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Solitary Pulmonary Metastatic Neuroendocrine Tumor with EML4-ALK Fusion Gene Mimicking Glioblastoma: A Case Report and Literature Review

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ABSTRACT

Lung cancer is the most frequently seen origin of intracranial metastatic tumors. Lung cancer with EML4-ALK fusion gene is mainly detected in adenocarcinomas, but is extremely rare in pulmonary neuroendocrine tumors. We report a case of a 60-year-old woman with a solitary intracranial pulmonary metastatic neuroendocrine tumor, with EML4-ALK fusion gene which should be differentiated from primary brain tumors such as glioblastoma. Because of the low incidence, gene testing of EML4-ALK fusion for such tumors is seldom prescribed by pathologists. However this may lead to the missing of effective target therapy. Literature regarding to the pathological and radiological features of such entity were reviewed to get a deep understanding of this entity and to avoid missing target therapy for the patients.

Keywords: Pulmonary neuroendocrine tumors, Intracranial metastasis, Target therapy, Differential diagnosis

INTRODUCTION

Lung cancers are responsible for approximately 50% of brain metastatic neoplasms [1]. However, intracranial metastatic lung neuroendocrine tumors are relatively rare. It is extremely rare that lung neuroendocrine tumor harbors EML4-ALK fusion gene (EML4-ALK fusion gene is responsible for 3%-5% non-small-cell lung cancer, especially adenocarcinomas). Neoplasms with EML4-ALK fusion gene are sensitive to Crizotinib, a targeted drug as an ALK inhibitor. We describe an incidentally found lesion of this rare kind of tumor, which may result in improper treatment. It is important to identify the radiological features of this rare entity to avoid improper diagnosis and treatment.

CASE PRESENTATION

History and Physical examination

A 60-year-old female was admitted to hospital for "incidentally found space-occupying lesions in the left frontal lobe for one week". Because of slight dizziness which could be relieved after rest, the patient visited the local hospital. CT scan indicates “left frontal lobe hemorrhagic mass lesion”.

Physical Examination revealed no nervous system or respiratory positive sign.

Radiographic evaluation

1) Head CT scan (**Figure 1A):** left frontal lobe 3.5 × 2.2cm high-density nodular mass, surrounded by edema;
2) Head MRI (**Figure 1B to F):** left frontal lobe, 3.6 × 2.7cm mass, with mixed signal on T1 and T2 weighted imaging; uneven contrast was seen after gadolinium injection. Left frontal lobe tumor with bleeding was considered.
3) Preoperative chest X-ray (**Figure 2A**) : the right hilar of lung was enlarged

Chest high-resolution CT scan (**Figure 2B):** right middle lobe of lung masses, right hilar lymph nodes enlargement

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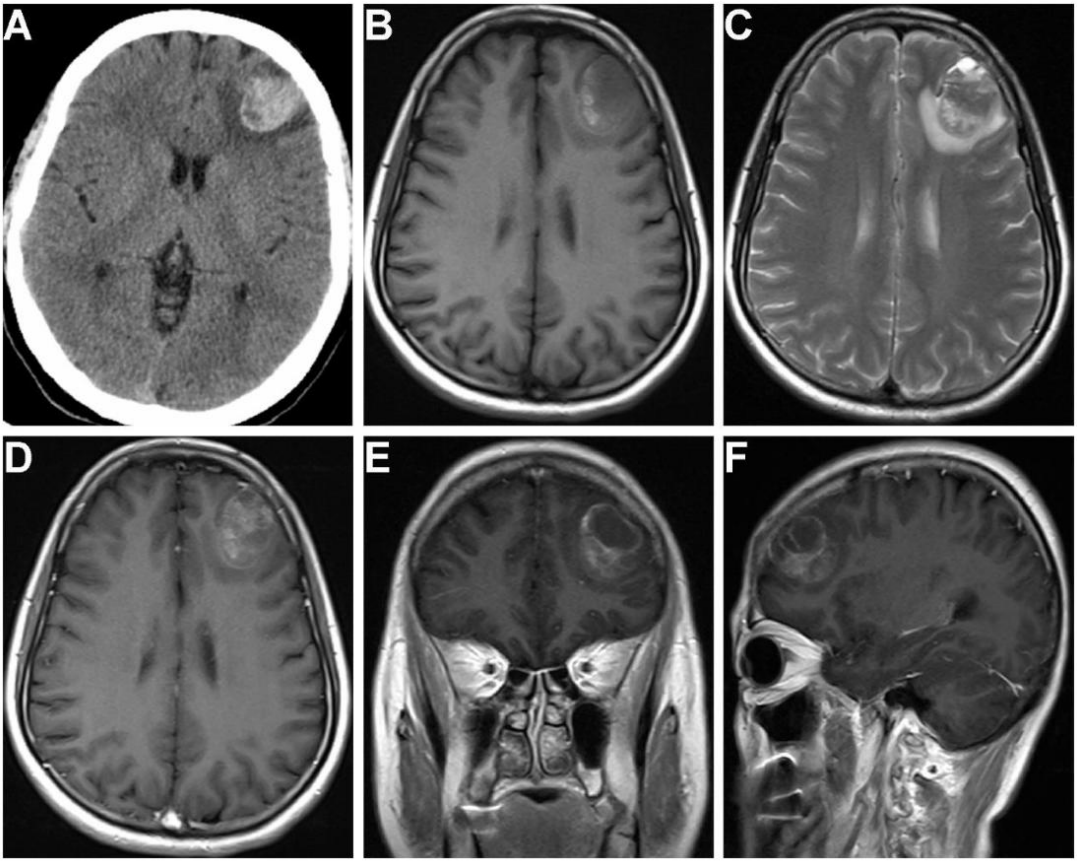

