CLINICAL NOTE

MENINGEAL CARCINOMATOSIS: UNUSUAL PRESENTATION OF ADENOCARCINOMA OF THE LUNG

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Abstract:
A case is presented of a patient with a history of low-intensity smoking, with an accumulated tobacco index of less than 5 packs-year and without other personal history of interest. She went to the emergency room several times over 2 months, complaining of a diffuse, oppressive and intermittent headache and diplopia accompanied by occasional blurred vision, being diagnosed with ischemic paralysis of the fourth cranial nerve of the left eye and initiating treatment with antiplatelets. Despite treatment, she returned to the emergency room within a week, as she had been suffering from progressive dizziness, instability when walking, loss of vision mainly in the left eye and a greater feeling of weakness in the upper limbs. Finally, admission to Neurology was decided upon with the suspicion of subacute tuberculous meningoencephalitis. However, after various diagnostic tests, it was concluded that it was a pulmonary adenocarcinoma, which began as meningeal carcinomatosis without presenting associated respiratory symptoms.

Key words: Lung cancer, meningeal carcinomatosis, lung adenocarcinoma.

CARCINOMATOSIS MENÍNGEA: FORMA INUSUAL DE PRESENTACIÓN DEL ADENOCARCINOMA DE PULMÓN

Resumen
Se presenta el caso de una paciente con antecedentes de ser fumadora de baja intensidad, con índice acumulado de tabaco menor de 5 paquetes/año y sin otros antecedentes personales de interés. Acudió en diversas ocasiones durante 2 meses a urgencias, refiriendo cefalea difusa, opresiva e intermitente y diplopía acompañada de visión borrosa ocasional, siendo diagnosticada de parálisis isquémica del IV par craneal del ojo izquierdo e iniciando tratamiento con antiagregante. A pesar del tratamiento, a la semana acudió de nuevo a urgencias, ya que progresivamente había ido presentado mareos, inestabilidad en la marcha, pérdida de visión con predominio en ojo izquierdo y mayor sensación de debilidad en miembros superiores, Finalmente, se decidió ingreso en Neurología ante la sospecha de meningoencefalitis subaguda tuberculosa, pero tras diversas pruebas diagnósticas se llegó a la conclusión de que se trataba de un adenocarcinoma pulmonar, que debutó en forma de carcinomatosis meníngea sin haber presentado sintomatología respiratoria asociada.

Palabras clave: cáncer de pulmón, carcinomatosis leptomeningea, Adenocarcinoma pulmonar.

INTRODUCTION

Lung cancer (LC) is the most common tumor and the one which causes the highest mortality rate in the developed world[1], with 1,800,000 new cases per year and 1,600,000 deaths in 2012. In Spain[3], there were 33,370 new cases diagnosed in 2015, making it the third most prevalent tumor in our country. The incidence rate is variable according to sex, in such a way that in 2015, 22,430 men were diagnosed compared to 5,917 women. It is the most common malignant tumor in men, and ranks third place in women[3]. Additionally, during the next decade, incidences are expected to continue increasing for both sexes. The mortality rate for both woman and men hasn't stopped rising in our country since 1980 and is currently the type of tumor that causes the highest number of deaths in the general population, both in Spain and on a global level[4]. Of the new cases at the time of diagnosis, only 20% are found in early stages (Stage I-II of the TNM classification) and up to 40% of cases already have distant metastasis. The survival rate of patients with lung cancer is very low and it's because of this that the proportion of mortality to incidence maintains a

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stable relationship which is close to the same in our country and the rest of the world (0.86)[5]. Tobacco smoke is the most important risk factor for the development of LC, with smokers being approximately 20 times more at risk of developing the disease than non-smokers. In the same way, the passive inhaling of tobacco smoke increases the risk of developing LC between 20% and 30% compared to the non-exposed population.

Adenocarcinoma is the most common histological type, constituting 38% of the cases of LC diagnosed at present, also being the lineage that is least related to the consumption of tobacco in comparison with squamous cell carcinoma or with small cell carcinoma.

The first symptoms are often extrathoracic, given its propensity to develop early metastases, and it is not uncommon for it to start with neurological symptoms due to brain metastasis, with a range of occurrence of these symptoms between 3-21%[6, 7].

Paraneoplastic syndromes appear in less than 1% of patients with cancer and the majority of them present with carcinoma of the lung (generally small cell), breast or ovary. They are not limited to the nervous system, but they affect it frequently.

