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Case Report: An Atypical Case of Carney Complex

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 54-year-old
Final Diagnosis: Carney complex (CNC)
Symptoms: Cough • dyspnea • heart failure • lightheadedness • palpitation
Medication: —
Clinical Procedure: Mitral valve repair • open heart surgery • transesophageal echocardiogram • transthoracic echocardiogram
Specialty: Cardiac Surgery • Cardiology • Endocrinology and Metabolic • Genetics

Objective: Rare disease

Background: Intracardiac tumors are a rare entity, with myxomas being the most common among them (approximately 50% of intracardiac tumors). Up to 80% of myxomas originate within the left atrium and while most are incidental or isolated findings in asymptomatic patients, others may result in clinical manifestations of heart failure or emboli. Moreover, in some cases, myxomas can be part of a genetically inherited syndrome known as Carney complex (CNC), and present with varied phenotypes, including skin, endocrine, and neuroendocrine tumors.

Case Report: We present a case of a 54-year-old male patient who presented with a several-month history of non-specific cough, dyspnea on exertion, and palpitations along with several skin tags, nevi, and nodules. He was found to have a retrocardiac density on chest X-ray, which was revealed to be a large left atrial myxoma on echocardiography. The myxoma was surgically excised and genetic testing for a mutation of the *PRKAR1A* gene (the most common mutation underlying CNC) was negative. However, 2 major clinical criteria for diagnosis of CNC were fulfilled based on cardiac myxoma and spotty skin pigmentation. In this report, we focus on the clinical manifestations of CNC, including guidance on tumor surveillance and genetic variants of CNC.

Conclusions: While CNC is most commonly associated with an inactivating mutation of the *PRKAR1A* gene, it can be diagnosed clinically in the absence of an identifiable genetic mutation. In patients presenting with atypical cardiac tumors, the early recognition of cutaneous manifestations can raise the index of suspicion for CNC, which can facilitate early diagnosis, treatment, and initiation of surveillance for neoplasia development.

Keywords: Atrial Myxoma, Familial • Carney Complex • PRKAR1A Protein, Human

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933744

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Background

Intracardiac tumors are rare entities, but when they do occur, among the most common are myxomas (about 50% of intracardiac tumors), which are gelatinous tumors consisting of stellate or globular cells within a mucopolysaccharide stroma [1-3]. Up to 75-80% of these myxomas originate within the left atrium and can result in emboli, heart failure, or non-specific constitutional symptoms. Less commonly, however, myxomas can be familial (~10%), and be associated with concurrent facial freckles or adenomas of the pituitary and thyroid [4-6].

Carney complex (CNC) is a rare syndrome most commonly inherited in an autosomal dominant fashion via an inactivating mutation of the *PRKAR1A* gene responsible for the protein kinase A (PKA) regulatory alpha-1 subunit, which results in multiple neoplasias (cutaneous, endocrine, and cardiac) and facial nevi [1,7]. Conversely, almost a quarter (~25%) of CNC cases are attributable to de novo mutations and nearly 30% of patients diagnosed with CNC do not have identifiable mutations of the *PRKAR1A* gene [6,8]. Moreover, there are controversial reports of CNC "variants" associated with arthrogryposis [9-11]. Clinically, cardiac myxomas associated with CNC are diagnosed at an early age, may be multiple and involve multiple cardiac chambers, and often tend to recur after resection. In patients with seemingly idiopathic heart failure symptoms and the cutaneous manifestation of nevi, clinicians should consider screening for myxoma and possible evaluation for CNC.

In this case report, we present an atypical case of CNC in which the patient's chief concern of dyspnea was attributed to bronchitis and community-acquired pneumonia. Subsequent imaging based on astute clinical suspicion revealed an intracardiac tumor and led to a diagnosis of CNC in the absence of any *PRKAR1A* gene mutation. We will discuss the skin findings and family history, which may have provided early clues to his diagnosis.

