Angioedema and flushing in the elderly patient. From "allergy" to carcinoid tumor. The importance of a differential diagnosis

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Abstract

Aging influences the variety of pathologies observed in any internal medicine department, and Allergology is no exception. Adverse drug reactions are one of the primary reasons for the referral of elderly patients to the Allergology service. Renin-angiotensin-aldosterone blockers are widely used in the treatment of patients with cardiovascular pathology, and angioedema is one of the possible side effects. We present the case-report of a 71-year-old woman with recurrent angioedema following emergency room treatment of hypertensive crisis with captopril, which was controlled after eviction of this drug. Subsequently, she presented flushing episodes, which were interpreted by her medical assistant as an allergic reaction and she was referred to Allergology service for further investigation. Neuroendocrine tumor was diagnosed and collaboration with different specialties was needed for adequate treatment. The authors discuss the etiology of the angioedema and flushing, and the treatment options.

Key words: angioedema, carcinoid, high blood pressure, flushing.

Introduction

Immunoallergological diseases are traditionally considered a pathology affecting the younger age group, but in reality, the patients referred to the Immunoallergology service of our hospital have an average age of 46 years (2007 data). The phenomenon of population ageing is currently having repercussions on the range of diseases seen in any medical clinic, and involves a vast differential diagnosis, particularly in the case of immunoallergological patients.

Adverse drug reactions are one of the most frequent causes of referral of elderly patients to the Immunoallergological Service.

Angiotensin-converting enzyme inhibitors (ACEI) play an increasingly important role in controlling cardiovascular disease. Their beneficial effects depend on bradykinin, the same agent that is responsible for the adverse reactions, notably chronic cough and non-allergic angioedema. The frequency of ACE-induced angioedema in the Caucasian race is 0.1-0.7% (0.5% for captopril).[1] This drug is commonly used in the Emergency Services to treat hypertensive crises.[2]

Inflammatory cutaneous reactions have a vast differential diagnosis, and in the context of previous adverse drug reactions, can prompt the clinic to investigate a possible allergic reaction. The case reported here refers to a patient with various episodes of ACE-induced labial angioedema, and subsequently, a state of flushing interpreted by the assistant doctor as anaphylaxis.

The evaluation algorithm of a patient with cutaneous flushing first involves excluding malignant (though less frequent) pathologies, despite being commonly associated with benign situations, such as post-menopause, febrile syndrome, or the ingestion of alcohol or certain foods.[3]

Clinical case

Female patient, aged 71 years, Caucasian, admitted to the Immunoallergology Service in April 2006 for recurrent labial angioedema. The patient had been diagnosed with arterial hypertension from the age of 69, which was medicated with valsartan (ARB) 160 mg per day but was not controlled, and she had come to the Emergency Service due to persistent epistaxis. On entry, she presented AP of 180/90 mm Hg, for which she was medicated with antihypertensive

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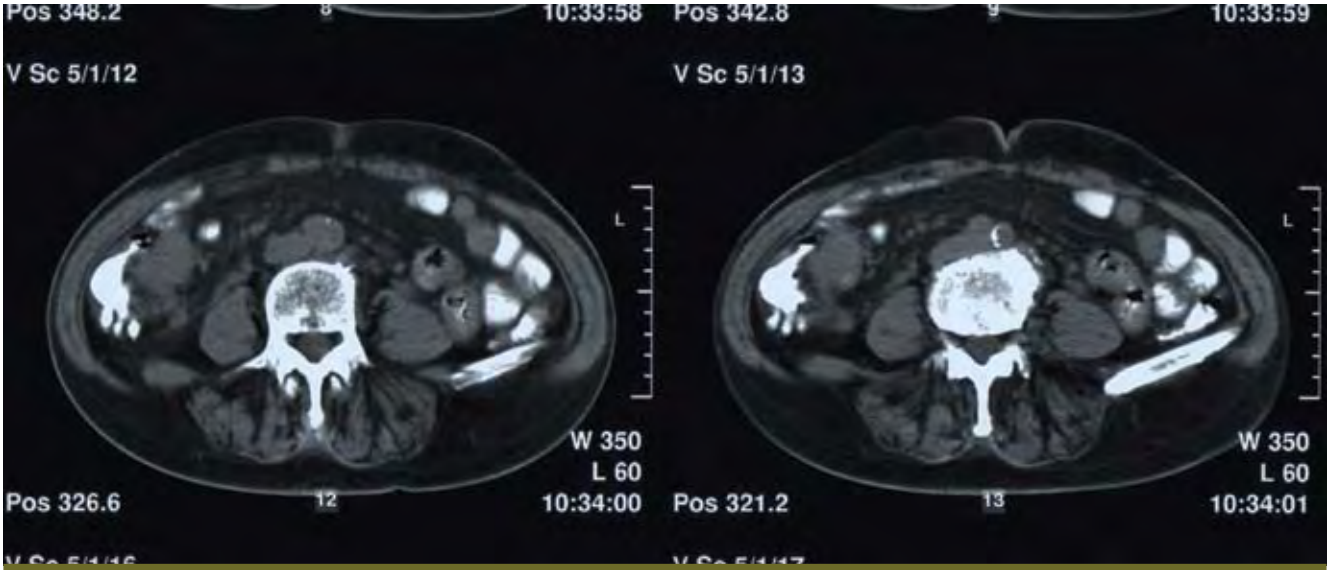