The effects at the central nervous system (CNS) level include progressive dementia, behavior alterations, convulsions and, on a lesser scale, focal motor or sensory signs.

The main outlying effects are muscular weakness and peripheral neuropathy. The diagnosis is usually by exclusion, unless autoantibodies are detected in the patient's serum or cerebrospinal fluid (CSF). The differential diagnosis includes metabolite disorders, meningeal carcinomatosis and progressive multifocal leukoencephalopathy. There is no specific treatment, although patients can occasionally improve with treatment of the primary neoplasm[8, 9].

Nowadays, the anatomopathological diagnosis of lung cancer is a multi-step process, beginning with the morphological diagnosis to determine the histological type and then refining with immunohistochemistry, which is required to perform an appropriate characterization of the tumor. This increasingly complex diagnosis algorithm poses many changes for the management of patients with lung cancer.

Nowadays, we know that a significant proportion of patients with lung cancer suffer from tumors with molecular characteristics (mutations, gene fusions, etc.) which allow us to establish a therapeutic target. Currently, the vast majority of those molecular abnormalities that are susceptible to specific therapeutic processes are presented, for the most part, in adenocarcinoma of the lung. Laboratory studies based on predictive biomarkers, which identify said abnormalities to be able to respond with targeted therapies, represent an example of change in lung cancer diagnosis and have become an important evolution in this pathology.

Active mutations in the growth factor receptor gene (EGFR) *tyrosine kinase* appear in 10-16% of cases of adenocarcinoma in European patients[10]. However, in squamous cell carcinoma, these mutations very scarcely appear in a reliable form. The cause of the EGFR mutation is unknown, but it's not related to tobacco. Thus, these mutations are more common, although not exclusive, in non-smokers or long-time former smokers and in young women. Independent of this data, recent evidence indicates that patients with any type of lung cancer, including small cell, that have a minimal or remote history of smoking should be considered for said gene test[10].

Studies in phase III which include patients from Asia, Europe and America with metastatic disease, whose tumors have the mutated EGFR, have demonstrated higher response ratios (approximately 70%) and a higher survival rate, without significant progression in patients initially treated with EGFR *tyrosine kinase* inhibitors (EGFR TKIs) (gefitinib, erlotinib, afatinib), compared to those who received chemotherapy[11-13]. The use of EGFR TKIs is currently well established in clinical practice, requiring routine tests in appropriate cases.

CLINICAL CASE

A female, 55-year-old patient, allergic to acetylsalicylic acid, pyrazolones, non-steroidal anti-inflammatories, penicillin and derivatives, cephalosporin, gentamicin and fosfomycin. Very sporadic smoker. She did not refer to any other personal history of interest nor active treatment. She visited the emergency room several times over two months, suffering from a diffuse, oppressive and intermittent headache and diplopia accompanied by occasional blurred vision. She was initially diagnosed with ischemic paralysis of the fourth cranial nerve of the left eye after performing a nuclear magnetic resonance (MRI) scan. Treatment began with clopidogrel. Despite this, she returned to the emergency room a

week later, as the signs had progressively worsened. She presented further dizziness, instability when walking, loss of vision mainly in the left eye and a greater feeling of weakness in the upper limbs, therefore a spinal tap was performed in the emergency room, obtaining cerebrospinal fluid (CSF) with predominantly mononuclear cellularity. With the suspicion of tuberculous meningitis, admission to the Neurology department was decided and empirical antituberculous treatment was initiated.

At first, the signs of the physical and neurological examination were normal, but the day of admission for physical examination she displayed hypo-reactive pupils, especially the left, which appears to be Marcus Gunn pupil. It's difficult to explore the extrinsic ocular motility due to loss of visual acuity. Furthermore, it is accompanied by facial paresis of the upper and lower right bundle branch, together with weakness of the soft palate and a certain nasalization of the voice. She also presents weakness in neck flexion, absence of peripheral motor reflexes in extremities and cutaneous extensor plantar reflexes.

Once she was admitted, the following set of diagnostic tests was carried out. No alterations in the hemogram nor the biochemistry were found. The acetylcholine antireceptor antibody was negative. An anterior-posterior chest and left anterior oblique x-ray showed a consolidation-mass located in the right upper lobe (RUL) of approximately 4 cm in maximum diameter. A chest CT scan was carried out. A cranial CT scan was carried out, without observing pathological findings. A Doppler ultrasound of supra-aortic trunks was performed, with no alterations in either carotids or vertebral arteries. In the transcranial Doppler ultrasound, there were also no alterations in the examination of the cerebral arteries.

