Prolactin-Secreting Lung Adenocarcinoma Metastatic to the Pituitary Mimicking a Prolactinoma: A Case Report

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BACKGROUND AND IMPORTANCE: Metastasis to the pituitary gland is uncommon in patients with systemic disseminated cancer. Individual articles have reported cases of pituitary metastasis mimicking a prolactinoma, but no case of a prolactin-secreting tumor metastasizing to the pituitary mimicking a prolactinoma has been reported so far.

CLINICAL PRESENTATION: This article reports a 67-yr-old man with a recent onset of headaches, ophthalmoplegia, hypopituitarism, and hyperprolactinemia who was initially diagnosed with prolactinoma and given bromocriptine in the local hospital. Because of vomiting after taking drugs, he was transferred to our hospital for further diagnosis and treatment. Serum prolactin was elevated up to 1022 ng/mL, and pituitary magnetic resonance imaging revealed a 2.9 × 2.8 × 2.3 cm sellar mass with pituitary apoplexy, for which endoscopic transsphenoidal surgery was performed. Postoperative pathology and western blotting disclosed a prolactin-positive metastatic lung adenocarcinoma. Whole exome sequencing revealed a number of gene mutations including KRAS, PIK3CA, ALK, and CTNNB1. The patient died of deterioration of the lung disease 3 mo after the initial diagnosis.

CONCLUSION: To the best of our knowledge, this is the first report of a prolactin-secreting tumor metastasizing to the pituitary mimicking a prolactinoma as confirmed by both immunohistochemistry and western blot. Prolactin secretion is rare and elusive, and may associate with specified gene mutations.

KEY WORDS: Pituitary, Metastasis, Hyperprolactinemia, Lung adenocarcinoma

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Sellar tumors are usually pituitary adenomas and rarely metastasize from other organs.[1] Clinicians often try to differentiate between primary and secondary tumors based on initial presentation. But it can be difficult, especially when the metastatic tumor itself produces hormones. Production of GHRH and ACTH in cancers metastatic to the pituitary has been well documented,[2,3] but no case of a prolactin (PRL)-producing tumor metastasizing to the pituitary has been reported so far. This article reports the first case of metastatic lung adenocarcinoma attributing to pituitary apoplexy and mimicking a prolactinoma, in which PRL secretion was confirmed by immunohistochemistry and western blotting. In addition, whole exome sequencing (WES) was performed to explore the underlying mechanism.

ABBREVIATIONS: DRD5, dopamine receptor D5; **DRD2,** dopamine receptor D2; **HPRL,** hyperprolactinemia; **MRI,** magnetic resonance imaging; **PMs,** pituitary metastases; **PRL,** prolactin; **WES,** whole exome sequencing; **T1WI,** T1-weighted images; **T2WI,** T2-weighted images

CLINICAL PRESENTATION

A 67-yr-old man reported headache, insomnia, and left eye ptosis in the recent 3 mo, and headache became more severe in the recent week, especially in the left retro-orbital area, accompanied with an episode of severe vomiting, without visual symptoms and polyuria. He also reported a decrease in libido. The patient was first admitted to a local hospital, where computer tomography scan showed an isodense pituitary mass with suprasellar extension.