Thoracic/abdominopelvic TC. Heterogeneous nodule formation involving the ileocecal region.

FIG. 1

drugs administered under the tongue, and underwent nasal packing in the Ear Nose and Throat Service, after which she was discharged. After five hours, she returned to the Emergency Service with vomiting of digested blood and lipothymia, presenting, on objective examination, labial angioedema (without urticaria or other symptoms) and pale mucosa. Nasogastric intubation was carried out, which did not reveal the presence of blood in the stomach. In the laboratory evaluation, normochromic, normocytic anemia was highlighted (Hb 9.6 g/dl, MCV 96 fl, hematocrit 29.3%), and it was decided to admit the patient for tests and control of the clinical evolution. The patient reported two similar episodes in the four months prior to admittance: Intense epistaxis, not controllable in the home, which led to observation, and medication with sublingual antihypertensive drugs, at the Health Center, with appearance of labial angioedema without urticaria. The angioedema cleared up in two days, without treatment.

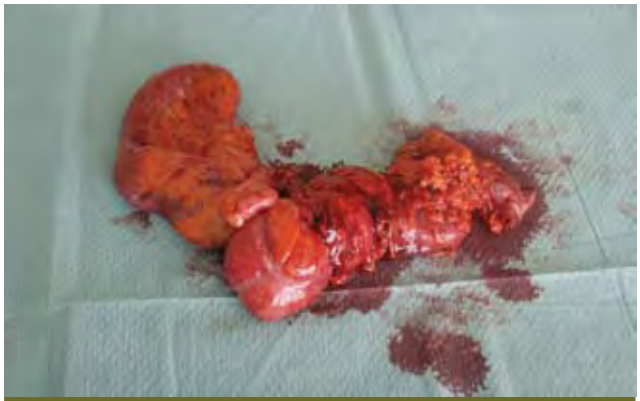
The additional laboratory evaluation revealed a non-elevated total IgE value, thyroid function and study of the complement system without alterations.

During hospitalization, the patient was treated with: prednisolone 75 mg/day IV, aminocaproic acid 2500 mg de 8/8 h IV, ranitidine 50 mg 12/12 h IV, hydroxyzine 25 mg 8/8 hours PO. The patient was discharged with a diagnosis of angioedema ACE-induced angioedema, medicated with valsartan 160 mg/day in association with hydrochlorothiazide 12.5 mg and written indication for eviction of ACEis.

In the Immunoallergology Consultation in June 2006, two months after hospitalization, the patient reported no new episodes of angioedema; AP values were within the normal parameters under instituted therapy; hemogram and study of iron metabolism did not reveal any pathological alterations. The cutaneous tests carried using the standard battery of aeroallergens and food allergens were negative.

In February 2007, the patient was referred to our clinic by her family doctor, for episodes of sudden appearance of erythematous-violaceous coloration of the face and chest, sensation of slight itching and warmth, lasting several minutes, with frequency of 1-5/month, and without any apparent trigger factors. These episodes were interpreted by the assistant doctor as a probable allergic reaction. The patient reported no weight loss, respiratory complaints, abdominal pain or visible blood loss, and around 2 to 3 episodes per month of liquid feces with 2-3 bowel movements a day.

Thus, the diagnostic investigation focused on clarifying the main clinical problems presented by the patient: Flushing and intestinal transitory altera-



Surgically removed piece showing the tumor mass and mesenteric involvement.