Case Report

An otherwise healthy 54-year-old fair-skinned man presented to an urgent care center with a 2-year history of intermittent, productive cough. He reported having worsening dyspnea on exertion for the preceding 2 to 3 months and was only able to walk a few feet without dyspnea. During that time, he experienced palpitations and intermittent lightheadedness, but no chest pain, fevers, chills, or upper-respiratory infection symptoms (eg, rhinorrhea, congestion). He denied any recent travel or a smoking history. Notably, since the onset of symptoms, he had visited urgent care centers on several occasions, where he was diagnosed with bronchitis or pneumonia, then treated with antibiotics and steroids without sustained relief. At this urgent care visit, the chest X-ray identified an apparent retrocardiac opacity (**Figure 1A**), which a followup computed tomography (CT) scan of the chest revealed to be an abnormal filling defect in the left atrium (approximately 5.1×6 cm) with extension into the left ventricle. At that time, the patient was urgently referred to our medical center for cardiology evaluation.

On physical examination, the patient was afebrile with a heart rate of 94 beats per minute (bpm), blood pressure of 136/81 mmHg, and oxygen saturation of 99% on room air. He was a well-appearing man without respiratory distress. A cardiac exam revealed normal heart rate and regular rhythm, normal S1 and S2 heart sounds without tumor plop, but a 2/4 low-pitch, rumbling diastolic murmur was appreciated at the left lower sternal border. No jugular venous distension or peripheral edema

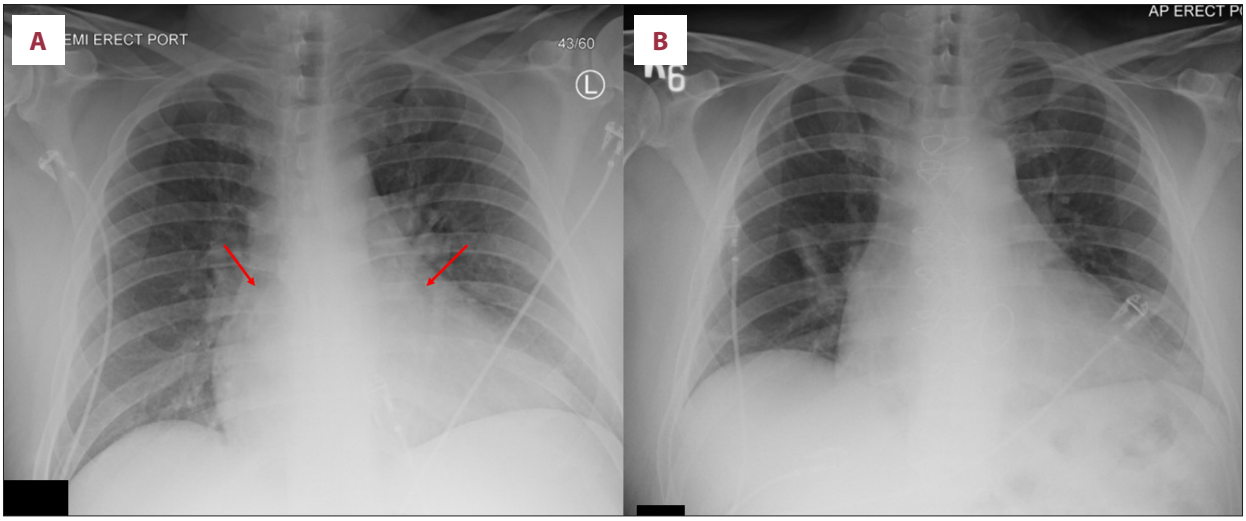

Figure 1. (**A**) Initial chest X-ray, demonstrating subtle, but well-circumscribed, opacity underlying the cardiac silhouette (red arrows). (**B**) Postoperative chest X-ray without the density.

