

# Advanced Atherosclerosis with Leriche Syndrome, in a Patient with Carney Complex

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## ABSTRACT

Carney complex (CNC) is a rare autosomal dominant syndrome. Spotty skin pigmentation is the major clinical manifestation of CNC, followed by cardiac myxomas, benign tumors that usually present with features from the classical triad of obstructive cardiac, embolic and non-specific constitutional symptoms (NCS). NCS are caused by the overproduction of interleukin-6 (IL-6), a pro-inflammatory cytokine which mediates the induction of intercellular adhesion molecule 1 (ICAM-1) and promotes endothelial dysfunction and atherosclerosis. Thus, myxomas may be directly linked to an increased risk of atherosclerotic events.

We report here a case of a 74-year-old woman with left atrial myxoma, skin pigmentary abnormalities, thyroid disorder and extensive atherosclerosis, with non-embolic occlusion of infrarenal abdominal aorta.

**Keywords:** Carney complex, critical limb ischemia, Leriche syndrome, cardiac myxoma, atherosclerosis, autoimmune thyroid disorder.

## INTRODUCTION

Cardiac myxomas are the most common primary tumors of the heart; 7% of all cardiac myxomas are associated with Carney complex (CNC), an autosomal dominant syndrome consisting of spotty skin pigmentation, endocrinopathy and tumors, including myxomas (1-3).

Due to an increased expression of inflammatory cytokines, mainly interleukin-6 (IL6) (4), myxomas are associated with a chronic inflammatory status, which accelerates the development of atherosclerosis.

We describe here the case of a CNC patient with left atrial myxoma and severe atherosclerosis, who had critical Leriche syndrome (LS), coronary artery disease (CAD) and non-critical in-

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involvement of carotid, upper extremity limbs and renal arteries. □

**CASE REPORT**

A 74-year-old woman was admitted to the emergency department (ED) with a month old critical limb ischemia (CLI), symptomatic by severe pain and dry gangrene at the second left toe. She also reported fatigue, dizziness, one episode of loss of consciousness a month ago, and episodes of angina pectoris a few years before. Her medical history included Basedow-Graves disease, treated with radioactive iodine, currently with permanent hypothyroidism, a heart tumor known by 10 years, essential arterial hypertension, dyslipidemia and active smoking.

Physical examination revealed an underweight patient, with light exophthalmia and no obvious goiter. Skin exam showed a generalized hyperpigmentation with café-au-lait spots, multiple lentiginos predominantly on her upper body, mainly on the back, and a solitary nodule on the left cheek, suggestive of cutaneous myxoma (Figure 1). Cardiovascular examination was notable for a high blood pressure of 220/110 mmHg at the right arm, with systolic blood pressure difference in upper limbs >100 mmHg, systolic murmurs at bilateral carotid arteries and left subclavian artery. The arterial pulse was absent at both femoral arteries with dry gangrene at the second left toe.

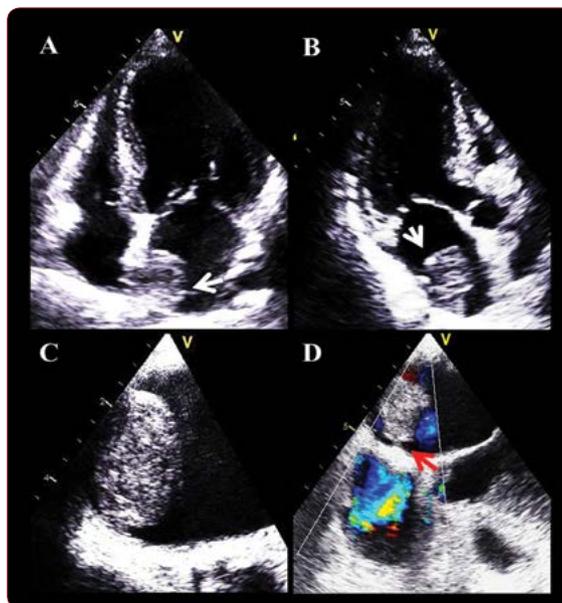
The ECG showed normal sinus rhythm with left ventricle hypertrophy (LVH). Blood tests revealed increased NTproBNP (560 pg/mL) and severe anemia, with a baseline hemoglobin (HGB) level of 7.1 g/dL, increased ESR (75 mm/h) and thrombocytosis (497000/μL). The biological picture associates severe hypothyroidism, with TSH > 50 μIU/mL, stage III kidney disease (eGFR=47.8 mL/min/1.73 m<sup>2</sup>), hypercholesterolemia (LDL=126 mg/dL), and hypertriglyceridemia (TRIG=180 mg/dL).

