



No Intraparenchymal Mass Lesion in a Patient with Lung Adenocarcinoma with Treatment-Resistant Seizures: What Next?

Tedaviye Dirençli Nöbetlerden Muzdarip Akciğer Adenokarsinomlu Bir Hastada İntraparankimal Kitle Lezyonu Yok: Ne Yapmalı?

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Abstract

Leptomeningeal carcinomatosis (LMC) is a relatively rare complication of advanced-stage cancer. The diagnosis of LMC is based on clinical and radiologic findings and cytologic examinations. The diagnosis may be difficult because the clinical findings may be subtle initially, and the specificity of the diagnostic modalities is low. A 41-year-old male patient with metastatic lung adenocarcinoma presented with headache, confusion, and treatment-resistant seizures. There was no intraparenchymal mass lesion or leptomeningeal contrast enhancement in brain magnetic resonance imaging. The presence of LMC was demonstrated in a cytopathologic examination of cerebrospinal fluid. The seizures were controlled with antiepileptic treatment, but the patient was referred to the palliative care center due to poor oncologic prognosis.

Keywords: Leptomeningeal carcinomatosis, lung adenocarcinoma, cerebrospinal fluid cytology, possible non-convulsive status epilepticus

Öz

Leptomeningeal karsinomatozis (LMK), ileri evre kanserlerin görece nadir bir komplikasyonudur. Bu tanı klinik ve radyolojik bulgular ile sitolojik incelemelere dayanarak koyulur. Klinik bulguların başlangıçta silik olabilmesi ve tanı modalitelerinin spesifitesinin düşük olması nedeniyle tanı koymada güçlük yaşanabilir. Metastatik akciğer adenokarsinomlu, 41 yaşında bir erkek hasta baş ağrısı, konfüzyon ve tedaviye dirençli nöbetlerle başvurdu. Beyin manyetik rezonans görüntülemesinde intraparankimal kitle lezyonu ya da leptomeningeal kontrast tutulumu saptanmadı. Beyin omurilik sıvısının sitopatolojik incelemesi ile LMK varlığı gösterildi. Antiepileptik tedavi ile nöbetleri kontrol altına alındı ancak onkolojik prognozunun kötü olması nedeniyle hasta, palyatif bakım merkezine sevk edildi.

Anahtar Kelimeler: Leptomeningeal karsinomatozis, akciğer adenokarsinomu, beyin omurilik sıvısı sitolojisi, olası non-konvulsif status epileptikus

Introduction

Several systemic malignancies can cause metastases in the central nervous system and leptomeninges, and lung cancer is one of the most common (1,2). Leptomeningeal carcinomatosis (LMC), also known as carcinomatous meningitis or leptomeningeal metastasis, is a relatively uncommon but well-known complication of advanced-stage cancer (1,3). The incidence of LMC varies by tumor type (4), and 1-10% of patients with non-small cell lung cancer (more common in adenocarcinoma), develop LMC (5,6). The diagnosis of LMC is based on clinical findings, imaging,

and cerebrospinal fluid (CSF) cytology (1,4,7). Common clinical findings are headache, nausea-vomiting, alterations in mental status, cranial nerve palsies, seizures, and spinal cord signs such as limb weakness, dermatomal sensory loss, radicular pain, bowel, and bladder dysfunction (1,4,6). Treatment options for LMC include radiotherapy, systemic or intrathecal chemotherapy, but the prognosis is poor with an average survival of 2 to 4 months (2,6,7). Here, we present a patient with lung adenocarcinoma who developed headache and seizures due to LMC.

This manuscript was presented at the 55th National Neurology Congress held in Antalya, Turkey on 15th-21st November 2019, and was published in abstract form in the proceedings of the congress.

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Received/Geliş Tarihi: 02.09.2020 **Accepted/Kabul Tarihi:** 16.03.2021

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Turkish Journal of Neurology published by Galenos Publishing House.

Case Report

A 41-year-old male patient with metastatic lung adenocarcinoma for three years presented with subacute onset headache, confusion, and generalized tonic-clonic seizures. He had undergone radiotherapy, and he was still on osimertinib chemotherapy. His headache and seizures had begun approximately four months ago. He had been prescribed levetiracetam (3x1000 mg/day) and carbamazepine (2x400 mg/day) at another medical center when he presented with recurrent seizures. However, he had discontinued the drugs because of drowsiness and ineffectiveness. Two months later, he experienced convulsive status epilepticus and was hospitalized in the intensive care unit of a medical center. Valproate (2x400 mg/day), topiramate (1x25 mg/day), and phenytoin (3x100 mg/day) were initiated. The convulsions diminished, but he was obtunded. Later, he was admitted to the emergency department of our hospital after a generalized tonic-clonic seizure. Lethargy, opisthotonus, and papilledema were remarkable findings in the examination.

