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Carcinomatous Meningitis from Unknown Primary Carcinoma

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Key Words
Carcinomatous meningitis · Unknown primary carcinoma · Lumbar puncture · Magnetic resonance imaging

Abstract
Carcinomatous meningitis (CM) occurs in 3 to 8% of cancer patients. Patients present with a focal symptom, and multifocal signs are often found following neurological examination. The gold standard for diagnosis remains the demonstration of carcinomatous cells in the cerebrospinal fluid on cytopathological examination. Despite the poor prognosis, palliative treatment could improve quality of life and, in some cases, overall survival. We report on a patient who presented with vertigo, tinnitus and left-sided hearing loss followed by progressive diffuse facial nerve paralysis. Lumbar cerebrospinal fluid confirmed the diagnosis of CM. However, no primary tumor was discovered, even after multiple invasive investigations. This is the first reported case in the English-language medical literature of CM resulting from a carcinoma of unknown primary origin.

Introduction

Carcinomatous meningitis (CM) is a well-known, but devastating metastatic evolution of solid tumors. Between 3 and 8% of all solid cancer-bearing patients develop CM. Common primary tumors that metastasize to leptomeninges are lung cancer (especially small cell carcinoma), breast cancer and melanoma. Usually, leptomeningeal metastasis occurs late during tumor history, yet it can be the first disease manifestation in about 5 to 10% of CM. The presence of CM without any detectable primary tumor is exceptional. We present here the first case in the English-language medical literature of a patient whose CM resulted from a carcinoma of unknown primary.

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Case Report

A 45-year-old-man, with no past medical history, was referred to the hospital for a history of several months of vertigo, tinnitus and left-sided hearing loss. Neurological examination only revealed impaired hearing in the left ear. Magnetic resonance imaging (MRI) on T1-weighted images showed left internal auditory canal tumors with enhancement after gadolinium chelate injection (fig. 1). The diagnosis of acoustic nerve neurinoma was suspected. Nevertheless, a few weeks later, left facial nerve paralysis occurred. The patient quickly developed left eye blindness and bilateral facial nerve paralysis. Cranial and medullar MRI showed a diffuse and irregular thickening of the leptomeninges on T1-weighted images and diffuse enhancement after gadolinium chelate injection (fig. 2). Lumbar puncture found clear cerebrospinal fluid (CSF). Protein level was 1.06 g/l. Cytology found 35 cells/mm^3 with neoplastic cells consistent with adenocarcinoma, thus confirming the diagnosis of CM. On immunocytological examination, malignant cells were labeled with antibodies against cytokeratin 7 and cytokeratin 20, but not with antibodies against E-cadherin. This was consistent with a primary tumor of gastric or pancreatic origin (fig. 3). Then, an extensive work-up to identify the primary malignancy was started. Thoracic, abdominal and pelvic computed tomography as well as PET scan were unremarkable. Gastric fibroscopy with systematic biopsy and colonoscopy were normal. Over the following days, headache, nausea, vomiting, and weakness appeared, associated with a deterioration of the patient's mental condition. The patient was treated with biweekly intrathecal methotrexate injections. Shortly after the first injection, neurological functions improved. However, two weeks after starting the treatment, neurological degradation re-occurred, leading to the death of the patient within a few days.

Discussion

CM is a common complication of cancer, and the primary tumor is almost always known or easy to discover. Here, we present the first case in the English-language medical literature of CM of unknown primary. Despite the histological arguments for an upper digestive tract tumor, we could not find any primary on CT scan, PET scan or colonoscopy. Moreover, upper digestive fibroscopy with systematic biopsy was unremarkable, thus eliminating the classical association of gastric linitis adenocarcinoma and CM. CM is not a rare event and, according to autopsy findings, 19% of patients with cancer and neurological symptoms have evidence of meningeal involvement. Cancer cells diffuse to the meninges by various mechanisms: by hematogenous spread, by lymphatic spread, by growing around and along nerves or by spreading from adjacent bone or brain parenchyma.

