

Received: 2017.08.24
Accepted: 2017.10.19
Published: 2018.01.26

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 99-104
DOI: 10.12659/AJCR.906803

Hemorrhagic Brain Metastases in a Patient with Anaplastic Lymphoma Kinase (ALK)-Rearranged Invasive Mucinous Adenocarcinoma of the Lung

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Mingxia Shi**
B 1 **Hongzhi Xu**
BD 2 **Angela DiPoto Brahmbhatt**
D 3 **Eduardo Gonzalez-Toledo**
BCDEF 1 **Maria-Magdalena Georgescu**

1 Department of Pathology and Translational Pathobiology, Louisiana State University Health Science Center, Shreveport, LA, U.S.A.
2 Division of Anatomic Pathology, Children's National Medical Center, Washington, DC, U.S.A.
3 Department of Radiology, Louisiana State University Health Science Center, Shreveport, LA, U.S.A.

Corresponding Author: Mingxia Shi, e-mail: mshi@lsuhsc.edu
Conflict of interest: None declared

Patient: Female, 44
Final Diagnosis: Brain metastases from invasive mucinous adenocarcinoma of the lung
Symptoms: Coughing
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Rare co-existence of disease or pathology
Background: Invasive mucinous adenocarcinoma (IMA) is a rare variant of adenocarcinoma of the lung. It frequently shows KRAS mutations, while ALK rearrangement is exceedingly rare. We present a case of ALK-rearranged IMA of the lung presenting with an unusual pattern of brain metastases, radiologically mimicking a cavernous angioma.
Case Report: A 44-year-old non-smoker female was first diagnosed with lung right lower lobe IMA with ALK rearrangement. Five years after surgery followed by chemotherapy, she developed a sudden onset headache. Brain imaging revealed a hemorrhagic left frontal mass, suspicious for a cavernous angioma. However, the pathology of the resected lesion showed an ALK-rearranged brain metastasis from the IMA of the lung. Interestingly, the metastases showed perivascular tumor infiltrates, accompanied by focal mural invasion, vascular disruption, and hemorrhage.
Conclusions: To our knowledge, this is the first reported case of brain metastasis from an ALK-rearranged IMA of the lung. Further investigation of the clinical and pathological characteristics of the ALK-rearranged IMA, including awareness of the possibility for development of brain metastases with tumor-associated vasculopathy and hemorrhage, is warranted.

MeSH Keywords: Adenocarcinoma, Mucinous • Gene Rearrangement • Lung Neoplasms • Neoplasm Metastasis

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/906803>

 1712  —  4  19



Background

Invasive mucinous adenocarcinoma (IMA), formerly known as mucinous bronchioloalveolar carcinoma, has been introduced as a new category in the most recent International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATC/ERS) multidisciplinary classification system [1]. This variant of adenocarcinoma of the lung, accounting for approximately 5% of lung adenocarcinomas [2], has distinct clinical, radiological, pathological, and genetic characteristics. IMAs frequently show KRAS mutation (in up to 90% of cases) [1,3], whereas nonmucinous adenocarcinomas are more likely to show epidermal growth factor receptor (EGFR) mutation. Recently, CD74-NRG1 fusions have been discovered in invasive mucinous adenocarcinoma, providing further evidence of a distinctive subtype [4].

In non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK) is rearranged to create the EML4-ALK oncogene that causes the increased growth of cancer cells. EML4-ALK fusion gene is a potent oncogenic driver, reported in about 3% to 7% of all NSCLC patients [5]. Other fusion partners for ALK have also been discovered in NSCLC. ALK rearrangements are mutually exclusive with EGFR or KRAS mutations [6]. Most ALK-rearranged NSCLC are adenocarcinomas, which have a younger age of onset, high-stage disease, and most patients are never smokers or have a limited smoking history [7]. Crizotinib is the ALK tyrosine kinase inhibitor that has shown marked and durable efficacy for the treatment of patients with NSCLC positive for ALK rearrangement. Despite their initial response, however, such patients treated with crizotinib eventually develop progressive disease, with the brain being the most common site for the occurrence of new lesions [8].

IMA of the lung harboring ALK rearrangement is exceedingly rare. There is no previous report of brain metastases from such patients. We present here a case of brain metastasis from ALK-rearranged IMA of the lung that also showed an unusual pattern of brain invasion radiologically mimicking a cavernous angioma.

