevi, cutaneous, mucosal and cardiac myxomas, schwannomas, liver, pancreatic, breast and endocrine neoplasias, such as follicular thyroid cancer, pituitary adenomas or hyperplasia, large-cell calcifying Sertoli cell tumours and the main endocrine manifestation of Carney complex, primary pigmented nodular adrenocortical disease (PPNAD) (Stratakis *et al.* 2001). Myxomas at multiple locations are the second most frequent manifestation of the Carney complex. Inactivating mutations in the 1a regulatory subunit of the protein kinase A gene (PRKAR1A), located in chromosome 17q22-q24, are found in 45–80% of Carney complex families (Bertherat *et al.* 2009;Kirschner *et al.* 2000).

CASE REPORT

A 13 year old boy was admitted to the department of pediatric cardiology from district hospital where he was observed for a week because of fever as well as unspecified chest and abdominal pains. Due to presence of the heart murmur the echo study was performed which showed a tumor like structure in his right atrium (Figure 1). Detailed echocardiographic examination revealed the large heterogeneous tumor 3.8×3.2 cm with the characteristics of myxoma, attached to the atrial wall by a narrow pedicle, protruding through the tricuspid valve during diastole into the right ventricle. The patient underwent cardiac operation with complete removing of the tumor from his right atrium. Histology confirmed heart myxoma with unusual location. As Carney complex was suspected the boy was referred to the endocrine unit. The interview with his parents revealed an 8-year history of episodes of increased appetite with weight gain, mood swings and growth rate inhibition. His past medical history revealed also that at the age of 7 years the lentigo lesion in his lower lip and inflammatory piloid cyst from his right arm were removed. At the age of 8 years he was referred to the endocrine unit in another endocrine centre where cyclic hypercortisolemia was confirmed but the boy was lost to follow-up due to family reasons. Auxological analysis at the age of 13 years revealed height: 158.8 cm (–0.2 SD), MPH: 177.5 cm (–0.25 SD), bone age 15 years and predicted adult height: 165.7 cm (–1.74 SD), weight: 57 kg, weight/height ratio: +18%, BMI: 22.6 (+0.87 SD) (Figure 2 and 3). On examination moon-like face with plethora, muscle wasting on extremities, scarce pigmented nevi and lentigines spots on trunk and head were found. Pubertal assessment revealed his right testis 18 ml, left testis 20 ml, pubic hair: IV, axillarche-(+).

Biochemically, cortisol circadian rhythm was abolished (Figure 4). In CRH test (+) 37% increase of cortisol was noted (basal: 66.4 ng/ml, max. 91.4 ng/ml) and abolished ACTH response to CRH (basal ACTH-28.9 ng/ml (n:10–60), max.value: 29.2 ng/ml) indicated primary adrenal autonomous hypercortisolemia. This was confirmed in Liddle`s test by lack of inhibition of serum cortisol after low (1 mg p.o., 8 am – 234.8 ng/ml) and high (2 mg p.o. every 6 h for a period of 48 hours) doses of dexamethasone (serum cortisol:

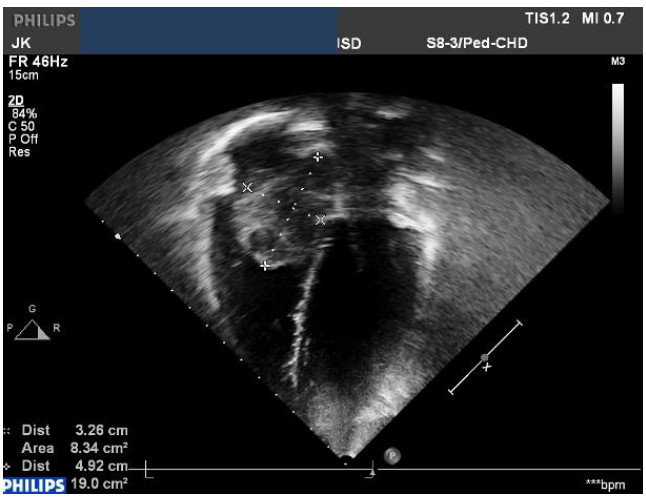

Fig. 1. Right atrial myxoma.

