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CASE REPORT

Large cell neuroendocrine carcinoma of the lung with metastasis to soft tissues. Case report

Carcinoma neuroendocrino de células grandes de pulmón con metástasis a partes blandas. Informe de caso

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ABSTRACT

Neuroendocrine carcinoma of large lung cells is a rare and aggressive lung tumor with a high metastatic capacity. Metastases to soft tissues as an initial form of presentation are exceptional. An 84-year-old female patient with a history of smoking, chronic obstructive pulmonary disease, epilepsy, and pacemakers due to complete atrioventricular block presented with increased volume in the right deltoid region. A percutaneous biopsy was performed once delimited by tomography occupying soft tissues, whose histological and immunohistochemical study established the diagnosis of large cell neuroendocrine carcinoma with primary pulmonary origin whose lesion in the right thigh was a metastasis to soft tissues. Immunohistochemistry is essential for the diagnosis of metastatic neuroendocrine tumors of uncertain origin. The reporting of similar cases is recommended to expand knowledge about this entity.

Keywords: Key words: Large cell neuroendocrine carcinoma; Immunohistochemistry; Metastasis to soft tissues; Synaptophysin.

RESUMEN

El carcinoma neuroendocrino de células grandes pulmonares es un tumor pulmonar infrecuente y agresivo, con alta capacidad metastásica. Las metástasis a partes blandas como forma de presentación inicial son excepcionales. Se presentó una paciente femenina de 84 años, con antecedentes de tabaquismo, enfermedad pulmonar obstructiva crónica, epilepsia y de marcaspasos por bloqueo auriculoventricular completo, que consultó por aumento de volumen en la región del deltoides derecho. Se realizó biopsia percutánea una vez delimitada por tomografía que ocupaba partes blandas, cuyo estudio histológico e inmunohistoquímico desarrolló el diagnóstico de carcinoma neuroendocrino de células grandes con origen primario pulmonar cuya lesión en muslo derecho se trató de una metástasis a partes blandas. El estudio inmunohistoquímico es fundamental para el diagnóstico de tumores neuroendocrinos metastásicos de origen incierto. Se recomienda el reporte de casos similares para ampliar el conocimiento sobre esta entidad.

Palabras clave: Carcinoma neuroendocrino de células grandes; Inmunohistoquímica; Metástasis a partes blandas; Sinaptofisina.

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INTRODUCTION

Neuroendocrine carcinomas of the lung represent a heterogeneous group of tumors that include small cell neuroendocrine carcinoma and large cell lung carcinoma (CNCGP). CNCGP is reported as a rare but highly aggressive neoplasm, with an estimated incidence of 1-3% of all lung tumors.

The most common symptoms include chest pain, hemoptysis, and cough, whereas dyspnea, weight loss, and fever are less common; however, up to 25% of patients may be asymptomatic. Its biological behavior is similar to that of small cell carcinoma, with a high rate of distant metastasis, most frequently to the liver, brain, bone, and adrenal glands. (1,2,3)

Diagnosis is made through histological and immunohistochemical (IHC) examination. Histological examination reveals a tumor with carcinoid morphology (nested, palisading, rosette-like, and trabecular patterns), abundant mitoses, and frequent necrosis. Immunohistochemical analysis shows positivity for TTF-1, CK7, CK20, and synaptophysin, which is useful to differentiate a pulmonary origin from other neoplasms with atypical metastases of unknown origin. In particular, synaptophysin corroborates the immunohistochemical diagnosis. (1,3,4,5)

For the reasons stated, we present the case of 1 patient with an immunohistochemical diagnosis of CNCGP of pulmonary origin, initially presenting as a metastatic lesion in soft tissues.

CASE REPORT

Background

An 84-year-old female patient, housewife, married, Catholic. History of smoking since age 30, with cessation 10 years ago, consuming 8 cigarettes per day. Past medical history includes chronic obstructive pulmonary disease (COPD) for 3 years, treated with salmeterol, fluticasone, ipratropium bromide, and home oxygen at 2 liters per day; hypothyroidism for 2 years treated with levothyroxine 25 mcg orally every 24 hours; idiopathic epilepsy for 2 years treated with levetiracetam and carbamazepine, under follow-up by neurology; and a dual-chamber pacemaker for 3 years due to complete atrioventricular block.