The transthoracic echocardiography revealed a sessile-like heterogeneous oval tumor in the left atrium, measuring 2,1x3 cm, close to the interatrial septum (IAS), in an otherwise normal-sized left atrium, with no obstruction of the mitral valve orifice. Along with these findings, LV hypertrophy has been noticed, with preserved EF and no significant valve disease. Further evaluation with transesophageal echocardiography revealed the presence of a short



**FIGURE 1.** Skin manifestations. Multiple pale brown to black lentiginos on the face (A-B) and back (D); solitary superficially bean-sized nodule on the left cheek, suggestive of cutaneous myxoma (B); café-au-lait spots (white arrows) with irregular borders, on the anterior chest wall and anterior axillary fold (C).

stalk (3 mm) attached to the IAS, explaining the poor mobility (Figure 2), and a soft atherosclerotic plaque in the thoracic descending aorta. The tumor was highly suggestive of myxoma,



**FIGURE 2.** Cardiac involvement. A-B. Transthoracic echocardiography, apical 4 chamber view (A) and 3 chamber view (B) showing a 2.1x3 cm mass (white arrow) in the left atrium (LA), away from the mitral valve and near the interatrial septum (IAS), but with an unclear attachment; C-D. Transesophageal echocardiography at the midesophageal level, which confirms the presence of a large ovoid and heterogeneous mass in LA (C), showing a more definite connection between the mass and IAS through a short and narrow stalk (D), without flow signal at color Doppler flow mapping (red arrow), suggesting the absence of blood supply.

considering its location and macroscopic features.

Taking into account the related neurological symptoms and a possible double source of embolism, from the cardiac myxoma and the unstable atherosclerotic plaque of the thoracic descending aorta, a non-contrast computed tomography (CT) of the brain was performed, excluding the presence of silent embolic strokes.

A peripheral angiography followed, which confirmed the clinical suspicion of Leriche syndrome, having infrarenal abdominal aorta occlusion (Figure 3), bilateral superficial femoral artery occlusion, with collateral loading of bilateral common femoral arteries. It also revealed a 60% stenosis of left internal carotid artery, a 70% proximal stenosis of left subclavian artery and a 50% ostial stenosis of left renal artery (Figure 3). Also, the coronary angiography pointed out a chronic total occlusion (CTO) of the proximal right coronary artery (RCA), distal vessel being retrograde loaded by epicardial and transeptal collateral from the left coronary artery, with no significant other lesions and no visible vascular supply of myxoma (Figure 3).

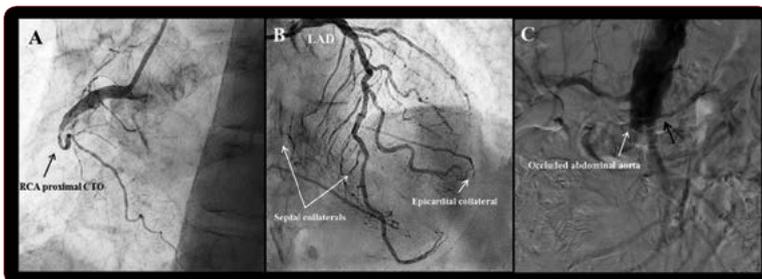
Surgical revascularization of the inferior limbs was recommended, but preceded by open-heart surgery, for RCA bypass and surgical excision of the myxoma, due to the high risk of embolization. Both surgical interventions were postponed until correction of associated pathologies, resis-

tant arterial hypertension, anemia and severe hypothyroidism.

