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Case Report

Familial Carney complex with biatrial cardiac myxoma

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ABSTRACT

We report a case of Carney complex (CNC) with biatrial cardiac myxoma. The patient had left and right atrial myxomas which were resected in a surgery. She showed bilateral adrenal tumors and multiple mammary tumors. She had pigmentation on her lower lip. Previously, her daughter was also diagnosed with CNC with cardiac myxoma. Both of them showed mutations in the PRKAR1A gene.
<**Learning objective:** Carney complex is a syndrome with skin pigmentation, myxomas, and endocrine abnormalities. It is an autosomal dominant disease and shows PRKAR1A gene mutation. We experienced a rare case of familial Carney complex with biatrial cardiac myxomas found by echocardiography and treated surgically.>

Introduction

Carney complex (CNC) is an autosomal dominant multiple neoplasia syndrome that includes cardiac myxoma, endocrine, cutaneous, and neural tumors [1,2]. Although the age at presentation may vary, CNC is usually diagnosed in young patients, predominantly in females [1]. Extra-cardiac manifestations of CNC include pigmented skin lesions, cutaneous myxomas, adrenal cortical disease, myxoid mammary fibroadenoma, and testes tumors in male patients [1].

Generally more than 75% of primary cardiac tumors are benign, and most of them are myxomas. The incidence of myxomas is 0.5 per million population per year. Up to 80% of them are localized in the left atrium while 7%–20% are found in the right atrium. Myxomas are found in the right ventricle in 2.5%–6% of cases, 8% in the left ventricle, 2.5% in two or more locations, and under 2.5% in both atria of the same patients [3].

We report a case of CNC with biatrial myxoma successfully treated by surgery.

Case report

A 51-year-old female patient visited our hospital with persistent fever for several weeks. There was no history of cardiovascular risk factors. Her lower lip had pigmentation (Fig. 1). Her daughter had skin myxoma without symptoms of heart failure and was diagnosed as having CNC with left atrial myxoma and mutations in the PRKAR1A gene. At the time of physical examination, the patient's temperature rose to 38.7 °C with swelling of the cervical lymph nodes. White blood cell count was 4,770/μL. Viral infection was suspected. She returned to normal temperature in two days without medication.

In spite of antimicrobial treatment for the lymphatic swelling, the symptoms persisted but swelling of lymph nodes disappeared in 4 days. As we found that the patient's daughter had CNC, we decided to perform a transthoracic echocardiography to understand the etiology behind the symptoms. The echocardiography showed a large mass (23 × 34 mm) in her left atrium and a small mass (18 × 11 mm) in her right atrium (Fig. 2A). A contrast-enhanced computed tomography (CT) showed two low density

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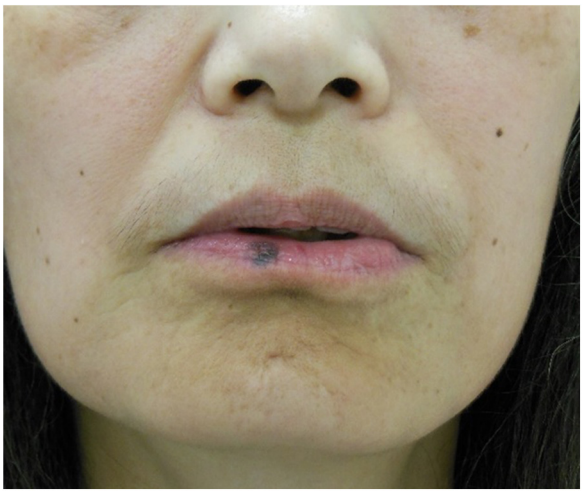

Fig. 1. Lip pigmentation. About 5-mm pigmentation was seen in the lower lip.

shadows in both atria. Cardiac myxoma was suspected. Both tumors were found to be growing from near the fossa ovalis but were independent from each other by transesophageal echocardiography (Fig. 2B and C). The left atrial tumor was attached to the mitral valve in diastole but did not cause a functional mitral obstruction. B-type natriuretic peptide (BNP) was 48 pg/mL (normal 0–18.4 pg/mL) and D-dimer was 0.8 μg/mL (normal 0–1 μg/mL). Left ventricular ejection fraction was 56% but the patient complained of no symptoms of heart failure or embolism. After surgery the ejection fraction was 62% and BNP was 50–60 pg/mL.

