

Evaluation and management of Carney's complex: an illustrative case

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■ Carney's complex is characterized by cardiac and cutaneous myxomas, mammary myxoid fibroadenomas, spotty mucocutaneous pigmentation, primary pigmented adrenocortical disease, large-cell calcifying Sertoli cell tumors of the testis, growth hormone-secreting pituitary adenomas, and psammomatous melanotic schwannomas. We present an illustrative case of Carney's complex in a 26-year-old woman who at age 20 underwent bilateral adrenalectomy for Cushing's syndrome. Six years later, she suffered multiple central nervous system embolic episodes secondary to three cardiac myxomas, which led to her death. Appropriate evaluation and management of patients with Carney's complex is outlined.

□ INDEX TERM: CARNEY'S COMPLEX □ CLEVE CLIN J MED 1991; 58:248-256

CARNEY'S COMPLEX is characterized by cardiac and cutaneous myxomas, mammary myxoid fibroadenomas, spotty mucocutaneous pigmentation, primary pigmented adrenocortical disease, large-cell calcifying Sertoli cell tumors of the testes, growth hormone secreting pituitary adenomas,^{1,2} and psammomatous melanotic schwannomas.³ Carney's complex is familial and probably autosomal dominant.^{1,4,5} Early recognition may prevent or delay the development of complications. We present an illustrative case of Carney's complex, review the diagnostic criteria in the literature, and recommend appropriate management.

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CASE PRESENTATION

A 26-year-old single woman had cutaneous "tumors" excised from her right ear and thigh in early childhood. The pathologic materials of the cutaneous lesions were unavailable for review. She developed secondary amenorrhea at age 13 but complete examination at a university medical center was negative. At age 20, she was evaluated for moon facies, purple striae, male escutcheon, and persistent amenorrhea.

■ See Sheeler (p 214).

Her family history was entirely unremarkable. The findings included normal blood pressure, glucose tolerance test, and urinary 17-hydroxy-corticosteroids (17OH) and 17-ketocorticosteroids (17KS). Hirsutism and a buffalo hump developed when the patient was 21 years old. Repeat testing revealed a diabetic glucose tolerance test and elevated 17OH and 17KS.

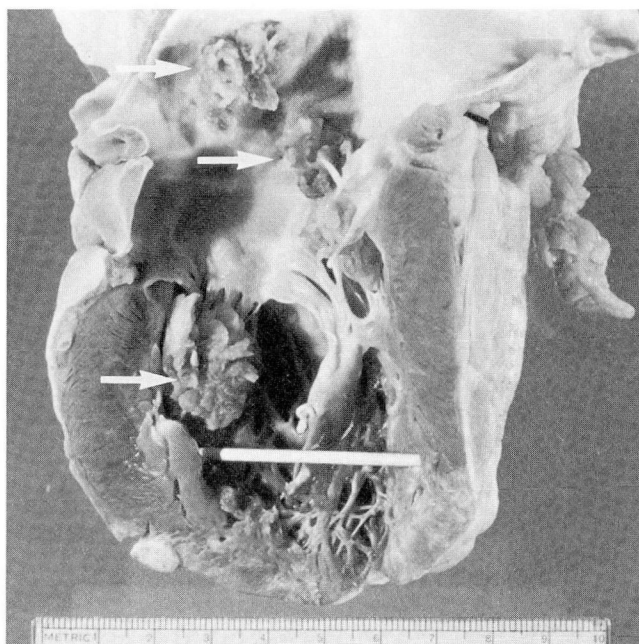


FIGURE 1. Three reddish-gray, moderately firm, friable, fungating masses characteristic of cardiac myxoma (arrows) are present on the interatrial septum and the papillary muscle and chordae of the anterior leaflet of the mitral valve.

Upon surgical exploration at the University of Michigan Medical Center, the right adrenal gland was found to contain a brown nodule with surrounding cortical atrophy. Multiple small brown nodules were found in the left adrenal gland. A total right and partial left adrenalectomy, which removed all grossly visible nodules, was performed. Ten months later, stigmata of Cushing's syndrome had regressed and menses recurred.

Two years later, in 1957, she was admitted to the Cleveland Clinic because of a stroke, thought to be caused by thrombosis of the right superior cerebellar artery. Oral anticoagulants were started, but 2 months later she suffered a myocardial infarction. A left central retinal artery occlusion developed 1 year later. Anticoagulants were continued and she had no other complications until 2 years later, when another stroke resulted in right-sided hemiplegia.

