

CARCINOMATOUS ENCEPHALITIS AS CLINICAL PRESENTATION OF OCCULT LUNG ADENOCARCINOMA

Case report

Henrique Barbosa Ribeiro¹, Tadeu Ferreira de Paiva Jr¹, Gustavo Pignatari Rosas Mamprin², Milton Luiz Gorzoni¹, Antônio José da Rocha³, Carmen Lucia Penteado Lancellotti²

ABSTRACT - Carcinomatous encephalitis is a rare entity, originally described by Madow and Alpers in 1951, which is characterized by tumoral spreading perivascular, without mass effect. Clinical manifestations such as hemiparesis, seizures, ataxia, speech difficulties, cerebrospinal fluid findings as well as computed tomography are nonspecific. This leads the physician to pursue more frequent diseases that could explain those manifestations – toxic, metabolic, and/or infectious encephalopathy. A magnetic resonance imaging (MRI) with gadolinium, the method of choice, presumes the diagnosis. Previous reports of this unusual form of metastatic disease have described patients with prior diagnosis of pulmonary adenocarcinoma. We present the case of carcinomatous encephalitis in a 76-years-old woman as the primary manifestation of occult pulmonary adenocarcinoma with its clinical, imaging, and anatomopathological findings.

KEY WORDS: brain metastases, carcinomatous encephalitis, lung adenocarcinoma, miliary brain metastases.

Encefalite carcinomatosa como apresentação inicial de adenocarcinoma de pulmão oculto: relato de caso

RESUMO - A “encefalite” carcinomatosa é entidade rara, descrita originalmente por Madow e Alpers em 1951 e caracterizada pela disseminação tumoral perivascular, sem causar efeito de massa. As manifestações clínicas como hemiparesia, convulsões, ataxia, alterações de fala, os achados do líquido cefalorraquidiano e da tomografia computadorizada de crânio são inespecíficos, o que faz buscar outras causas mais frequentes que justifiquem o quadro -encefalopatia tóxica, metabólica e/ou infecciosa. A ressonância magnética com gadolínio é o exame de eleição, frente à suspeita clínica. Todos os casos de “encefalite” carcinomatosa foram relatados em pacientes com diagnóstico prévio de adenocarcinoma de pulmão. Nesse sentido. Apresentamos caso de encefalite carcinomatosa, em mulher de 76 anos como manifestação primária de adenocarcinoma de pulmão oculto, com seus aspectos clínicos, de imagem e anatomopatológicos.

PALAVRAS-CHAVE: metástase cerebral, encefalite carcinomatosa, tumor primário de pulmão, mecanismo de metástase, metástase miliar.

Carcinomatous encephalitis is an unusual form of cerebral miliary metastatic dissemination, characterized by the presence of tumoral micronodules spreading into the perivascular Virchow-Robin (VR) spaces, parenchyma, as well as meninges, without constituting a tumoral mass. The most frequently associated primary tumor is lung cancer^{1,2}. Moreover, it has also been described associated with other tumors such as melanoma³. Several terms were proposed to describe this entity in literature, e.g., “miliary carcinoma” and “metastatic meningoencephalitic carcino-

miosis without tumefaction”. Nevertheless, none of them describes this form of metastatic tumors properly. In this sense, Madow and Alpers, in 1951, proposed the expression “carcinomatous encephalitis”, as the most adequate term, despite the fact that no inflammatory reaction is involved². This diagnosis was again emphasized with the advent of imaging methods, particularly magnetic resonance imaging (MRI) with gadolinium^{1,4-6}.

Carcinomatous encephalitis clinical manifestations vary and the cerebrospinal fluid is usually nonspecif-

¹Department of Medicine, ²Department of Pathology, and ³Department of Radiology, Santa Casa de São Paulo, Faculty of Medical Sciences, São Paulo, Brazil.

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Dr. Carmen Lucia Penteado Lancellotti - Santa Casa de São Paulo / Faculty of Medical Sciences, Department of Pathology - Rua Dr. Cesário Mota Jr. 112 - 01221-900 São Paulo SP - Brasil. E-mail: luciapl@uol.com.br

ic⁷, making the diagnosis difficult. In the reviewed literature (MEDLINE), all the reported carcinomatous encephalitis cases, related to lung adenocarcinoma, occurred in patients with its previous diagnosis^{4,6}. We present a review of the literature and a case report of carcinomatous encephalitis as the primary manifestation of pulmonary adenocarcinoma in correlation with clinical, imaging, and anatomopathological findings.

