

Angioedema as a single manifestation of carcinoid syndrome in a bronchial carcinoid tumor

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ABSTRACT

Background: The association of bronchial carcinoid tumours with carcinoid syndrome is extremely rare especially in the absence of metastatic disease, and the angioedema is not a typical sign of this syndrome.

Methods and results: We report the case of a 39 year-old woman referred to our allergy department with recurrent episodes of angioedema.

The aetiological study of angioedema did not show evidence of hypersensitivity to common inhalants, food allergens and latex. C1-inhibitor, C3, C4, C1q, proteinogram and immunoglobulins (IgA, IgG, IgM) all were normal. TSH determination gave normal results, too. Faecal analyses for parasites were negative. The haemogram showed moderate leucocytosis and hypochromic microcytic anaemia.

The thoracic radiography showed a mediastinal node image in the right paratracheal region. Histology analyses of the samples were diagnostic of a typical carcinoid tumor. Levels of 5-hydroxyindolacetic acid (5-HIAA) were slightly increased. A su-

perior lobectomy was performed and no new episodes of angioedema appeared after surgical intervention.

Conclusions: We report the first case of typical bronchial carcinoid tumour, without metastatic disease, with angioedema as a single manifestation of carcinoid syndrome.

In our knowledge, only one case of Quincke's edema as part of typical carcinoid syndrome has been reported, in a case of primary midgut carcinoid tumor with metastatic disease to liver. It is very important to include complementary tests, as thoracic radiography, in the routine study of angioedema to reject malignant diseases.

Key words: Angioedema. Carcinoid syndrome. Carcinoid tumor. Thorax radiography.

RESUMEN

La presencia de síndrome carcinoide asociado a tumores bronquiales es poco frecuente, sobre todo en ausencia de enfermedad metastásica; y el angioedema no es una manifestación típica de dicho síndrome.

Métodos y resultados: Presentamos el caso de una paciente de 39 años de edad con episodios recurrentes de angioedema.

En el estudio etiológico de angioedema no se evidenció hipersensibilidad frente a inhalantes, alimentos ni látex. La determinación de fracciones séricas de complemento (C3, C4, C1q y C1-inhibidor) e inmunoglobulinas mostró resultados normales. Los va-

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lores de TSH estaban, asimismo, dentro de la normalidad. En análisis de parásitos en heces fue negativo. En el hemograma se apreciaba una leucocitosis moderada y una anemia microcítica e hipocroma.

La radiografía de tórax mostraba una imagen nodular mediastínica a nivel paratraqueal derecho. El estudio histológico fue diagnóstico para carcinóide típico. Los niveles de ácido 5-hidroxiindolacético (5-HIAA) en orina de 24 horas, estaban discretamente elevados. A la paciente se le practicó una lobectomía superior derecha, no volviéndose a presentar nuevos episodios de angioedema tras la intervención.

Conclusiones: Presentamos el primer caso de tumor carcinóide bronquial típico, sin enfermedad metastásica asociada, con angioedema como única manifestación de síndrome carcinóide.

Sólo tenemos conocimiento de un caso de edema angioneurótico de Quincke asociado a síndrome carcinóide en un caso de tumor primario intestinal con metástasis hepáticas. Creemos que es importante incluir determinados exámenes complementarios, como la radiografía de tórax, en el estudio de rutina del angioedema para descartar enfermedades malignas subyacentes.

Palabras clave: Angioedema. Síndrome carcinóide. Tumor carcinóide. Radiografía de tórax.

INTRODUCTION

Carcinoid tumours are neoplasms of the neuroendocrine system. They are usually small in size and slow growing. They can be found in different locations, such as intestines, respiratory airways, the urinary system and gonads. The incidence varies depending on the series, although is estimated that it is about 1.5 per 100.000 inhabitants¹. They are more frequent in women than in men (1.6:1)² and are not related to smoking³. Almost 2 % of the bronchial tumours are carcinoids⁴.

In the majority of cases, they are accidentally found in necropsies and in surgical operations because they do not show any symptoms.

There are two kinds of carcinoid tumours, the so called "typical", with a high degree of differentiation, and the "atypical", with a major mitotic activity and a tendency to metastasize.

Like neuroendocrine tumours, the carcinoids synthesize biogenic amines that develop the carcinoid syndrome when they are released into the systemic circulation. This syndrome is characterized by diar-

rhoea, flushing and pain, although other atypical manifestations, such as wheezing or cardiac failure, are possible. Although not in every case, in the majority of cases, the syndrome is developed in the presence of liver metastasis⁵.

The association of bronchial carcinoid tumors with carcinoid syndrome is extremely rare especially in the absence of metastatic disease, and the angioedema is not a typical sign of this syndrome.