A resection of the cardiac tumors was performed and intraoperative findings showed two pedunculated tumors that adhered near to the fossa ovalis. Pathological analysis showed sporadic vascular structures with myxoid stroma in the background. Final histological diagnosis was myxoma (Fig. 3). Based on this diagnosis and her daughter's history with mutations of the PRKAR1A gene, we suspected the patient had CNC.

The patient had elevated levels of insulin-like growth factors-1 (IGF-1) and the growth hormone levels increased paradoxically after 75 g of oral glucose load (OGTT). No pituitary tumor was observed by magnetic resonance imaging. The growth hormone level did not change after resection of myxomas. Acromegaly was suspected and somatostatin was administered. She showed normal serum cortisol level with decreased adrenocorticotropic hormone (ACTH) level [morning cortisol levels: 10.3 μg/dL (NR: 6.2–19.4 μg/dL), ACTH: < 2.0 pg/mL (NR: 7.2–63.3 pg/mL). Thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and luteinizing hormone-releasing hormone (LHRH) loading test showed no abnormal response. Dexamethasone suppression test showed paradoxical increase of urinary cortisol. CT and adsterolscintigram demonstrated bilateral adrenal hyperplasia. They were compatible with primary pigmented nodular adrenocortical disease (PPNAD). Metyrapone 250 mg per day was administered for PPNAD. Mammary ultrasonography showed multiple oval low echoic areas. Needle biopsy class was III. The patient did not wish to continue the investigation and was followed by mammary ultrasonography. No thyroid tumor was detected by ultrasonography.

We investigated her PRKAR1A gene. Mutation g.106901(c.124) C > T hetero p.Arg 42 Ter in PRKAR1A gene was identified and the diagnosis of CNC was confirmed. Her daughter showed the same mutation. The patient was discharged in good condition.

Discussion

CNC was proposed by Carney et al. in 1985 [1]. Familial CNC is about 70% of CNC cases with an average age of diagnosis at 20 years [4]. Her daughter was diagnosed with CNC with left atrial myxoma and adrenal tumor at the age of 25 years.

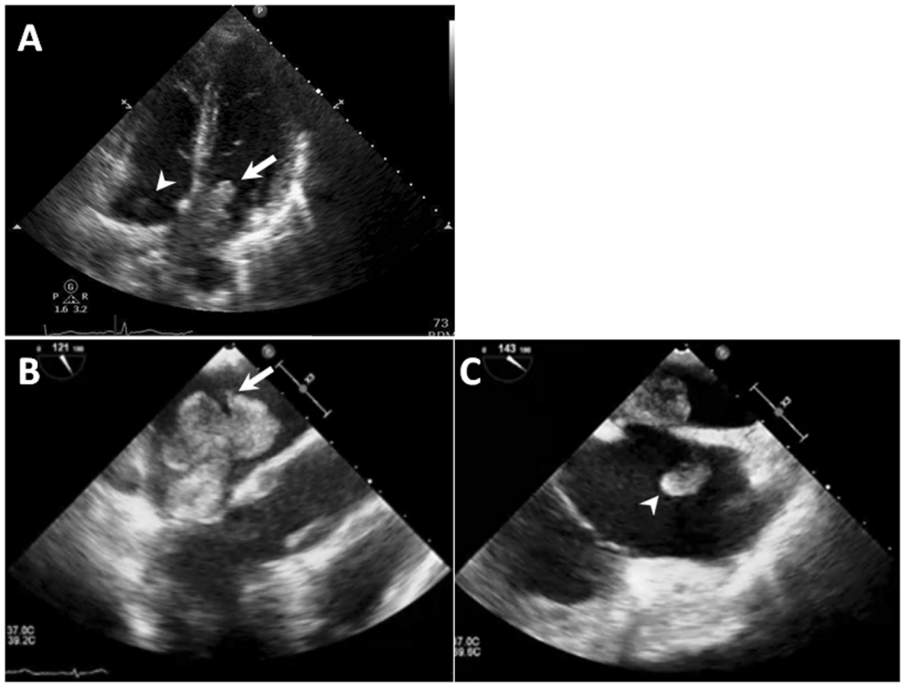

Fig. 2. Echocardiographic findings. (A) Four-chamber view of trans-thoracic echocardiography. An arrow indicates left atrial mass and an arrow head indicates right atrial mass. (B) Left atrial mass in trans-esophageal echocardiography. An arrow indicates left atrial mass. (C) Right atrial mass in trans-esophageal echocardiography. An arrow head indicates right atrial mass.