CASE

A 76-year-old white female presented with a 3-week history of mental confusion, somnolence, diffuse headache, and diplopia. She reported untreated high blood pressure and denied tobacco use. On physical examination the patient was in a regular general state, febrile (38.5°C), blood pressure within normal parameters, rhythmic heart rate at 80 beats per minute, confused, and withdrawn. Chest auscultation showed crepitant rales on the left lung base. The neurological examination revealed hemiparesis to the left (grade III motor strength) and paralysis of the left VI cranial nerve.

Chest X-ray showed parenchymal condensation on the left hemithorax, and the patient was submitted to antibiotic therapy, after presumed diagnosis of pneumonia. Computed tomography (CT) of the brain demonstrated hydrocephalus with no deviation of the medial structures or focal lesions. Cerebrospinal fluid (CSF) revealed cells of 6/mm³, with lympho-monocytic predominance. Glucose and protein levels were 50 mg/dL and 30 mg/dL, respectively. Direct study and culture for bacteria and fungi were negative, as well as the study for neoplastic cells. Additional evaluation using MRI of the brain revealed areas with hypersignal in the T2 and FLAIR sequences, with innumerable punctate

foci in the topography of the VR perivascular spaces of the pons, mesencephalon, nucleus-capsular regions, thalamus, and in the semi-oval centers. It was also observed the focal compromising of the leptomeninges in the convexity, characterized by the gadolinium enhancement. Furthermore, the supratentorial ventricular system was dilated with incipient signs of CSF hypertension (Fig 1).

Regarding these clinical conditions and imaging studies, the diagnostic possibility of meningitis by *Cryptococcus sp* was considered due to the distribution pattern of the lesions in the perivascular spaces of VR, as well as leptomeningitis, and hydrocephalus. However, new CSF specimen kept the same aforementioned characteristics, including negative China ink, latex, and culture for *Cryptococcus sp*.

After two weeks of the admission, the patient's condition deteriorated with consciousness level reduction, cardiopulmonary arrest, and death. Autopsy was done after the patient's family had signed the informed consent, which was registered in her records.

In the autopsy it was detected frontoparietal cerebral atrophy with moderate dilation of the cerebral ventricles, secondary to micrometastases in the same sites revealed by MR in the parenchyma, VR spaces, and leptomeninges, with no tumoral mass formation (Fig 2). The patient presented a peripheral pulmonary nodule on the left inferior lobe whose histopathological study revealed acinar adenocarcinoma. In addition, metastases to the liver, mediastinal and abdominal lymph nodes were observed.

DISCUSSION

Parenchymal cerebral metastases are usually characterized by nodules or single masses in the white and gray matter junction, as a result of hematogenic dissemination. It is estimated that 20% to 30% of



Fig 1. Axial FLAIR image (A) demonstrates signs of hydrocephalus and small hyperintense foci in the thalamus and nucleus-capsular regions (arrowheads) in the topography of the Virchow-Robin perivascular spaces. The injection of gadolinium (B) demonstrated abnormal micronodular enhancement in the same regions (arrows). Also note the asymmetric enhancement of the leptomeninges in the left occipital regions (arrowheads).