CASE REPORT

We report the case of a 39 year-old woman, a smoker, referred to our allergy department with recurrent episodes of angioedema for the last six months. Angioedema occurs in different locations, including eyelids, lips, and soles, on different occasions; which spontaneously disappeared after one day.

The aetiological study of angioedema did not show evidence of hypersensitivity to common inhalants, food allergens and latex. C1-inhibitor, C3, C4, C1q, proteinogram and immunoglobulins (IgA, IgG, IgM) all were normal. TSH determination gave normal results, too. Faecal analyses for parasites were negative. The haemogram showed moderate leucocytosis and hypochromic microcytic anaemia.

The thoracic radiography showed a mediastinal node image in the right paratracheal region. In order to confirm these findings a thorax computerised tomography was performed, showing a solid mass of six centimetres as a major diameter, located in the anterior and middle mediastinum. It is of interest that it contacted the right pulmonary artery, without invading its wall. A mass with tendency to bleed was visualised by bronchoscopy, which nearly occupied the whole right bronchus. Histology analyses of the samples were diagnostic of a typical carcinoid tumor. As such, a carcinoid tumor was suspected as the cause of angioedema episodes, as a carcinoid syndrome manifestation. Certainly, levels of 5-hydroxyindolacetic acid (5-HIAA) were slightly increased, 11.1 mg/day, respect to normal values between 2-8 mg/day³. Determination of serotonin in platelets gave normal results. A superior lobectomy was performed and, as suspected, no new episodes of angioedema appeared after surgical intervention.

DISCUSSION

Patients with classic carcinoid syndrome usually present diarrhoea, flushing and localised or generalised pain. Biogenic amines such as serotonin, hist-

amine, kallikrein, substance P, prostaglandins and catecholamines are excessively synthesized⁶, stored and released into the systemic circulation.

Some of them, mainly histamine, are implicated in the pathogenesis of the angioedema, possibly manifesting itself as a part of a carcinoid syndrome.

The histamine is the predominant mediator in angioedema, because the quantities in blood are 100 to 1000 times higher than the others constituents⁷.

Until Feldman et al reported in 1982 three cases of carcinoid syndrome without liver metastasis, only carcinoid tumours with metastatic disease had been associated to this clinical situation⁸. It is of interest that gastro-intestinal carcinoids usually produce the syndrome only when they spread to the liver, because from there they can release tumour products into the systemic circulation avoiding liver breakdown, and metastasize to the lungs, bones and other organs.

But, as said, the development of the syndrome is possible in the absence of metastasis, if the tumour discharges the active products directly into the systemic circulation and circumvents hepatic metabolism. This situation is possible in extra-intestinal locations such as lung, gonads and the retroperitoneum⁹.

Carcinoid tumors arising in the lung specifically produce serotonin, gastrin, adrenocorticotrophic hormone and histamine¹, probably involved in the genesis of angioedema in this case. Therefore, bronchial carcinoid tumors could develop this syndrome, releasing tumor factors directly into the systemic circulation. In our patient's case, it is obvious that the tumor can easily access it through the pulmonary artery next to which is located. However, the association of bronchial carcinoid tumors with carcinoid syndrome is extremely rare and it has been reported in only one patient with metastatic disease². Acquired angioedema has been reported as a manifestation of malignant disease in monoclonal gammopathies by auto-antibodies against C1-inhibitor, but in to the best of our knowledge, only one case of Quincke's edema as part of typical carcinoid syndrome has been reported, in a middle-aged man with a primary midgut carcinoid tumor with metastatic disease to liver¹⁰.

The biochemical diagnosis of carcinoid tumours is based on the measurement of the serotonin metabolite 5-HIAA in a 24 hour urine collection (Normal value = 2-8 mg/day), with a sensitivity of about 73 % and specificity of 100 %³. The measurement of platelet serotonin level is useful because it seems to have a higher sensitivity, especially with tumours that are characterised by a low rate of

serotonin production^{3,11}. In our patient's case, the levels of 5-HIAA (5-hydroxyindoleacetic) were slightly elevated, although normal for serotonin. However, there are atypical forms of carcinoid syndrome in which those biochemical markers are normal and it is necessary to determine other metabolites of tryptophan as 5-HTP (5-hydroxytryptophan) or 5-HT (serotonin).

In conclusion, we report the first case of typical bronchial carcinoid tumour, without metastatic disease, with angioedema as a single manifestation of carcinoid syndrome. So, it is very important to include complementary tests in the routine study of angioedema to reject malignant diseases. In our case, the thoracic radiography was the basis of the diagnosis of recurrent angioedema due to bronchial carcinoid tumor.

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