Hydrocortisone replacement was started and the patient was operated for recurrent intranasal mass. Mesenchymal tumor containing otherwise normal. Endocrinologic evaluation showed ACTH deficiency, peak cortisol level was 13,4 µg/dl by a low dose ACTH stimulation test. All other pituitary hormone levels were normal except gonadotropins which were prepubertal due to GNRH analogue treatment. The first presentation of our case was osteochondromyxoma, a very rare component of CNC, without typical manifestations of CNC. We want to emphasize osteochondromyxoma, as a component of CNC.

Abstract

Carney complex (CNC) is multiple neoplasia syndrome characterized by pigmented lesions of the skin and mucosa, cardiac, cutaneous and other myxomas, and multiple endocrine and non–endocrine tumors. Most of the cases have an inactivating mutation in PRKAR1A gene. Osteochondromyxoma (OMX) is an extremely rare myxomatous tumor of bone, affecting 1% of CNC patients. Large cell calcifying Sertoli cell tumor (LCCSCT) is a testicular tumor affecting more than 75 % of males with CNC. Here, we report a atypical case of CNC without typical pigmented skin lesions, presenting with a bone based tumor as the first manifestation. At first, the patient had recurrent, local invasive intranasal tumor without definite diagnosis. Further clinical developments during follow up, central precocious puberty and testicular tumor with calcification, led the diagnosis of LCCSCT, a CNC related tumor. Histopathologic examination of intranasal tumor was reevaluated with this knowledge and OMX was diagnosed. Coexistence of OMX and LCCSCT suggested CNC. Genetic analysis revealed heterozygous non-sense p.Trp 224* (c.672G>A ) in PRKAR1A gene. In our case, the diagnosis of OMX was delayed, because it is extremely rare and little is known about this tumor. In this report, we wanted to emphasize osteochondromyxoma, as a component of CNC.

Keywords: Carney complex, Osteochondromyxoma, Large cell calcifying Sertoli cell tumor, Central puberty precocious

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What is already known on this topic?

Carney complex (CNC) is a rare multiple endocrine neoplasia syndrome characterized by distinctive pigmented lesions of the skin and mucosal surfaces, cardiac and noncardiac myxomatous tumors, and multiple endocrine tumors.

What this study adds?

The first presentation of our case was osteochondromyxoma, a very rare component of CNC, without typical manifestations of CNC. We want to emphasize osteochondromyxoma, as a component of CNC.

Introduction

Carney complex (CNC) is a rare multiple neoplasia syndrome with an autosomal dominant inheritance (1). However, approximately 30 % of cases occur sporadically, as a result of de-novo mutations (2). Most patients with CNC, have inactivating mutations in PRKAR1A gene. PRKAR1A may act as a tumor suppressor gene by regulating protein kinasa A activity, which in turn can suppress or stimulate cell growth and differentiation (3). Carney complex is characterized by sporadic pigmentation of the skin, endocrinopathy, and endocrine and nonendocrine tumors. Patients often have tumors of two or more endocrine glands, including adrenal cortex, pituitary and thyroid. This syndrome is associated with many other nonendocrine tumors, including cardiac myxomas, testicular tumors (primarily LCCSCT), psammomatous melanotic schwannoma, breast myxomatosis, and abnormal pigmentation (lentiginous) or myxomas of the skin (2,4).

Here we report an atypical case of CNC. He had initially presented with an intranasal tumor, the pathologic diagnosis of which could not be established clearly. During, follow up, LCCSCT, a CNC related tumor, was detected in the testes and with this knowledge, intranasal tumor was reevaluated histopathologically and it was found to be a osteochondromyxoma (OMX), a rare component of CNC. Coexistence of OMX and LCCSCT suggested CNC, and a previously known mutation, c.672G>A(p. Trp224*) was detected heterozygously in the PRKAR1A gene.

Case report

A 9-year-old male was referred to our pediatric endocrinology department because of partial empty sella on pituitary MRI, detected during follow up of an intranasal tumor.