FIG. 2

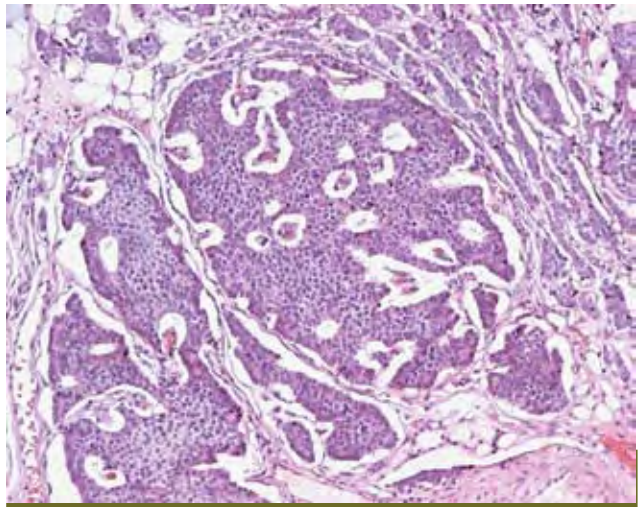
tion. The laboratory evaluation carried out showed an increase in 5-hydroxyindolacetic acid (5-HIAA): 58.0 mg in the urine at 24h (normal value: 0,7-8,2). Other parameters, notably hemogram, study of iron metabolism, hepatic and renal function, tryptase, serotonin and vanilmandelic acid were within the normal limits.

Thoracic-abdominal-pelvic computed tomography showed "a heterogeneous nodule formation involving the ileocecal region infiltrating the last ileal ansa, with a significant reduction in its lumen" *(Fig. 1)*, additionally evidencing retroperitoneal involvement and absence of any hepatic lesions. Echocardiogram excluded the involvement of the valves of the right side of the heart.

Diagnoses of carcinoid tumor (ileon) were established, with carcinoid syndrome, hypertension and angioedema by ACEi.

To mitigate the risk of intestinal occlusion, it was decided to carry out right hemicolectomy. During surgery, extensive mesenteric metastization was identified *(Fig. 2)* with histological confirmation *(Fig. 3)* and immuno-histochemical conformation (positivity for neuroendocrine differentiation markers) of the gastroenteropancreatic neuroendocrine (carcinoma).

The patient is currently receiving therapy with octreotide and antihistaminic H1, with good control of flushing, and has presented no more symptoms of angioedema since the indication for eviction of the ACEis.



Histological exam (hematoxylin-eosin): Gastroenteropancreatic neuroendocrine tumor (carcinoma)
Caption: Tumor with insular pattern consisting of uniform cells, polygonal cells with vast cytoplasm, round nuclei, with finely and coarsely granular chromaffin, with slight nuclear pleomorphism.

FIG. 3

Discussion

According to the latest data, ACE-induced angioedema has an incidence of around 0.1-0.7% in the Caucasian race,[1,4] and is higher among the Negro race.[5] ACEis and type II angiotensin receptor antagonists (ARA II) are 1st level evidence drugs in therapy for arterial hypertension, acute coronary accident, congestive cardiac insufficiency and diabetic nephropathy.[6] The angiotensin-converting enzyme has two main proteolytic functions: Generation of angiotensin II and bradykinin degradation. Therapy with ACEis (but also with ARA II) increases the plasma levels of bradykinin, one of the most potent vasodilators.[1] The action of bradykinin in the pancreatic beta cells with an increase in insulin production by elevation of intracellular calcium in response to the hyperglycemia,[1] which also makes ACEis useful in the treatment of metabolic syndrome, was demonstrated.

The stimulation of the type 2 bradykinin receptors (BKR-2), besides the beneficial effect in patients with cardiovascular pathology, can lead to various secondary effects, such as cough (due to the release of pro-inflammatory peptides and histamine locally, with hyper-reactivity of the cough reflex) and angioedema by vasodilation and increase in vascular permeability. In 10% of patients with ACE-induced angioedema,

TABLE I

Important anamnesis data, objective examination and laboratory evaluation in the most frequent and/or less severe causes of Flushing