An initial lumbar puncture was carried out, which showed high cellularity with mononuclear, hyperproteinorrachy and hypoglycorrhachia predominance, with leukocytes: 15 leu/dL (polymorphonuclear 13%, mononuclear 87%), red blood cells: 0 hem/dL, proteins: 64.2 mg/dL and glucose: 31 mg/dL. The fundus of the eye didn't show any evidence of papilledema or other alterations.

In the cranial MRI with contrast, pachy and leptomeninges involvement was observed that posed as the differential diagnosis between infectious meningitis and granulomatous processes such as sarcoidosis and carcinomatosis. Furthermore, an early subacute ischemic lesion was evident on the left side of the protuberance, compatible with probable vasculitis associated with meningitis (Figure 1).

The electroencephalogram showed signs of mild generalized cerebral electrical involvement, predominantly in anterior areas of both hemispheres and a certain right predominance.

A second lumbar puncture was carried out that showed findings similar to the previous one, with high cellularity of mononuclear, hyperproteinorrachy and hypoglycorrhachia predominance and with higher red blood cell content (leukocytes: 10 leu/dL [95% mononuclear], red blood cells: 100 hem/dL, proteins: 220 mg/dL and glucose: 16 mg/dL). Additionally, a rise in adenosine deaminase (ADA) with a value of 9.2 (normally 0-7) was found. The determination of microbacteria through the polymerase chain reaction (PCR) in CSF was negative, as were the stains and microbacteria, bacteria and fungus cultures.

The cytology of the CSF was positive, compatible with meningeal carcinomatosis of adenocarcinoma.

The chest CT scan showed a 3.3 x 2.7 x 4.5 cm mass in the right upper lobe (RUL), which comes into contact with the mediastinal pleura on an approximate surface of 2 cm. Furthermore, a dense lesion with sclerotic appearance was described on the posterosuperior side of the D1 vertebral body and a discrete pseudonodular thickening of the left adrenal gland with undetermined characteristics was observed. If it was a neoplasm, it would be stage IB (T2a, N0, Mx).

The positron emission tomography (PET)-CT showed a metabolically positive pulmonary mass in the CSF with ipsilateral mediastinal lymphatic and osseous involvement (vertebra D1, L5 and right iliac bone), suggestive of malignancy. There was pseudonodular thickening without significant uptake in the left adrenal gland, indicating a low probability of malignancy (Figure 2).

Finally, a CT-guided biopsy of the pulmonary mass was carried out, with cytology compatible with adenocarcinoma of pulmonary origin, with mutation of the positive endothelial growth factor receptor (EGFR).

The definitive diagnosis was stage IV (T2a, N2, M1b) adenocarcinoma of the lung, with osseous metastasis (D1, L5 and right iliac bone) and carcinomatous meningoencephalitis.

Once the diagnosis was decided, treatment began with the instillation of intrathecal dexamethasone and erlotinib. Levetiracetam was also added after the patient presented an absence seizure on one occasion during

hospitalization.

The patient evolved, developing a new absence seizure after a month as she had decreased the dose of antiepileptic medication without medical supervision. Two months after discharge, she was diagnosed with left iliofemoral deep vein thrombosis, requiring admission to start anticoagulation, being stable from the neurological and pulmonological point of view.

Three months after starting treatment, a control chest CT scan was carried out, evidencing signs of partial response, with shrinking of the CSF tumor mass to diameters of 21 x 17 mm (33 x 27 mm in previous study). No radiologically significant lymphadenopathies appeared in the study. Bone lesions had increased their degree of sclerosis, a modification which could be in relation to internal reparative changes. Furthermore, the study showed signs of pulmonary thromboembolism in some segmental arteries, with partial occupation of the lumen of the vessels, without appreciable parenchymal repercussions or signs of right cardiac overload. A control cranial NMR was also performed, in which the disappearance of the hyper-uptake and leptomeningeal thickening seen in the previous study can be noted at the cranial level. This highlights the presence of signs of subcortical atrophy and increased small vessel ischemic leukoencephalopathy in the cerebral study. Also highlighted was the relative increase of the ventricular system, uniformly and globally, compared to the previous study.

In the final progressive test, the patient continued the treatment with erlotinib, presenting grade 3 cutaneous toxicity of the scalp and grade 2 paronychia , therefore the dose was reduced as the patient was neurologically stable and showed asymptomatic breathing.

