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CASE REPORT

Leonine Facies in Carcinoid Syndrome

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KEYWORDS

Carcinoid syndrome;
Leonine facies

Abstract

Carcinoid syndrome is a rare disorder caused when elevated levels of vasoactive substances secreted by a carcinoid tumor fail to be metabolized by the liver. This can occur for a variety of reasons including metastatic invasion of the organ. Carcinoid syndrome results in elevated levels of 5-hydroxyindoleacetic acid in the urine. Clinical manifestations include: flushing, diarrhea, bronchospasm, and heart failure. We describe a patient with carcinoid syndrome and hepatic metastases, in whom the key symptom of persistent facial edema resulted in conspicuous leonine facies; there was a partial response to treatment with oral isotretinoin and intramuscular lanreotide. Differential diagnosis was made with other conditions causing facial edema. A review is performed of the various skin manifestations of carcinoid syndrome, highlighting their role in the early diagnosis and treatment of the disorder.

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PALABRAS CLAVE

Síndrome carcinoide;
Facies leonina

Facies leonina en el síndrome carcinoide

Resumen

El síndrome carcinoide es un proceso infrecuente que se produce por la presencia en el organismo de niveles elevados de sustancias vasoactivas secretadas por un tumor carcinoide y no metabolizadas por el hígado, debido a diversas circunstancias, entre ellas la invasión metastásica del mismo. Se traduce en una elevación del 5-hidroxi-indolacético en orina. Clínicamente cursa con síntomas cutáneos (episodios de rubefacción-*flushing*), digestivos (diarrea), respiratorios (broncoespasmo) y cardiovasculares (insuficiencia cardíaca). Describimos el caso de un paciente con síndrome carcinoide con metástasis hepáticas cuyo síntoma guía fue el edema facial, que se hizo persistente otorgándole una facies leonina muy llamativa, que respondió parcialmente al tratamiento con isotretinoína por vía oral y lanreótida intramuscular. Realizamos diagnóstico diferencial con otros

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cuadros que cursan con edema facial y revisamos las diversas manifestaciones cutáneas que pueden surgir en el síndrome carcinoide, destacando su importancia para realizar un diagnóstico y tratamiento precoces del proceso.

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The approximate incidence of carcinoid tumors is estimated at 1.5 per 100,000 population, and less than 10% of the patients with these tumors develop an associated carcinoid syndrome,¹ which is therefore an uncommon condition. Carcinoid tumors are of neuroendocrine origin, arising from enterochromaffin cells. They secrete various vasoactive substances (serotonin, histamine, bradykinin, prostaglandins) that, when not metabolized by the liver, reach the systemic circulation and cause the clinical symptoms. This situation may be due to the presence of liver metastases, the production of mediators by extra-abdominal tumors, or large or multiple intra-abdominal tumors that produce an excessive quantity of neuroendocrine substances that exceeds the metabolic capacity of the liver.^{1,2}

Carcinoid syndrome manifests mainly in the skin, the digestive tract, and the respiratory and cardiovascular systems. Skin manifestations can be grouped into 4 categories: episodes of flushing and associated disorders; pellagra-like lesions related to niacin deficiency; a specific variant of scleroderma; and a range of various less common disorders.¹

We describe a patient with carcinoid syndrome who was diagnosed as a result of his skin condition.

Case Description

The patient was an 81-year old man with a history of right lung lobectomy for a malignant bronchial carcinoid tumor 9 years earlier; the tumor had been in remission for 7 years. The patient had hypertension that had been treated with enalapril for several years and a grade III adenoma of the prostate.

During the previous 2 years he had come to the emergency department on 5 occasions for lingual edema that on the most recent occasion, had been associated with facial edema with no other concomitant symptoms. The patient was referred to the allergy department, where blood tests and other additional tests were performed and he was diagnosed with angioedema probably related to the ingestion of angiotensin-converting enzyme (ACE) inhibitors. His antihypertensive treatment was changed and oral antihistamines and systemic corticosteroids were administered, leading to a partial remission of the symptoms.

The patient came to the dermatology outpatient clinic with a 6-month history of persistent seborrhea, edema, and facial erythema, which had become persistent and had given rise to metophyma, producing a leonine facies appearance. Macroglossia was observed and there was thickening of the eyelids and palpebral ptosis that restricted

his field of vision (Figure 1). The patient also reported marked hypoacusia of recent onset, episodes of diarrhea, and unquantified weight loss since the skin symptoms had started. He also complained of a degree of depression as the facial changes meant he was not recognized in public.