The patient recovered partially. Seven months later she had an episode of lethargy and aphasia from which she recovered fully in 2 hours. Physical examination at the time of this episode revealed excess hair and brown spotty pigmentation on the upper lip, striae over both thighs, and a rounded face. Ocular fundoscopic ex-

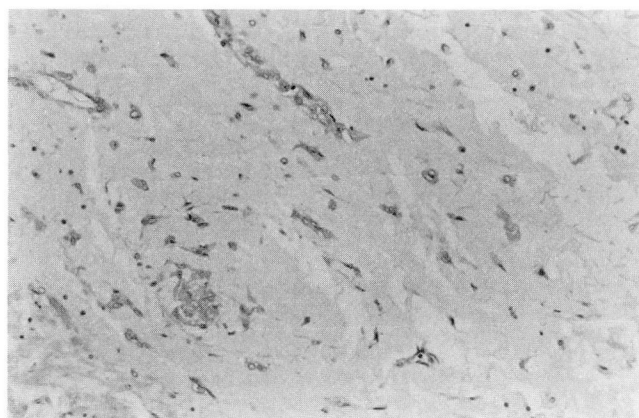


FIGURE 2. Cardiac myxoma characterized by spindled to stellate cells set in a basophilic, edematous, myxomatous stroma. Capillaries and inflammatory cells are variably present (hematoxylin-eosin, $\times 50$).

amination revealed a left central artery occlusion. Cardiac examination revealed no murmurs or tumor plop. Peripheral vascular examination revealed absence of the ulnar pulses bilaterally. Neurologic examination demonstrated a weakened right arm and leg with hyperactive reflexes.

The prothrombin time was 36 seconds (normal, 14 seconds); 24-hour urine values for 17KS and 17OH were within normal limits and did not change in response to administration of adrenocorticotrophic hormone (ACTH). Radiographs of the skull and chest were negative. Muscle biopsies were negative for vasculitis. The patient was discharged on warfarin, 5 mg and 7.5 mg on alternate days; hydrocortisone, 20 mg daily; and 9- α fluorohydrocortisone, 0.05 mg twice weekly.

She did well for 3 weeks but sustained numbness in her left arm and leg, and a sudden loss of consciousness prompted readmission. Eight days later, there was sudden development of drowsiness, dysphasia, and complete left-sided motor paralysis, which progressed to a comatose state with generalized rigidity, irregular respiration, and death.

Autopsy findings

A complete autopsy was performed. Focal areas of pale gray mottling were present throughout the left ventricle, particularly in the apex. These areas surrounded small intramyocardial vessels with dark red centers. Within the left atrium overlying the foramen ovale, there was a papillary, pale reddish-gray,

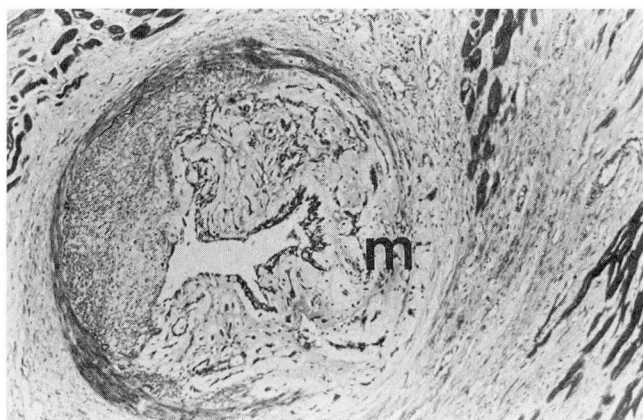


FIGURE 3. The smooth muscle and elastic laminae of a small coronary artery are partially obliterated (M) by myxoma (Movat, $\times 15.5$).