Case Report

A 44-year-old non-smoker female was found to have an infiltrate in right lung lower lobe by chest imaging, and was diagnosed with IMA by lung biopsy. One year later, the patient underwent right thoracotomy and lobectomy (Figure 1). Histopathological examination of the resected specimen revealed neoplastic cells with a goblet and columnar cell morphology with abundant intracytoplasmic mucin and small basally located nuclei (Figure 2A). Abundant singly dispersed and clusters of signet ring cells were also present. Tumor cells showed

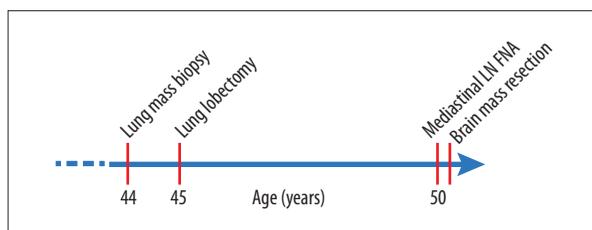


Figure 1. Time course of clinical progression of the IMA.

a predominant lepidic growth with mixture of acinar and solid growth patterns. Spatial proximity between the bronchus and the tumor with frequent tumor cell infiltration of the adjacent bronchial epithelium was observed. Occasionally, the tumor cells showed a continuation with the non-neoplastic bronchiolar epithelium (Figure 2A, right image). By immunohistochemistry (IHC), the tumor was positive for CK7, TTF1, napsin A, p63 and was negative for p40 (Figure 2B) and CK20. A diagnosis of pulmonary IMA with hilar lymph node metastases (stage IIA) was rendered. Molecular studies of the tumor revealed the presence of an ALK rearrangement by fluorescence *in situ* hybridization (FISH) (Figure 2C) and the absence of EGFR and KRAS mutations by sequencing. Expression of epithelial to mesenchymal transition (EMT)-related markers such as E-cadherin and vimentin were also evaluated. Focal absence of E-cadherin expression and gain of vimentin expression in tumor cells (Figure 2D) were observed, suggesting EMT phenotype.

The patient subsequently underwent paclitaxel and carboplatin chemotherapy for four cycles. Five years later, surveillance imaging detected 18F-fluorodeoxyglucose (FDG)-avid mediastinal lymphadenopathy. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) of station 7 lymph nodes was performed, and a cytological diagnosis of metastatic mucinous adenocarcinoma of the lung with signet ring features (Figure 3) was rendered. The tumor cells were positive for CK7 and napsin A, focally positive for TTF1 and negative for CK20. ALK rearrangement and EGFR mutation were not detected.

Two months later, the patient presented to the emergency department with a sudden onset headache. A brain magnetic resonance imaging (MRI) revealed a hemorrhagic left frontal mass with cortical and subcortical deposits of hemosiderin (Figure 4A), suspicious for a cavernous malformation (cavernous angioma). The patient underwent left frontal craniotomy for the resection of the mass. Histopathological examination of the resected brain lesion revealed growth of mucinous tumor cells in the subarachnoid space around the small and large leptomeningeal vessels and diffuse invasion of the brain along the Virchow-Robin perivascular spaces (Figure 4B, left panel). Focal mural invasion, vascular disruption, and hemorrhage (Figure 4B, right and bottom panels) were present inside