Brain magnetic resonance imaging (MRI), including unenhanced T1, T2, T2 fluid-attenuated inversion recovery (FLAIR) and contrast-enhanced (CE) T1 sequences, showed enlarged lateral ventricles, bilateral periventricular confluent T2 hyperintensities, bilateral tortuous optic nerves, optic nerve sheath distension, and optic nerve head protrusion indicating increased intracranial pressure. There was no parenchymal mass lesion or leptomeningeal contrast enhancement (Figure 1). There were sclerotic-osteoblastic metastases in iliac bones and all vertebrae in spinal MRI. Electroencephalography revealed a moderate slowing of background activity with diffuse theta rhythms and anteriorly prominent generalized quasi-rhythmic delta activity. To exclude the presence of non-convulsive status epilepticus (NCSE), he was given 5 mg of intravenous diazepam. The background activity improved considerably; however, there was no change in his clinical status, suggesting possible NCSE. Levetiracetam and lacosamide were started in addition to valproate treatment. Phenytoin and topiramate were tapered off gradually and discontinued. We performed a lumbar puncture (LP) to assess for infectious pathologies and LMC. CSF opening pressure was dramatically

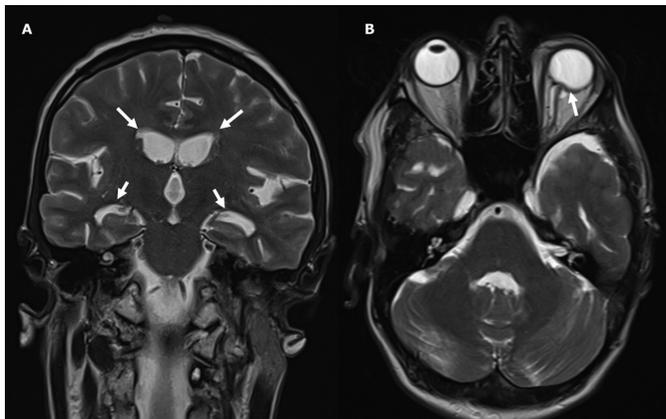


Figure 1. A, B) Brain magnetic resonance imaging (MRI) of the patient. Coronal (A) T2-weighted (W) brain MRI shows dilatation of body and temporal horns of the lateral ventricles (arrows), and axial (B) T2W image shows posterior scleral flattening and optic nerve head protrusion indicating increased intracranial pressure (arrow)

increased (360 mm H₂O). Protein level was high (121.8 mg/dl, normal range: 15-40 mg/dl) and CSF glucose was low (43 mg/dl; simultaneous blood glucose: 117 mg/dl). Oligoclonal bands were negative, and the immunoglobulin G index was normal. Complete blood count, serum biochemistry and CSF culture tests were unremarkable. However, the CSF cytology revealed atypical epithelial cells compatible with the infiltration of lung adenocarcinoma (Figure 2), and he was diagnosed as having LMC. He was intubated because of respiratory distress. Midazolam infusion was started because of possible NCSE. Although rhythmic delta activity disappeared, the patient did not fully regain consciousness. He remained on osimertinib chemotherapy, but intrathecal chemotherapy was not given because his Eastern Cooperative Oncology Group performance status score was high, and his life expectancy was low. Tracheostomy and gastrostomy were performed. The patient was sent to a palliative care center and was lost to follow-up.

Discussion

Due to the improvements in treatment modalities and prolonged lifespan, LMC will be more commonly encountered in every day clinical practice (1,7). Although LMC is characterized by a poor prognosis, early detection is important to establish appropriate therapy and improve the life expectancy of the patients. However, the diagnosis of LMC can be challenging because clinical manifestations may be subtle initially (6), and no test is sensitive enough to rule out leptomeningeal involvement (4).

Frequently, MRI with or without CE is performed to ascertain LMC. The sensitivity of MRI is 65-87% (8,9), and the specificity is 75-94% (9,10,11). MRI findings can be definite, suggestive or negative for LMC according to the classification system (12). Definite findings are clear leptomeningeal involvement of cerebrum, cerebellum or spinal cord, whereas focal or diffuse dural enhancement, subtle leptomeningeal enhancement, and communicating hydrocephalus are suggestive findings (1,12). A

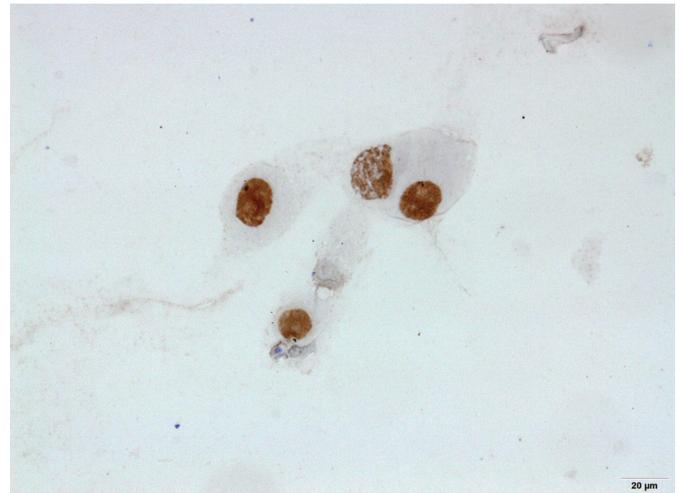


Figure 2. Cerebrospinal fluid cytology. The smear prepared from cerebrospinal fluid shows atypical epithelioid cells with irregular nuclear contours and large cytoplasm. These cells have positive nuclear staining for thyroid transcription factor-1 (TTF-1). The cytomorphologic and immunocytochemical studies are consistent with lung adenocarcinoma metastasis