A skin biopsy was taken from the right side of the forehead and showed marked sebaceous hyperplasia with no other abnormalities (Figure 2). Blood tests were requested, including C1q inhibitor, thyroid hormones, autoantibodies, and tumor markers, and a 24-hour urine sample for vanillylmandelic acid, catecholamines, and 5-hydroxyindoleacetic acid (5-HIAA). The results showed mild anemia, an erythrocyte sedimentation rate of 70, and very high levels of 5-HIAA in the urine (339 mg/24h vs a control of 1-8.2 mg/24h). On chest x-ray there was a residual image in the right perihilar region that was stable on comparison with previous studies. Computed tomography (CT) of the chest and abdomen showed the presence

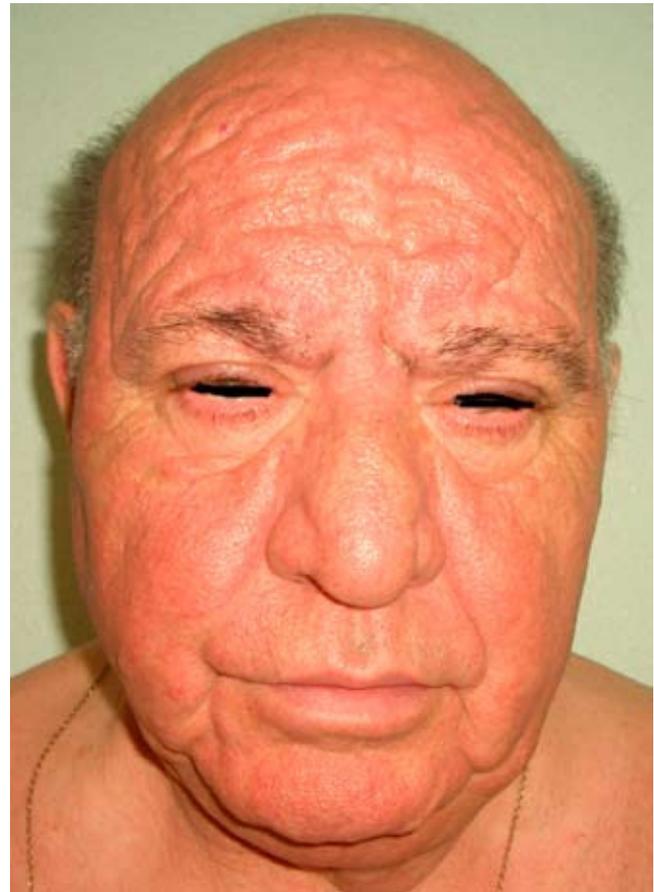


Figure 1 Metophyma, facial edema, and thickening of the eyelids.



Figure 2 Sebaceous hyperplasia affecting the full thickness of the dermis. Hematoxiline-eosin, original magnification $\times 200$.

Figure 3 Computed tomography of the abdomen showing liver metastases.

of liver metastases not visible on the CT of 8 months previously (Figure. 3). The otorhinolaryngology department diagnosed conductive deafness due to edema in both external auditory canals. On ophthalmologic evaluation

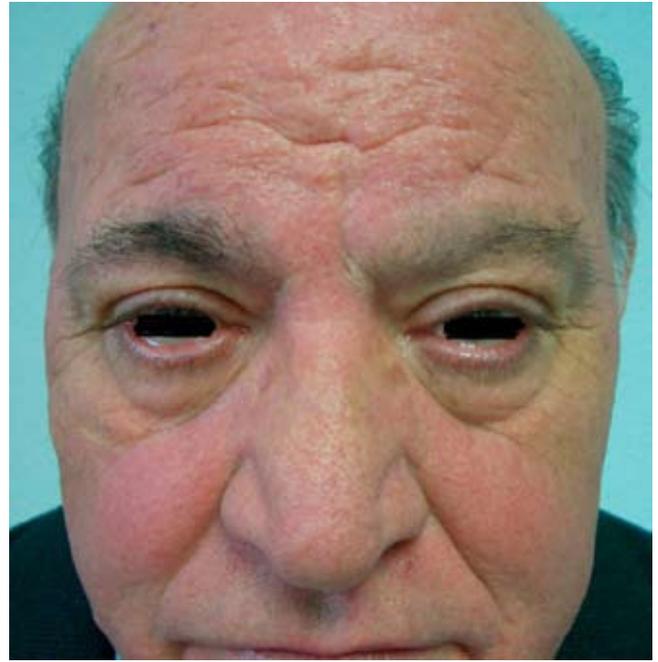


Figure 4 Improvement in the facial changes following treatment.

there was a reduction of the visual field due to thickening of the eyelids. Bone marrow biopsy was normal.

Based on these findings, the patient was diagnosed with carcinoid syndrome with cutaneous and digestive tract manifestations and treatment was started with oral isotretinoin 30 mg/d and a degreasing facial cleanser. After 1 month there was a substantial improvement in the alterations of the skin (Figure 4), with the consequent improvement in mood.

The oncology department subsequently started treatment with intramuscular lanreotide, a synthetic somatostatin analog and serotonin antagonist, at a dose of 120 mg every 4 weeks. The urinary 5-HIAA levels initially declined, though they did not normalize; in subsequent monthly measurement, the levels remained elevated and the patient continued to present variable cutaneous symptoms associated with weight loss and persistent diarrhea.