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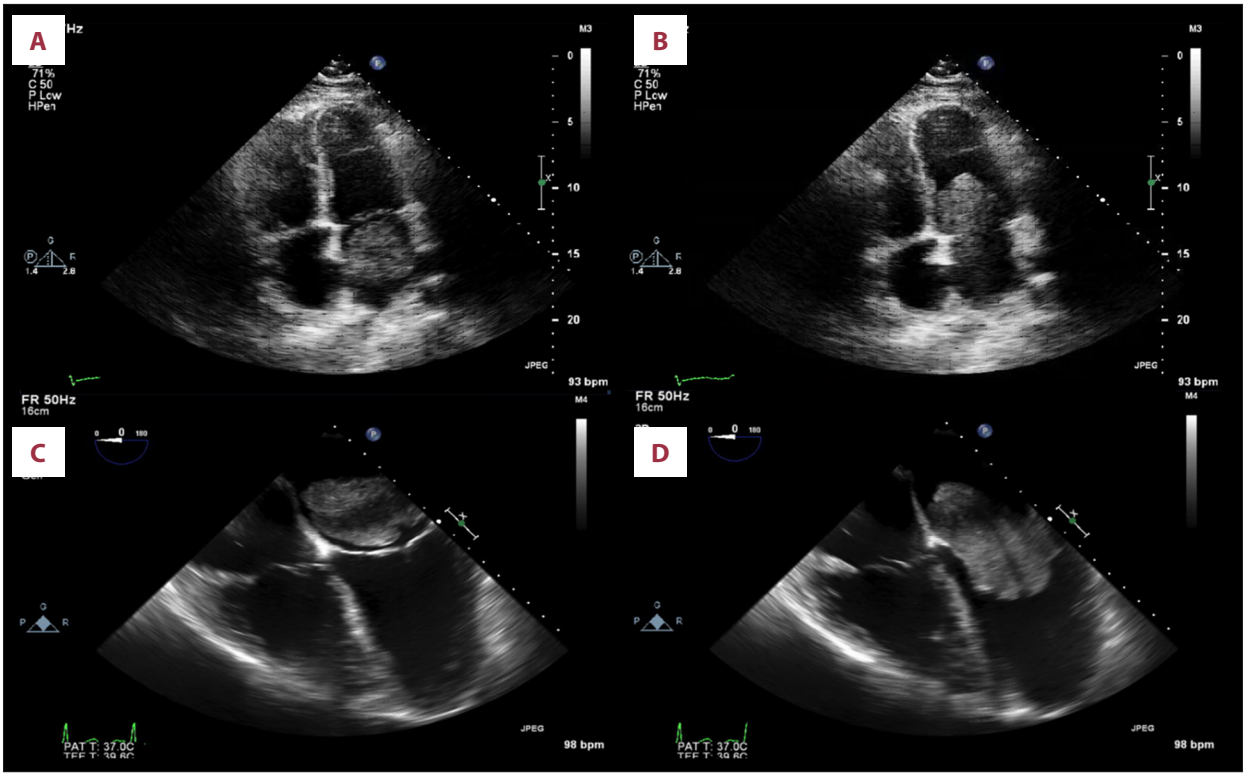

Figure 2. (**A, B**) Initial transthoracic echocardiogram demonstrating a large left atrial mass (9×4 cm) prolapsing into the left ventricle. Right ventricular systolic pressure was 95 mmHg. (**C, D**) Perioperative transesophageal echocardiogram demonstrating a 7.5×4.5 cm mass attached to the atrial septum. Left ventricular ejection fraction was 40-45%.

was noted. A lung exam revealed good inspiratory effort and no crackles or rales to posterior auscultation. The skin exam was notable for multiple flesh-colored skin tags around the circumference of his neck and anterior to the left ear, innumerable pigmented and non-pigmented rubbery nodules on his back, multiple perioral hyperpigmented ink-like lentigines, and a small hyperpigmented macule at the right upper cheek.

The patient did not have any prior medical history or active outpatient medications. However, his family history was significant for diffuse skin tags in his father and an unknown congenital heart disease in his infant daughter (deceased).