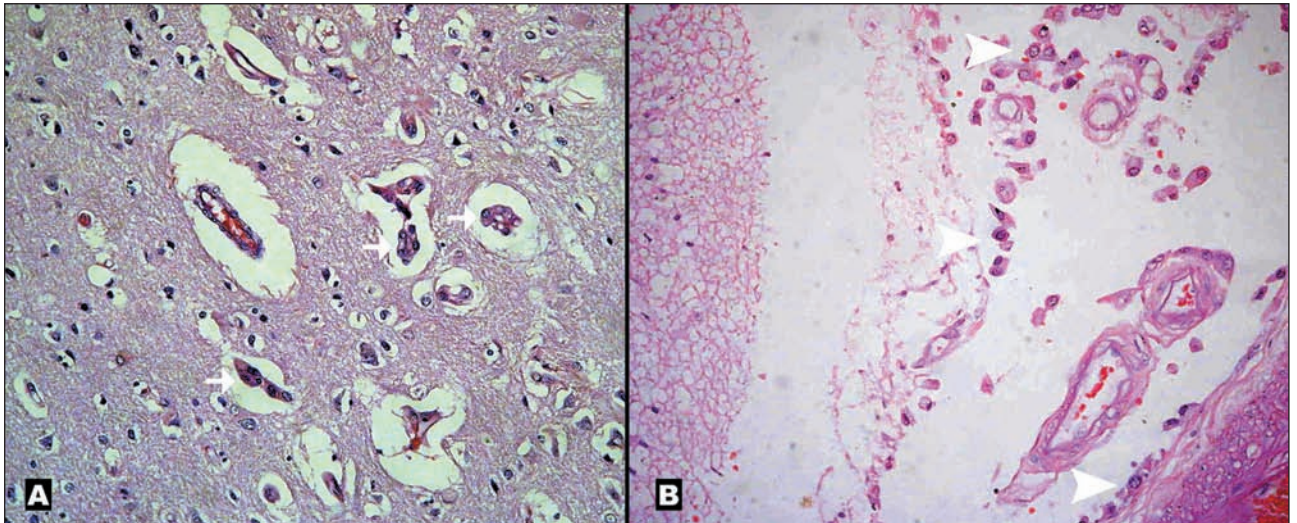


Fig 2. Histopathological findings of the cerebral tissue: (A) observe typical presence of neoplastic cells in the perivascular spaces of Virchow-Robin, without perilesional edema (arrows), or tumoral mass (hematoxylin and eosin; original magnification X 200); (B) leptomeningeal carcinomatous dissemination (arrowheads); (hematoxylin and eosin; original magnification X 200).

the patients with solid cancer present cerebral metastasis at the time of death⁸. Miliary metastatic pattern describes the occurrence of several faint nodules disseminated in the brain parenchyma. Carcinomatous encephalitis is a particular form of brain metastasis that could be included among miliary pattern. It is quite uncommon and affects the perivascular spaces of VR, parenchyma, and meninges, without causing perilesional edema or mass effects¹⁻⁹.

The clinical manifestations vary and can be described as organic mental syndrome^{6,7}, hemiparesis², convulsions^{2,10}, speech abnormalities¹, and gait abnormalities^{7,9}, being found generally in patients with the previous diagnosis of a systemic neoplasia. In contrast, our case did not show any neoplastic antecedents, and the first clinical manifestations were related to the cerebral metastases. The variability of clinical presentations makes the diagnosis difficult, especially in the absence of previously defined neoplasia. This probably explains its reserved prognosis, ranging in the literature from 14 days⁸ to 7 months¹⁰.

The CSF analysis is normally nonspecific, differentiating from carcinomatous meningitis that usually presents abnormalities, either with the presence of positive cytology, that is only negative in 16% of patients after repeated lumbar puncture¹¹⁻¹², or increased total protein level. Although not specific, the finding of increased total protein level might be valuable, mainly in patients with a negative first CSF cytologic examination¹¹⁻¹³.

Regarding the neuroradiological findings, the CT does not generally detect the micronodules, only the

hydrocephalus that may result from meningeal and cerebral perivascular damage that alters CSF circulation. It must be emphasized that the MRI using gadolinium is the exam of choice facing clinical suspicion of the disease. Therefore, the reports in the literature are contradictory, and the parenchymal and meningeal lesions may^{1,4} or may not¹⁰ be enhanced by the contrast. Also, they may be calcified¹³⁻¹⁶, hemorrhagic⁹, or even be normal¹⁷. Nakamura et al. proposes that the MRI with contrast should be repeated in cases with strong clinical suspicion, even if the initial study is normal¹⁷.

The main MRI differential diagnosis is meningitis by *Cryptococcus sp* because of the distribution pattern of the lesions in the perivascular spaces of VR in the pons, mesencephalon, basal nucleus, and in the semi-oval centers, as well as in the leptomeninges, and the presence of hydrocephalus. But, in such cases the CSF is normally altered and may yield increased number of cells, positive China or India ink test, culture or positive antigen assay¹⁸⁻²⁰.

The reviewed literature and analysis of the presented case allow us to conclude that the symptoms of carcinomatous encephalitis are nonspecific and that the prognosis is reserved. MRI using gadolinium constitutes the imaging method of choice, and it is able to reproduce the pathological features of this uncommon pattern of cerebral neoplastic dissemination, in the VR perivascular spaces. Moreover, it should be included in the differential diagnosis of such cases, even without any known systemic neoplastic involvement.

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