Clinical manifestations are pleiomorphic due to the cerebral hemispheres, cranial nerves or spinal cord dysfunctions. Hydrocephalus is a frequent complication due to focal tumors that block CSF outflow. The diagnosis is obtained by cytopathological analysis of CSF. Other analyses of CSF, such as an increase in leukocytes and protein, are suggestive. Nevertheless, the cytopathological analysis of CSF frequently remains negative. Indeed, at the first lumbar puncture, the sensitivity of CSF cytopathological analysis to detect tumor cells is 70%, and reaches 90 and 95% if the puncture is repeated twice or three times [1]. Increasing the volume of removed fluid could enhance the sensitivity of the procedure (from 68 to 97% with increasing the removed volume from 3.5 to 10.5 ml) [1].

MRI with gadolinium chelate injection is useful for the diagnosis of CM. Cranial and spinal MRI must be performed, with T1-weighted images before and after gadolinium chelate injection, combined with T2-weighted sequences [2]. Most of the time, lesions include parenchymal brain volume loss, dural enhancement, which can be focal or generalized, cisternal deposits and, more rarely, tentorial and ependymal enhancement. Large numbers of nodules can be seen typically in the subarachnoid and parenchymal regions. Secondary hydrocephalus can be observed. These images are not specific to CM and can be observed during infection, inflammatory disease, trauma and even lumbar puncture. MRI sensitivity to detect CM is far superior to cranial CT scan (70 vs. 30%) [3].

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The prognosis of neoplasic meningitis remains dramatic, and the goal of treatment remains essentially symptomatic. Neurological deficit is the main cause of death with CM, and without treatment, median survival ranges between 4 and 6 weeks. Three therapeutic possibilities exist: radiotherapy, intrathecal chemotherapy and systemic chemotherapy.

Radiotherapy is a valuable strategy to relieve CSF flow blocks due to localized bulky tumors [4]. Whole cerebrospinal axis irradiation is not frequently performed because of high toxicity, so localized radiotherapy is mostly used for palliation of symptoms.

Intrathecal local chemotherapy can be delivered via lumbar puncture or using an intraventricular (Ommaya) reservoir. Complications of intrathecal chemotherapy include complications of the ventricular reservoir, such as malposition (3–12%), obstruction and infection, mostly involving *Staphylococcus epidermidis* (2–13%) [5]. Intrathecal methotrexate injections induce a risk of myelosuppression, which can be prevented by folinic acid rescue (10 mg every 6 h for 24 h), and of chemical aseptic meningitis, a frequent complication that could be prevented by oral dexamethasone [6]. Late neurotoxicity and leuko-encephalopathy have been described, especially in long-term survivors [7].

Methotrexate is the intrathecal benchmark drug. A randomized trial comparing intrathecal methotrexate versus thiotepa demonstrated that both treatments appeared to be equivalent. Nevertheless, such a result is quite surprising as TEPA, the active metabolite of thiotepa, is formed when thiotepa is administrated intravenously, but not intrathecally [8]. Monotherapy is as effective as combined therapy in most studies [9].

Aracytine has also been tested but has been regarded as a less interesting drug than methotrexate. Yet, methotrexate is known to provide a longer exposure and to penetrate more deeply into the meninges and brain parenchyma [10]. A liposomally encapsulated formulation of aracytine (Depo-AraC, Depocyt®) has been developed and seems to be at least as effective as intrathecal methotrexate injections [11]. Depo-AraC is given once every two weeks [6]. Interestingly, Depo-AraC achieves cytotoxic concentrations in the ventricles if administrated by lumbar puncture, a condition that is not guaranteed with methotrexate [12].

Systemic chemotherapy is not frequently used because chemotherapeutic drugs have poor meningeal penetration. The characteristics of a drug that determine its penetrance into the CSF after intravenous administration include the degree of protein binding, the lipid solubility of the drug and its ionization. For methotrexate, only 3% of an intravenous dose enters the CSF. Thus, to reach cytotoxic concentrations in the CSF, high doses of methotrexate need to be given intravenously with folinic acid rescue to minimize the systemic toxicity. Current published reports to evaluate the role of high-dose methotrexate compared to intrathecal regimen remain largely inconclusive. Indeed, one retrospective study comparing patients treated with systemic chemotherapy and radiotherapy versus patients treated with intrathecal chemotherapy failed to demonstrate any statistically significant difference between the two groups [13]. By contrast, Glantz et al. [14] found a significant advantage with better response rate and survival for patients treated by systemic methotrexate perfusion.