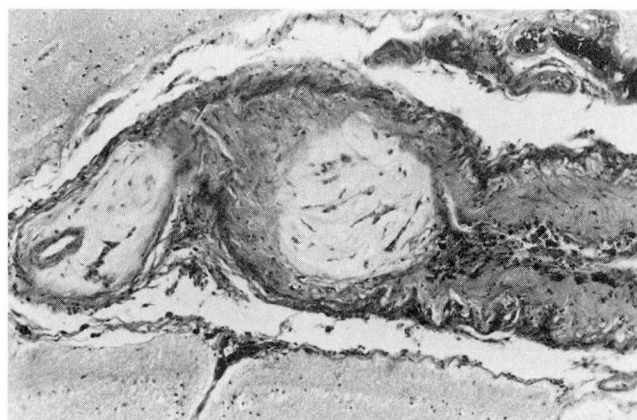


FIGURE 4. An embolus of cardiac myxoma occludes a small cerebral artery. Similar emboli were found in small renal arteries. (Luxol fast blue-cresyl violet-eosin, $\times 31.2$).

moderately firm, friable mass measuring 2.0 cm \times 2.0 cm. Similar masses were found on the left side of the inferior interatrial septum, the left ventricular anterior papillary muscle, and chordae tendineae of the mitral valve (Figure 1).

Examination of the brain revealed transtentorial herniation and cerebellar tonsillar herniation, a remote left parieto-occipital infarct, and a recent hemorrhagic right frontotemporal infarct.

Residual adrenal tissue was noted bilaterally adjacent to the kidneys. Both breasts and the pituitary gland were unremarkable. The right ovary contained a large hemorrhagic follicular cyst but otherwise the ovaries were normal.

Microscopically, the cardiac mass lesions consisted of spindled to stellate cells set in a basophilic, myxomatous, and edematous stroma characteristic of myxoma (Figure 2). The masses invaded the atrial and ventricular cardiac muscle in several areas. Sections of the coronary arteries demonstrated emboli of myxoma which invaded and destroyed the vascular smooth muscle, elastic laminae, and surrounding cardiac muscle adjacent to areas of recent and remote infarct (Figure 3).

Similar emboli of myxoma were present in the cerebral arteries near recent and remote infarcts (Figure 4) and in small renal arteries. The adrenal gland sections contained sharply demarcated nodules of large eosinophilic cells with large nuclei and nucleoli and focal pigment accumulation in the cytoplasm, characteristic of primary pigmented adrenocortical disease (Figure 5).

DISCUSSION

In 1985, Carney and associates² reported a series of 40 patients with multiple myxomas, spotty pigmentation, and endocrine overactivity. Most of the patients were young and had multicentric tumors; when paired organs were involved, the involvement was bilateral. Most patients manifested three to five components of the complex. Nine (23%) patients died as a result of cardiac myxomas. By 1987, Carney had identified a total of 67 cases⁶ and since that time, at least 10 more cases have been reported in the literature.⁷⁻¹³ Of these 10 cases, cardiac myxomas caused 1 death.

In retrospect, our patient fulfilled the criteria for Carney's complex, with multiple cardiac myxomas, primary pigmented adrenocortical disease, perioral cutaneous pigmentation, and cutaneous "tumors." Bilateral subtotal adrenalectomy cured her Cushing's syndrome, but her cardiac myxomas were not detected, and embolic central nervous system events contributed to her death.

Diagnostic criteria

Cardiac myxomas are found in 76% of patients with Carney's complex. The cardiac myxomas associated with Carney's complex differ from other cardiac myxomas in that they occur in young individuals, tend to be multiple, and involve multiple chambers. In contrast, sporadic cardiac myxomas occur in older persons, are single, and usually are located in the left atrium (86%).¹⁴ Histologically benign cardiac myxomas may recur, locally invade and extend, or embolize to distant

sites to form tumor masses. At the embolic site, the myxoma may invade and destroy an artery, causing microaneurysms, as happened in our case.

Primary pigmented adrenocortical disease, a cause of ACTH-independent Cushing's syndrome, is present in approximately 37% of patients with Carney's complex. Both adrenal glands are involved and are characterized by grossly visible small brown-black nodules separated by atrophic adrenal cortex.