Transthoracic echocardiogram (TTE) confirmed a single 9×4 cm left atrial mass (**Figure 2A**) with mildly reduced left ventricular ejection fraction (LVEF ~ 40%), mild mitral regurgitation (normal mitral valve leaflets), and right ventricular systolic pressure (RVSP) of 95 mmHg, consistent with severe pulmonary hypertension. The mass was noted to be prolapsing into the left ventricle during diastole (**Figure 2B**). Transesophageal echocardiogram (TEE) again confirmed the large left atrial mass (measured at 7.5×4.5 cm) with diastolic prolapse into the left ventricle (**Figure 2C, 2D**).

Left heart catheterization (LHC) was subsequently done to evaluate for coronary artery disease and demonstrated multivessel luminal irregularities without obstructive coronary disease. Additionally, the LHC confirmed normal left ventricular end-diastolic pressure (LVEDP). In the setting of an elevated RVSP, a dilated left atrium, but normal LVEDP and normal mitral valve leaflets, the etiology of the patient's severe pulmonary hypertension was determined to be from functional mitral stenosis caused by the left atrial mass (WHO group 2 pulmonary hypertension).

The patient was taken for urgent surgical excision of the mass by cardiothoracic surgery, who performed the open excision with cardiopulmonary bypass support. The tumor stalk was attached to the inter-atrial septum and had dilated the mitral valve annulus. A portion of the inter-atrial septum was resected along with the intact tumor. Subsequently, the inter-atrial septum was repaired with a square bovine pericardial patch and the mitral valve annulus was repaired with a semi-rigid annuloplasty ring.

Intra-operative TEE demonstrated successful removal of the left atrial mass with mild improvement of ejection fraction (**Figure 3C, 3D**). Postoperative TTE confirmed the mass excision (**Figure 3A, 3B**) and improvement of pulmonary hypertension

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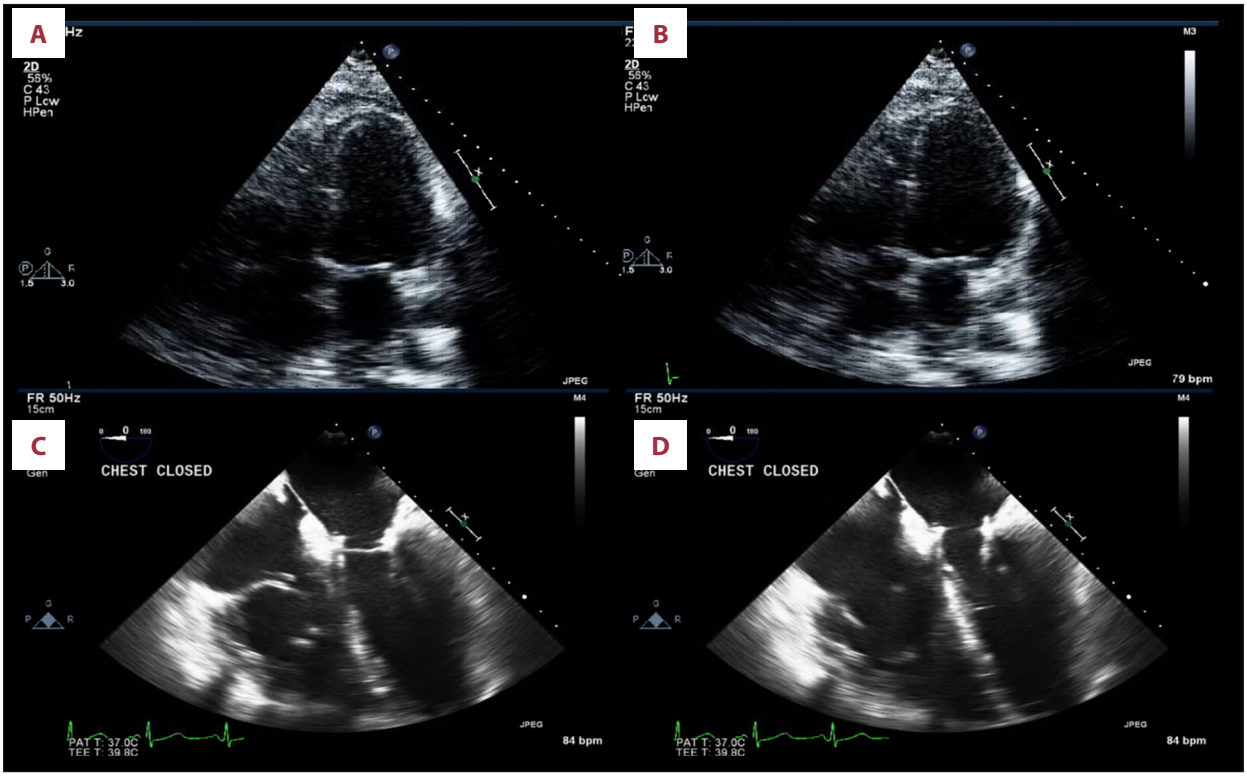