The pharmacokinetics of cytarabine differs from methotrexate in that penetration of the intravenous agent into the CSF is greater and the half-life is longer. Active CSF concentration of cytarabine can be achieved by high-dose intravenous administration, but the hematological toxicity, the limited range of susceptible tumor types and the lack of systemic rescue agents limit the use of high-dose cytarabine for the treatment of CM.

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To date, intrathecal methotrexate is still the standard of care for treatment of CM. The development of new therapies that could diffuse into the CSF remains a major challenge. New drugs are currently under investigation, such as temozolomide, gemcitabine and topotecan. The role of target therapy must be also studied and intrathecal trastuzumab injections may be potentially interesting for HER2-overexpressing breast carcinoma [15].

Fig. 1. On this axial post-contrast T1-weighted image, enhancement observed within the left internal auditory canal (arrow) led to the diagnosis of acoustic nerve neurinoma.

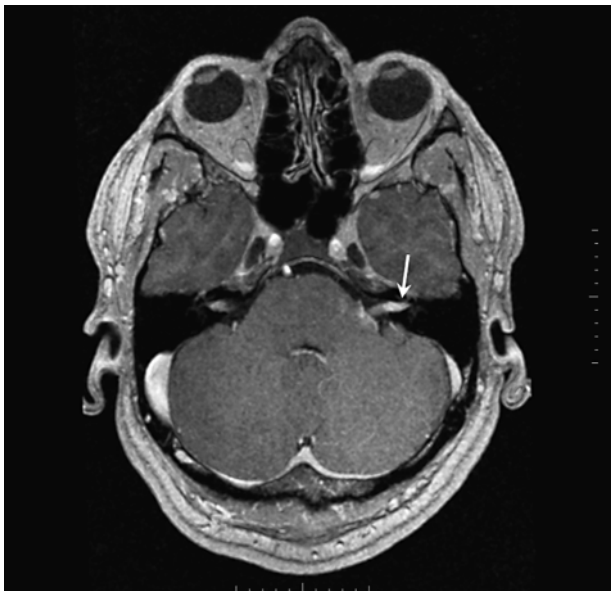

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Fig. 2. a On this axial T1-weighted image performed after administration of gadolinium, leptomeningeal enhancement follows the convolutions of the gyri in the left lateral cerebellum (arrow). **b** This sagittal post-contrast T1-weighted image of the dorsolumbar region shows irregular and diffuse leptomeningeal enhancements (arrows).