Additionally, multiple geriatric syndromes were identified, including fall syndrome and mild dependence for basic and instrumental activities, with follow-up by geriatrics. Surgical history includes laparoscopic cholecystectomy 6 years ago and appendectomy 2 years ago, both without apparent complications. Furthermore, no history of fractures, transfusions, allergies, other previous hospitalizations, or gynecological-obstetric history was documented in the center's reports.

History of present illness

She comes to the service because she reports abdominal pain for about a week, in the right iliac fossa region, of moderate intensity, relieved with analgesics, intermittent in nature, non-radiating, occurring several times a day and of short duration. This condition was accompanied by nausea and vomiting with food remains, without foul odor and without blood, as well as weight loss of about a month without quantification.

Positive physical examination

An increase in volume was found in the right deltoid region, well-defined, about 3 cm, located in the subcutaneous tissue, with signs of inflammation, hard consistency, pitting edema, painful to palpation, and impairing the mobility of said limb.

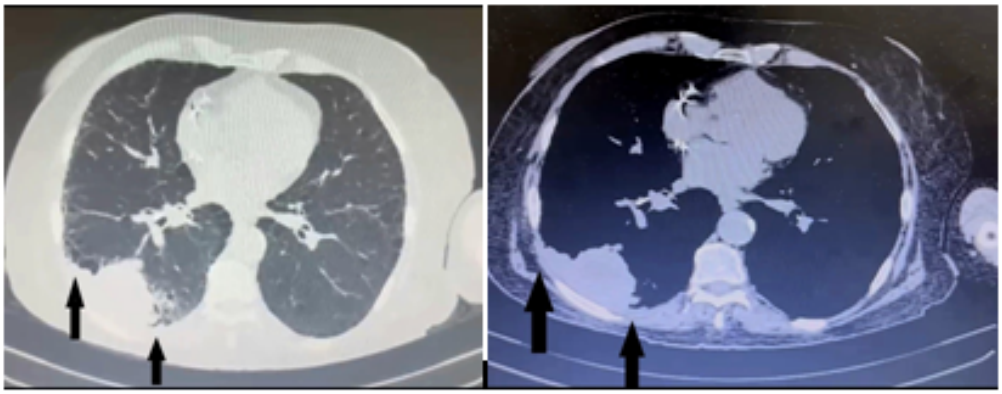
Diagnostic evaluation

On the same day, laboratory tests were performed (Table 1) which showed moderate leukocytosis with a predominance of neutrophils, suggestive of infection or systemic inflammatory process; at the same time, mild hypoglycemia was found. Three weeks later, a computed tomography (CT) scan of the chest was performed (Figure 1a) to delineate and locate the inflamed area and guide subsequent actions, which showed that the lesion occupied soft tissues, with no other findings. The next day, the patient was prepared for a percutaneous core needle biopsy (Tru-Cut) of the lesion.

Table 1. Complementary tests on patient admission.

Complete blood count	Blood chemistry	Tumor markers
Hemoglobin: 14.9 g/L	Blood glucose: 64 mg/dL	Prolactin: 25.4 ng/mL
Hematocrit: 45.1 %	Urea: 24.8 mg/dL	ACE: 3.42 ng/mL
Platelets: 274 x 109/L	Creatinine: 0.61mg/dL	Ca 15 – 3: 22.03 U/mL
Leukocytes: 16.10 x 109/L	Sodium: 135 mEq/L	Ca 19 – 9: 18.99 U/mL
Neutrophils: 81 %	Potassium: 4.24 mEq/L	Alpha-fetoprotein: 1.72 ng/mL
-	Chloride: 97.8 mEq/L	CA 125: 14.62 U/L
-	Calcium: 8.11 mg/dL	-
-	Phosphorus: 4.04 mg/dL	-
-	Magnesium: 1.96 mg/dL	-

Figure 1. Non-contrast chest CT. A peripheral hyperdense image is observed (delineated by black arrows), with pleural anchoring and thickening, irregular contours, approximately 3 cm, located in the posterior segment of the right upper lobe.