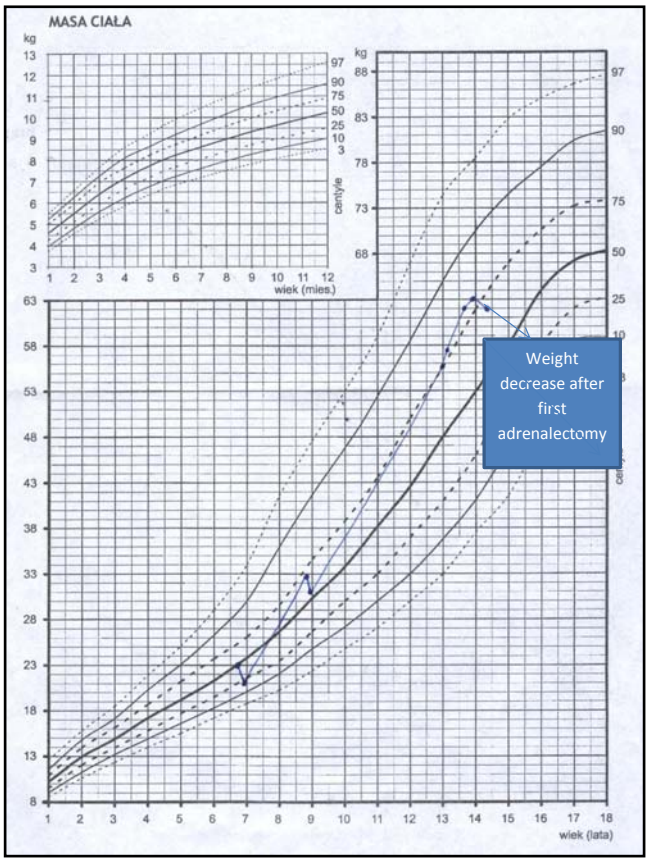

Fig. 2. Growth chart of patient`s body weight with episodes of weight gain.

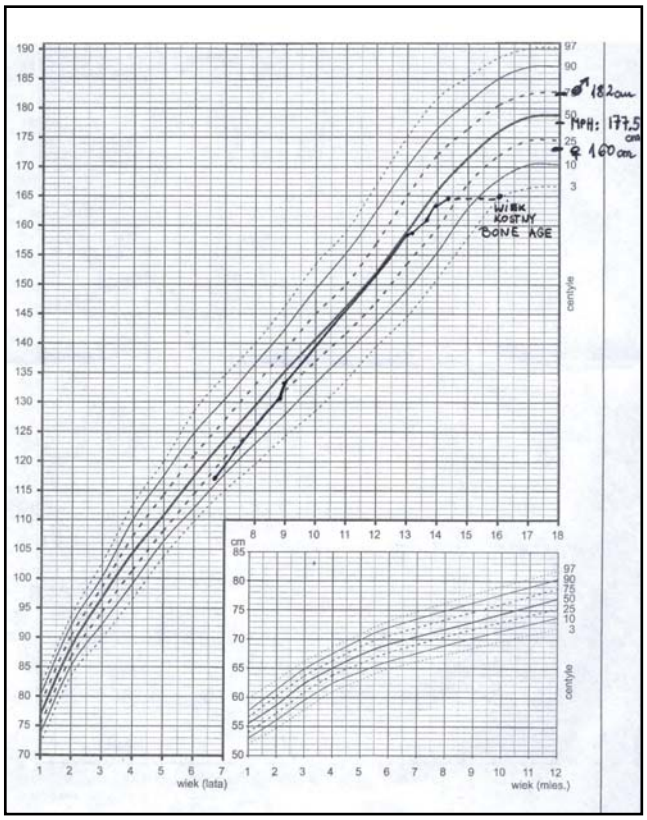

Fig. 3. Growth chart of patient presenting compromised final height, below MPH (mid-parental height).

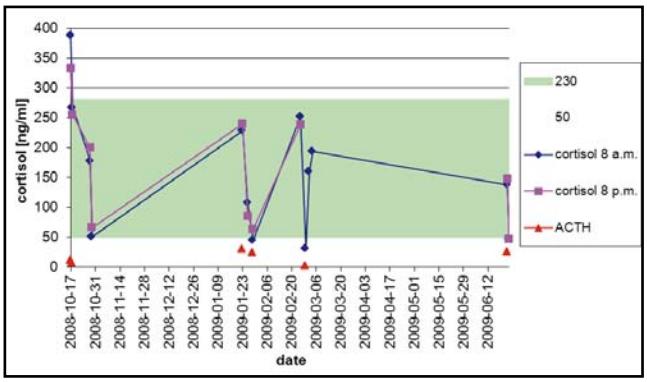

Fig. 4. Episodes of hypercortisolemia and cortisol circadian rhythm abolished. Legend: 50–230 ng/ml – normal range of morning cortisol.