Discussion

Cutaneous symptoms are not uncommon with carcinoid syndrome. It is a proven fact that episodes of chronic flushing like those experienced by our patient, can even become permanent and lead to severe rosacea with the development of metophyma, rhinophyma, and zygophyma.² The differential diagnosis should include other conditions that lead to facial edema (Table), and the diagnosis is based on a detailed patient history, blood tests, and imaging studies.³⁻⁵

Pellagra-like changes can also occur in the skin (hyperkeratosis, xerosis, desquamation, glossitis, and hyperpigmentation) related to excessive dietary tryptophan in these patients, as 60% of ingested tryptophan is

Table 1 Differential Diagnosis of Facial Edema

Cutaneous Disorders	Systemic Disorders
Urticaria and angioedema	Thyroid disease
Eczema	Hypervolemia and hypoproteinemia: cardiac failure, hepatic insufficiency, nephrotic syndrome
Light-induced rashes	Drugs: ACE Inhibitors, nifedipine, rifampicin, ARB
Connective tissue diseases: SLE and DM	Superior vena cava syndrome
Rosacea (Morbihan syndrome)	Carcinoid syndrome
Melkersson-Rosenthal syndrome	Pheochromocytoma
Scleromyxedema	Mastocytosis
Erysipelas/cellulitis	

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; DM: diabetes mellitus; SLE: systemic lupus erythematosus.

metabolized to serotonin and its urinary metabolite 5-HIAA. This leads to niacin and protein deficiency, as tryptophan is needed for their synthesis. Pellagra can be prevented with niacin supplements. These should be provided in the form of nicotinamide rather than nicotinic acid, as the latter may induce episodes of flushing.^{1,6,7}

There is a type of scleroderma associated with carcinoid syndrome; it is characterized by an absence of Raynaud phenomenon and involvement of the lower limbs before it affects the upper limbs. There also tends to be no visceral involvement except for cardiac abnormalities due to endocardial fibrosis. Evaluation of the pathogenesis of carcinoid syndrome must therefore include a study of alterations of tryptophan and serotonin metabolism, genetic predisposition, and other neuroendocrine mediators.^{1,2}

Other possible skin abnormalities in carcinoid syndrome include pachydermoperiostosis with clubbing accompanied by thickening of the skin and periosteal bone lesions, none of which was present in our patient.^{8,9} Brownish or orange plaques may develop on the forehead, back or wrists in later stages of the disease. Symptoms such as pruritus, urticariform lesions, erythema annulare centrifugum, pyoderma gangrenosum, lichen planus, lichen sclerosus et atrophicus, acrocyanosis, and skin metastasis may also occur.^{1,2,4,6,10}

Intestinal symptoms can precede or coincide with the skin manifestations of carcinoid syndrome. The most common of these is chronic watery diarrhea associated with weight loss, as experienced by our patient.^{1,2}

Respiratory symptoms include bronchospasm, dyspnea, and cough. Cardiovascular symptoms are due to endocardial fibrosis, which results in valve damage that can lead to cardiac failure, and occasionally may cause attacks of tachycardia.^{2,1}

Arthritis, psychiatric symptoms, osteoblastic lesions, acromegaly, neurofibromatosis, Cushing syndrome, and ocular disorders are less common additional findings.^{1,2,11}

Definitive diagnosis of carcinoid syndrome is established by biochemical evidence of excess serotonin production, which can be demonstrated by the detection of an elevated urinary excretion of 5-HIAA following a 3-day exclusion

diet of foods and drugs that may influence urinary 5-HIAA levels.^{1,2}

The treatment of choice for these patients is tumor resection, though this is not possible in most cases of carcinoid syndrome due to the presence of hepatic metastasis, as was found in our patient. Palliative, symptomatic treatment is therefore used, administering systemic corticosteroids, antihistamines, and niacin (nicotinamide); however, the most effective treatment is based on the serotonin antagonists (methysergide, parachlorophenylalanine, cyproheptadine, somatostatin, and lanreotide). In the present case, lanreotide—a long-acting synthetic somatostatin analog that inhibits the secretion of mediators by the carcinoid tumor—was administered and a partial improvement was observed.¹² Treatment is complemented with the avoidance of factors that trigger flushing, such as hot food and drinks, spicy products, chocolate, cheese, tomatoes, walnuts, and alcohol. Reduction of emotional stress and avoidance of the Valsalva maneuver are also recommended.^{1,2} Some selected patients show improvement following hepatic artery embolization, which prolongs survival and reduces hormone-related symptoms.¹³

This article is interesting because the skin disorder was the key symptom that led to the diagnosis of carcinoid syndrome. This diagnosis brought together the other systemic symptoms reported by the patient in previous consultations with various specialist departments (allergy, gastroenterology, otorhinolaryngology). The importance of a good patient history must be stressed, as this provided us with details of the exact nature of the pulmonary intervention. We also draw attention to the need to establish an appropriate differential diagnosis in this type of case, particularly if the primary tumor has not been previously diagnosed.

Conflict of interest

The authors declare that they have no conflict of interest.

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