

Carcinomatous Meningitis, A Rare Etiology of Rapidly Progressive Dementia

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Abstract- Most dementias often develop slowly and progressively, but in some cases we are faced with presentations whose worsening is very rapid. The neoplastic origin of a rapidly progressive dementia is rare, its occurrence is related to a spread of the tumor to the meninges and cerebrospinal fluid (CSF). This article presents the clinical case of a 75-year-old man with multiple comorbidities and a small cell bronchial adenocarcinoma under treatment, which presents a rapidly progressive cognitive decline over a few weeks and progressing to aggravation. The neurological examination did not find any signs of focusing and the neuropsychological tests show a severe alteration of the memory and executive cognitive functions. Cerebral MRI reveals stage 3 medial temporal atrophy, a diffuse cortico-subcortical atrophy associated and a few demyelinating lesions with a degenerative appearance. Infectious, deficiency, autoimmunity and thyroid tests were carried out and returned without abnormality. The search for anti-neuronal antibodies is negative. Cytological analysis of the cerebrospinal fluid (CSF) showed a sheet of blastoid cells of medium to large hetero size with the presence of a few images of mitosis. Based on the "medical" history "of the patient" and the results of CSF cytology, the diagnosis of carcinomatous meningitis secondary to metastatic lung cancer is retained. Our case underlines the importance of the study of CSF, especially cytology in patients with an atypical dementia in search of tumor cells.

Keywords- Carcinomatous meningitis, rapidly progressive dementia, neoplasia, CSF

I. INTRODUCTION

Dementia is a slow, progressive decline in cognitive functions, with impaired memory and behavioural disorders. In some cases, however, the symptoms worsen rapidly over a period of months or weeks, defining rapidly progressive dementia. The outcome of these symptoms is variable and depends essentially on the etiology.

Several causes are incriminated in this case, such as autoimmune, inflammatory, infectious, metabolic or toxic. On the other hand, direct neoplastic origin through leptomeningeal dissemination is rare. [1]

Carcinomatous meningitis (CM) is often associated with solid tumors, notably breast, lung and malignant melanoma, or with lymphoma. The incidence rate is estimated at between 5% and 8% in patients being followed for solid cancer, and between 5 and 15% in patients with leukemia or lymphoma. Autopsies performed on patients with tumours showing neurological signs have revealed higher incidence of 20% [2].

It should be noted that dementia is a rare manifestation of carcinomatous meningitis, and we report here the case of a patient with lung cancer whose CM was revealed by a dementia syndrome.

II. OBSERVATION

The case involved a 75-year-old patient with a 30-year history of active smoking (weaned in 2014), type 2 diabetes, benign prostatic hypertrophy, chronic obstructive pulmonary disease and small-cell bronchial adenocarcinoma treated by lobectomy and radio-chemotherapy in 2004. He had been undergoing chemotherapy for ten months for a recurrence of his neoplasia.

He was admitted to our unit for the diagnosis of an rapidly progressive dementia syndrome, with fluctuating memory disorders of recent events, lack of words and agitation, as well as sleep disturbances.

On admission, the patient was conscious, uncooperative and disoriented in time and space; neurological examination revealed no signs of focalization, and neuropsychological tests revealed severe impairment of mnemonic and executive cognitive functions. Brain MRI revealed moderate diffuse cortico-subcortical atrophy associated with a few degenerative demyelinating lesions.