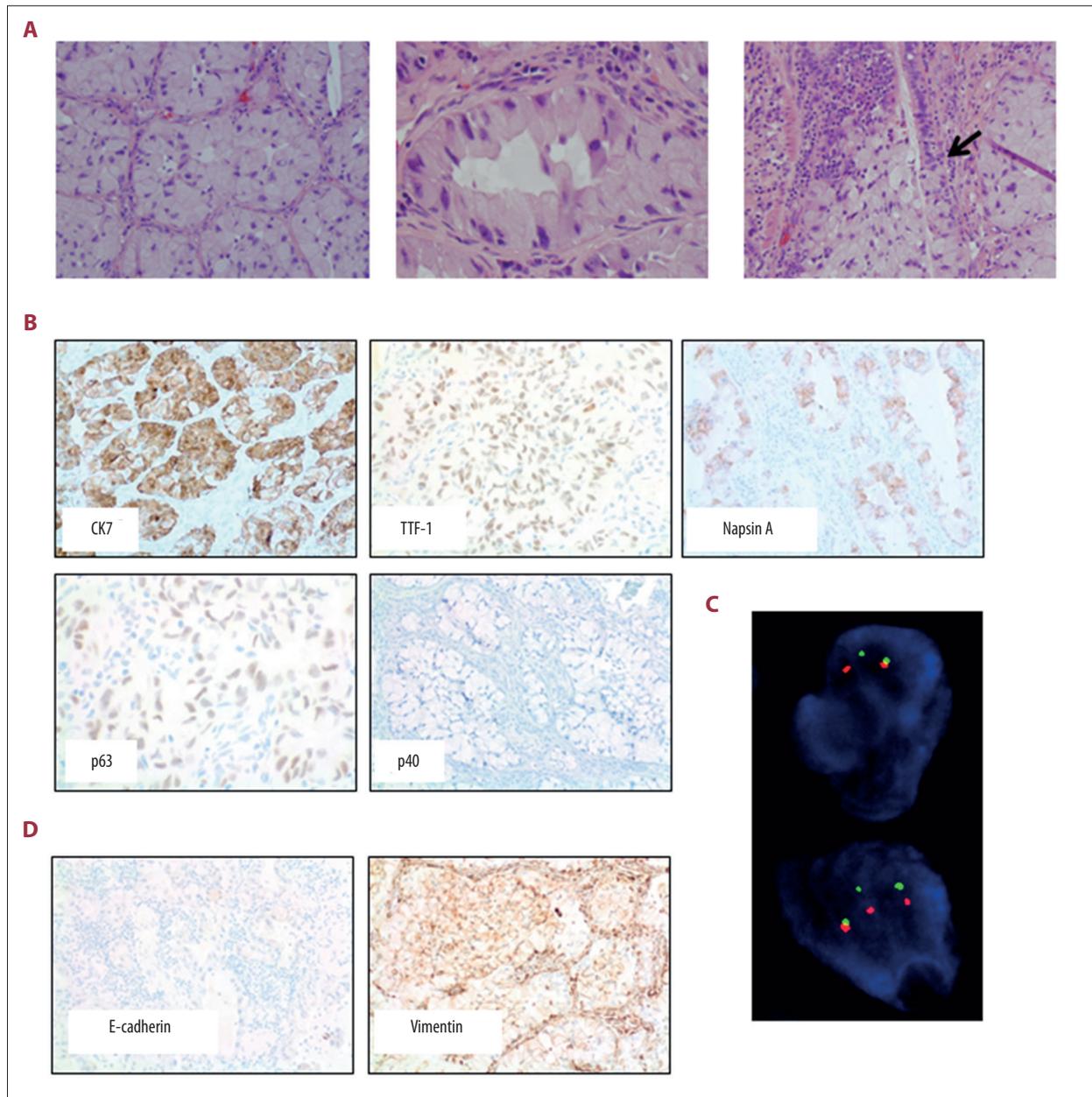


Figure 2. IMA of the lung. (A) Shows neoplastic cells with a goblet and columnar cell morphology with abundant intracytoplasmic mucin and small basally located nuclei. The mucinous tumor cells continued with the non-neoplastic bronchiolar epithelium (black arrow in right image). (B) The neoplastic cells are positive by IHC for CK7, TTF1, napsin A, p63, and negative for p40. (C) Positive ALK FISH break-apart test is shown with split red and green signals, signifying the presence of an ALK rearrangement. (D) The neoplastic cells are positive for vimentin and negative for E-cadherin by IHC. Images in (A), (B), and (D) were acquired at 20× magnification except for center image in panel A and CK7 in panel B that was acquired at 40× magnification with an Olympus BX43 microscope.

and outside the brain parenchyma. The tumor cells were positive for TTF1 and napsin A, and showed presence of ALK gene rearrangement by FISH. The pathological findings confirmed brain metastases from the ALK-rearranged IMA of the lung.

