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CASE REPORT

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Extraordinary linear non-enhancing brainstem leptomeningeal metastasis from lung adenocarcinoma: A case report

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Key Clinical Message

In patients with lung adenocarcinoma, angiogenesis-altering drugs can alter the appearance of leptomeningeal metastasis on magnetic resonance imaging (MRI) scans. In the ventral brainstem, this can manifest as a unique, linear, non-enhancing T2-hyperintense signal.

KEYWORDS

adenocarcinoma, brain, lung, magnetic resonance imaging, metastasis, tyrosine kinase inhibitors

1 | INTRODUCTION

Although leptomeningeal metastases typically appear as enhancing lesions on magnetic resonance imaging (MRI) scans, the use of anti-angiogenic therapies has recently been reported in association with non-enhancing forms.[1,2] Herein, we describe a case of leptomeningeal metastasis from lung adenocarcinoma with an extraordinary appearance on MRI scan, manifesting as a symmetrical, non-enhancing, linear, T2-hyperintense signal outlining the anterior aspect of the pons and middle cerebellar peduncles. In addition to previously reported idiosyncratic associations such as tyrosine kinase inhibitor (TKI) therapy, our patient also had exposure to patritumab deruxtecan, an anti-HER3 drug which may also have contributed to the unique appearance on MRI.

2 | CASE HISTORY/EXAMINATION

A 66-year-old man with a history of right lung adenocarcinoma presented to the emergency department with a 1-day history of behavioral change and confusion, as well as a 1-month history of poking headache. Other than lung adenocarcinoma, he had no other significant past medical history. On examination, he was superficially relevant, but was not oriented to time, could not recall his own address, and could not retain a simple memory phrase. The rest of the neurological examination was unremarkable. There was no fever or neck stiffness.

Seven years ago, he had been diagnosed with right lung adenocarcinoma and underwent right lung upper

lobectomy by means of video-assisted thoracoscopic surgery. Histological examination showed that the tumor was 2.3 cm in size, with uninvolved resection margins. The post-surgical staging was T1 N0 M0. An epidermal growth factor receptor (EGFR) mutation (exon 21 L858R substitution) was detected. No chemotherapy was administered but the patient was put on regular surveillance. Three years after diagnosis, he was discovered to have recurrence of the disease in the form of multiple bilateral lung nodules on computed tomography (CT) imaging. Since then, the disease had progressed, with the emergence of new metastatic foci in the peritoneum and para-aortic lymph nodes, despite sequential treatment with gefitinib, osimertinib, pemetrexed, carboplatin, and an anti-HER3 drug known as patritumab deruxtecan. A repeat CT-guided transthoracic biopsy of one of the lung nodules, performed 5 years after diagnosis, returned a pathologic yield of the same adenocarcinoma, this time with an additional EGFR mutation detected (exon 20 T790M). At the time of presentation for altered mental status, he had just completed his eighth cycle of patritumab (having received the last dose 8 days prior to presentation), and had not been on any other cancer treatment for at least 5 months.

3 | INVESTIGATIONS AND TREATMENT

Blood tests revealed bicytopaenia (hemoglobin of 10.3 g/dL and platelet count of 68×10^9/L), which was a known side-effect of patritumab. Other blood test results such as urea, electrolytes, vitamin B12 level, and folate level were unremarkable. C-reactive protein was only mildly elevated (12.5 mg/L) and procalcitonin was normal (0.09 μg/L). Electroencephalography (EEG) showed intermittent generalized slowing, a non-specific finding of encephalopathy. A CT scan of the brain was performed, and was unremarkable.

MRI of the brain showed peculiar-looking linear, non-enhancing T2-hyperintense lesions outlining the anterior aspects of the brainstem and middle cerebellar peduncles (Figure 1). These lesions were associated with mild restricted diffusion.

A lumbar puncture was performed, revealing an opening pressure of 11 cmH_2O. Cerebrospinal fluid (CSF) studies showed a mild monocytic pleocytosis (CSF white blood cell count of 11/μL, 96% monocytes), low CSF glucose level (CSF glucose 3.4 mmol/L, compared to paired serum glucose of 7.1 mmol/L) and normal CSF protein

