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CLINICAL CASE REPORT

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Symmetrical Curvilinear Cytotoxic Edema Along the Surface of the Brain Stem: A Probable New Magnetic Resonance Imaging Finding of Leptomeningeal Carcinomatosis

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Abstract: Lung cancer is one of the most common neoplasms to appear leptomeningeal metastasis (LM). Contrast-enhanced magnetic resonance imaging (MRI) is better diagnostic choice for LM and usually shows focal nodular or diffuse linear enhancement on the leptomeninges along the sulci and tentorium in the brain. We experienced atypical 2 cases of lung cancer in patients who showed unusual brain MRI finding of symmetrical curvilinear or band-like, nonenhancing cytotoxic edema along the surface of the brain stem. This finding is unique and different from the general findings of leptomeningeal metastasis.

This unique imaging finding of symmetric curvilinear nonenhancing cytotoxic edema along the brainstem is extremely rare and represents a new presentation of leptomeningeal carcinomatosis.

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Abbreviations: ADC = apparent diffusion coefficient, CE = contrast-enhanced, CNS = central nervous system, CSF = cerebrospinal fluid, DWI = diffusion-weighted images, FLAIR = fluid-attenuated inversion recovery, LM = leptomeningeal metastasis, MRI = magnetic resonance imaging, PNDs = paraneoplastic disorders, PRES = posterior reversible encephalopathy syndrome.

INTRODUCTION

The incidence of leptomeningeal metastases (LM) of solid tumors has increased owing to prolonged patient survival because of increasingly effective systemic chemotherapy, but its prognosis remains poor. Lung cancer is the most common primary tumor leading to brain metastases[1] and is one of the most common neoplasms that metastasize to the leptomeninges.[2] LM occurs in approximately 5% of nonsmall cell lung cancers, including adenocarcinoma.[3]

Even though the gold standard for the diagnosis of LM is cerebrospinal fluid (CSF) cytology, contrast-enhanced (CE) brain magnetic resonance imaging (MRI) is the first diagnostic choice for LM evaluation in clinical practice. On CE MRI, LM usually appears as a focal or diffuse, nodular or linear enhancement of the leptomeninges along the brain sulci and cisterns.[3] However, CE MRI yields approximately 30% of false-negative findings.[4] We report unfamiliar brain MRI findings, a symmetrical curvilinear or band-like cytotoxic edema without enhancement along the surface of the brain stem and middle cerebellar peduncles, in 2 patients with leptomeningeal metastases from lung cancer, which is considered a probable new finding suggestive of leptomeningeal carcinomatosis.

CASE REPORTS

Case 1

A 75-year-old man was diagnosed with lung adenocarcinoma with bone metastases in December 2011. At that time, brain MRI did not show evidence of metastasis. He was treated with chemotherapy using Iressa (gefitinib) for 8 weeks, and showed partial response of the tumor after 1 year, in November 2012. However, 1 month later, he was admitted to the hospital with headache and dizziness. Brain MRI revealed previously unreported curvilinear or band-like parenchymal lesions of high signal intensity on T2-weighted images and diffusion-weighted images (DWI), with restricted diffusion along the anterior and posterior surface of the midbrain, pons, and on both sides of the anterolateral surface of the middle cerebellar peduncles (Figure 1). There was no contrast enhancement in the brain parenchyma and the leptomeninges, and no hydrocephalus was observed. Therefore, we initially suspected chemotherapy-induced toxic encephalopathy and paraneoplastic syndrome rather than LM. On cytological examination of CSF, there were malignant metastatic adenocarcinoma cells. Serum antineuronal antibodies (anti-Hu, anti-Ri, and anti-Yo) were negative. One month later, he showed respiratory failure and expired.

