

the gastrointestinal system and the bronchi.

The incidence of carcinoid tumors is estimated in 1:75,000 inhabitants, 50% of whom develop carcinoid syndrome, and in turn, 50% of these develop carcinoid heart disease which typically causes abnormalities in the right heart chambers.

Cardiac manifestations are caused by the paraneoplastic effects of humoral substances released by the carcinoid tumor, such as serotonin, histamine, bradykinin, and prostaglandins. These are usually inactivated by the liver, lungs, and brain, but the presence of liver metastases may allow large quantities of these substances to reach the right heart chambers.

Vasoactive substances extend to the left heart chambers only in 5-10% of the patients with multiple liver metastases, bronchial carcinoid, or a patent foramen ovale.

Typically, symptoms are characterized by facial flushing, diarrhea, bronchospasm, and right heart failure.

Many carcinoid tumors follow a prolonged course of up to 20 years from the onset of carcinoid symptoms. However, the development of heart disease in the carcinoid patient heralds a rapid decline in the clinical condition and survival rate is much lower.

Valve regurgitation is the most common complication; about 95% of the patients display moderate to severe tricuspid regurgitation. Pulmonary regurgitation is less common. Both are responsible for right heart failure.

Diagnosis is made with Doppler echocardiography, and is confirmed with serotonin and urinary 5-hydroxyindoleacetic acid assays. Additional complementary tests are only indicative.

In the early phase of the disease, surgical resection of the carcinoid tumor tends to be curative. In some cases, resection or embolization of hepatic metastases can be an option. In patients with the carcinoid syndrome, treatment tends to be palliative; octreotide, analogous of somatostatin, is used for reduction of vasoactive substances and relief of symptoms. Once heart disease has developed, treatment is focused on heart failure.

In selected cases of tricuspid or pulmonary valve stenosis, balloon valvuloplasty produces symptomatic improvement, although recurrent symptoms have been observed after some time. Early valve surgery is the only definitive treatment for severe heart failure. Bioprosthetic valves are preferable, as anticoagulation, which would increase the risk of bleeding secondary to metastasis, can be avoided, and the life expectancy of the patient is likely to be shorter than that of the valve. Patients usually die of severe tricuspid regurgitation rather than of carcinomatosis.

Finally, our diagnostic triad for this disease consists of anamnesis, physical examination and Doppler echocardiography. However, it is even more important for cardiologists to consider carcinoid syndrome as a possible differential diagnosis in tricuspid and pulmo-

nary valve diseases, because it is the only way to provide a better prognosis to our patients.

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Cardioembolic Ischemic Stroke Associated with Mitral Annular Calcification

Mitral annular calcification (MAC) is a chronic degenerative process of the valve fibrous skeleton. MAC has been associated with high risk of systemic embolism, among which cerebral embolism leads to ischemic stroke. We describe a case of stroke secondary to calcific embolization, possibly originated in MAC.

A 78-year-old female patient, receiving eplerenone 25 mg, atorvastatin 10 mg, losartan 50 mg and inhaled bronchodilators on a daily basis, presented with recurrent episodes of expressive aphasia lasting approximately 1 minute. She had several comorbidities, including hypertension (HT), dyslipidemia (DLP), and chronic obstructive pulmonary disease. Twenty days before hospitalization, the patient had been admitted for multiple injuries due to a car accident whereupon a computed tomography (CT) scan of the brain showed no abnormalities (Figure 1). On admission, the neurological examination and lab tests were normal. The ECG showed sinus rhythm, without significant changes. CT scan on admission (Figure 2) revealed bihemispheric subcortical microangiopathic sequelae, mild involutional changes, and punctate calcifications in the cerebellar tentorium and in the M1 segment of the left middle cerebral artery (MCA). During hospitalization, the patient repeated four similar episodes of aphasia with recovery ad integrum. The electroencephalogram revealed left temporal

intermittent slowing, and lamotrigine was prescribed. Magnetic resonance imaging (MRI) of the brain with diffusion sequences showed several acute ischemic lesions at the temporal, lenticular and in the left convexity level, and the magnetic resonance angiography (MRA) of intracranial vessels showed no signal in the left MCA. The magnetic resonance angiography of neck vessels was normal. Total cholesterol was 212 mg/dL, HDL 56 mg/dL, LDL 141mg/dL and triglycerides 77 mg/dL. Echo-Doppler of the lower limbs and iliac veins was normal. The transesophageal echocardiography showed MAC, severe mitral regurgitation, left atrial enlargement, diffuse aortic atheroma, and a 7×5 mm mobile calcification associated with the atrial side of the mitral annulus; the interatrial and interventricular septa were complete. A CT angiography of the intracranial vessels revealed partial obstruction in the M1 segment of the left MCA due to calcified embolism. The patient was diagnosed cardioembolic ischemic stroke due to possible calcified embolism. The case was reviewed by the Department of Cardiovascular Surgery, which discarded surgery. The patient was discharged, adding aspirin, atorvastatin, and lamotrigine to her usual therapeutic regimen.