The arterial hypertension was difficult to control after salt restriction, treatment with loop diuretics and maximal doses of angiotensin-converting enzyme inhibitors and dihydropyridine calcium antagonists, requiring addition of mineralocorticoid receptor antagonists and  $\alpha$ -2-adrenergic agonists (clonidine).

The anemia was characterized as microcytic (MCV=62.4 fL) with marked hypochromia (MCHC=28.9 g/dL), hyposideremia (FE=12  $\mu$ g/dL) and elevated TIBC (411  $\mu$ g/dL). Beta thalassemia was suspected, but the hemoglobin electrophoresis was inconclusive in the context of iron deficiency. Paradoxically, there was no evidence of active gastrointestinal bleeding, occult or macroscopic. Colonoscopy revealed the presence of hemorrhoids, but without bleeding stigmas. Other sources of bleeding were not detected. The patient received transfusion of one unit of packed RBCs, followed by i.v. iron substitution, partially correcting anemia up to a HGB value of 10,4 g/dL, with a corresponding increase in MCV to 76.6 fL, thus excluding thalassemia.

An evaluation by a specialist in endocrinology recommended increasing the dose of levothyroxine up to 125  $\mu$ g per day, with reassessing the TSH level after three months. The patient also received antiplatelet therapy with aspirin, statins, phosphodiesterase inhibitors (pentoxifylline) and pain relievers. She was advised to stop smoking and was discharged slightly improved. Unfortunately, after those three months, the patient informed us that she decided to reject surgery, choosing to continue the conservative treatment. In this situation, we were unable to provide a histopathological confirmation. There was no other family member available for screening, as the patient had no brothers, sisters or children.  $\square$



**FIGURE 3.** Selective angiography showing vascular involvement. **A.** Right coronary angiography, left anterior oblique view, with caudal angulation, showing a chronic total occlusion (CTO) of the proximal right coronary artery (RCA) (black arrow); **B.** Left coronary angiography, left anterior oblique view, with cranial angulation, showing retrograde filling of distal RCA through epicardial (simple white arrow) and septal collaterals (split white arrow) from the left anterior descending (LAD) artery; **C.** Abdominal aortography showing infrarenal abdominal aorta occlusion (white arrow) and a 50% ostial stenosis of left renal artery (black arrow).

## DISCUSSION

We presented a rare case of CNC with severe atherosclerosis, having CLI with occlusion of abdominal aorta, in a 74-year-old woman, which was unfortunately medically managed.

Carney complex is a rare syndrome caused mostly by mutations in the PRKAR1A gene, coding for the regulatory subunit type I alpha of the protein kinase A (PKA). These mutations are

inherited in an autosomal-dominant manner, in approximately 70% of cases, or occur sporadically as a result of a de novo genetic defect, in the remaining cases. For the majority of the PRKAR1A-negative CNC cases, the genetic cause remains unknown (2).

Currently, the diagnosis of CNC relies on clinical diagnostic criteria. A definite diagnosis is given when two or more major manifestations are present (2). Our patient had spotty skin pigmentation and cardiac myxoma as major manifestations, adding other findings possibly related to CNC such as café-au-lait spots and autoimmune thyroid disease (ATD). The facial cutaneous myxoma may be another major manifestation (2), but in the absence of a histological confirmation it does not contribute to diagnosis.

Cardiac myxomas are benign slow growing neoplasms with possible life-threatening complications. They are usually asymptomatic but can break the silence through one or more elements of the triad: embolic, obstructive and non-specific constitutional symptoms (NCS) (5).

Unusually, our patient was asymptomatic with advanced age till the admission with Leriche syndrome with infrarenal abdominal aorta occlusion and CLI. After further thorough investigations, we discovered an extensive atherosclerosis, having CAD with CTO of proximal RCA and other sites of the peripheral artery disease involved, like carotid, upper extremity limbs and renal ones.

The concomitant presence of atherosclerosis has also been reported in previous studies, and may be added to the above mentioned triad as a fourth category of events. The prevalence of CAD in patients with myxoma is ranging between 20.3% and 36.6% (6).