Case 2

A 47-year-old woman was diagnosed with lung adenocarcinoma with brain metastases approximately 3 months before admission to our hospital. Initial brain MRI showed multiple small enhancing metastatic nodules on both sides of the cerebral and cerebellar hemispheres, and multiple short linear enhancements in the cerebellar sulci, suggesting leptomeningeal metastases without hydrocephalus. Chemotherapy with a combination of docetaxel and carboplatin was initiated. She was also treated with palliative whole brain radiotherapy up to a total dose of 30 Gy in 10 fractions over 2 weeks for brain metastases. After 3 cycles of chemotherapy for approximately 3 months, she presented persistent general weakness. A second brain MRI

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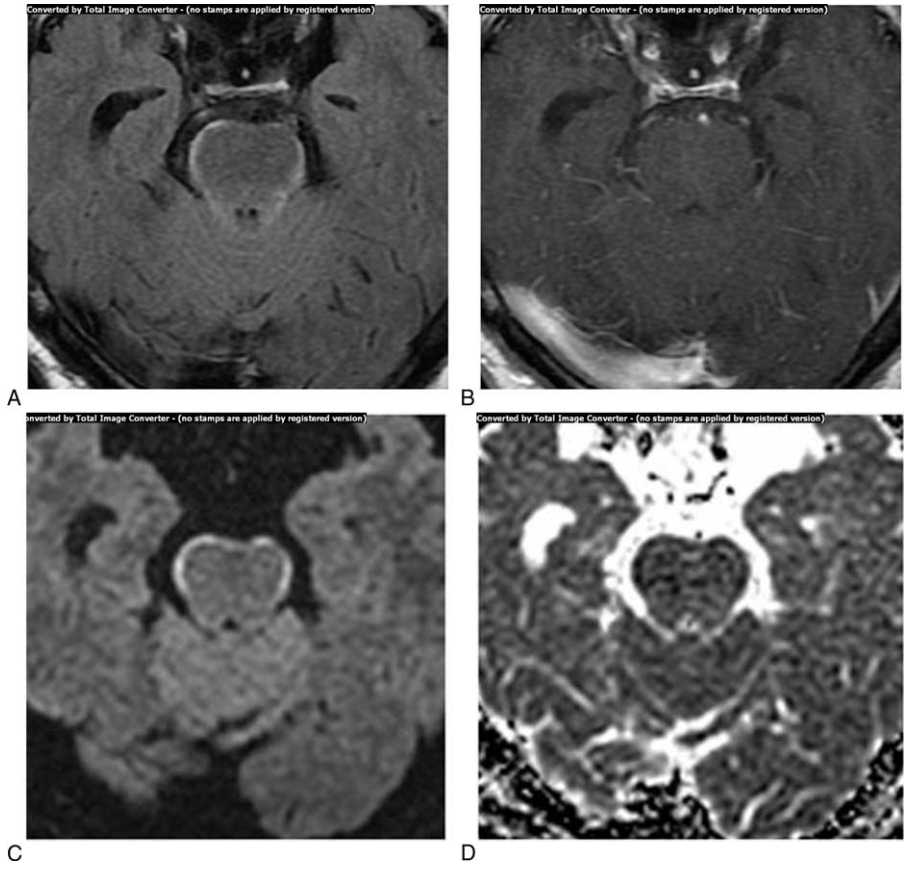

FIGURE 1. Case 1. A 75-year-old man with lung adenocarcinoma. (A) A T2-FLAIR (fluid-attenuated inversion recovery) image shows bilateral symmetrical curvilinear high signal intensity along the surface of the pons. (B) A contrast-enhanced T1-weighted image reveals no enhancement in the lesion. (C) DWI. (D) An ADC map shows symmetrical curvilinear cytotoxic edema along the pons.

showed new findings of bilateral symmetrical curvilinear high signal intensity on T2-weighted images and DWI ($b = 1000$ s/mm^2) with a low apparent diffusion coefficient (ADC) along the surface of the pons and on both sides of the middle cerebellar peduncles. However, the lesions showed no definite parenchymal or leptomeningeal enhancement (Figure 2). Additionally, hydrocephalus developed, with slight increases in the size and the number of multiple small parenchymal metastases as well as more prominent leptomeningeal enhancement along the cerebellar folia. Serum and CSF antibody examination for the evaluation of paraneoplastic syndrome was not performed. The patient presented with recurring seizures and persistent drowsiness despite antiepileptic medication. Eventually, she was transferred to hospice care.