Mitral annular calcification (MAC), described in 1908, is a degenerative fibrocalcification of the mitral valve. Presumably, it is originated as a result of mechanical endothelial disruption followed by migration of macrophages and T-lymphocytes, generating a localized chronic inflammatory response that causes remodeling of the extracellular matrix with reactive fibrosis and calcification. Risk factors (RF) for MAC development are the same as those for cardiovascular disease: HT, diabetes (DM), DLP, smoking, physical inactivity, and age. The main non-modifiable RF is age (which proportionally increases incidence), and the main modifiable RF is HT (some studies consider

it an independent RF). (1) Higher prevalence of MAC has been described in chronic inflammatory diseases (such as collagen diseases) and in those altering the phospho-calcium metabolism (such as chronic kidney failure). It was in 1946 that Rytand and Lipsitch described an ischemic stroke in a patient presenting MAC. In 1984, Furlan poses two conclusions about the association between MAC and ischemic stroke: 1) it may be difficult to prove the association between them, and 2) MAC may be better viewed as a marker of atherosclerosis rather than an embolic mechanism. (2) The SSS-TOAST classification system for ischemic stroke (3) assigned MAC a low or undetermined risk for stroke, based on a study from 1992, (4) in which MAC was associated with a 2.2 relative risk of ischemic stroke. In that study, Benjamin et al. analyzed the Framingham cohort population and determined that MAC is an independent cause of ischemic stroke after adjusting for age, sex, systolic blood pressure, DM, smoking, atrial fibrillation, coronary artery disease, and congestive heart failure (RR 2.10, 95% CI 1.24-3.57; $p = 0.006$). However, MAC is a marker of systemic vascular disease as an association was found between the presence of MAC and carotid stenosis greater than 160%, (5) a variable for which no adjustments were made in the study of Benjamin et al. Kizer et al (6) retrospectively analyzed 2,723 patients from the Strong Heart Study cohort, who were free of prevalent cardiovascular disease. They concluded that MAC provided high risk of ischemic stroke (incidence rate ratio, 3.12, 95% CI 1.77-5.25) after risk adjustment for age, sex, obesity, DLP, serum creatinine, HT, DM, and smoking. MAC was also associated with reduced time to the first ischemic stroke after adjustment for the variables described above and C-reactive protein, fibrinogen (HR 2.42; 95% CI, 1.39-4.21) and echocardiographic markers (left ventricular hypertrophy and left atrial enlargement; HR 1.89; 95% CI, 1.04-3.41). In other studies, when MAC is adjusted with other known RF for stroke, the risk is not increased. MAC was not significantly associated with ischemic stroke (HR 0.76%, 95% CI 0.42-1.36; $p = 0.3$) in the study by Boon et al, (7) after adjustment of RF for systemic vascular disease, with and without adjustments for RF as carotid artery stenosis, cardioembolic source and atrial fibrillation. In this work, carotid artery stenosis was identified as a potential confounder that explained previous reports of associations between MAC and ischemic stroke. A study published in 2003 demonstrated that the presence of MAC predicts cardiovascular events and death due to cardiovascular disease, and claims that MAC is a marker of subclinical cardiovascular disease. (8) While it is controversial whether MAC is associated with independent increased risk for stroke, there are plenty of studies on ischemic stroke in which a causal association with MAC is postulated. (9, 10) In our case, the absence of calcified lesions in the M1 segment of the left MCA in the CT scan performed 20 days before



Fig. 1. CT scan on admission. The arrows show endoluminal hyperdense calcification in the M1 segment of the left middle cerebral artery.

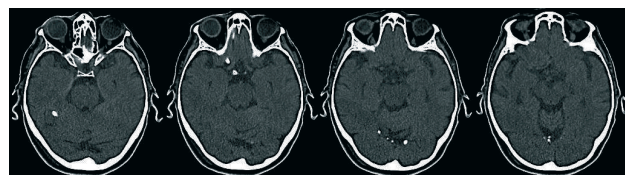


Fig. 2. CT scan prior to admission: hyperdense images consistent with dystrophic calcification in the free edge of the cerebellar tentorium.

hospitalization due to ischemic stroke, suggests an association with MAC. We therefore postulate that the presence of a mobile mass of MAC would increase the risk of detachment and possible embolization. MAC could be not only a marker of vascular disease but also a cause of medium to low risk of cardioembolism in patients with extensive, mobile calcifications.

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