Cause	Anamnesis	Objective exam	Laboratory evaluation
Benign cutaneous flushing	Related to emotions, exercise, foods	Non-specific	—
Rosacea	Typical trigger factors, ocular symptoms	}Papules, pustules, telangiectasias, flushing restricted to the face.	—
Menopause	Woman in the 5th, 6th or 7th decades of life, short, frequent episodes, profuse sweating	Flushing of the face, neck and chest	Increase in follicle-stimulant hormone
Carcinoid	Hypotension, tachycardia, abdominal cramps, diarrhea, bronchospasms	Red-brown or bright red flushing, may be diffuse, with involvement of the palms of the hands, telangiectasias of the face	24-hour urine for 5-HIAA
Pheochromocytoma	Hypertension, sweating, palpitations, thoracalgia, abdominal pain, nausea, vomiting, headache	Non-specific	24-hour urine for metanephrine, norepinephrine, epinephrine, dopamine, vanilmandelic acid
Mastocytosis	Abdominal pain, nausea, vomiting, diarrhea, fatigue, myalgia, weight loss, neuropsychiatric symptoms, hypotension	Cutaneous mastocytosis (urticaria pigmentosa, telangiectasia maculaaris eruptive perstans, etc.)	Persistently high serum tryptase
Anaphylaxis	Hypotension, respiratory symptoms (dyspnea)	Urticaria, angioedema	Tryptase increase during the episode
Medullary Carcinoma of the thyroid	Personal or family history of medullary carcinoma, pheochromocytoma, hyperparathyroidism (MEN)	Flushing or discoloration and telangiectasias of the face, thyroid nodule	Serum calcitonin testing after IV administration of calcium and pentagastrin
Carcinoma of the pancreas (VIPoma)	Prolonged watery diarrhea, abdominal pain, nausea, vomiting, drowsiness, asthenia	Non-specific	High serum VIP
Carcinoma of the renal cells	Hematuria, flank pain	Abdominal mass	Hematuria and imagiological studies

Adapted from Izikson et al.

concomitant irritative cough present.[7]

In relation to the clinical characteristics of angioedema, the involvement of the face, neck, lips, tongue, pharynx and in rare cases, the larynx should be reported. In the latter case, nasal or orotracheal intubation to control the respiratory state is particularly difficult.[7] Cases of visceral angioedema were also described, with symptoms of abdominal pain, nausea and diarrhea, and absence of mucocutaneous angioedema. The diagnosis is suggested by the presence rapid-onset abdominal pain with thickening of the intestinal wall, when other apparent causes are excluded.[8] The fact that there is no obvious temporal relationship between the start of taking ACEis and the state of angioedema (some cases occur years after the start of medication with ACEis) suggests a need to clarify, to the patient, at the time the ACEis are prescribed, the possibility that this secondary effect could occur.

In cases where adverse effects appear, alternative treatment should be considered.

ARA II trigger angioedema less frequently than

TABLE II

Differential diagnosis of Flushing

Common causes
Benign cutaneous flushing Emotional Alterations in temperature Food or food supplements Rosacea Menopause Fever Alcohol
Less common, less severe causes
Carcinoid Pheochromocytoma Mastocytosis Anaphylaxis Medullary carcinoma of the thyroid Carcinoma of the pancreas (VIPoma) Carcinoma of the renal cells
Other causes
Ingestion of fish (scombroid) Psychiatric disturbances or anxiety Idiopathic flushing Neurological causes Parkinson's disease Migraine Multiple sclerosis Lesion of the trigeminal nerve Horner's Syndrome Frey's Syndrome Dysautonomic crises Orthostatic hypotension Streeten's syndrome Medication Vasodilators, calcium canal blockers, beta-blockers, anti-Inflammatories, non-steroids, anti-emetics (metoclopramide), nicotine, opiates, chemotherapy, etc.
Very rare causes
Mitral stenosis, dumping, arsenic poisoning, POEMS syndrome, basophilic granulocytic leukemia, bronchogenic carcinoma, malign histiocytoma, malign neuroblastoma, malignant ganglioneuroma, periaortic surgery, Leigh's syndrome, Rovsing's syndrome
Adapted from Izikson et al.[3]

ACEis, and one study has estimated the frequency of angioedema by valsartan in 0.2% (0.5% for captopril).[9] It is believed that the risk of angioedema by ARA II is slightly higher than in patients with a history of ACEi angioedema. However, according to recent studies, due to the benefits in controlling arterial hypertension and decreasing albuminuria, ARA II can be prescribed, albeit with caution, in this group of patients.[10]