DISCUSSION

We report an unusual MRI finding with symmetrical curvilinear or band-like cytotoxic edema along the surface of the brain stem. The most reasonable etiology is leptomeningeal carcinomatosis. To our knowledge, only one case with similar MRI findings has been recently reported.[5] The pathogenesis of the cytotoxic edema along the brain stem surface is unknown. We think there are 3 possible explanations for our finding: microinfarctions secondary to tumor cell infiltration in the perforating vessels, paraneoplastic encephalopathy involving the brain stem, and toxic encephalopathy caused by chemotherapy. First, we hypothesized that the findings would be explained by microinfarctions. In LM, the tumor cells are usually concentrated in the subarachnoid cisterns along the surface of the brain stem. The brain stem has many short circumferential perforating arteries originating from the basilar artery and both the superior cerebellar arteries on the anterior, lateral, and posterior aspects of its surface.[6] The malignant cells in the CSF cistern around the brain stem could directly infiltrate the microvessels or extend into the subpial space, causing perivascular inflammatory reaction and thrombosis.[7,8] Crombe et al[5] reported of a patient diagnosed with lung adenocarcinoma who showed diffuse high signal intensity on T2-weighted images and DWI, only along the anterior surface of the brain stem and on both sides of the middle cerebellar peduncles. However, our patient showed high signal intensity along the entire surface of the brain stem. Therefore, it would be presented by curvilinear or band-like cytotoxic edema along the surface of the brain stem without leptomeningeal enhancement. Paraneoplastic disorders (PNDs) are a second possible etiologic factor potentially responsible for the cytotoxic edema in the brain stem. Most PNDs are known to be autoimmune-mediated, the best evidence of which comes from the demonstration of antineuronal antibodies in the CSF and serum of patients. PNDs present with various patterns such as limbic encephalitis, cerebellar degeneration, and brain stem encephalitis. Brain stem encephalitis is uncommon compared with other PNDs.[9] Brain stem encephalitis is usually not observed on initial MRI images,