Once the sample was obtained, it was taken to the Pathological Anatomy Service for histological study (Figure 2a-b), which showed an infiltration by large round and blue cell neoplasm. However, the histological study was inconclusive due to the variety of patterns observed, its similarity to other metastases of unknown origin, and the fact that it did not coincide with soft tissue neoplasms, which suspected that the lesion was a metastasis. Therefore, the IHC study was carried out to identify the primary origin.

Figure 2a. Cytological study showing accumulation of cells arranged in groups forming nodules or islands. The pattern is predominantly composed of cells with weakly eosinophilic cytoplasm, round or ovoid nuclei, an abundant desmoplastic stroma, speckled chromatin, and an irregular punctate nucleolus.

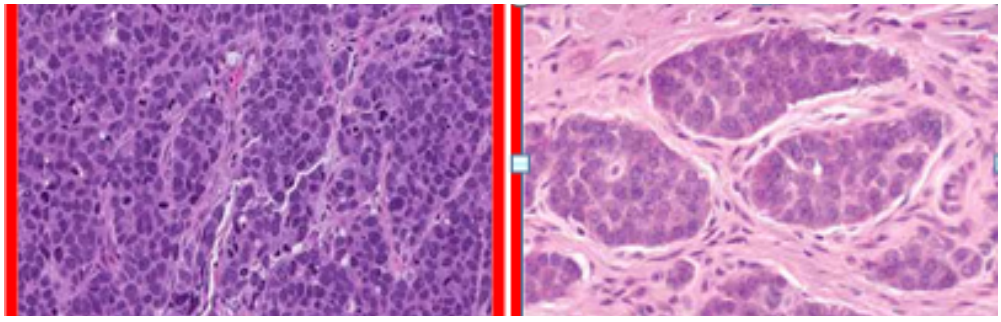
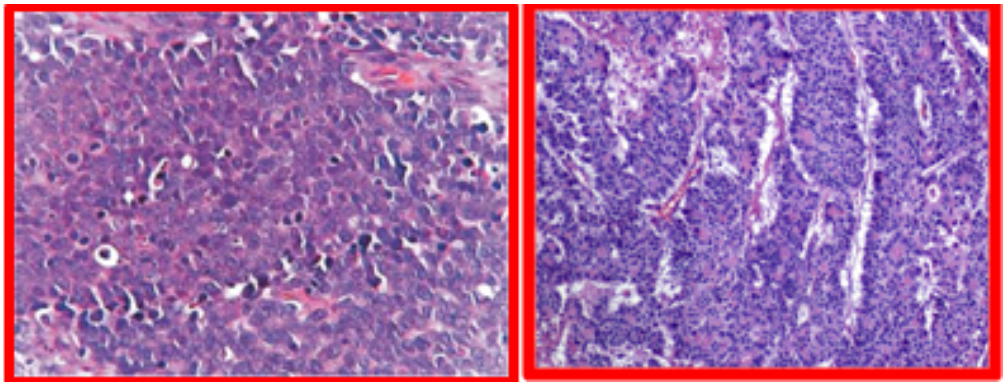