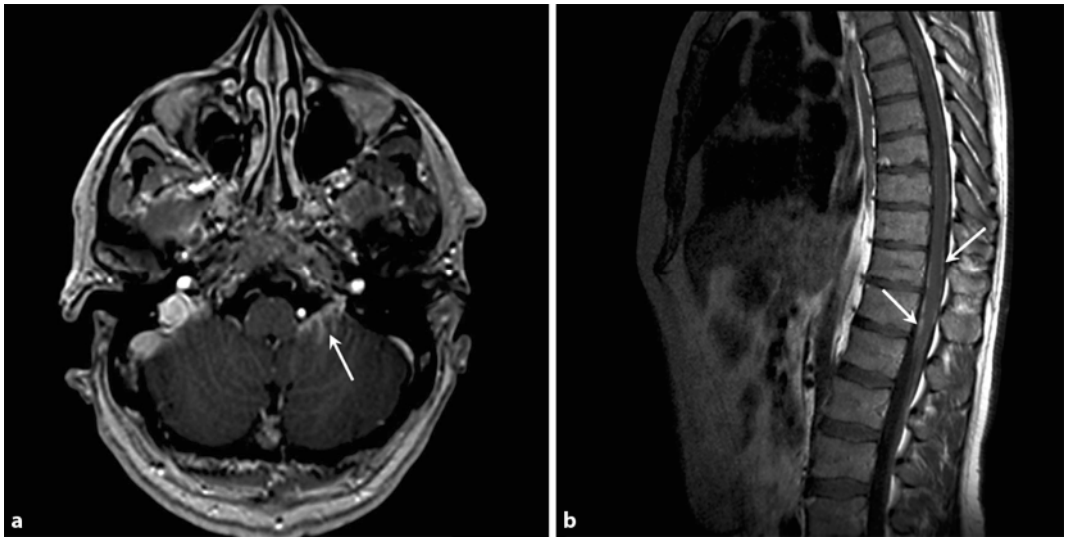

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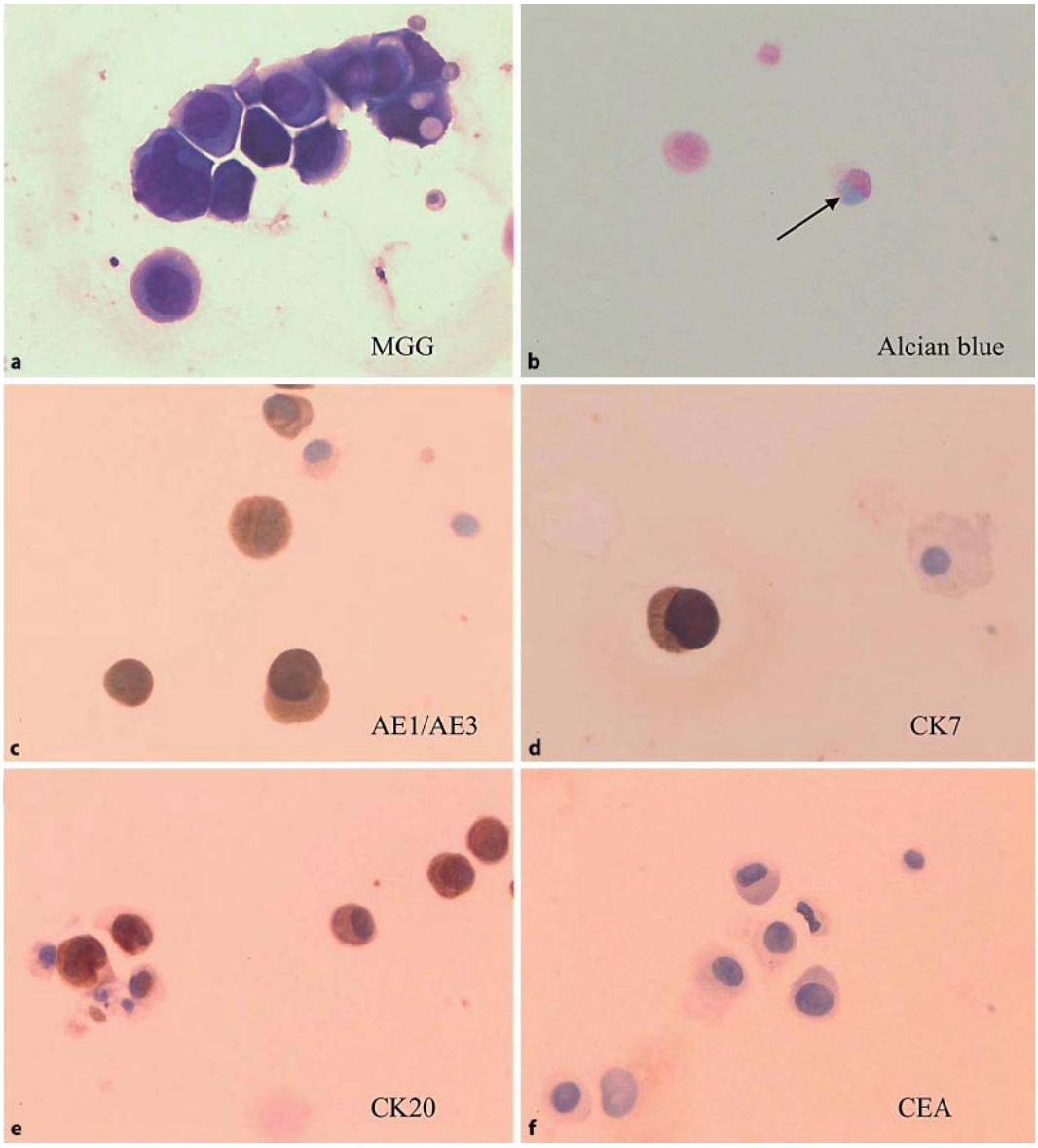
Fig. 3. a Microphotography of the cerebrospinal fluid cytology using May Grünwald Giemsa (**a**) and alcian blue staining (**b**). On immunocytological examination, malignant cells were labeled with antibodies against cytokeratin (AE1/AE3) (**c**), cytokeratin 7 (**d**) and cytokeratin 20 (**e**) but not with antibodies against carcino-embryonic antigen (CEA) (**f**).



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