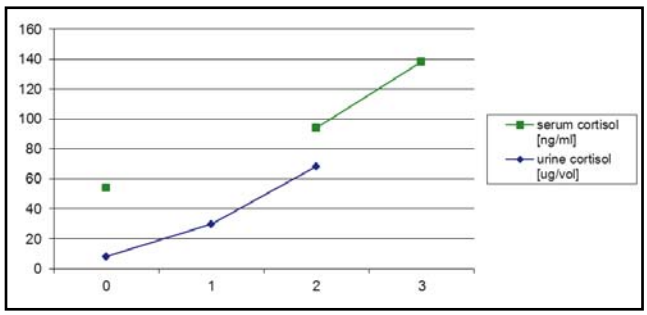

Fig. 5. The Liddle`s test – lack of inhibition of serum cortisol after high (2 mg p.o. every 6 h for a period of 48 hours) dose of dexamethasone and a paradoxical increase in urinary glucocorticoids after dexamethasone administration.

54 ng/ml, after 48 hrs: 94.1 ng/ml). Additionally a paradoxical increase in urinary glucocorticoids after dexamethasone administration during the Liddle's test was noted: cortisol in urine: basal – 29.7 μg/vol (n: 5–55), after 48 hrs: 68.3 μg/vol (Figure 5). Ultrasound and magnetic resonance imaging failed to demonstrate an adrenal lesion. The results of MR of pituitary gland, ultrasonography of thyroid gland, breasts, abdomen and testes were normal. Densitometry of L2–L4 revealed decreased bone mass (age matched Z-score: –1.3 SD). Ambulatory blood pressure monitoring was within the normal range. His karyotype was male: 46, XY. Primary pigmented nodular adrenocortical disease was suspected based on clinical and biochemical analysis. Bilateral adrenalectomy was planned in a two-stage procedure according to a protocol in our centre (Kumorowicz-Czoch *et al.* 2011). Histology of the first adrenal removed was typical for PPNAD (Figure 6 and 7). Molecular analysis performed in the USA confirmed inactivating mutation in the 1a regulatory subunit of the protein kinase A gene (PRKAR1A).

DISCUSSION

Cardiac tumors in infants and children are rare (below 0.027–0.08% of all neoplasms) (Marx *et al.* 2013). Myxomas, representing 10–15% of cardiac tumors, are the second (after rhabdomyomas) most common primary cardiac tumors in pediatric patients (Marx *et al.* 2013; Vargas-Barron *et al.* 2008). In the largest series presented by Vargas-Barron 79 % of cardiac myxomas were situated in left atrium, 7.9% in the right atrium, 4.7% in ventricles (Vargas-Barron *et al.* 2008). The Carney complex (CC) was suspected in 7.9% patients with an atypical presentation of myxomas (outside the left atrium). The authors present also characteristic features of cardiac myxomas in CC: a tendency to the reccurence, multiplicity and multiple sites of location, as well as the development at an earlier age (in childhood) than in cases of isolated myxomas (in adulthood) (Vargas-Barron *et al.* 2008). In the presented case a single heart myxoma was found in rare location in right atrium.

PPNAD causing the adrenocorticotropin hormone (ACTH)-independent Cushing's syndrome is an endocrine disorder most commonly associated with Carney complex, affecting 60% of patients with the disease, mostly children and young adults (Stratakis *et al.* 2001; Bertherat *et al.* 2009; Kirschner *et al.* 2000; Courcoutsakis *et al.* 2013). Histological evidence of PPNAD has been reported, however, in almost every patient with Carney complex who underwent an autopsy (Stratakis *et al.* 2001; Bertherat *et al.* 2009; Kirschner *et al.* 2000). PPNAD has a bimodal age of distribution. Most cases are diagnosed during the second and third decade of life; however, a substantial proportion of patients presents during early childhood (2–10 years) (Kirschner *et al.* 2000). The formation in both right and left

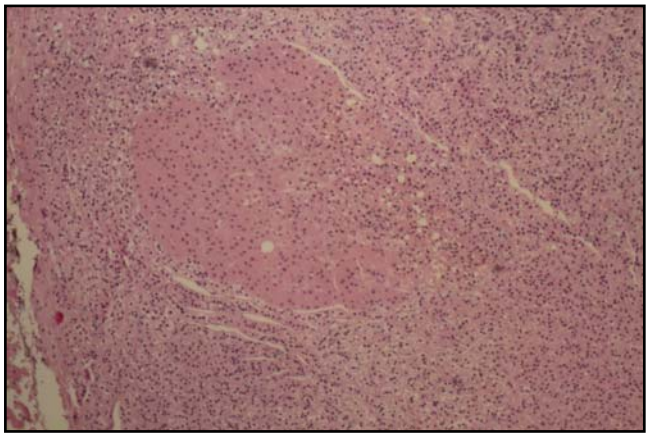

Fig. 6. Primary pigmented nodular adrenocortical disease. Nodule with cells containing brown pigment. (HE, ×40).