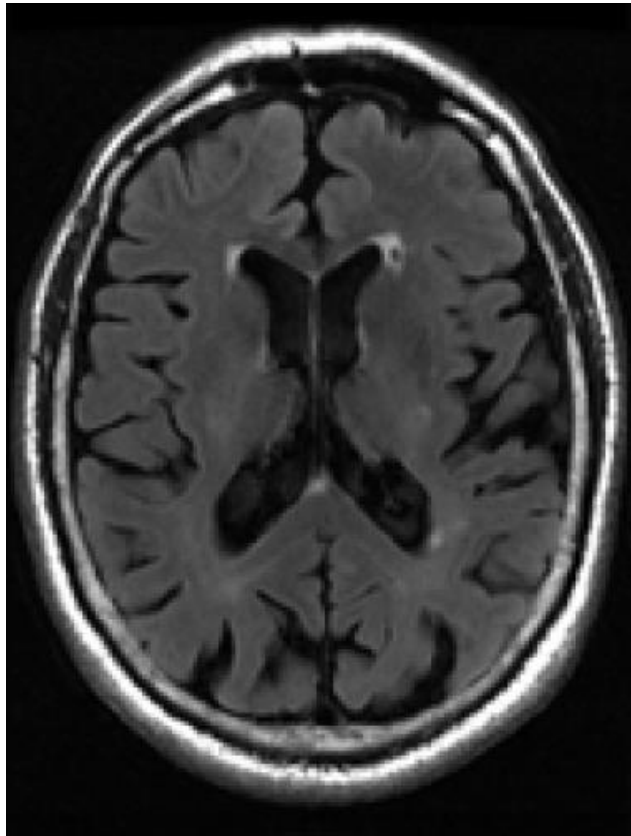


Fig1 : Moderate diffuse cortico-subcortical atrophy

Standard blood tests were performed and showed no abnormalities: WBC: 5×10^3 /mm³ (N=4000-10000 /mm³) RBC: 5.12 million/mm³ (N=4.5-6 million/mm³) Hb: 16 g/dl (N=12-18 g/dl) BUN: 0.43 g/l (N=0.10-0.50 g/l) Creatinemia: 12 mg/l (N=9-13 mg/l) CRP: 2.9 mg/l (N 6mg/l) TSH=3 mUI/l (N=0.4 -4 mUI) Vitamin B12=300 ng/l (N=190-800 ng/l) ANA=negative

NMDA and VGKC antibody tests were negative.

A lumbar puncture was performed with biochemical, cytological and cytopathological analysis of the CSF, with the following results: Glycorachy: 0.29 g/l and Proteinorachy: 1.3 g/l and 90 red blood cells with 100 leukocytes/mm³ The cytopathological study revealed a cluster of medium to large heterogeneous blastoid cells with a high N/P ratio (nucleus to plasma ratio) and the presence of some images of mitosis.

In view of the results of the investigations and the clinical context, the diagnosis of carcinomatous meningitis was retained and the patient was referred to oncology for therapeutic management. Unfortunately, he died 2 weeks later in respiratory distress.

III. DISCUSSION

Carcinomatous meningitis is a rare and serious complication of cancer. It is more frequent in hematological diseases (acute lymphoid leukemia and non-Hodgkin's lymphoma) and solid tumors, notably lung cancer (small-cell bronchial adenocarcinoma), breast cancer and malignant melanoma. [3]

The occurrence of CM is becoming increasingly frequent, probably for several reasons:

- Improved survival of oncology patients thanks to advances in therapy
- Improved diagnostic techniques, especially imaging techniques such as MRI.

CM corresponds to tumor infiltration of the meninges, with the presence of cancer cells in the CSF, most often by hematogenous dissemination via the arachnoid arterial vessels or choroid plexuses, or retrogradely via the venous sinuses.

Other diffusion routes are also possible: the peri-neuronal route, with diffusion along the cranial pairs (trigeminal and facial nerves+++), with invasion of the meningeal layers. A direct route exists via: diffusion from cerebral or medullary metastases already present in contact with the meninges, or by contiguity with bone involvement. [4]

Diagnosis is often difficult, given the clinical and radiological heterogeneity. The meningeal syndrome with stiff neck, nausea and vomiting is found in only 20% to 30% of cases [5]. Other neurological signs may include headaches, convulsions, muscle weakness, sensory disturbances, radicular pain, cauda equina syndrome, delirium, mental confusion, dementia, vertigo, tinnitus, gait ataxia and extrapyramidal symptoms (e.g. tremors).

However, patients may present with a single symptom or, inversely, no symptoms at all, meaning that diagnostic guidance can be difficult in this case [6].

Symptoms are generally explained by an increase in intracranial CSF pressure, parenchymal irritation or an inflammatory process in the CNS, or by the 3 associated mechanisms resulting from infiltration of cancer cells [7].

In our case, the patient presented with a rapidly progressive form of dementia, with memory and neuropsychological disorders. Several differential diagnoses can be evoked in the face of this clinical picture. The reversible and potentially curable cause to be considered first is autoimmune encephalitis, in which case antineuronal antibody tests should be performed as soon as possible. Crutzfeld-Jacob disease can also present in a similar way, requiring an electroencephalogram.

Cerebral-medullary MRI may show abnormalities in 50% of cases, such as meningeal thickening (T2/FLAIR hypersignal, enhancing after injection) > 1 mm and nodular, extensive and continuous or subarachnoid nodules [8], although normal MRI does not eliminate the diagnosis. MRI with abnormal features and suggestive clinical signs is often sufficient for diagnosis. However, the sensitivity of MRI is often insufficient, and a CSF study is required to confirm the diagnosis.

Lumbar puncture may generate meningeal enhancements lasting several months. Patients with suspected carcinomatous meningitis should undergo neuroimaging beforehand to avoid confusion. [9]

CSF study may show pleocytosis with hyperproteinorrachia, or even hypoglycorrachia. In most cases, a cytological study of the CSF provides a definitive diagnosis, finding heterogeneous abnormal tumour cells with an irregular nuclear membrane and a high N/P (nuclei to cytoplasm) ratio.