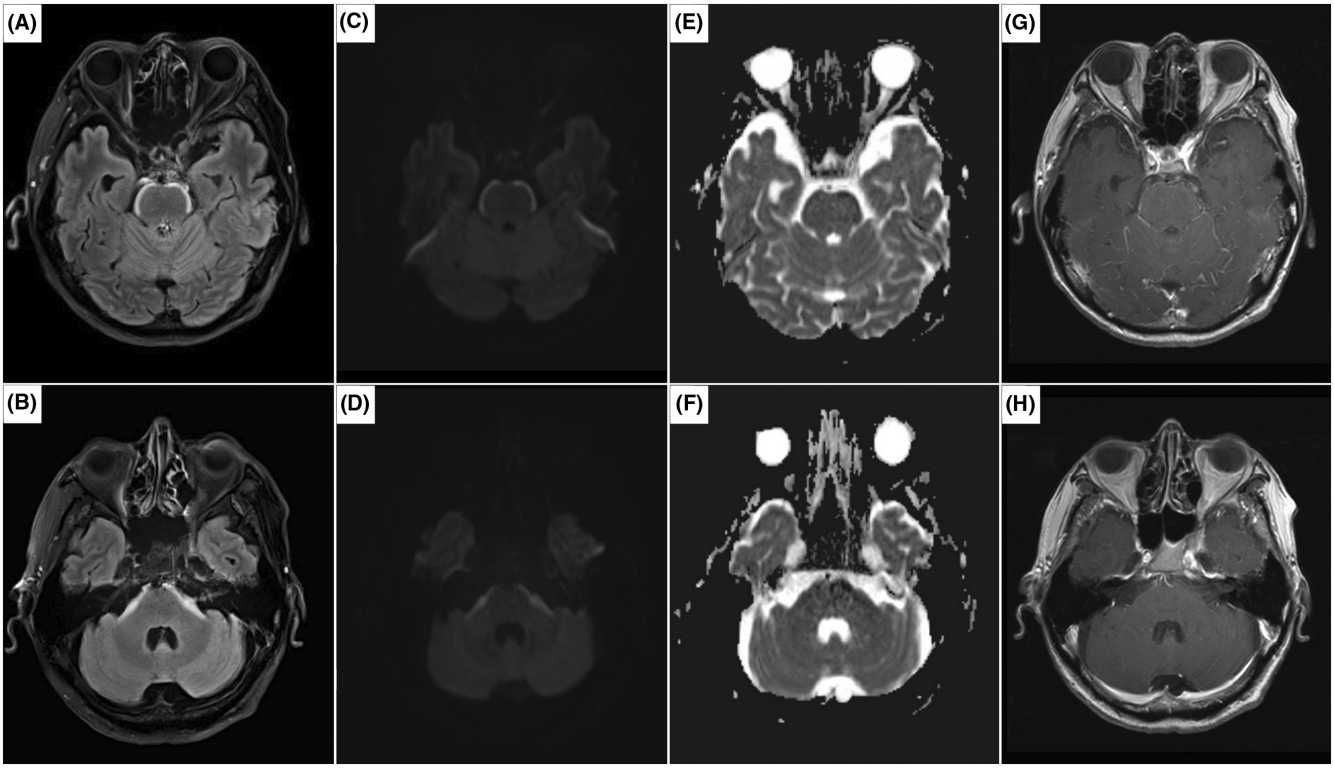

FIGURE 1 Magnetic resonance imaging of the brain showing "bloomy rind sign." (A, B) T2 fluid-attenuated inversion recovery sequences, showing linear hyperintensities outlining the anterior aspects of the pons and middle cerebellar peduncle, respectively. (C, D) Diffusion weighted sequences, showing restricted diffusion over the same areas. (E, F) Apparent diffusion coefficient sequences, showing hypointensity over the same areas. (G, H) Gadolinium-enhanced T1 sequences, showing lack of abnormal enhancement over the same areas.

level (CSF protein 0.37 g/L). CSF microbiological assays were unyielding. Most importantly, CSF cytology revealed the presence of rare malignant cells on Pap and Diff-Quik-stained smears, as well as on TTF1 immunostain performed on cytospin, consistent with metastatic lung carcinoma (Figure 2).

4 | OUTCOME

Having confirmed the presence of intracranial metastasis, patritumab deruxtecan was stopped and the patient underwent whole brain radiotherapy. Transient improvement in the patient's mental status was noted, but 1 week after the completion of radiotherapy, the confusion recurred with progressive worsening. In view of the poor prognosis, no further chemotherapy or radiotherapy was attempted. The patient demised 3 months after onset of altered mental status (2 months after completion of whole brain radiotherapy).

