Genetic Analysis in a Patient With Recurrent Cardiac Myxoma and Endocrinopathy

Yasushi Imai, MD; Tsuyoshi Taketani, MD*; Koji Maemura, MD; Norihiko Takeda, MD; Tomohiro Harada, MD; Takefumi Nojiri, MD; Daiji Kawanami, MD; Koshiro Monzen, MD; Dobun Hayashi, MD; Yuji Murakawa, MD; Minoru Ohno, MD; Yoshinobu Hirata, MD; Tsutomu Yamazaki, MD**; Shinichi Takamoto, MD*; Ryozo Nagai, MD

A 60-year-old male was referred for treatment of a cardiac myxoma in the right atrium. He had a past history of left atrial cardiac myxoma at age 49 and pituitary microadenoma related to acromegaly at age 55. He did not have a family history of cardiac neoplasm or endocrinopathy. The intracardiac tumor was resected and its pathology was compatible with myxoma. A diagnosis of Carney complex (CNC) was made because the diagnostic criteria of this neoplastic syndrome were satisfied by the presence of recurrent cardiac myxoma, endocrine tumor and spotty skin pigmentation. In genetic analysis novel frame-shift mutation was detected in exon 2 in a heterozygous fashion in the causative gene of CNC, protein kinase A regulatory subunit 1 (PRKAR1A). This genetic mutation is thought to cause haplo-insufficiency of PRKAR1A resulting in tumorigenesis. Although it is the most common, usually benign, cardiac tumor, myxoma can cause a critical clinical situation and thus detecting the PRKAR1A mutation can assist with prognosis.

Key Words: Acromegaly; Cardiac myxoma; CARNEY complex; PRKAR1A mutation

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carney complex (CNC), a neoplastic syndrome first characterized in 1985, consists of (1) myxomas in the heart and other locations (breast or skin), (2) spotty pigmentation (lentigines, pigmented nevi, or both), (3) endocrine overactivity (pituitary adenoma, primary pigmented nodular adrenocortical disease, or testicular tumors involving the endocrine components). Although cardiac myxoma is the most common, usually benign, tumor of the heart, it can cause a critical clinical situation. We present a case of recurrent cardiac myxoma that was identified as CNC with a genetic mutation.

Case Report

A 60-year-old Japanese male was referred for further evaluation of intracardiac mass in the right atrium. He had a past history of resection of a left atrial cardiac myxoma in 1992 (Fig 1A), at which time he suffered a cerebral hemorrhage caused by multiple cerebral aneurysms from myxoma tissue embolism. Because some of those cerebral aneurysms were gradually increasing in size, a series of angiographies incidentally detected a new intracardiac tumor in the right atrium (Fig 1B). He did not have a family history of cardiac myxoma or endocrinopathy.

During physical examination we observed acromegaly especially in the limbs and face. There were neither cardiac murmurs nor abnormal respiratory sounds. Remarkable skin pigmentation was noted. Blood tests showed slight elevation of the erythrocyte sedimentation rate and a significant increase in the interleukin-6 (IL6) concentration (81.9 pg/ml (normal range <4.0 pg/ml)), which is a useful biochemical marker of cardiac myxoma. Preoperative cardiac catheterization revealed normal coronary arteries without evident tumor-feeding arteries and normal left ventricular function. All of these findings strongly suggested recurrent cardiac myxoma.

The intracardiac tumor was surgically resected and the pathological findings were compatible with myxoma. His postoperative course was uneventful and the IL6 concentration decreased significantly to 9.7 pg/ml. Since discharge, he has been leading a normal life and routine ultrasonographic studies have not revealed any sign of tumor recurrence.

The patient’s recurrent cardiac myxomas, pituitary adenoma and skin pigmentation satisfy the clinical criteria for CNC. Protein kinase A regulatory subunit 1 (PRKAR1A) has been identified as one of the causative genes of CNC so after obtaining written informed consent from the patient, we sequenced the 10 exons of PRKAR1A using DNA extracted from his blood. We identified one heterozygous base pair deletion in exon 2, which produced a frame shift and premature stop codon with consequent PRKAR1A haploinsufficiency (Fig 2). This mutation site has not been reported in the literature. In addition, a base pair substitution (C to T) 3 base pairs downstream from the deletion site was also detected. The presence of a genetic mutation of
PRKAR1A strongly supports our clinical diagnosis.

Discussion

Myxoma is the most common type of primary cardiac tumor, comprising 30–50% of the total in most pathological series. Most myxomas occur in the left atrium and are usually attached to the fossa ovalis. However, myxomas may occasionally be found in the right atrium and, less often, the right or left ventricle. Some patients with cardiac myxoma have CNC. Syndromic myxomas, usually genetically transmitted, constitute approximately 10% or less of all myxomas. Patients with CNC tend to be younger and are more likely to have myxomas in locations other than left atrium.

Genetically, CNC is thought to be inherited in an autosomal dominant fashion and the responsible genes have been mapped to 2p16 and 17q22–24. In the latter candidate locus, PRKAR1A has been identified as one of the causative genes for CNC. The R1 regulatory subunit binds to the catalytic subunits of protein kinase A, inactivating the holoenzyme PRKAR1A. Thus, genetic mutations of PRKAR1A cause an increase in cAMP-stimulated activity of protein kinase A, ultimately leading to tumorigenesis. In the present case there was a novel frame shift mutation in exon 2 of PRKAR1A, which is a ‘hot spot’ previously identified in several pedigrees of CNC. Unfortunately, further evaluation of genetic mutation in his family was impossible because he has neither children nor siblings. However, the lack of a family history of syndromic cardiac myxoma or endocrinopathy suggests sporadic occurrence.

Although cardiac myxoma is usually benign, tumor embolism, intracardiac obstruction or other neoplastic formation can cause a critical situation. Therefore, a genetic survey of PRKAR1A mutations in patients with cardiac myxoma will assist with clinical decision making.

References