Microscopically, the nodules consist of large cortical cells with eosinophilic cytoplasm and large, hyperchromatic nuclei. Nucleoli are often present. The cytoplasm is rich in lipofuscin pigment¹⁵ and possibly neuromelanin.¹⁶

Plasma ACTH is usually undetectable. Adrenal steroid production is not suppressed with high-dose dexamethasone and responds poorly to metyrapone.^{17,18} Computed tomography (CT) shows adrenal glands of normal or slightly enlarged size.¹⁷ Because symptoms are frequently mild, there may be a long interval between onset of symptoms and diagnosis. The cause may be related to circulating IgG immunoglobulins directed at ACTH receptors.¹⁹

Skin lesions include cutaneous myxomas, spotty pigmentation, and blue nevi. Spotty pigmentation is present in 66% of patients and appears as brown to black irregular macules that may be distributed over the entire body surface; more often they are found around the eyes, mouth, and vermilion border of the lip. Lentigines and blue nevi are the most common pigmented lesions. Cutaneous myxomas are present in 43% of patients and are found most commonly on the eyelid as sessile nodules or pedunculated lesions. Myxoid fibroadenomas of the breast are found in 21% of cases and may be bilateral and multifocal.

Psammomatous melanotic schwannomas, recently described by Carney³ but not found in our case, are identified in 14% of patients with the complex. The lesions may be located in the alimentary tract, especially the stomach, bone, or dorsal spinal roots.³ Psammomatous melanotic schwannomas manifest at a younger age than classic schwannoma and may present with neurologic symptoms, mechanical dysfunction, or pain. The tumor is well circumscribed, black to gray in color, and rubbery to firm in consistency. The course is indolent and invasion is usually localized, but four patients have died of metastatic disease.³ Surgical resection usually is curative.

Large-cell calcifying Sertoli cell tumors of the testis are found in 46% of male patients with Carney's complex, and may present with precocious puberty or as a

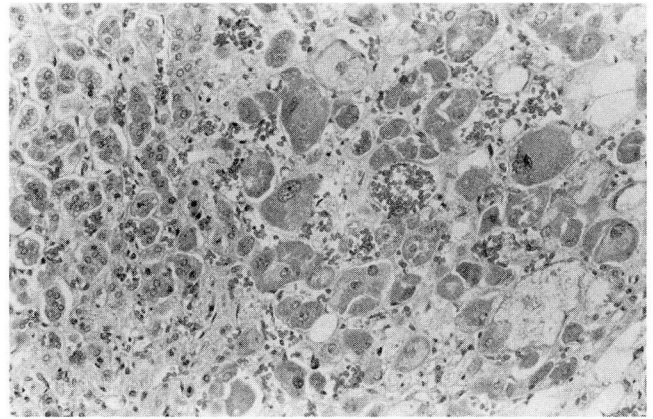


FIGURE 5. Adrenal gland containing nodules of large eosinophilic cells with large hyperchromatic nuclei, large nucleoli, and accumulation of cytoplasmic pigment characteristic of primary pigmented adrenocortical disease (hematoxylin-eosin, $\times 62.2$).

palpable testicular mass. The tumors are well circumscribed, yellow-tan, and characterized by large cells with abundant eosinophilic cytoplasm and calcification.²⁰ Large-cell calcifying Sertoli cell tumors are often bilateral and multifocal. Metastases are rare.

Growth hormone-secreting pituitary tumors, which are found in 9% of patients with Carney's complex, may cause acromegaly. Possible signs or symptoms from an invasive pituitary mass might include headache, chiasmal compression, temporal lobe seizures, or cavernous sinus invasion with third, fourth, or sixth cranial nerve injuries.

Management

Our patient presented with Cushing's syndrome caused by autonomously functioning adrenal glands. Primary pigmented adrenocortical disease can be diagnosed on surgical resection and pathologic examination. This diagnosis should precipitate a thorough search for cardiac myxomas, testicular tumors in males, and pituitary and soft tissue tumors. All patients with the typical pigmentation, primary pigmented adrenocortical disease, or large-cell calcifying Sertoli cell tumors should be investigated for cardiac myxomas.²

First-degree relatives (parents, siblings, and children) of affected patients should have a complete examination, including evaluation of the cardiovascular system and adrenal glands.¹ The examination should be repeated yearly. Cardiac evaluation should include an imaging procedure such as echocardiog-

raphy, angiography, or magnetic resonance imaging.

Surgical management of the cardiac myxomas of Carney's complex should include "(1) a thorough search of each cardiac chamber for myxoma; (2) complete excision of the area of attachment with the atrial septum (when the myxoma arises from this location) and either primary or patch closure of the atrial septal defect; and (3) excision of myxoma(s) and underlying endocardium for myxoma(s) arising on the free wall of the atria or ventricles."²¹

Early recognition of Carney's complex may prevent or delay future complications such as central nervous system embolic disease and local destruction or metastases from the associated tumors.

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