In the history, 3 years ago, he had been admitted to another hospital with the complaint of swelling around his right orbita. Orbital MRI had revealed an intranasal tumor filling the nasal sinuses and destructing cribriform plate and orbita medial wall. This tumor was excised and osteochondroid tissue with osteoblasts, which suggested fibrous dysplasia histopathologically, was identified. One year after the operation, when he was 8 years old, he presented with pubic hair. His physical examination revealed increased testicular volume. Central precocious puberty (CPP) was diagnosed with increased LH and LH/FSH ratio in the GnRH test and GnRH analogue treatment was started. Cranial and pituitary MRI screenings were normal. Scrotal USG revealed multiple macrocalcifications in the testes bilaterally. At the age of 9, he presented with difficulty in nasal breathing which was due to the recurrence of the intranasal tumor. Paranasal sinus CT revealed a lobulated, 22x25x28 mm mass with amorphous calcification, adjacent to the right frontal lobe, which extended to the base of the sphenoid sinus and destructed surrounding tissues. Pituitary MRI was compatible with partial empty sella. At that point, the patient was referred to our clinic for endocrinologic evaluation and then followed up together with pediatric oncology and otorhinolaryngology department. He was the first child of nonconsanguineous parents. His birth history was unremarkable and family history was not significant for tumor occurrence. On physical examination, his height was 146 cm (1, 93 SD), weight was 38,5 kg (1,25 SD) and body mass index was 18kg/m2(0,23 SD). On his right lateral lumbar area, there were two domed, soft papules, the largest diameter of which was 5 mm (Figure 1). Bilateral testes volumes were 6 cc and the stretched length of the penis was 7cm. General examination was otherwise normal. Endocrinologic evaluation showed ACTH deficiency, peak cortisol level was 13.4 µg/dl by a low dose ACTH stimulation test. All other pituitary hormone levels were normal except gonadotropins which were prepubertal due to GnRH analogue treatment. Hydrocortisone replacement was started and the patient was operated for recurrent intranasal mass. Mesenchymal tumor containing
chondroid component was observed in pathologic examination (Figure 2). Because of the tumoral infiltration of the host bone (Figure 2 a, b, d), focal osteoid-like matrix within the tumor (Figure 2c), recurrence of tumor and the radiological findings, diagnosis of osteosarcoma could not be excluded. Nevertheless, clinical findings during the follow-up were not compatible with osteosarcoma and it was decided to follow the patient closely without giving any chemotherapy. By that time tests were re-evaluated with scrotal ultrasonography. Numerous coarse parenchymal calcifications in both testes and a 6x5 mm hypoechoic heterogenous solid lesion in the left testis were detected. Two months after operation, cranial MRI revealed 31x 13 mm residue mass. Therefore, PET-CT scan was used to evaluate the malignancy potential of the lesion. 18F-FDG-PET imaging revealed normal uptake value in the tumor and also in other parts of the body. The patient was reoperated for the tumoral lesion in the nasal cavity and testicular biopsy was performed from the testicular lesions, considering that these lesions might be due to metastases of the primary disease. In pathological examination of intranasional lesion, only granulomatous tissue and reactive bone formation were observed without cutaneous nodules. However, histopathological examinations were compatible with LCCSCT without malignant features (necrosis and mitosis) (Figure 3). The diagnosis of LCCSCT raised the possibility of CNC. Pathological diagnosis for the bone lesion was not clear, thus the specimens were re-evaluated for the possibility of OMX which is a rare CNC associated bone tumor, most frequently located in the nasal sinuses and diaphyses of the long bones. Pathologic re-examination revealed osteoid and chondroid predominant lobular areas and focal mesenchymal spindle cells that suggested OMX. OMC was reevaluated for fulfillment of the diagnostic criteria of CNC. The lesions on his back were cutaneous myxomas which are common components of CNC. Presence of OMX and LCCSCT, which are two major criteria, confirmed the diagnosis of CNC. Thus patient was evaluated for the association of other endocrinopathies, and growth hormone (GH) excess was detected. Pituitary MRI did not show any adenoma. Despite GH excess, growth velocity was not increased and other clinical manifestations related to GH excess were not found. There were no other endocrinologic dysfunctions related to CNC such as hyperprolactinemia and hypercortisolemia. On the contrary, he had ACTH deficiency. For the molecular confirmation, genetic analysis was performed and heterozygous nonsense mutation c.672G>A (p. Trp224*) was detected in the PRKAR1A gene. In our case, malignancy potential of LCCSCT was histopathologically low and maximum diameter of the tumoral lesion was 45 mm. Therefore, the lesions were followed up with scrotal USG without intervention and the size of the tumoral lesions did not change during 18 months follow-up. The patient was also screened for other CNC-associated tumors and no additional tumor was found.