Figure 3. (**A, B**) Postoperative transthoracic echocardiogram showing that the mass is now absent, with right ventricular systolic pressure improved to 50 mmHg. (**C, D**) Perioperative transesophageal echocardiogram confirming removal of echodensity and mild improvement of the left ventricular ejection fraction to 45-50%.

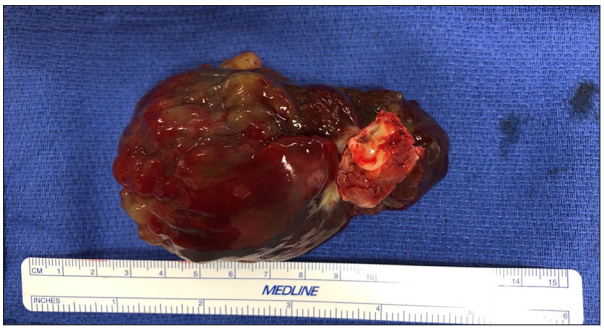

Figure 4. Postoperative image of pedunculated myxomatous tumor measuring 7.0×4.5×3.8 cm.

from RVSP 95 mmHg (pre-operatively) to RVSP 50 mmHg (post-operatively), which is near the age-adjusted upper limit of normal (15 mmHg to 45 mmHg for ages 50 to 75). Following excision, a post-operative chest x-ray (**Figure 1B**) no longer demonstrated the retrocardiac density seen pre-operatively (**Figure 1A**).

The excised mass (**Figure 4**) was subsequently sent to pathology for further analysis. Immunohistochemistry stains were positive for calretinin, an immunohistochemistry marker strongly expressed in cardiac myxomas, as well as CD34, which confirmed the diagnosis of cardiac myxoma.

Following successful surgical resection of the atrial myxoma, the patient was extubated and began ambulating on postoperative day 1. A genetics consultation was obtained postoperatively due to concern about CNC. Genetic testing for an inactivating mutation or large deletion in *PRKAR1A* was negative, but major clinical criteria were fulfilled for the diagnosis of CNC.

The patient was successfully weaned off the nasal cannula and discharged home with close followup. One year after resection, he was evaluated by cardiology and underwent repeat TTE, which was notable for moderately decreased right ventricular function with normal cavity size, but negative for recurrent cardiac myxoma. At that visit, he denied chest pain, peripheral edema, or limitations of functional capacity, although he continued to experience mild dyspnea with heavy exertion (several flights of stairs). We attempted to contact the patient to offer further genetic studies (linkage and exome testing, including evaluation of CNC2), but he declined any additional testing at this time.

Discussion

As previously mentioned, while cardiac tumors are rare entities, atrial myxomas are among the more common among

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these tumors. These gelatinous tumors, comprised of stellate or globular cells within a mucopolysaccharide stroma, can be pedunculated. Up to 80% of cardiac myxomas originate within the left atrium, which can lead to complications such as systemic emboli and clinical heart failure. While the majority of myxomas are isolated, approximately 3% to 10% are associated with cutaneous manifestations and thyroid/pituitary adenomas in a familial inheritance pattern, such as CNC [5,6].