Discussion

IMA of the lung is typified by columnar and/or goblet cell morphology with abundant intracytoplasmic mucin and small basally located nuclei. Nuclear atypia is usually inconspicuous or absent. Alveolar spaces often contain mucin. Patients with IMA

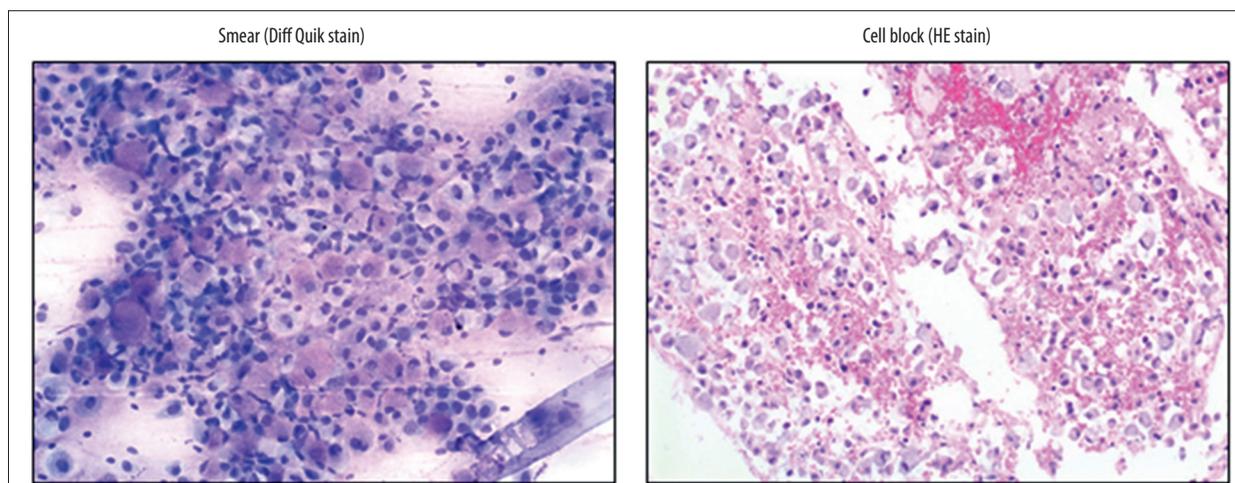


Figure 3. Aspirates of the metastatic IMA in mediastinal lymph node consist of abundant signet ring cells (magnification 20×).

frequently present with a pneumonia-like pattern and multifocal and multilobar lesions [9]. The tumor may show the same heterogeneous mixture of lepidic, acinar, papillary, and micropapillary growth as non-mucinous tumors, but the lepidic pattern is most common, and solid growth is rare. Identical morphology may be seen in metastatic mucinous adenocarcinomas from sites such as the colon, pancreas and ovary, and therefore clinical and radiologic correlation should be made to exclude primary tumors in these locations. The immunoprofile of invasive mucinous adenocarcinoma of the lung may be different from that of other adenocarcinoma subtypes. The tumor is typically positive for CK7 (90%) and CK20 (50%), and less frequently express TTF1 (15%) and napsin A (11%) [10–12]. MUC 2-5-6 positivity is often seen due to its origin of bronchiolar mucinous goblet cells [1]. In the present case of ALK-positive IMA of the lung, the tumor cells demonstrated similar immunoprofile to nonmucinous adenocarcinoma, showing positivity for CK7, TTF1, napsin A, and negative for CK20.

ALK rearrangement is shown to be associated with a solid predominant growth pattern and signet ring cell features [7,13]. It has been reported that approximately 70% of pulmonary adenocarcinoma demonstrate ALK gene rearrangement when signet ring cells comprised >10% of the tumor cells [14]. Proper recognition of this feature may be important in determining whether further molecular testing is advisable. In the present case, the ALK-rearranged IMA showed largely lepidic pattern with foci of acinar and solid growth, and abundant signet ring cells. The EMT phenotype seen in this case, as well as in other cases with ALK rearrangement [13], could potentially contribute to tumor progression, metastasis, and drug resistance in ALK-rearranged tumors. Some studies reported that ALK-rearranged tumors have significantly higher p63 immunoreactivity compared to tumors that are negative for ALK rearrangement [5,13,15]. In contrast, positivity of p40 was rarely observed in ALK-rearranged tumors. Similar to these reports,