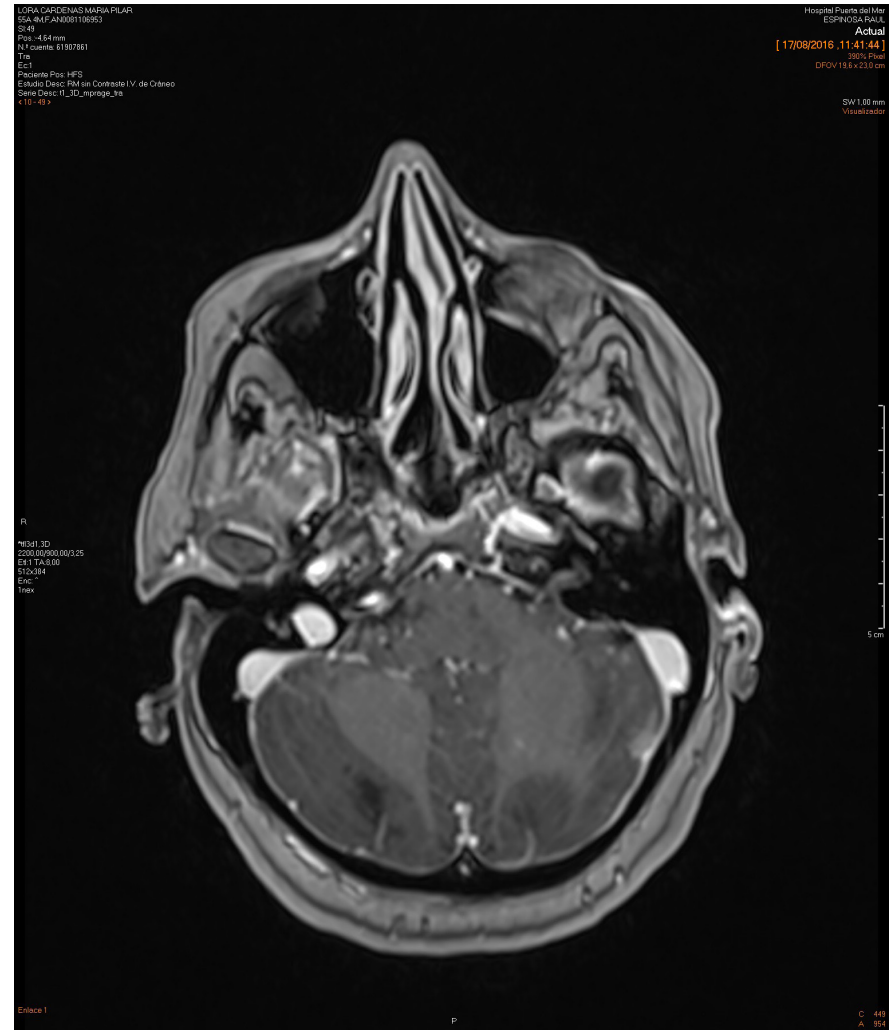

Figure 1. Cranial NMR, which highlights a diffuse and linear enhancement of the dura mater, as well as diffuse leptomeningeal enhancement with a linear predominance that adopts a pseudonodular pattern at the level of the folia of the cerebellum.