normal MRI can be seen in up to 20% of cases (6). Some clinical studies also established the value of CE-FLAIR imaging in the diagnosis of LMC (13,14). However, as a limitation, CE-FLAIR sequence was not performed in our case because it was not included in the routine CE MRI procedure in our institution. The brain and spinal MRI of our patient revealed no diffuse or focal leptomeningeal enhancement but showed the signs of increased intracranial pressure. Then, we performed LP for differential diagnosis. CSF examination was abnormal with elevated opening pressure, high protein, and low glucose levels. These findings could be seen both in LMC and infectious pathologies (4,6). Abnormalities in CSF protein and glucose levels are seen in almost 90% (6), and an elevated opening pressure is seen in 50-70% of patients with LMC (4).

The detection of neoplastic cells in CSF is the gold standard for the diagnosis of LMC (6,7,15). Although the sensitivity of the first CSF cytology is low (15), it increases to >90% after three high-volume LPs (1,4). Taking a sufficient amount (at least 10 ml) of CSF volume and processing the CSF sample as soon as possible are recommended to minimize false-negative results (4). False-positive cytology results may rarely be obtained in infectious or inflammatory conditions (1,4), and immunocytochemical studies help to prevent this phenomenon (6), as was the case in our patient.

In conclusion, the lack of intraparenchymal mass lesion or leptomeningeal contrast enhancement in brain MRI, despite treatment-resistant seizures, made the diagnosis challenging in this case. Nevertheless, CSF cytology was positive in the first sampling and helped make the diagnosis of LMC. If the clinical suspicion for LMC is high, we highly recommend repeating the procedure if the initial cytology is negative or any other diagnosis cannot better explain the clinical picture.

Ethics

Informed Consent: Written informed consent was obtained from the next of kin of the patient. No picture or information that could identify the patient was used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.İ., G.E.T.K., N.D., Concept: N.D., Design: B.İ., N.D., Data Collection or Processing: B.İ., G.E.T.K., Analysis or Interpretation: B.İ., G.E.T.K., N.D., Literature Search: B.İ., Writing: B.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ko Y, Gwak HS, Park EY, et al. Association of MRI findings with clinical characteristics and prognosis in patients with leptomeningeal carcinomatosis from non-small cell lung cancer. *J Neurooncol* 2019;143:553-562.
2. Hochmair M. Medical treatment options for patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer suffering from brain metastases and/or leptomeningeal disease. *Target Oncol* 2018;13:269-285.
3. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am* 2011;22:1-6, v.
4. Wang N, Bertalan MS, Brastianos PK. Leptomeningeal metastasis from systemic cancer: Review and update on management. *Cancer* 2018;124:21-35.
5. Nagpal S, Riess J, Wakelee H. Treatment of leptomeningeal spread of NSCLC: a continuing challenge. *Curr Treat Options Oncol* 2012;13:491-504.
6. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: A continuing challenge in the personalized treatment era. *Cancer Treat Rev* 2017;53:128-137.
7. Le Rhun E, Galanis E. Leptomeningeal metastases of solid cancer. *Curr Opin Neurol* 2016;29:797-805.
8. Singh SK, Leeds NE, Ginsberg LE. MR imaging of leptomeningeal metastases: comparison of three sequences. *AJNR Am J Neuroradiol* 2002;23:817-821.
9. Chamberlain MC. Leptomeningeal metastasis. *Curr Opin Oncol* 2010;22:627-635.
10. Straathof CS, de Bruin HG, Dippel DW, Vecht CJ. The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. *J Neurol* 1999;246:810-814.
11. Maroldi R, Ambrosi C, Farina D. Metastatic disease of the brain: extra-axial metastases (skull, dura, leptomeningeal) and tumour spread. *Eur Radiol* 2005;15:617-626.
12. Freilich RJ, Krol G, DeAngelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. *Ann Neurol* 1995;38:51-57.
13. Kremer S, Abu Eid M, Bierry G, et al. Accuracy of delayed post-contrast FLAIR MR imaging for the diagnosis of leptomeningeal infectious or tumoral diseases. *J Neuroradiol*. 2006;33:285-291.
14. Masaki K, Nakada M, Hayashi Y, et al. Contrast-enhanced fluid-attenuated inversion recovery MRI is useful to detect the CSF dissemination of glioblastoma. *J Comput Assist Tomogr* 2001;25:953-956.
15. Glantz MJ, Cole BF, Glantz LK, et al. Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. *Cancer* 1998;82:733-739.