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 leukocytosis and hypocromic 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 superior 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-
lores de TSH estaban, asimismo, dentro de la norma-

dad. En análisis de parásitos en heces fue negativo.

En el hemograma se apreciaba una leucocitosis mo-
derada y una anemia microcítica e hipocroma.

La radiografía de tórax mostraba una imagen no-
dular mediastínica a nivel paratraqueal derecho. El

estudio histológico fue diagnóstico para carciñoide

típico. Los niveles de ácido 5-hidroxiindolacético

(5-HIIA) en orina de 24 horas, estaban discretamen-
te elevados. A la paciente se le practicó una lobecto-
mia superior derecha, no volviéndose a presentar

nuevos episodios de angioedema tras la interven-
ción.

Conclusiones: Presentamos el primer caso de tu-
mor carciñoide bronquial típico, sin enfermedad me-
tastásica asociada, con angioedema como única ma-

nifestación de síndrome carciñoide.

Sólo tenemos conocimiento de un caso de ede-

ma angioneurótico de Quincke asociado a síndrome
carcinoide en un caso de tumor primario intestinal
con metástasis hepáticas. Creemos que es impor-
tante incluir determinados exámenes complementa-
rios, como la radiografía de tórax, en el estudio de
rutina del angioedema para descartar enfermedades
malignas subyacentes.

**Palabras clave:** Angioedema. Síndrome carciñoide.

**INTRODUCTION**

Carcinoid tumours are neoplasms of the neuroen-
docrine system. They are usually small in size and
slow growing. They can be found in different loca-
tions, such as intestines, respiratory airways, the uri-
nary system and gonads. The incidence varies de-
pending on the series, although is estimated that it
is about 1.6 per 100.000 inhabitants\(^1\). They are more
frequent in women than in men (1.6:1)\(^1\) and are not
related to smoking\(^2\). Almost 2 % of the bronchial tu-
mours are carcinoids\(^1\).

In the majority of cases, they are accidentally
found in necropsies and in surgical operations be-
cause 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 syn-
thesize biogenic amines that develop the carcinoid

syndrome when they are released into the systemic
circulation. This syndrome is characterized by diar-

hoea, flushing and pain, although other atypical man-
ifestations, 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 metastasis\(^3\).

The association of bronchial carcinoid tumors with
carcinoid syndrome is extremely rare especially in
the absence of metastatic disease, and the an-
gioedema 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 re-
current episodes of angioedema for the last six
months. Angioedema occurs in different locations,
including eyelids, lips, and soles, on different occa-
sions; which spontaneously disappeared after one
day.

The aetiological study of angioedema did not
show evidence of hypersensitivity to common in-
halants, food allergens and latex. C1-inhibitor, C3, C4,
C1q, proteinogram and immunoglobulins (IgA, IgG,
IgM) all were normal. TSH determination gave nor-
mal results, too. Faecal analyses for parasites were
negative. The haemogram showed moderate leuco-
cytosis and hypocromic microcitic anaemia.

The thoracic radiography showed a mediastinal
node image in the right paratracheal region. In order
to confirm these findings a thorax computerised to-
mography 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 in-
vading 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 syn-
drome manifestation. Certainly, levels of 5-hydrox-
indolacetic acid (5-HIIA) were slightly increased,
11.1 mg/day, respect to normal values between
2-8 mg/day\(^3\). Determination of serotonin in platelets
gave normal results. A superior lobectomy was per-
formed and, as suspected, no new episodes of an-
gioedema appeared after surgical intervention.

**DISCUSSION**

Patients with classic carcinoid syndrome usually
present diarrhoea, flushing and localised or gener-
alised pain. Biogenic amines such as serotonin, hist-
amine, kallikrein, substance P, prostaglandins and catecholamines are excessively synthesized, 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 constituents.

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 situation. It is of interest carcynoid tumours with metastasic disease had been reported in only one patient with metastatic disease. Acquired angioedema has been reported as a manifestation of malignant disease in monoclonal gammapathies 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 in the absence of liver metastasis has been reported in a primary midgut carcinoid tumor with metastatic disease to liver.

The biochemical diagnosis of carcinoid tumours is based on the measurement of the serotonin metabolite 5-HIIA in a 24 hour urine collection (Normal value = 2-8 mg/day), with a sensitivity of about 73 % and specificity of 100 %.

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. In our patient’s case, the levels of 5-HIIA (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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REFERENCES