

ALK-positive adenocarcinoma of the lung expressing neuroendocrine markers and presenting as a “pituitary adenoma”

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Key words

Lung • Adenocarcinoma • Immunohistochemistry • Neuroendocrine • ALK • Pituitary gland • Metastasis

Summary

We report an ALK-rearranged adenocarcinoma of the lung presenting as a pituitary metastasis, clinically simulating a pituitary adenoma. The patient, a 50 year-old, former-smoking woman was admitted with a Parinaud’s syndrome characterized by progressive oculomotor impairment of visual verticality, bitemporal hemianopsia and nystagmus. Imaging studies showed a sellar tumor and the biopsy revealed a TTF-1 and napsin positive lung adenocarcinoma strongly expressing synaptophysin and CD56, also harboring ALK rearrangement. A subsequent CT scan dis-

closed the primary lung mass of the left upper lobe. The patient progressed after 4 cycles of cisplatin/pemetrexed as first line treatment, but showed a partial response and a significant clinical benefit from the combination of ceritinib and nivolumab in a phase Ib trial.

Despite its central nervous system tropism, ALK-rearranged adenocarcinoma manifesting with pituitary gland involvement was never reported. Second generation ALK inhibitors seem the best therapeutic strategy.

Introduction

Primary lung carcinoma presenting as a metastasis to the pituitary gland is exceedingly rare and generally represents a diagnostic challenge for pathologists. In addition, immunohistochemical stains may be misleading since TTF-1 expression is observed in some primary pituitary tumors². We describe here the case of a 50-year-old, former smoker woman presenting with neurologic symptoms due to a sellar mass clinically suggestive of a pituitary adenoma. The tumor biopsy revealed an adenocarcinoma with acinar pattern expressing TTF-1 and napsin, but also neuroendocrine markers (synaptophysin, CD56) and ALK protein. ALK gene rearrangement was confirmed at FISH testing and a pulmonary mass was subsequently identified at chest CT-scan. To our knowledge, this is the first ALK-positive lung adenocarcinoma manifesting with pituitary gland metastasis. The concurrent neuroendocrine differentiation at immunostains and the site-related therapeutic strategies were discussed.

Case report

A 50 year-old women, former smoker, was admitted to the Neurology Unit with polydipsia and progressive ocular impairment in visual verticality. Ophthalmologic examination revealed bitemporal hemianopsia and nystagmus. A magnetic resonance imaging (MRI) with gadolinium (Fig. 1) showed a 2.2 cm sellar lesion, clinically suggesting a pituitary adenoma with compression of the optic chiasm.

Routine laboratory test were unremarkable. The tumor was, then, partially removed through a trans-sphenoidal approach. Histological examination (Fig. 2) showed an adenocarcinoma with an acinar pattern expressing TTF-1 (clone 8G7G3/1), napsin (clone MRQ60), synaptophysin (clone SP11) and CD56 (clone 123C3). Chromogranin (clone LK2H19) was negative. All primary antibodies were tested using an automated immunostainer (UltraView, Ventana Medical system, Tucson, AZ, USA). A diagnosis of pituitary metastasis from an adenocarcinoma consistent with lung primary was made

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Fig. 1. Contrast-enhanced magnetic resonance (sagittal-T1-weighted images) shows a 2,2 cm lesion of the pituitary region suggestive of pituitary macroadenoma.



and predictive biomarkers were ordered as reflex test. Tumor cells were strongly positive (score 3+) for ALK protein (clone D5F3) and ALK rearrangement was further confirmed by fluorescence in-situ hybridization (FISH) technique (46% of tumor cells with classic split signals). Extractive molecular analysis by MALDI-TOF method ((Sequenom, LungCarta Panel v1.0, Agena Bioscience, San Diego, CA) did not evidence gene alterations of *EGFR*, *KRAS*, *BRAF*, *HER2*, *PI3KCA*, *NRAS*.

A left upper lobe nodular opacity was noted and chest X-rays and computed-tomography (CT) (Fig. 3) confirmed a mass of 3.5 cm of maximum diameter with ipsilateral hilar lymphadenopathies. The patient started first-line chemotherapy with cisplatin (75 mg per square meter) and pemetrexed (500 mg per square meter of body-surface area). After 4 cycles, CT scan showed a progression of residual sellar lesion and disease stability of the primary site.