our case of ALK-rearranged lung adenocarcinoma showed TTF1 and p63 co-expression and no reactivity to p40. It is known that EGFR-mutated tumors are originated from terminal respiratory units (TRU), which is positive for TTF1 but typically negative for p63. A close relationship to the adjacent bronchial epithelium was reported as a unique feature of ALK-rearranged tumors. In our case, we also observed spatial proximity between bronchus and the tumor with frequent tumor cell infiltration of the adjacent bronchial epithelium. Occasionally, the tumor cells showed a continuation with the non-neoplastic bronchiolar epithelium. These findings suggest that ALK-rearranged tumors might originate from different cell type, and may represent non-TRU-type adenocarcinoma. It was proposed that a cell type dually expressing TTF1 and p63 may be the cell origin of ALK-rearranged tumors [5,13]. However, a specific cell type of ALK-rearranged tumors and the significance of p63 expression remain to be clarified. With regards to diagnosis, the frequent presence of the solid growth pattern with positive p63 immunoreactivity in ALK-rearranged tumors may make it difficult to differentiate from squamous cell carcinoma in a limited specimen. Being aware of these features may prove helpful for accurate diagnosis.

Studies showed a high concordant rate of ALK rearrangement between primary tumors and their corresponding metastases [7,17]. However, discordance has also been reported, indicating intratumor heterogeneity of ALK rearrangement. Hou et al. identified two patients with discrepancy of ALK rearrangement showing an ALK fusion positive in primary tumor while not in paired metastatic lymph nodes [7]. Two patients were reported showing ALK rearrangement negative on primary lung tumor while harboring ALK fusion in metastatic peritoneal and soft tissue lesion, respectively [16,17], indicating that ALK alteration and ALK expression can be acquired during metastatic progression in NSCLC. A recent study reported that ALK rearrangement detected by IHC and RT-PCR was discordant among