Figure 1. Head CT showed left frontal lobe high-density abnormal signal (A); MRI without contrast: T1 (B), T2 (C) weighted images showed left frontal mass high-low-mixed signals; Head MRI with contrast: coronal (E), sagittal (F) images suggested left frontal tumor with bleeding.

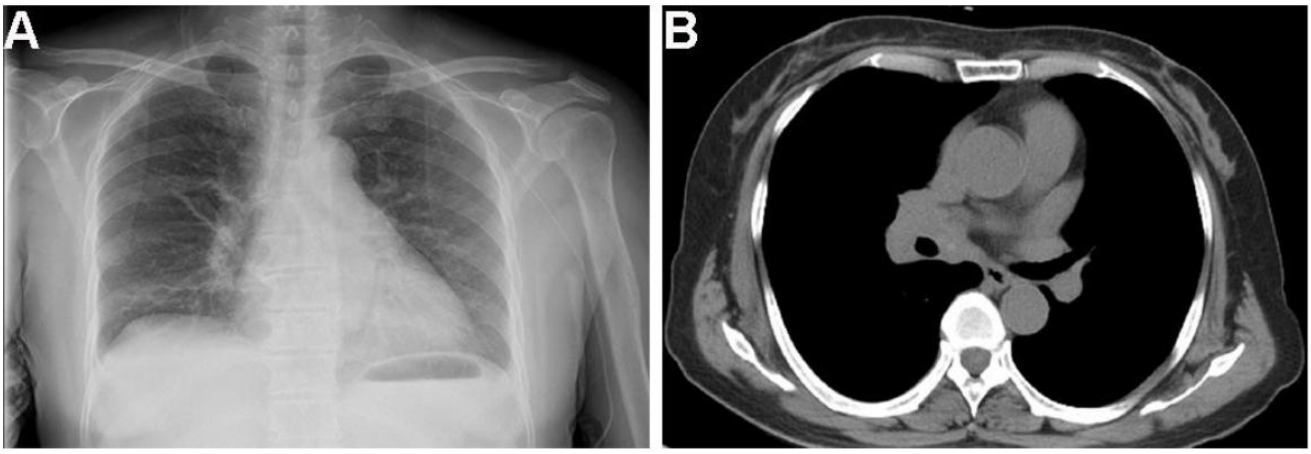

Figure 2. Chest X-ray implied the right side of the hilar enlargement (A); Chest high-resolution CT: right middle lobe mass and lymph nodes swelling (B).

SURGICAL FINDINGS AND PATHOLOGY

Left frontal lobectomy under general anesthesia was performed. The tumor was located in the left frontal lobe, sized about 4×3×3 cm, and grey-red colored cyst with brown-red non-coagulated liquid component. The tumor was obscurely demarcated with surrounded brain tissue with abundant blood supply. The tumor was gross totally removed en bloc (For post-operative MRI, **Figure 3**).

Intraoperative frozen section pathology indicated epithelial tumors, brain metastasis was suspected.

Paraffin embedded section pathology: (left frontal lobe) metastases, lung non-small cell metastatic neuroendocrine tumor was considered (**Figure 4**).