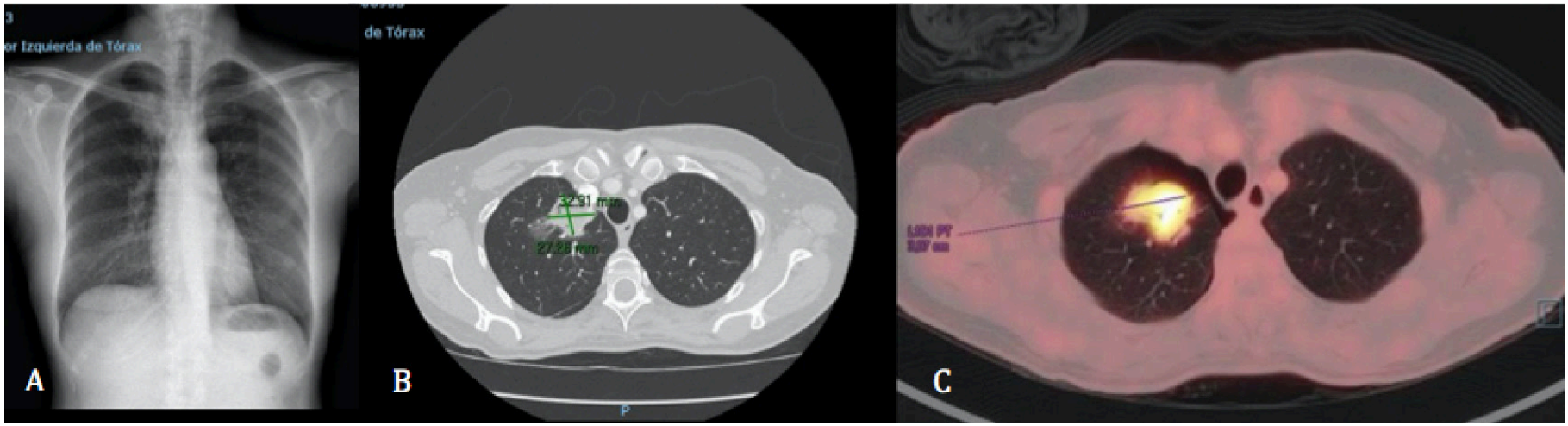

Figure 2. A) PA chest x-ray with image of an approximately 4-cm consolidation-mass located at right upper lobe level. B) Chest CAT scan with 3.3 x 2.7 x 4.5 cm mass in right upper lobe. C) Pulmonary section of PET-CT, with image of metabolic hyper-uptake in CSF.

DISCUSSION

Meningeal carcinomatosis (MC) is more commonly present in patients with disseminated neoplastic disease (70%), but it can occur after a disease-free interval (20%) and even be the first sign of cancer (5-10%)[14]. Similarly, several autopsy studies indicate that up to 19% of patients with cancer associated with neurological signs and symptoms have evidence of meningeal involvement due to MC. Furthermore, the incidence of MC in patients with cancer ranges from 5% to 8%. The first tumors that usually indicate MC in the adult population are breast (30-50%) and lung (15-25%), mainly small cell carcinoma and adenocarcinoma, followed by melanoma (11%) and gastric cancer (0.16-0.69%)[14].

It is especially interesting to note how the patient's initial clinical symptoms focused the pathology towards the central nervous system, at first suspecting a possible intracranial expansive lesion, which was ruled out after the complementary examinations. It is worth noting that the patient was completely exempt from respiratory symptoms, which made the initial diagnosis difficult and, therefore, delayed an adequate therapeutic approach.

This case is interesting because it can help us to take meningeal carcinomatosis into account, within the differential diagnoses of the pathology that simulates symptoms of intracranial neoplasia.

Furthermore, MC in non-small cell carcinoma of the lung (NSCCL) is a difficult illness to treat and is a very serious entity in the course of these tumors. The survival rate of these patients is approximately 3 months, which is shorter than that of patients with meningeal involvement in other illnesses like breast cancer or malignant hematological illnesses[15]. These patients are frequently treated with holo-cranial radiotherapy, intrathecal chemotherapy with methotrexate, cytarabine or thiotepa (or both), although this is less common. The survival rate remains poor, independent of the use of treatments or not. Thus, although holo-cranial radiotherapy may play an important role in terms of symptom control, there is little evidence to support its survival benefit[16]. There is also no clear evidence of the advantages of intrathecal chemotherapy in terms of the survival of these patients[17].

However, there are studies, reports and case series whose data suggests that patients with meningeal carcinomatosis with the EGFR mutation, treated with EGFR TKIs like erlotinib or gefitinib, had a higher average survival rate (3 months)[18-21].

We specifically mention a study with 11 patients with meningeal carcinomatosis in the context of NSCCL which was treated with erlotinib or high doses of gefitinib. The results of the study show, among other things, that the survival rate of 8 of the patients was more than 6 months and, additionally, another 2 patients survived +2.5 and +4.4 months. Clinical improvement was documented in 9 of the patients. Thus, the results suggest that treatment with erlotinib or an increased dose of gefitinib is an effective therapeutic option for selected patients with this pathology[15].

In this way, taking the clinical evidence into account, since the positive result for the EGFR mutation was obtained in our patient, treatment with erlotinib was started. Subsequent tests showed a good response to the therapy, with improvement both in the pulmonary and metastatic lesions and, for the time being, with an above-average survival rate compared with patients who can't be treated with this therapy due to absence of the EGFR mutation.

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