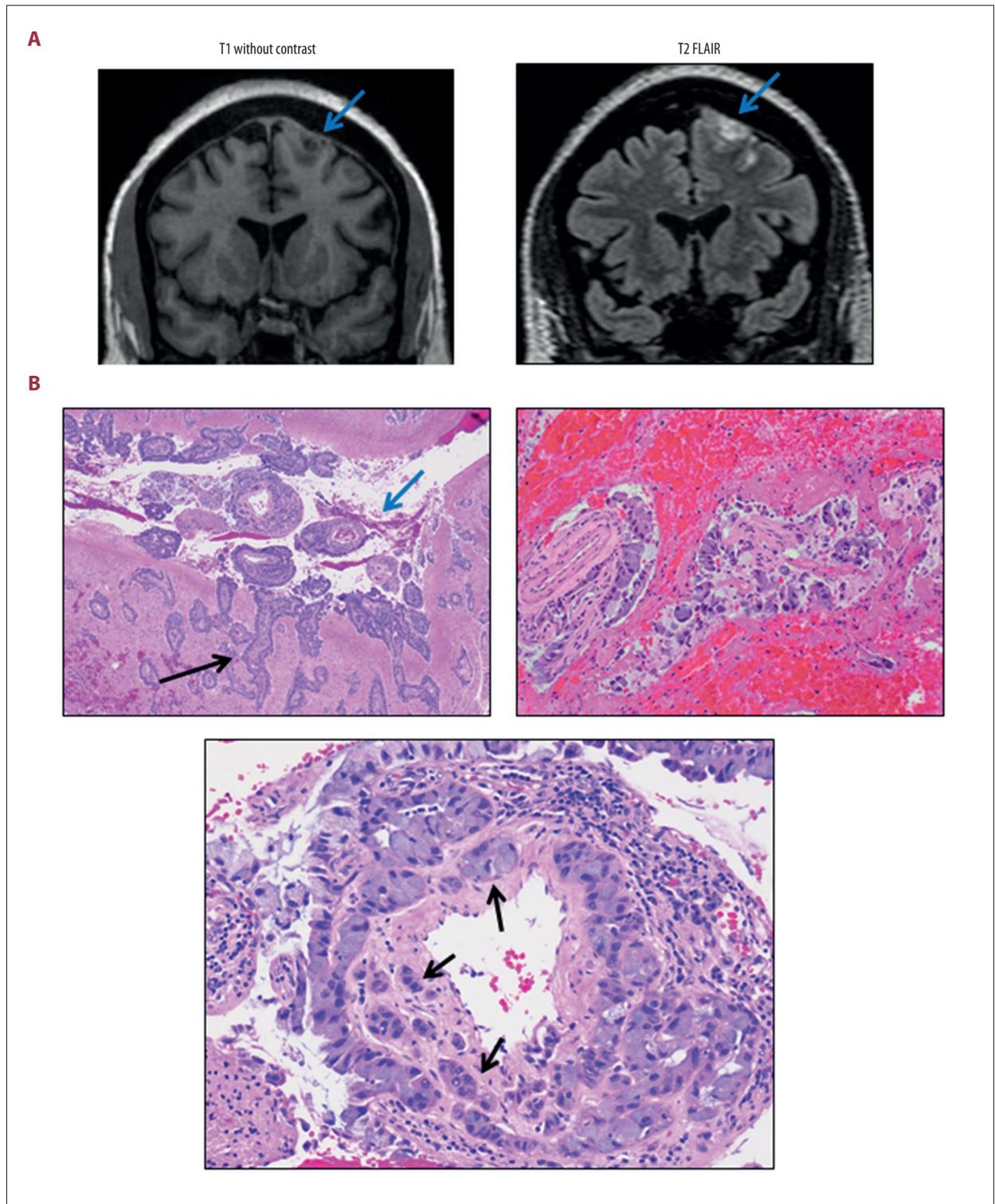


Figure 4. (A) Brain MRI shows hyperintense deposits of hemosiderin (arrow) on T1 images without contrast in a superficial intraaxial and extraaxial lesion located in the left frontal lobe. T2 FLAIR (fluid attenuated inversion recovery) images show the hyperintense superficial lesion. (B) Brain metastases show growth of mucinous tumor cells around the subarachnoid leptomeningeal vessels (blue arrow in **left panel**, 10×) and diffuse invasion of the brain along the Virchow-Robin perivascular spaces (black arrow in **left panel**). Mural invasion (black arrow in **bottom panel**, 40×), vascular disruption and hemorrhage (**right panel**, 20×) are present.

spatially separated tumor areas in the same primary tumor of ALK-positive patient. In the present case, the patient with ALK-rearranged primary lung tumor showed ALK rearrangement in the brain metastases, and no ALK rearrangement in the tumor metastatic to the mediastinal lymph node. It seems reasonable to infer that metastatic tumor cells in the lymph node may come from a clone of ALK-negative tumor cells within the primary lesion. Therefore, genetic intratumoral heterogeneity with different tumor clones may account for this discrepancy.

Brain metastasis usually occurs at the gray and white matter junction or in the vascular border zone regions. This supports the notion that metastatic emboli tend to lodge in areas of reduced blood flow, such as those with sudden reduction of vascular caliber (gray/white matter junction) or areas of the most distal vascular field (border zone) [18]. In our case, the brain metastases from an ALK-rearranged IMA of the lung demonstrated an unusual pattern of brain metastases, with tumor cells seeding in the subarachnoid space, growing around the

leptomeningeal vessels, and diffusely invading the brain along the Virchow-Robin perivascular spaces. This is a pattern of solid tumor metastases that is sometimes seen in melanoma or in breast metastatic to the brain, and rarely in lung cancers [19]. However, in our IMA case, the perivascular tumor infiltrates were accompanied by focal mural invasion, vascular disruption, and hemorrhage. This tumor-associated vasculopathy might be responsible for the radiological mimicry of cavernous angioma.

Conclusions

To our knowledge, the present case is the first reported instance of hemorrhagic brain metastasis in patients with lung IMA positive for ALK rearrangement. Further investigation of the clinical and pathological characteristics of the ALK rearrangement positive IMA and awareness of the possibility for the development of brain metastases with tumor-associated vasculopathy and hemorrhage in such patients are warranted.