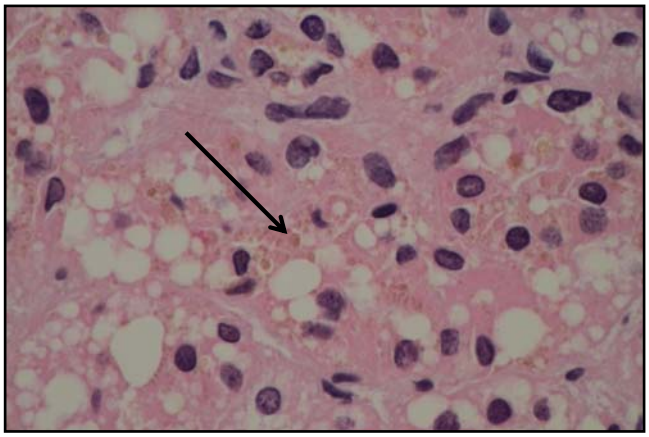

Fig. 7. Primary pigmented nodular adrenocortical disease. Nodule with cells containing brown pigment (an arrow). (HE, ×400).

adrenal cortices of small pigmented and benign nodules is characteristic of PPNAD (Stratakis *et al.* 1998; Shenoy *et al.* 1984). The hypercortisolism can manifest as the classic constellation of Cushing's characteristics or with isolated features, like mild growth retardation (short stature), severe precocious osteoporosis and severe muscle and skin wasting (Stratakis *et al.* 1998). Clinically our patient presented with typical features of Cushing's syndrome including also low bone mass, muscle wasting and typical for pediatric patients compromised prognosis of his final height. Biochemically the patient presented with cyclical ACTH-independent hypercortisolemia that started at around 5 years of age, that is common among patients with PPNAD (Stratakis *et al.* 1998). The results of Liddle test with a paradoxical increase of urinary free cortisol were typical for PPNAD, that was finally confirmed histologically (Stratakis *et al.* 1999; Grant *et al.* 1986).

Tab. 1. Diagnostic criteria of Carney complex (Stratakis *et al.* 2001).

MAIN CRITERIA
• Typically distributed lentigines (lips, conjunctiva, oral and genital mucosa)
• Myxoma (in skin or mucosa)
• Cardiac myxoma
• Breast myxomatosis on MRI image (in fat suppression mode) suggesting diagnosis
• PPNAD or paradoxical positive corticosteroid response in urine after dexamethasone administration during Liddle test
• Acromegaly secondary to GH-secreting adenoma
• large-cell calcifying Sertoli cell tumours or presence of characteristic calcifications in testicular ultrasound
• Thyroid carcinoma or presence of multiple hypoechoic nodules in thyroid ultrasound in a young patient
• Psammomatous melanocytic schwannoma
• Blue nevus, multiple epithelioid blue nevi
• Multiple ductal adenomas of the breast
• Osteochondromyxoma
ADDITIONAL CRITERIA
• First-degree relative affected
• Inactivating mutation in the PRKAR1A gene.

The diagnostic criteria for CC are included in Table 1, as established by Stratakis *et al.* (2001). The diagnosis of CC is established when a patient exhibits either: (1) two of the manifestations of the disease listed in the Table 1 or (2) one of these manifestations and one of the supplemental criteria.

The presence of confirmed histologically primary pigmented nodular adrenal dysplasia and heart myxoma, lentigo lesions and nevi on skin fulfilled the clinical criteria of Carney syndrome in presented patient.

The differential diagnosis in our patient included syndromes that present with multiple endocrine neoplasias, like MEN syndromes (thyroid, pituitary and adrenal involvement), or with similar manifestations from skin, bones and other tissues, like Peutz-Jeghers syndrome (lentigines) and McCune-Albright syndrome (cafe-au-lait spots, bone tumours, pituitary, thyroid and adrenal involvement) (Stratakis *et al.* 2001;Courcoutsakis *et al.* 2013; Bourdeau *et al.* 2003).

As recommended treatment for patients with PPNAD is bilateral adrenalectomy (Grant *et al.* 1986; Sarkar *et al.* 1990) the patient was subjected to a two-step procedure developed in our center (Kumorowicz-Czoch *et al.* 2011).

CONCLUSION

Carney complex should be suspected in patients with intracardiac myxoma, especially in an atypical location.

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