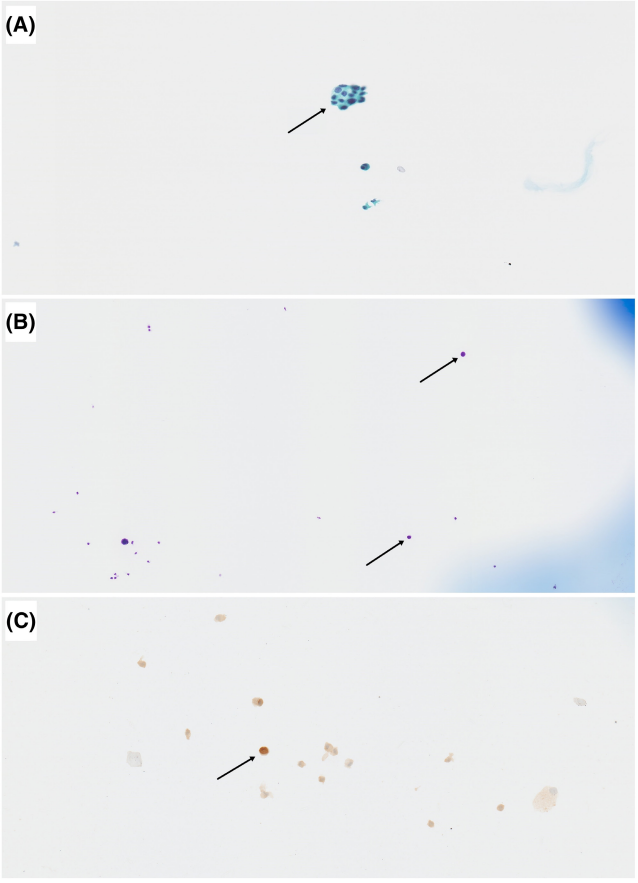

FIGURE 2 Cerebrospinal fluid cytology showing malignant cells consistent with metastatic lung carcinoma. (A, B) Papanicolaou and Diff-Quik stains showing atypical cells (arrows) with enlarged irregular nuclei and hyperchromasia, respectively. (C) Thyroid transcription factor-1 (TTF-1) immunostain performed on cytospin highlighting few atypical cells (arrow), consistent with a lung origin.

5 | DISCUSSION

Due to the unusual appearance of our patient's MRI findings, the etiology was not immediately clear. As the lesions were not enhancing, we had initial doubts about the likelihood of intracranial metastasis. Infective cases were deemed unlikely as the patient was not clinically septic, the blood inflammatory markers were unimpressive, and the CSF microbiological studies were negative. The presentation with an acute onset, 1-day history of altered mental state was atypical for autoimmune or paraneoplastic processes. Metabolic and toxic causes were also explored, but there were no potential culprits identified. Patritumab has not been reported to be associated with confusion or brainstem changes on MRI scans.[3]

However, we discovered from a literature search that our patient's MRI scan bore semblance to a recently described, rare, and little-known non-enhancing form of leptomeningeal metastasis that has been imaginatively described to be like bloomy rind on cheese. This appears on MRI scans as symmetrical, fluid-attenuated inversion recovery hyperintense bands along the anterior and lateral surfaces of the brainstem, extending to the cerebellar peduncles.[4,5]

In our literature review, we found that 19 of 20 cases of "bloomy rind sign" in lung adenocarcinoma with reported EGFR statuses were positive for EGFR mutations.[4–7] The single case without EGFR mutation had an anaplastic lymphoma kinase mutation instead. An additional three cases had unreported driver mutation statuses.[5] Despite the strong association with EGFR-positive lung adenocarcinoma, the non-enhancing nature of bloomy rind sign is unlikely to be related to the EGFR mutation itself, given that EGFR mutation has not been reported to alter its appearance on contrast-enhanced sequences.[8]

Instead, the non-enhancing nature of bloomy rind sign is more likely to be a treatment-related finding. Previous reports of bloomy rind sign occurred in patients with lung adenocarcinoma who had received systemic therapy in the form of TKI or anti-angiogenic antibodies such as bevacizumab.[5] It has been suggested that leptomeningeal metastasis is contrast-enhancing because of (1) intravascular enhancement secondary to increased vascularity and (2) extravascular enhancement due to angiogenesis of new blood vessels with a leaky blood–brain barrier.[2] Hence, bloomy rind sign may be a form of non-enhancing leptomeningeal metastasis due to the use of targeted therapy that inhibits neovascularization.[5]

Our patient's treatment regimen prior to the emergence of bloomy rind sign included gefitinib, osimertinib, and pemetrexed, all of which have been reported in association with bloomy rind sign, but the role of patritumab is less clear.[5] Given that patritumab targets

HER3, a protein that is part of the epidermal growth factor (EGF) receptor, and that EGF receptors participate in tumor angiogenesis among other pathways, it is also possible that patritumab had a role to play in our patient.[9]

Leptomeningeal metastasis has a poor prognosis, early detection and early treatment are important to maximize the chances of survival.[10] Although the detection of malignant cells on CSF cytology is the gold standard for the diagnosis of leptomeningeal disease, MRI is non-invasive, may have a higher sensitivity, and is generally the first-line investigation.[11] Hence, recognition of an unusual but characteristic way that leptomeningeal metastasis can appear on MRI can be helpful, and we hope to add to the limited literature on bloomy rind sign.

AUTHOR CONTRIBUTIONS

Zhibin Tan: Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Shawn Zhi Zheng Lin:** Formal analysis; validation; writing – review and editing. **Yihan Li:** Data curation; writing – review and editing. **Si Wei Kheok:** Formal analysis; supervision; validation; writing – review and editing.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest, no affiliation or financial involvement with any commercial organizations, and no financial interest in the subject or materials discussed in the manuscript.

DATA AVAILABILITY STATEMENT

For this case report, There were no associated datasets to avail.

ETHICS STATEMENT

The subject of this case report was deceased at the time of writing. Although the authors' institution does not require written consent to be taken for case reports involving less than three subjects, the authors nonetheless tried to contact the patient's next-of-kin repeatedly for 3 months, but to no avail. All effort has been made to anonymize the report as much as possible.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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