In approximately 70% of cases, CNC is an autosomal dominant condition resulting from an inactivating mutation of the *PRKAR1A* gene (also known as the CNC1 locus on chromosome 17q2) encoding the protein kinase A (PKA) regulatory alpha-1 subunit, which leads to multiple neoplasias (eg, cutaneous, endocrine, and cardiac) and facial nevi/spotty pigmentation [1]. The PKA regulatory subunit serves as a tumor suppressor under normal circumstances, which is why inactivation results in the proliferation of neoplasia. However, up to 25% of CNC cases can be a result of de novo mutations in the *PRKAR1A* gene rather than the autosomal dominant inheritance pattern. Of note, while 70% of patients diagnosed with CNC have an identifiable mutation (inactivation or large deletion) in the *PRKAR1A* gene, the remainder of cases do not [1,5-8]. Per Correa et al, it is postulated that there may be a second locus (known as CNC2) within the short arm of chromosome 2 (2p16) responsible for a percentage of CNC cases; this locus has been associated with CNC through linkage studies [8]. Matyakhina et al have identified amplification of the 2p16 locus in tumors from CNC patients with and without *PRKAR1A* mutations. However, the exact gene responsible for these neoplastic changes (at the 2p16 locus) has yet to be identified [7]. To further underscore the genetic heterogeneity of CNC, Veugelers et al described a CNC variant in a large family with familial cardiac myxomas and distal arthrogryposis associated with a missense mutation in the myosin heavy-chain gene (*MYH8*) [9]. Conversely, subsequent studies have failed to identify *MYH8* mutations in CNC patients and, thus, argue that the syndrome described by Veugelers et al was not a CNC variant [10,11].

Clinical manifestations of CNC are exhibited via cutaneous lesions, endocrine tumors, and neuroendocrine tumors. Approximately 70% to 80% of patients with CNC develop lentiginous skin pigmentation within 2 decades of life, which are small, well-demarcated tan-to-black pigmented macules [4,12]. The lentigines associated with CNC have a predilection for perioral and periocular distribution, particularly at the vermilion borders of the lips and eyelid, which is uncommon of macules found within the general population. Our patient was noted to have small tan and black lentigines above his upper and lower lips, which had self-reportedly been present since his late teenage years. A smaller proportion of CNC patients (~40%) may have cutaneous myxomas (subcutaneous nodules), a multitude of blue nevi (blue-gray papules), and café-au-lait spots [4,5]. As previously mentioned, our patient's back exam was notable for several rubbery nodules of various pigmentations, as well as a flesh-colored tag anterior to his left ear. Skin biopsy was deferred at the time, but the most likely differential for these nodules certainly included cutaneous myxoma and neurofibroma. Additionally, our patient was found to have a small nevus at his right upper cheek, which he reported had developed over recent years and was concerning for blue nevus. Endocrine disturbances are the hallmark of CNC, with the spectrum of disease including Cushing's syndrome from nodular adrenocortical tumors leading to overproduction of cortisol (25-45% of CNC cases), hypersecretion of growth hormone (~67% of CNC cases), testicular Sertoli cell tumors (~75% of male CNC cases), and thyroid nodules (~75% of CNC cases). While these patients may develop Cushing's phenotype and late-onset acromegaly, the majority of gonadal and thyroid tumors are benign with a roughly 10% to 20% risk of becoming malignant [8,12,13]. Our patient's metabolic panel (Hgb A1c 5.90%, thyroid stimulating hormone [TSH] 1.83 mIU/L, and normal lipid studies) did not suggest any overt manifestations of endocrine dysfunction and further gonadal studies were not performed apart from a prostate-specific antigen of 1.40 ng/mL, which is below the upper limit of normal (4.00 ng/mL). Finally, neuroendocrine tumors are highly characteristic of CNC, including cardiac, breast, and osteochondral myxomas, as well as malignant melanotic nerve sheath tumors predominantly in the gastrointestinal tract and spinal nerve roots [12,13]. Based on recent literature, about 7% of all cardiac myxomas are associated with CNC, which becomes more clinically relevant when considering that CNC-associated cardiac myxomas have an earlier age of onset, potential for simultaneous multichamber involvement, and increased risk of recurrence following excision [2,3,5,6,14]. Our patient's single left atrial mass had histopathological confirmation as a myxoma.

