Leptomeningeal metastasis as a presenting manifestation of adenocarcinoma of the lung: a case report

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Introduction
Leptomeningeal metastasis (LM) is becoming known as a more frequent clinical situation in neuro-oncology. The rising incidence seems to be caused by prolonged survival due to improved supportive care and chemotherapy, and the inadequacy of current available systemic agents to penetrate the blood-brain barrier. LM usually manifests in patients with widely-metastatic and end-stage cancer (70%), but it can occasionally be the earliest manifestation of cancer (5%–10%), sometimes even in the absence of detectable systemic diseases symptoms.

Case Report
A 62-year-old male farmer presented with diplopia, blurred vision, and headache to our outpatient clinic. He attributed the onset of his headache to getting hit in the head with a bat and a deep 10-cm laceration in his left parietal scalp almost 2 months ago. The brain computed tomography (CT) scan was normal at that time, and the wound had healed uneventfully, with the headache persisting. Diplopia had appeared one week before presentation. He denied any weight loss, dyspnea, and history of smoking while reporting malaise, occasional non-productive cough, and dyspepsia during the past month. Physical examination revealed bilateral sixth cranial nerve palsy and bilateral papilledema. The only abnormal finding in routine laboratory studies was an elevated erythrocyte sedimentation rate (ESR) (61 mm/h).

Automated perimetry showed a mean deviation of −5 dB in the right eye and -7 dB in the left eye, and bilateral enlarged blind spots without any scotoma or visual field defects.

The brain magnetic resonance imaging (MRI) (with and without gadolinium enhancement) was normal. The MR venography showed no evidence of venous outflow obstruction, sinus thrombosis, or stenosis. The chest x-ray showed a diffuse ground-glass appearance in the right hemithorax without tracheal deviation. The cerebrospinal fluid (CSF) study showed mildly elevated protein to 65 mg/dL, an elevated opening pressure of 23 cmH₂O, and negative CSF-PCR for mycobacterium tuberculosis. Two CSF cytological studies revealed no abnormalities. The third cytological study of the CSF identified a few variably sized signet-shaped cells (eccentric nuclei) with clear vacuoles, large hyperchromatic nuclei, and clear cytoplasm, arranged in loosely attached clusters, arousing suspicions about malignant cells. Immunohistochemistry (IHC) staining showed diffuse and strong immunoreactivity of the suspicious cells for cytokeratin (CK) and carcinoembryonic antigen (CEA), in favor of metastatic adenocarcinoma, while being negative for CDX-2, rejecting the origin of the cells from gastrointestinal tissues (Figure 1). An endoscopic study of the upper and lower gastrointestinal tract was unremarkable. A chest, abdominal, and pelvic CT with contrast injection was requested. It was indicative of soft tissue lesion at...
periphery and lymphangitic carcinomatosis of right hemithorax (Figure 2). Additionally, lytic bone metastases were detected in some lumbar vertebrae and acetabulum. Flexible bronchoscopy showed no endobronchial lesion, with a normal biopsy and washing cytology study. Finally, he underwent CT-guided transbronchial lung biopsy, which established a diagnosis of poorly differentiated adenocarcinoma of the lung, supported by the IHC tumor markers of CK7+, CK20-, thyroid transcription factor-1 (TTF-1)+, and paired box 8 (PAX8).

His intracranial hypertension was refractory to symptomatic medical treatment and lumbar punctures, with his visual function deteriorating in the control perimetry. He was a candidate for lumboperitoneal shunting, which he and his family declined. After discussing the very poor prognosis of his condition, he was discharged to undergo home care with the consent of himself and his family.

Discussion
Headache is a common problem in medical practice and is among the 10 most frequent chief complaints in outpatient clinics. Headache as a symptom of disease can originate from paroxysmal, relatively benign etiologies to chronic, incapacitating causes which is sometimes an indicator of a life-threatening underlying disease.

Headaches are classified into two major primary and secondary categories and several subcategories by the International Headache Society (IHS). The four major primary types of headaches include migraine (with and without aura), tension-type headache (episodic and chronic), trigeminal autonomic cephalalgias, and other primary headache disorders. Secondary headache disorders may be due to grave underlying etiologies, such as neoplasm or intracranial hemorrhages. Secondary headaches are classified by IHS based on their etiology which may be attributed to: trauma or injury to the head and/or neck, cranial and/or cervical vascular disorder, non-vascular intracranial disorder (including increased CSF pressure due to LM), a substance or its withdrawal, infections (including meningitis or systemic infections), disorders of homoeostasis, head, eyes and neck or other facial or cervical structures disorders (including glaucoma, acute rhinosinusitis, and temporomandibular disorder), psychiatric disorders (somatization or psychotic disorder), lesions of the cranial nerves, other facial pain and as the last category other headache disorders (not elsewhere classified).

LM also known as meningeal carcinomatosis is a malignant infiltration of the pia mater and arachnoid membrane, diagnosed in almost 5% of patients with advanced cancer. The most frequent primary tumors associated with LM are breast, lung, and melanoma. The pathognomonic neurologic presentation of LM is in the form of multifocal neurologica signs and symptoms. Some of the most frequent presenting symptoms are headaches, nausea and vomiting, weakness, ataxia, altered mental state, diplopia, and facial weakness. Seizures are less frequent. LM is usually a late manifestation of systemic cancer, often accompanying relapse elsewhere in the body but might exceptionally be a presenting manifestation of a type of cancer.

Contrast medium-enhanced MRI of the brain and spine is recommended in all patients suspected of having LM before lumbar puncture (LP). The diagnostic findings on MRI study include linear and nodular leptomeningeal enhancement, thickening and enhancement of cranial nerves or nerve roots, including the cauda equine, and hydrocephalus. CSF analysis in many patients with LM shows abnormalities including mild pleocytosis, elevated total protein, decreased glucose, and elevated opening pressure. The diagnosis of LM is unequivocally ascertained by identifying malignant cells in the CSF, despite the absence of diagnostic clinical or imaging characteristics. However, cytology might be negative in up to 20% of cases. In rare cases with negative cytology and without evidence of advanced cancer, an open leptomeningeal biopsy might be indicated.

Conclusion
There were salient points of consideration in our case.
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LM in our patient was the presenting manifestation of his adenocarcinoma of the lung, which was unknown beforehand. To the best of our knowledge, no similar case in non-small cell lung cancer has been reported previously. Most cases are a late manifestation or at most diagnosed in the early stages of cancer in large series.\(^5^,^6\) Neuroimaging studies were negative in our case. Contrast-enhanced T1-weighted MR has a 41% false-negative rate; however, a negative study does not exclude the diagnosis of LM.\(^7\) A high index of clinical suspicion and repeating CSF studies are the key to the diagnosis.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors' Contribution
MH and ESH: Clinical study, supervision and work-up. BS: pathological reporting. ASB: radiological reporting. NF: clinical follow-up.

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