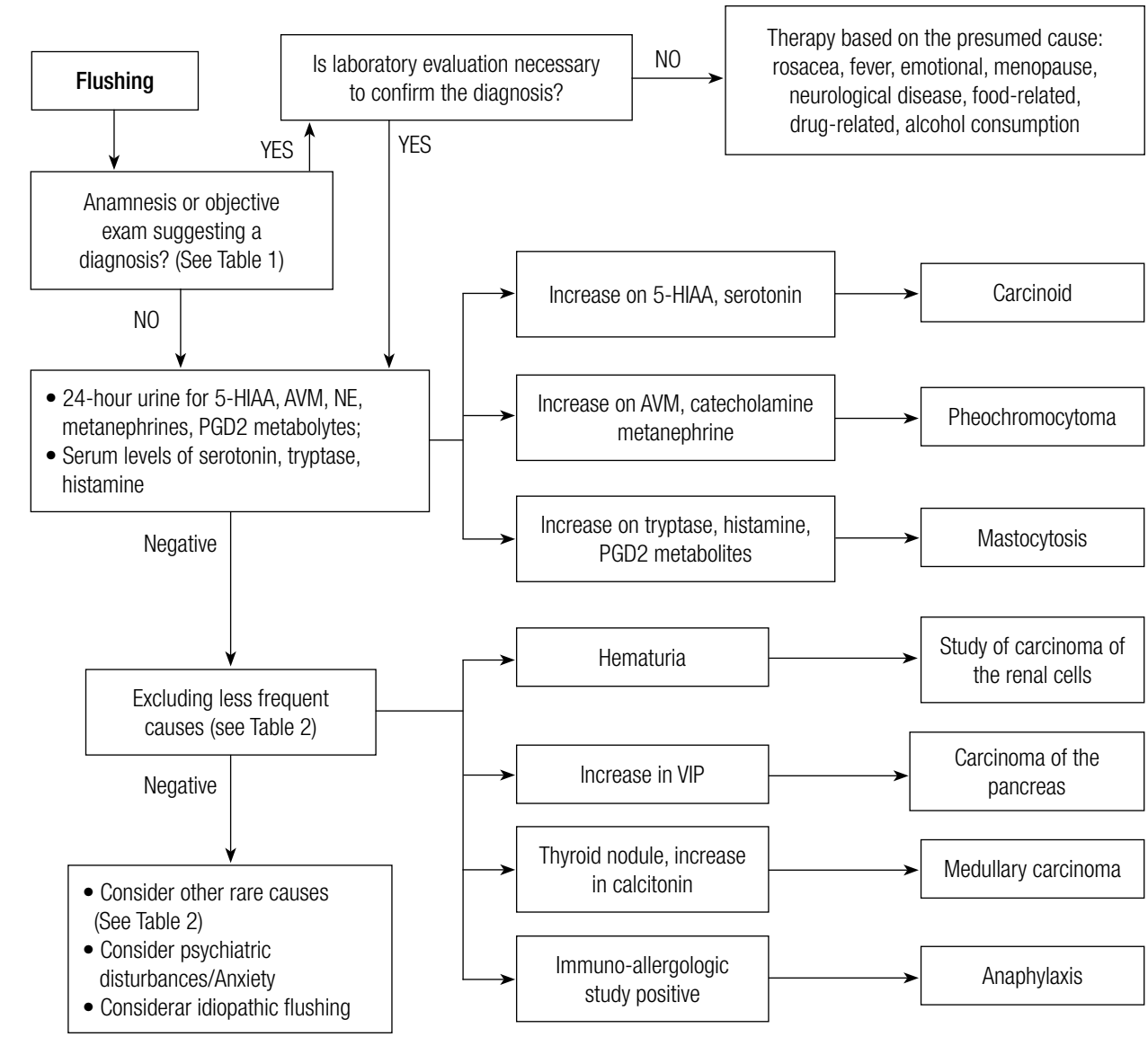
The etiopathogenesis of angioedema associated with ARA II is controversial. These drugs can also inhibit bradykinin degradation. One of the proposed mechanisms is to increase the level of circulating angiotensin II, by interrupting the physiological feedback mechanism of the control of its renin synthesis. Another hypothesis is the increased stimulation of the type 2 angiotensin II receptors in the context of inhibition of the type I receptors, with a consequent decrease in bradykinin degradation.[10] In the case described, the patient did not have angioedema related to the valsartan. The association of valsartan with hydrochlorothiazide enabled good control of the arterial hypertension.