In terms of prevalence, there are approximately 700 to 800 individuals identified with CNC. Diagnosis of CNC requires the fulfillment of at least 2 major clinical criteria, or 1 major clinical criterion plus either a first-degree relative with CNC or a *PRKAR1A* inactivating gene mutation, or a pathogenic variant identified in the *PRKAR1A* gene (**Table 1**). Our patient was found to have perioral and labial lentigines, along with pathological confirmation of cardiac myxoma, thus fulfilling 2 major diagnostic criteria for CNC. His numerous back nodules and tag anterior to the left ear were highly suspicious for cutaneous myxomas, as was the suspected blue nevus at his right cheek (which may fulfill a third and/or fourth major criterion). However, dermatologic biopsies of those lesions have not been performed to our knowledge at this time. Additionally, his father's history of having similar cutaneous manifestations may represent an affected first-degree relative with CNC, but this is speculative without his father's complete medical

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Table 1. Diagnostic criteria for Carney complex (CNC) [4]. [Adapted from Mateus et al. 2008].

Major Diagnostic Criteria for Carney Complex (CNC) [4]
1. Spotty skin pigmentation with typical distribution (lips, conjunctiva, inner/outer canthi, vaginal and penile mucosa)
2. Cutaneous and mucosal myxoma*
3. Cardiac myxoma*
4. Breast myxomatosis* or fat-suppressed MRI suggestive
5. Primary pigmented nodular adrenocortical disease (PPNAD)* or paradoxical positive response of urinary glucocorticoid excretion following dexamethasone administration
6. Acromegaly due to growth-hormone producing adenoma*
7. Large-cell calcifying Sertoli cell tumor (LCCSCT)* or calcifications on testicular ultrasound
8. Thyroid carcinoma* or multiple hypoechoic nodules on thyroid ultrasound (< 18 y.o.)
9. Psammomatous melanotic schwannomas (PMS)*
10. Blue or epithelioid blue nevus*
11. Breast ductal adenoma*
12. Osteochondromyxoma*
Supplementary Criteria for CNC
1. Affected first-degree relative
2. Inactivating pathogenic variant in PRKAR1A gene

* Following histologic confirmation.

history or examination. Although no inactivation or deletion was found at *PRKAR1A* for the patient, it is possible he may have a pathogenic variant of the gene, copy number changes at the CNC2 locus, or an as-yet unidentified mutation responsible for CNC neoplasia [7].

In patients with CNC, management consists of surgical resection of existing tumors, as well as continued surveillance for systemic manifestations of the disease [3,5,8,12,13]. The treatment of cardiac myxomas, suspicious thyroid nodules, melanotic schwannomas, adrenocortical disease, and malignant Sertoli cell tumors is surgical resection. While strict guidelines regarding CNC surveillance are lacking, it is recommended that patients receive annual TTE for screening of new or recurrent myxoma and annual thyroid ultrasounds to screen for suspicious nodules. If there is a personal or family history of CNC in adolescence, then screening for nodules via annual testicular ultrasound, screening for adrenocortical disease with 24-h urinary free cortisol, and annual screening for overactive pituitary (insulin-like growth factor-1 and prolactin) are also recommended starting in adolescence.

Conclusions

Cardiac tumors can often be incidental findings in asymptomatic patients; alternatively, they can be familial and cause significant symptoms. Clinicians should have a high index of suspicion for workup of CNC in patients with early identification of a cardiac myxoma, concurrent cutaneous manifestations, and/or presence of extracardiac neoplasia. While an inactivating mutation of *PRKAR1A* is commonly associated with CNC, the diagnosis can be made in the absence of an identifiable genetic mutation. While the initial presentation may be non-specific, early diagnosis can allow for appropriate surgical treatment and possible screening of first-degree relatives.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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