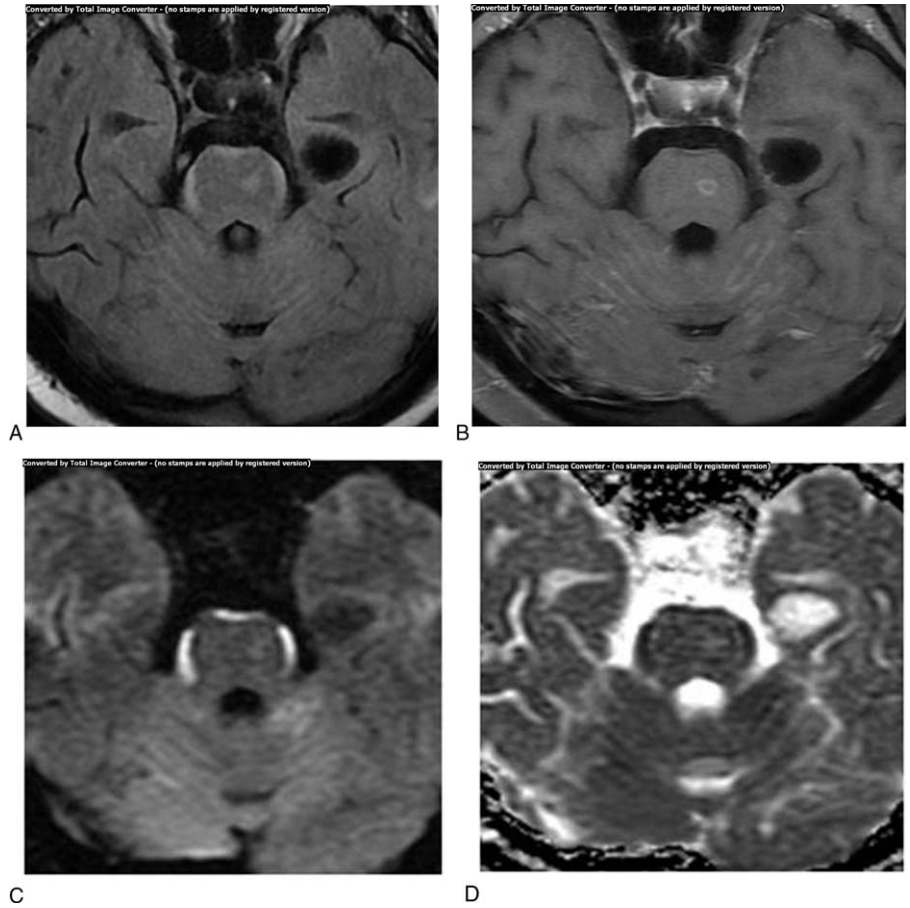

FIGURE 2. Case 2. A 47-year-old woman with lung adenocarcinoma. (A) A T2-FLAIR image reveals bilateral symmetrical curvilinear high signal intensity on the surface of the anterior pons. (B) A contrast-enhanced T1-weighted image shows no enhancement. There are diffuse linear enhancing lesions along the cerebellar folia, consistent with leptomeningeal metastasis. (C) DWI. (D) An ADC map demonstrates symmetrical band-like cytotoxic edema along the surface of the pons.

showing mostly normal findings, but later presents with progressive ascending involvement of the brainstem.[10] MRI reveals high T2 signal intensity in the midbrain tectum, periaqueductal gray matter, pons, medulla, and superior and middle cerebellar peduncles, with or without nodular enhancement.[9] However, circumferentially peripheral involvement of the brain stem with cytotoxic edema has never been reported. Paraneoplastic brainstem encephalitis is usually associated with serum anti-Hu (ANNA-1), anti-Ri (ANNA-2), or anti-Ma antibodies. Case 1 was negative for antineuronal antibodies. Therefore, we suppose that PND is a less likely etiologic factor.

The last hypothesis is toxic encephalitis caused by chemotherapy. The most common chemotherapeutic agents causing central nervous system (CNS) toxicity include methotrexate, vincristine, ifosfamide, cyclosporine, cytarabine, and 5-fuorouracil. It is well known that intrathecal or high-dose methotrexate may cause transient or persistent diffuse white matter degeneration.[11] In addition, calcineurin inhibitors such as cyclosporine or tacrolimus can lead to posterior reversible encephalopathy syndrome (PRES), mainly involving the subcortical regions of the occipital, posterior temporal, and parietal lobes.[11] Both patients in our report were treated with different chemotherapy regimens: one with gefitinib, the other with docetaxel plus carboplatin. There are a few reports about the adverse effects of gefitinib or of the docetaxel–carboplatin combination in the CNS. The most common adverse effects associated with gefitinib use are rash, acne, and diarrhea, while those associated with docetaxel–carboplatin use are hematologic effects related to myelosuppression and alopecia. Docetaxel–carboplatin occasionally can cause peripheral neuropathy but its CNS toxicity is rare.[12] Moreover, gefitinib is less neurotoxic than docetaxel–carboplatin.[13] We could not find any reports in the English literature describing brain stem encephalitis resulting from gefitinib and docetaxel–carboplatin on brain MRI, although PRES due to carboplatin and/or docetaxel has been rarely reported.[14] Toxic encephalopathy is less likely to cause cytotoxic edema in the brain stem.

In conclusion, MRI finding of curvilinear or band-like cytotoxic edema without LM enhancement may be an extremely rare new MRI finding of leptomeningeal carcinomatosis. The findings likely reflect microinfarctions caused by perivascular tumor infiltration on the surface or the subpial regions of the brain stem.

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