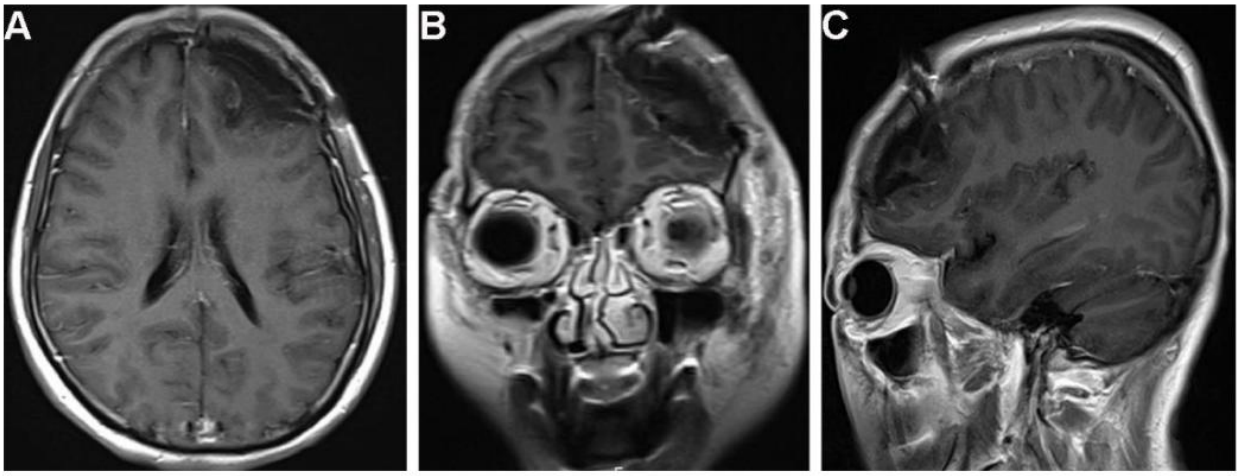

Figure 3. postoperative head MRI with gadolinium enhancement: axis (A), coronal (B), sagittal (C)

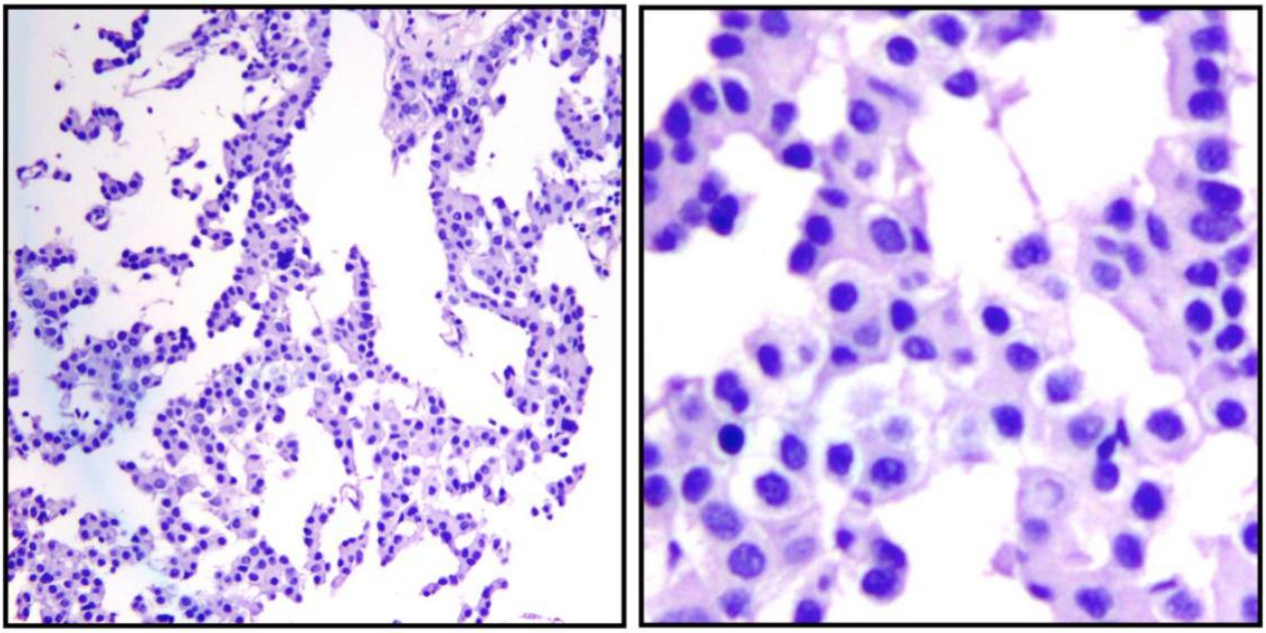

Figure 4. Erosin-hematoxylin staining of paraffin-bedded section: (left frontal) metastatic tumor. Neuroendocrine tumor considered , lung origin.