Discussion

Carney complex is a rare multiple endocrine neoplasia syndrome with autosomal dominant inheritance. It is characterized by pigmented lesions of the skin and mucosa, cardiac, cutaneous and other myxomas, and multiple endocrine and non-endocrine tumors. To confirm the diagnosis, patients must meet at least 2 major criteria or 1 major and 1 supplemental criteria (5). In our case, CNC was diagnosed clinically with a high likelihood of histologic proven OMX and LCCSCT as two major criteria and confirmed with genetic analysis. More than 80% of CNC patients develop spotty skin pigmements, which typically appear early in life and may be located anywhere on the body, typically on the face, lips, genital area and mucosa (6). Pigmented skin lesions of CNC were not present in our case. Only two myxomatous lesions were detected as cutaneous manifestations. Carney complex is characterized by endocrine overactivity. Primary pigmented nodular adrenocortical disease is the most common endocrine lesion and causes hypercortisolism (7). Our patient's adrenal imagings were normal and had hypocortisolism due to ACTH deficiency which was associated with partial empty sella. Asymptomatic GH hypersecretion occurs in approximately 2/3 of patients, in most cases without imaging evidence of pituitary adenoma (8), like our patient. In our patient, the first manifestation of CNC was OMX, which is an extremely rare myxomatous tumor of the bone, affecting 1/3 of CNC patients (9), but it is one of the 11 diagnostic criteria (5). Although he had presented with a bone tumor at the age of 6, diagnosis of OMX was delayed by 3 years, because of unrecognization of tumor. Knowledge about OMX is inadequate due to its rarity. Suspicion is needed for diagnosis. It is characterized as a painless mass and may be unnoticed unless it enlarges and surrounds vital structures. It may affect any bone, but most frequently seen in the nasal sinuses and long bones of extremities (8). In our patient, the unique localization of tumor in the nasal sinus suggested OMX and it was subsequently proven histopathologically. Although OMX is a benign neoplasm, it can exhibit local invasive characteristics (9). On imaging, OMX is well circumscribed, but can be destructive (8), as in our case. Osteosarcoma was considered in differential diagnosis, because of the local invasive and destructive nature of the tumor and radiological images. However, osteosarcoma was unlikely diagnosis since no metastases were observed during 3 years follow-up. Osteochondromyxoma has a good prognosis with complete excision, however local recurrence is very common with incomplete resection (8-10). Disease recurrence is therefore more likely at sites where complete resection is difficult as it has been in our case. Large cell calcifying Sertoli cell tumors, especially in children, present in association with CNC or Peutz-Jeghers syndrome (11). More than 75% of males with CNC may have LCCSCT (12). Maligantancy is not common. Rare in young patients with bilateral tumors or in association with a genetic syndrome (11,13). Malignant behaviour is associated with large size (> 4cm), necrosis, increased mitotic activity, atypia, and vascular invasion (14,15). In our case, bilateral multiple nodular lesions were present. The largest diameter of nodules was 6.7 mm. There was no evidence of malignancy histopathologically. Tumors may lead to premature epiphyseal fusion and induction of CPP due to increased aromatase activity (5,14). Our case also presented with CPP. At first, it was thought that CPP was related to excision of intranasional tumor close to sellar region, but then we realized that it may be associated with LCCSCT. Because of the low malignancy risk of tumor, only imaging surveillance was performed as recommended (14).

In conclusion, we reported a case of CNC presented with undiagnosed OMX as first manifestation. Osteochondromyxoma is a very rare tumor, but should be considered in the differential diagnosis of local invasive, recurrent intranasal tumor. Also the possibility of LCCSCT should be kept in mind in adenomatous calcified testis tumor presenting with CPP. We hope that the present report will be helpful in the diagnosis and treatment of CNC in the future.

References


**Figure 1.** Cutaneous myxomas, largest diameter of 5 mm

**Figure 2 (a-d).** In nasal cavity-osteochondromyxoma: Tumor consists of lobular areas, chondroid, osteoid predominant, focal mesenchymal spindled cells (H&E X200)
Figure 3 (a-d): In testis—Large cell calcifying Sertoli cell tumor. The neoplastic cells form solid and hollow tubules and are immersed in a loose, myxoid matrix and tumor is composed of large polygonal cells with abundant eosinophilic cytoplasm and eccentric nuclei (H&E X100-200)