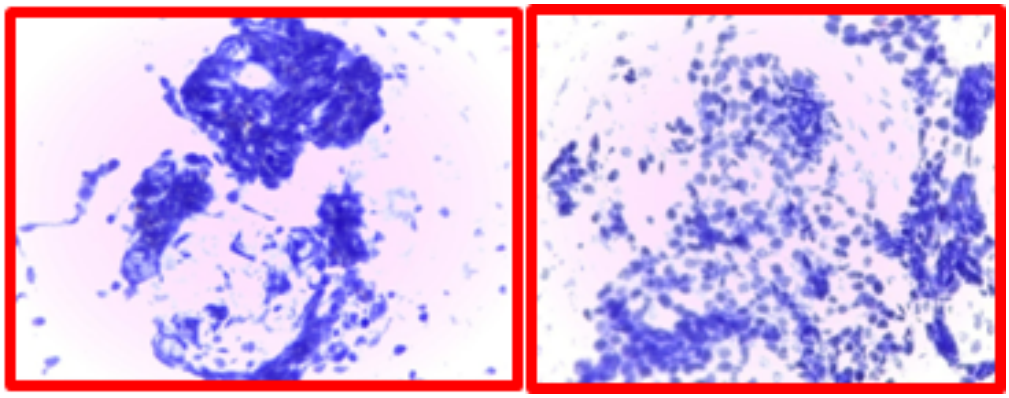
Figure 2b. Cytological study showing cells arranged in cords or trabeculae, or in a circular manner around a hyaline center, or with formation of a central lumen resembling rosettes. The cells have prominent nuclei, dispersed chromatin, and a high degree of mitosis.



For the IHC study, markers Cdx2, Ck20, Ck7, TTF-1, and Synaptophysin were included. Negative staining was obtained for Cdx2 (Figure 3a, left image), which ruled out colorectal, gastrointestinal, primary bladder, and bronchioloalveolar mucinous adenocarcinoma, as well as gastrointestinal carcinoid tumors of the appendix, ileum, and pancreas. Negative staining was also obtained for Ck20 (Figure 3a, right image), which ruled out Merkel cell carcinoma, intrahepatic bile duct carcinoma, gallbladder carcinoma, pulmonary bronchioloalveolar mucinous carcinoma, and endocervical, endometrial, bladder, colon, and esophageal adenocarcinoma, as well as mucinous tumors of the lower gastrointestinal tract and ovary.

In contrast, among the positive markers, diffusely positive Ck7 (Figure 3b, left image) was observed, which indicated the possibility of a primary pulmonary neuroendocrine carcinoma, as did the focal positivity of the Ttf1 marker (Figure 3b, center image), consistent with a high-grade neuroendocrine tumor of primary lung origin. Additionally, the positivity of synaptophysin (Figure 3b, right image) enabled a diagnosis compatible with metastatic large cell neuroendocrine carcinoma with an immunophenotype suggestive of primary pulmonary origin.

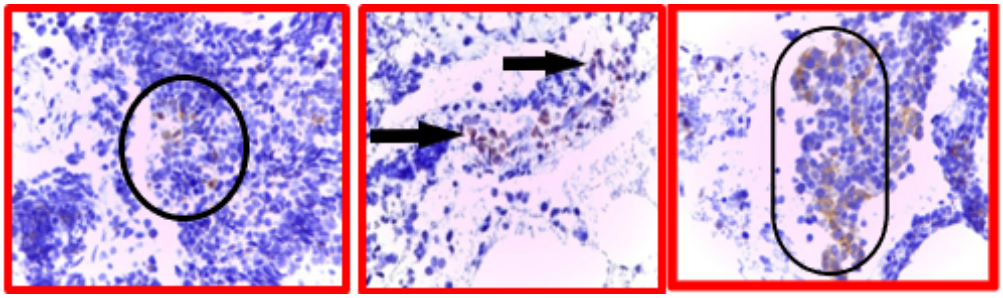
Figure 3a. Immunohistochemical study. Negative markers. Left image: negative Cdx2 marker. Right image: negative Ck20 marker.



Therapeutic intervention

After obtaining the diagnosis, the patient was referred to the Medical Oncology service for therapeutic conduct. Chemotherapy was indicated with carboplatin at a dose of 350 mg/m² and etoposide at 100 mg/m² intravenously, administered in cycles of 21 days, with the aim of controlling metastatic disease and improving quality of life.