Given the CNS involvement at the diagnosis, the patient was enrolled in a phase Ib study with a second generation ALK inhibitor (ceritinib, 750 mg taken orally once daily) plus the anti-PD-1 nivolumab (240 mg IV every two weeks) until disease progression or intolerable toxicity.

Fig. 2. The biopsy of pituitary mass revealed a metastatic adenocarcinoma (A, H&E stain) expressing TTF-1 (B), Napsin (C), synaptophysin (D) and ALK (E).

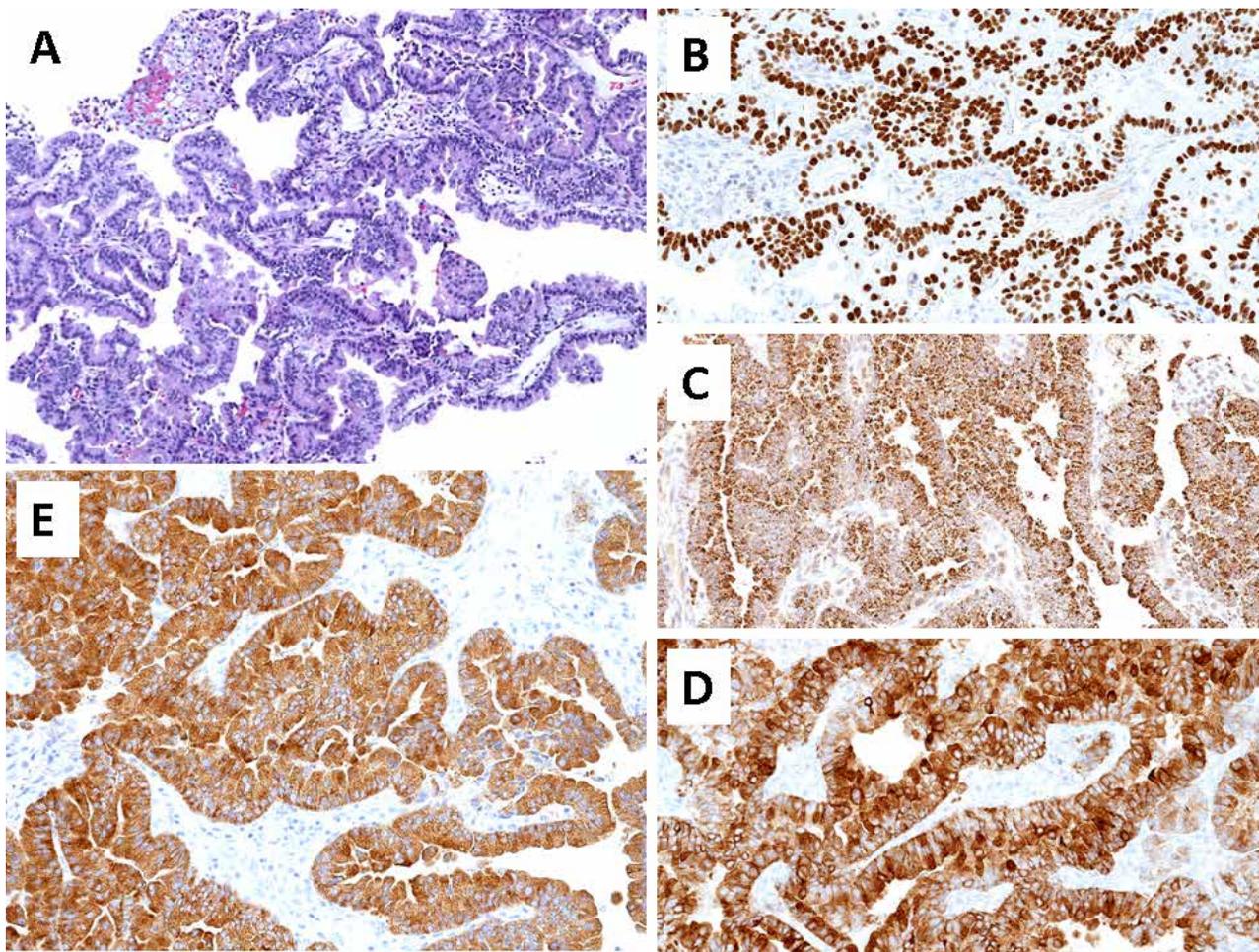


Fig. 3. Contrast-enhanced computed tomography scan of the thorax reveals a 3,5 cm pulmonary lesion of the left upper lobe associated with ipsilateral hilar lymphadenopathies.