Immunohistochemistry

CK（AE1/AE3）+, CK 5/6 -, CK7 +, CK 20 +, TTF-1 +, Napsin A -, CDX-2 -, PAX-8 +, CD56 +, GATA-3 -, CgA -, Syn +, NSE +, Ki-67 30%, Thyroglobulin –

Gene testing

EGFR mutation (-)

EML4-ALK fusion gene (+)

ROS1 fusion gene (-)

Postoperative multi-disciplinary team discussion suggested:

1. Biopsy of lung cancer via bronchoscopy recommended (patient declined);
2. Crizotinib was the first line treatment option (patient declined);
3. Chemotherapy option: EP regimen (Etoposide 0.14 g × 3 day + cisplatin 35 mg × 3 day)
4. Radiotherapy can be postponed due to the gross total resection and effective targeted therapy.

The patient was transferred to the Center of Lung Cancer of our hospital. The first cycle of EP regimen was completed on Nov. 20, 2017. The patient was discharged and followed up.

DISCUSSION

Definition of neuroendocrine tumor

Neuroendocrine tumors are tumors that originate from neuroendocrine cells, which are known as some specialized neurons (not endocrine cells) that secrete bio-active substances which can regulate the function of other organs through blood circulation or local diffusion. The hypothalamic supraoptic nucleus and paraventricular nucleus cells are typical neuroendocrine cells. However, neuroendocrine cells are not confined to the hypothalamus, they can be distributed throughout the body, and the majority of the neuroendocrine cells are in gastrointestinal tract [2]. The respiratory neuroepithelial cells are scattered in the respiratory tract from the nasal cavity to the alveoli [3,4], Neuroendocrine cells in the lung can serve as airway receptors to regulate the lung immune function [5].

Pathological classification of pulmonary neuroendocrine tumors

Pulmonary neuroendocrine tumors can be classified into: low-grade neuroendocrine tumors (typical carcinoids), intermediate-grade neuroendocrine tumors (atypical carcinoids), and high-grade neuroendocrine tumors. High-grade neuroendocrine tumors have two typical manifestations: small cell lung cancer and large cell lung cancer. Pulmonary neuroendocrine tumors of any grade manifest typical characteristics under light microscope. However, the pathological diagnosis needs to be confirmed by immunohistochemistry [6].

Radiological features of intracranial metastatic neuroendocrine tumors

Intracranial metastatic neuroendocrine tumors accounts for about 1.5%-5% of all intracranial metastasis [7]. Most of them originated from the lung. Pulmonary neuroendocrine tumors are responsible for about 87% of them [7,8], other origins include breast, esophagus. In some cases, no origins were founded even after 2 years of treatment and observation [7]. Within all a cases, about 2/3 of them are multiple tumors, 1/3 of them a solitary tumors [8]. In this case, a solitary incidentally found mass with uneven contrast may be misdiagnosed as primary brain tumors such as glioblastoma.

Since intracranial metastatic neuroendocrine tumors are very rare, no large cohort of cases was analyzed for the radiological features were published. But this case showed a unique manifestation mimicking hemorrhagic and glioblastoma.

Treatment for pulmonary neuroendocrine tumors

Treatments for neuroendocrine tumors and other cancers are different, so the correct pathological diagnosis is very important. **Table 1** summarizes the treatment options for different levels of pulmonary neuroendocrine tumors and the 5-year survival rate.

Table 1. Treatment options for different levels of pulmonary neuroendocrine tumors and the 5-year survival rate

Types of Neoplasms	Treatment	5-year Survival Rate (%)
Typical carcinoid (low-grade)	bronchoscopy, surgical resection, lobectomy	92-100
Atypical carcinoid (intermediate level)	bronchoscopy, surgical resection, lobectomy	61-88
Large cell neuroendocrine tumors (high level)	chemotherapy, surgery	16-57
Small cell lung cancer	Radiotherapy and chemotherapy (surgery for phase I plausible)	2-31

Targeted Therapies regarding EML4-ALK fusion gene

EML4 (echinus microtubule-associated protein like 4) gene and ALK (anaplastic lymphoma kinase) fusion gene, commonly found in lung adenocarcinomas, is approximately responsible for 3% - 5% for non-small cell lung cancer, which is related to non-smokers, mild smokers, and young patients [9]. This gene fusion results in over expression of ALK tyrosine kinase.

EML4-ALK fusion gene-positive non-small cell lung cancer is sensitive to crizotinib, an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor. Clinical studies have shown that for patients with high-stage EML4-ALK fusion gene-positive non-small cell lung cancer, the objective response rate (ORR) of crizotinib is 50% to 61% [10].

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