In our case, the primary pulmonary neoplasia was known; but in other cases, CM can be a revelation of the primary cancer, the diagnosis of which can sometimes be difficult. The first step is to investigate the neoplasias most frequently associated with carcinomatous meningitis, such as bronchial cancer, breast cancer and malignant melanoma.

In the case of carcinomatous meningitis, the outcome is very unfavorable, and treatment is disappointing, allowing only prolonged survival. If left untreated, patients die within a month or so. With appropriate early treatment, survival at 2 years is only 6%, with a median of 4 months [2].

Carcinomatous meningitis is preferentially treated with intrathecal chemotherapy, which is of particular benefit in hematological malignancies, with significant improvement in neurological signs [10].

Systemic chemotherapy is preferred for solid tumors, allowing simultaneous action on other systemic metastatic sites [11]. Panencephalic or localized radiotherapy to symptomatic areas of the CNS, particularly in the case of masses, also improves CSF circulation and intra-thecal chemotherapy diffusion. [12]

Leukemia, lymphoma and breast cancer are the most sensitive tumors to the proposed therapies.

IV. CONCLUSION

Carcinomatous meningitis is a rare and potentially fatal complication of lung cancer. It has a poor prognosis and encompasses a wide spectrum of neurological manifestations, including rapidly progressive dementia. Diagnosis can be difficult, especially in the absence of known neoplasia.

Our case highlights the importance of CSF studies, including cytology, in patients with atypical dementia, in search of tumour cells.

REFERENCES:

1. C. Domblides, L. Masse, R. Veillon. Les méningites carcinomateuses dans le cancer du poumon. *Revue des maladies respiratoires* Doi : 10.1016/S1877-1203(17)30060-5
2. Mack F, Baumert BG, Schäfer N, Hattingen E, et al. Therapy of leptomeningeal metastasis in solid tumors, *Cancer Treatment Reviews*. *Cancer Treat Rev* 2016 Feb;43:83-91. doi: 10.1016/j.ctrv.2015.12.004. Epub 2015 Dec 24.
3. E Garcia Molina (2020). Neoplastic meningitis in solid tumours : Updated review of diagnosis, prognosis, therapeutic management, and future directions. *Neurologia (Engl Ed)* 2020 Jan 18;S0213-4853(19)30141-0. doi: 10.1016/j.nrl.2019.10.010.
4. PELLERINO A, BERTERO L, RUDÀ R, SOFFIETTI R. NEOPLASTIC MENINGITIS IN SOLID TUMORS: FROM DIAGNOSIS TO PERSONALIZED TREATMENTS. *THER ADV NEUROL DISORD*. 2018;11:1756286418759618. PUBLISHED 2018 MAR 7. DOI:10.1177/1756286418759618
5. Le Rhun E., Taillibert S., Chamberlain M.C. Carcinomatous meningitis: Leptomeningeal metastases in solid tumors *Surg Neurol Int* 2013 ; 4 : S265-S288
6. Leptomeningeal metastasis from systemic cancer: review and update on management. Wang N, Bertalan MS, Brastianos PK. *Cancer*. 2018 Jan 1;124(1):21-35. doi: 10.1002/cncr.30911. Epub 2017 Nov 22.

7. Leptomeningeal carcinomatosis in chronic lymphocytic leukemia: a case report and review of the literature. Naydenov AV, Taylor LP. *Oncologist*. 2019 Sep;24(9):1237-1245. doi: 10.1634/theoncologist.2018-0619. Epub 2019 Mar 6.
8. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM. Leptomeningeal metastases in the MRI era. *Neurology*. 2010 May 4;74(18):1449-54. doi: 10.1212/WNL.0b013e3181dc1a69. PMID: 20439847; PMCID: PMC2871005.
9. Trunet S, Litré CF, Tran H, Marnet D, Rousseaux P. Intracranial hypotension with subdural hematoma following lumbar puncture: case report. *Neurochirurgie*. 2008 Apr;54(2):85-8. French. doi: 10.1016/j.neuchi.2007.12.001. Epub 2008 Mar 7. PMID: 18329051.
10. Impact of clinicopathologic features on leptomeningeal metastasis from lung adenocarcinoma and treatment efficacy with epidermal growth factor receptor tyrosine kinase inhibitor. Kwon BS, Cho YH, Yoon SK, et al. *Thorac Cancer*. 2020 ;11 :436–442
11. Manisha Kak, Rita Nanda, Erika E Ramsdale, Rimas V Lukas. Treatment of leptomeningeal carcinomatosis: current challenges and future opportunities. *J Clin Neurosci*. 2015 Apr;22(4):632-7. doi: 10.1016/j.jocn.2014.10.022. Epub 2015 Feb 9.
12. Roth P, Weller M. Management of neoplastic meningitis. *Chin Clin Oncol*. 2015 Jun ;4(2) :26. Doi : 10.3978/j.issn.2304-3865.2015.05.02. PMID : 26112812.