Figure 3b. Immunohistochemistry. Positive markers. Left image: CK7 diffusely positive with membranous/cytoplasmic staining pattern (black circle delineating them). Center image: TTF-1 focally positive with nuclear staining pattern (black arrows). Right image: Synaptophysin positive with cytoplasmic staining pattern (black capsule delineating them).



Follow-Up and Results

The patient completed a total of 5 cycles of chemotherapy, which were apparently well tolerated, with no reported serious adverse events that would have necessitated dose modification or treatment discontinuation. During this period, the patient maintained her baseline functional status, with mild dependence for instrumental activities, and continued using home oxygen at 2 liters per minute, consistent with her history of COPD.

However, after completing the fifth cycle, the patient discontinued follow-up at the medical oncology outpatient clinic and did not attend the scheduled follow-up appointments. Despite attempts by the healthcare team to contact her, it was not possible to obtain additional information about her clinical progression, nor to perform imaging studies to localize the tumor. Meanwhile, the tumor origin remained suspected to be in the lung, but this was not confirmed by imaging.

DISCUSSION

The patient described constitutes a typical clinical profile of patients with large cell neuroendocrine carcinoma (CNCG). According to the literature, a history of smoking is one of the main risk factors, and its presentation is more frequent after 60 years of age. (1,4,6) On the other hand, the location of metastases in soft tissues is exceptional, although CNCG metastases have been described in rare sites such as the foramen magnum, (7) the breast, (8) and the skin (9).

This atypical presentation, without prior pulmonary symptoms, has been described in other reports. Examples include the cases reported by Yuan et al., (9) of one case of CNCG diagnosed exclusively from a cutaneous metastasis in a patient without respiratory symptoms, and Barrionuevo and Cáceres, (10) where the patient initially presented with diarrhea and later received an incidental diagnosis through tomographic studies, magnetic resonance imaging, and immunohistochemistry. These cases, together with the one presented, demonstrate that CNCG can present atypically, which hinders clinical suspicion and delays diagnosis, and also provide evidence that the absence of respiratory symptoms and a localized primary tumor do not rule out the diagnosis.

Regarding diagnosis and treatment, the presented case conforms to the standards in the literature. Immunohistochemical study is the determinant par excellence that guides diagnosis and oncological therapy. The positivity profile for CK7, TTF-1, and synaptophysin, with negativity for CK20 and CDX2, is consistent with a large cell neuroendocrine pulmonary origin, which enabled correct identification in this patient, as well as the effective establishment of carboplatin/etoposide-based treatment documented in several patient series. (8)

The main limitation of this report is the loss of patient follow-up; the patient abandoned oncology consultations after completing 5 cycles of chemotherapy. Moreover, no follow-up imaging studies are available to assess treatment response or to determine clinical evolution. In addition, although the chest CT showed a peripheral image suggestive of a pulmonary lesion, the primary tumor could not be pathologically confirmed, which constitutes another important limitation.

Despite these limitations, we consider that the case provides value due to the rarity of the clinical presentation and by demonstrating the utility of immunohistochemical study to guide the etiological diagnosis in metastases of unknown origin. At the same time, early diagnosis of CNCG remains a challenge, and reports of atypical cases such as the case presented contribute to broadening the clinical spectrum of this neoplasm and alerting clinicians to its unusual forms of presentation.

CONCLUSIONS

Large cell neuroendocrine carcinoma of the lung can metastasize to soft tissues as an initial presentation. Immunohistochemical study is a highly valuable diagnostic tool for identifying the origin of metastatic neuroendocrine tumors when the primary is unknown. Close and multidisciplinary follow-up is recommended in these patients, as well as continuing to report similar cases to enrich knowledge about this atypical presentation.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORSHIP CONTRIBUTIONS

Conceptualization, data curation, formal analysis, investigation, project administration, supervision, validation, writing – original draft, writing – review and editing: Nadia del Rosario Blanco Figueredo. Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing - original draft, writing - review and editing: José Grabiel Correa Rodríguez. Data curation, investigation, writing – original draft, writing – review & editing: Leonardo Manuel Castell Martínez.