The advanced atherosclerosis may be caused, like NCS, by an overproduction of growth factors and cytokine, mainly IL-6. The amount of circulating IL-6 correlates with the size of the tumor and so, with the severity of symptoms (4). IL-6 is a pleiotropic cytokine with four properties, being a potent B cell differentiation factor, which induces the synthesis of polyclonal immunoglobulins, possibly explaining the autoimmune conditions; a potent cell-proliferative factor, explaining a hypercoagulability state; a strong hepatocyte stimulating factor, inducing the release of acute-phase proteins; and an inducer of ICAM-1, a factor implicated in the mechanism of cellular

adhesion, promoting endothelial dysfunction (4).

In this case, the main differential diagnosis of the Leriche syndrome etiology was between an embolic cause and an atherosclerotic one.

Embolism occurs in 30-40% of patients with myxomas. Since most myxomas are located in the LA, systemic embolism is particularly frequent. The myxoma embolization generally displays a predilection for the central nervous system, but occlusions of the peripheral arteries and embolization into visceral, renal, and coronary arteries can also occur (6, 7). More prone for embolization are the papillary or villous myxomas (7, 8) than those with a smooth surface, like in our patient, being more brittle. However, embolic symptoms usually develop suddenly, while in our case they were progressive, already having coronary and femoral collaterals at the time of presentation.

Given the chronic inflammatory status induced by myxoma, the patient's risk factors for atherosclerosis (such as uncontrolled hypertension, dyslipidemia, active smoking and advanced age) and the diffuse atherosclerotic impregnation favor the diagnosis of atherosclerotic disease rather than myxoma embolization.

Another interesting thing is the slow rate of growth of our patient's myxoma, which was known for more than 10 years. The rate of growth of myxomas is not exactly known, but may be influenced by neovascularization, reported in 80% of myxoma cases (9). Although it is a common belief that benign neoplasms tend to be less vascularized than malignant tumors, cardiac myxomas have a strong angiogenic potential that favors tumor growth, driven by the release of vascular endothelial growth factor (VEGF) (10). An increase in size by 1.8–5.8 cm/year and in weight by up to 14 g/year was reported (11). Left-sided myxomas are mostly supplied by the left circumflex artery but atypical cases supplied solely by the RCA have been described (9, 12, 13).

In our case, we did not identify neovascularization at all. The lack of myxoma feeding vessels, either missing from the beginning or occluded at the same time as the RCA, can explain the slow rate of growth, with size less than 5 cm, without atrial enlargement or symptoms of intracardiac flow obstruction.

Non-specific constitutional symptoms, determined by overproduction of IL-6, have been re-

ported in 20-60% of all cases. Such symptoms may include fever, arthralgia, myalgia, Raynaud phenomenon and weight loss. Laboratory findings may include elevated erythrocyte sedimentation rate (ESR) (33%), normochromic anemia (15%), and thrombocytopenia (5%) (4, 14). Our patient presented weight loss, anemia and increased ESR. The anemia was not a normochromic one, but one with a severe iron deficiency, without any evidence of a bleeding source. Cases with this type of anemia have been described by now, with complete resolution after surgical removal of myxoma (15).

Thyroid is commonly involved in CNC, including a spectrum of disorders ranging from multiple thyroid nodules, most of which are non-functioning thyroid follicular adenomas, to carcinoma (1, 2). ATD has not been described so far. Our patient presented with severe primary hypothyroidism, after radical treatment of Basedow-Graves disease. It is presumed that myxomas cause local activation of the immune system, allowing the production of a heterogeneous group of antibodies by bystander activation, i.e., antiendothelial cell antibodies (AECA)

(16). Though we cannot confirm this hypothesis, it is intriguing to speculate that ATD may be mediated by myxoma. □

## CONCLUSION

It is rare that a CNC is associated with extensive atherosclerosis and autoimmune thyroid disease. At a first glance, it seems like coincidence but in fact, there may be an etiological link between them, which is worth further studies. Timing of surgery is controversial in a patient who needs removal of the myxoma and surgical limb revascularization. Moreover, surgery in a patient with severe anemia and severe hypothyroidism poses other difficult management problems. But no matter what needs to be done, the patient has the final say, and both sides need to agree on it. □

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