The high risk of iatrogenic blindness and long-term neurocognitive toxicity precluded a radiotherapy treatment of the metastatic site. The patient promptly experienced a clinical benefit and an improvement of visual acuity. Imaging studies showed a partial response of the lung adenocarcinoma (1.1 cm of maximum diameter) and a stability of the pituitary metastasis. After 6 months, the patient presented with neural symptoms and MRI documented a multifocal brain progression. The experimental treatment was stopped and the patient underwent whole-brain irradiation and started a third line treatment with crizotinib (250 mg orally twice daily). She is alive with disease after 14 months from the diagnosis.

Discussion

The case described here had different interesting points. First, although lung and breast cancers are the most common metastatic tumors to the pituitary gland ¹, a lung adenocarcinoma presenting with neurologic symptoms and simulating pituitary adenoma at imaging studies is exceedingly rare ². Since presenting symptoms of a pituitary lesion, either primary or metastatic, are related to the involvement of optic chiasm (visual impairment, bitemporal hemianopsia and occasionally development of dorsal midbrain syndrome/Parinaud's syndrome) ^{1,2}, the correct diagnosis substantially relies on pathologic findings.

Histologic recognition of a pituitary gland metastatic tumor in absence a medical history of a known primary elsewhere may be very challenging. Apart from the morphologic features overtly revealing an adenocarcinoma, then favouring a metastasis, the immunohistochemical coordinated expression of TTF-1 and neuroendocrine markers was somehow controversial. Indeed, although generally considered a specific markers of pulmonary tumors (among others), TTF-1 is also expressed in pitui-

tary tumors ³. By contrast, the finding of strong positivity for synaptophysin and CD56 is extremely uncommon in lung adenocarcinoma, rather supporting a pituitary adenoma.

However, the set of morphology and immunostains, reinforced by the reactivity of tumor cells with napsin A, were more consistent with a sellar metastasis from lung adenocarcinoma ⁴.

It is noteworthy that pioneering gene expression profiling studies on lung adenocarcinoma have correlated the presence of neuroendocrine differentiation to significant poor prognosis ⁵ and acquisition of a neuroendocrine phenotype seems to characterize ALK-positive lung adenocarcinomas resistant to crizotinib ⁶. Again, pulmonary neuroendocrine carcinomas harbouring ALK rearrangement do not respond to crizotinib ⁷, then suggesting the presence of neuroendocrine differentiation in ALK-positive carcinomas as a mechanism of primary or secondary resistance to ALK inhibitors.

ALK-positive adenocarcinomas account for about 5% of all NSCLC and are associated with a peculiar tropism for central nervous system (CNS) metastases (approximately 35-50%) ⁸.

However, it is not clear if patients with ALK-rearranged adenocarcinoma have *per se* more probability to develop CNS metastases independently from the received therapy or to the poor diffusion capacity of crizotinib through the brain-blood barriers ⁹.

The case here seems to support a peculiar metastatic potential of ALK-positive adenocarcinoma to neural involvement, including the pituitary gland.

The best therapeutic strategy when dealing with a metastatic ALK-rearranged adenocarcinoma metastatic to the pituitary gland may be quite problematic. Indeed, stereotactic radiotherapy may provoke significant vision alterations leading to a poor quality-of-life, especially in an active young patient. Promising results were reported using second-generation ALK-inhibitors in light of their higher diffusion capacity through the brain ¹⁰.

In summary, we report the first case of ALK-positive pulmonary adenocarcinoma with neuroendocrine differentiation presenting as a pituitary gland metastasis. Exceedingly rare occurrence, as here, may result very challenging on a diagnostic and therapeutic levels requiring a close cooperation between pathologist and clinician.

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