The importance currently attributed to drugs that act on the renin-angiotensin-aldosterone axis is so great that some authors indicate the need to use angioedema control drugs in cases of where this secondary effect occurs. Studies are currently being performed focusing on a specific and selective antagonist of the BKR-2 receptors, namely, Icatibant. However, in view of the existence of alternative medication and the high cost of Icatibant, its application in cases of ACE-induced angioedema seems unlikely.[1]

In the literature, we find only one reference to angioedema as a manifestation of carcinoid syndrome, in which the authors suggest an association between the production of biogenic amines, notably histamine, with the condition of angioedema.[11] Therefore, in the patient in question, there appears to be no relation between the angioedema and the carcinoid tumor by absence of recurrence of the symptoms after the eviction of ACEis.

The differential diagnosis of flushing syndrome (*Tables I and II*) is vast, and includes various benign and malignant entities, therefore it is essential to exclude, as a priority, the following severe pathologies: Carcinoid tumor, pheochromocytoma, anaphylaxis and mastocytosis.[3]

According to the evaluation algorithm of the patient with flushing, proposed by the American Academy of Dermatology *(Fig. 4)*, in the absence of anamnestic or clinical data suggestive of diagnosis, it is important to request testing of 5-HIAA, vanil-



Caption: 5-HIAA, 5-hydroxyindolacetic acid; AVM, vanilmandelic acid; NE, norepinephrine; PGD2, prostaglandin D2; VIP, vasoactive intestinal peptide.

Diagnosis algorithm of a patient with flushing.

FIG. 4

mandelic acid, norepinephrine and prostaglandin D2 metabolites in the 24-hour urine and serotonin, serum tryptase and histamine. If there are no alterations in these parameters, excluding hypotheses of carcinoid tumor, pheochromocytoma and mastocytosis, other severe causes, although less frequent, should be excluded, notably carcinoma of the renal cells, hepatocellular carcinoma, medullar carcinoma of the thyroid and anaphylaxis. If this study is negative, other rare causes should be considered, notably arsenic poisoning, basophilic granulocyte leukemia, malignant histiocytoma, and malignant neuroblastoma, among others.[3]

The patient's clinical history, in particular, recurrence of the symptoms and alterations in intestinal transit, was suggestive of carcinoid syndrome. According

to the classification of the World Health Organization, the term carcinoid tumor has now been replaced by gastroenteropancreatic neuroendocrine tumor (GEP NET). Benign GEP NETs or those of uncertain malignant potential, well-differentiated neuroendocrine carcinomas with low level of malignancy, and little-differentiated carcinomas (generally small-cell) with a high degree of malignancy are distinguished. The incidence of neuroendocrine tumors is 0.5-8.4 cases per 100,000 inhabitants/year (although present in 1% of autopsies). Its symptomatology is non-specific and vague, and 40-60% of all patients are asymptomatic, therefore it delays the diagnosis of carcinoid tumors taking from 2 to 22 years.[12]

The symptoms of NET are caused by the local effect of the tumor mass, characteristic fibrosis of the tumor tissue or secretion of bioactive substances. The flushing reported to by the patient is suggestive of hepatic metastization which, however, was not present. The existence of flushing is conditioned by the bioactive substances produced by the tumor cells which, in the absence of hepatic metastization, are metabolized by the hepatocytes.[3] Another condition of the presence of flushing is the tumor localization outlining the portal circulation. The absence of respiratory symptoms and the results of the imagiological exams enable bronchopulmonary involvement to be excluded. Retroperitoneal involvement may be an explicative factor, in that 5-hydroxytryptamine and other metabolites do not go through the portal circulation, and are therefore not metabolized in the liver and can cause systemic symptoms.

Surgical intervention was carried out with palliative aims, to prevent probably intestinal occlusion due to fibrosis of the surrounding tissue.

In the case described, the antecedents of the ACEi angioedema patient (not a rare situation) led to the interpretation, by the assistant doctor, of the underlying state of flushing as an allergic pathology, justifying the patient's referral to the Allergology service. The diagnosis of neuroendocrine tumor was established by clinical suspicion, laboratory and imaging exams and evidence of the tumor on its excision. The anatomopathological exam of the excised part confirmed the diagnosis of neuroendocrine tumor (carcinoma), previously designated atypical carcinoid.

Collaboration with the Imagiological, Anatomic Pathology, Surgery and Oncology Services enabled, in this case, the diagnosis of a rare pathology, which required a diagnostic approach and multidisciplinary treatment. ■

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