References:

1. Tang ER, Schreiner AM, Pua BB: Advances in lung adenocarcinoma classification: A summary of the new international multidisciplinary classification system (IASLC/ATS/ERS). *J Thorac Dis*, 2014; 6: S489–501
2. Siegel R, Ma J, Zou Z, Jemal A: Cancer statistics, 2014. *Cancer J Clin*, 2014; 64: 9–29
3. Kadota K, Yeh YC, D'Angelo SP et al: Associations between mutations and histologic patterns of mucin in lung adenocarcinoma: Invasive mucinous pattern and extracellular mucin are associated with KRAS mutation. *Am J Surg Pathol*, 2014; 38: 1118–27
4. Fernandez-Cuesta L, Plenker D, Osada H et al: CD74-NRG1 fusions in lung adenocarcinoma. *Cancer Discov*, 2014; 4: 415–22
5. Kim H, Chung JH: Overview of clinicopathologic features of ALK-rearranged lung adenocarcinoma and current diagnostic testing for ALK rearrangement. *Transl Lung Cancer Res*, 2015; 4(2): 149–55
6. Zhang X, Zhang S, Yang X et al: Fusion of EML4 and ALK is associated with development of lung adenocarcinomas lacking EGFR and KRAS mutations and is correlated with ALK expression. *Mol Cancer*, 2010; 9: 188
7. Hou L, Ren S, Su B et al: High concordance of ALK rearrangement between primary tumor and paired metastatic lymph node in patients with lung adenocarcinoma. *J Thorac Dis*, 2016; 8(6): 1103–11
8. Otterson GA, Riely GJ, Shaw AT et al: Clinical characteristics of ALK+ NSCLC patients (pts) treated with crizotinib beyond disease progression (PD): Potential implications for management. *J Clin Oncol*, 2012; 30(Suppl.): abstr 7600
9. Casali C, Rossi G, Marchioni A et al: A single institution-based retrospective study of surgically treated bronchioloalveolar adenocarcinoma of the lung: Clinicopathologic analysis, molecular features, and possible pitfalls in routine practice. *J Thorac Oncol*, 2010; 5: 830–36
10. Lau SK, Desrochers MJ, Luthringer DJ: Expression of thyroid transcription factor-1, cytokeratin 7, and cytokeratin 20 in bronchioloalveolar carcinomas: An immunohistochemical evaluation of 67 cases. *Mod Pathol*, 2002; 15(5): 538–42
11. Tsuta K, Ishii G, Nitadori J et al: Comparison of the immunophenotypes of signet-ring cell carcinoma, solid adenocarcinoma with mucin production, and mucinous bronchioloalveolar carcinoma of the lung characterized by the presence of cytoplasmic mucin. *J Pathol*, 2006; 209(1): 78–87
12. Wu J, Chu PG, Jiang Z et al: Napsin A expression in primary mucin-producing adenocarcinomas of the lung: An immunohistochemical study. *Am J Clin Pathol*, 2013; 139(2): 160–66
13. Kim H, Jang SJ, Chung DH et al: A comprehensive comparative analysis of the histomorphological features of ALK-rearranged lung adenocarcinoma based on driver oncogene mutations: Frequent expression of epitheliomesenchymal transition markers than other genotype. *PLoS One*, 2013; 8: e76999
14. Choi E, Lewis AL, Takei H, Ro JY: Leptomeningeal carcinomatosis as initial presentation in adenocarcinoma of lung with signet ring cell features: An autopsy case report. *Int J Clin Exp Pathol*, 2012; 5(9): 972–76
15. Sakai Y, Nakai T, Ohbayashi C et al: Immunohistochemical profiling of ALK fusion gene-positive adenocarcinomas of the lung. *Int J Surg Pathol*, 2013; 21(5): 476–82
16. Rossi A, Galetta D, Bottiglieri L et al: Evaluation of ALK gene status in primary lung adenocarcinoma and matched metastases. *J Thorac Oncol*, 2011; 6: 1146
17. Kim H, Xu X, Yoo S-B et al: Discordance between anaplastic lymphoma kinase status in primary non-small-cell lung cancers and their corresponding metastases. *Histopathology*, 2013; 62(2): 305–14
18. Hwang TL, Close TP, Grego JM et al: Predilection of brain metastasis in gray and white matter junction and vascular border zones. *Cancer*, 1996; 77(8): 1551–55
19. Taillibert S, Laigle-Donadey F, Chodkiewicz C et al: Leptomeningeal metastases from solid malignancy: A review. *J Neurooncol*, 2005; 75(1): 85–99