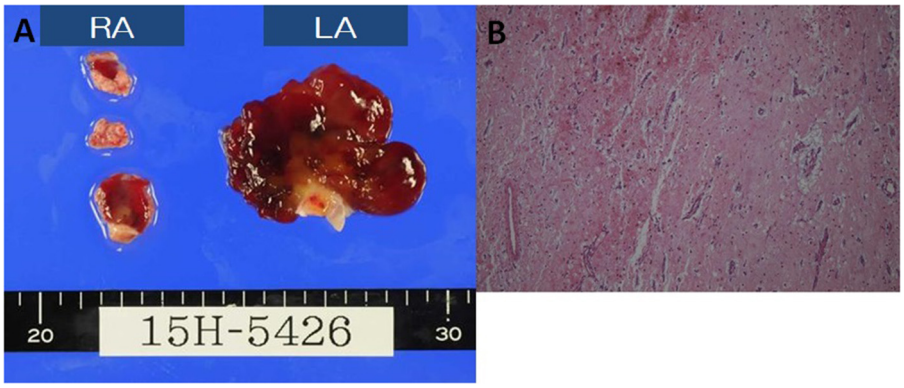

Fig. 3. Macroscopic and microscopic findings of myxoma. (A) Tumors resected from the right and left atria (RA, LA). A tumor from the right atrium was resected and separated into three pieces artificially. (B) Microscopic finding from the left atrial tumor. Dense vascular structures are observed in the myxoid interstitial tissue.

Cardiac myxomas are seen in about 30%–60% of CNC cases [5]. Usually cardiac myxoma is sporadic. However, multiple myxomas sometimes grow in multiple heart chambers in CNC cases. The patient had biatrial tumors which were suspected as cardiac myxoma. The fever and lymph node swelling seemed to have no relationship with myxoma because of their spontaneous relief. The patient showed no heart failure or embolism. The finding is one of the keys to suspect CNC if there was no familial history. Even after a complete resection of myxoma, recurrence rate is about 20% [6]. The recurrence is not only a residual one but also as a new lesion. Therefore, we have to follow up the patient by echocardiography every 6 to 12 months.

As for diagnosis, Carney proposed diagnostic criteria. It consists of 12 clinical signs and two supplementary items [5]. CNC is diagnosed if at least two clinical signs are met, or two clinical signs and one supplementary item are fulfilled. Our case met three clinical signs (lip pigmentation, cardiac myxoma, and paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration) and two supplementary items (affected first-degree relative and mutation of the PRKAR1A gene).

PPNAD and mammary tumors were detected as endocrine-related neoplasia. PPNAD is the endocrine tumor most often detected in CNC. With histologic confirmation, they are also included in the diagnostic criteria. In our case, both manifestations were suspected although they were not histologically confirmed. There was no pituitary tumor based on imaging diagnosis, but it is possible to appear in the future because of paradoxical increase of growth hormone after 75 g OGTT.

PRKAR1A gene is the gene encoding the protein kinase A type I-alpha regulatory subunit. Protein kinase A(PKA) activity in CNC tumors demonstrated a decreased basal activity, but an increase in cAMP-stimulated activity compared with non-CNC tumors. Germline mutations in PRKAR1A, an apparent tumor-suppressor gene, are responsible for the CNC phenotype in a subset of patients with this disease [7]. PRKAR1A gene mutation in the patient and her daughter firmly confirmed the diagnosis of CNC.

The patient did not undergo examination when her daughter was diagnosed with CNC. Since CNC is autosomal dominant, careful screening of the first-degree family members should be considered. Short- and long-term follow ups should also be carried out to detect recurrence and new neoplasms.

Conflict of interest

Authors have no conflict of interest.

Acknowledgment

This case was presented at the 121st Kinki Area Meeting of the Japanese Circulation Society.

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