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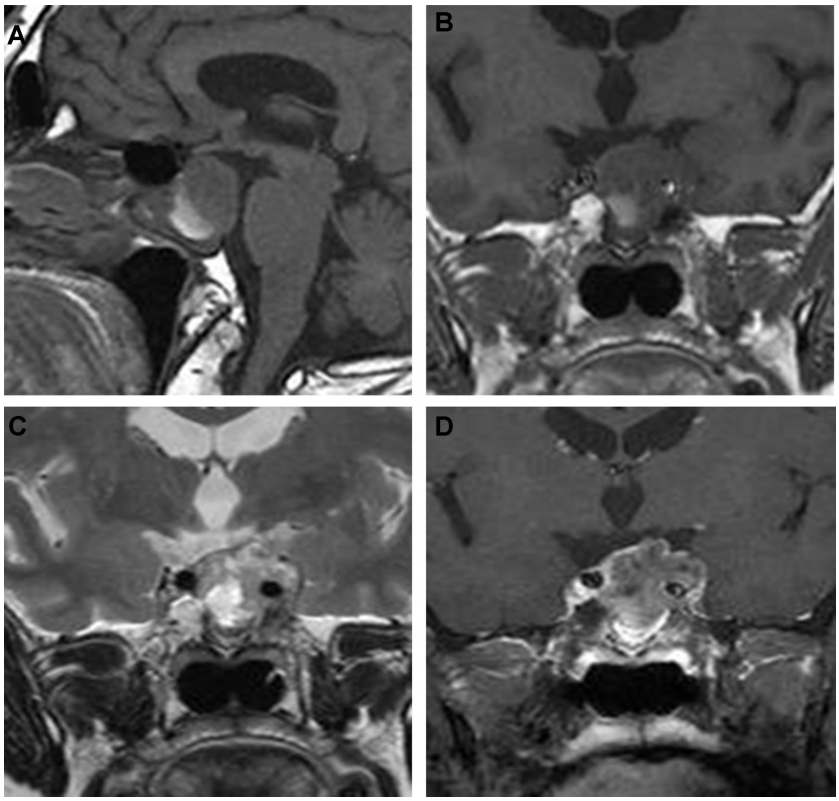

FIGURE 1. **A**, *Precontrast sagittal MRI T1WI;* **B**, *coronal T1WI;* **C**, *coronal T2WI;* **D**, *enhanced coronal T1WI show a pituitary macro-mass with suprasellar extension, invasion of the left cavernous, and apoplexy at the bottom.*

Pituitary function testing showed elevation of serum PRL level >200 ng/mL and hypopituitarism. He was diagnosed with prolactinoma, for which bromocriptine was administered. However, he experienced repeated vomiting after the use of bromocriptine. Then, the patient was transferred to our hospital. He was a heavy smoker and found to have asymptomatic lung masses 2 yr ago in a routine physical examination, for which fine-needle aspiration biopsy was performed; however, diagnosis of malignancy was not supported. Pulmonary auscultation showed enhanced respiratory sounds in the lower lobes of both lungs, and abdominal and neurological examinations were unremarkable. Ophthalmological examination demonstrated left oculomotor nerve palsy and left sixth cranial nerve palsy. Pituitary magnetic resonance imaging (MRI) revealed a 2.9 × 2.8 × 2.3 cm sellar mass. The tumor invaded the left cavernous sinus and encased the internal carotid artery. The tumor also extended into the suprasellar cistern. Precontrast T1-weighted images (T1WI) demonstrated an isointense signal intensity tumor with high signal in the bottom and inhomogeneous medium high signal on T2-weighted images (T2WI; Figure 1). Contrast-enhanced MRI showed inhomogeneous enhancement. Thoracic computer tomography confirmed masses in the 2 lungs. Hormone level testing showed corticotroph, gonadotroph, and thyrotroph cell insufficiency, while thyroid and growth hormone levels were within the normal range (Table 1). Serum PRL was elevated up to 1022 ng/mL (reference value < 20 ng/mL). Based on his clinical presentation and hormone profiling, the patient was diagnosed with pituitary apoplexy with hypopituitarism due to prolactinoma or a metastatic lesion. The patient underwent subtotal tumor removal via endoscopic transsphenoidal surgery. Macroscopic examination showed that the tumor was pulpy and hemorrhagic with rich vascularization, infiltrated the sella turcica, and adhered to the left internal carotid artery, suggesting a malignant nature.

Pathological examination (Figure 2) showed a malignant lung adenocarcinoma with a generally adenoid pattern infiltrating the pituitary parenchyma. The neoplastic cells were heavy irregular-shaped with hyperchromatic nucleus. The immune-phenotype of the tumor was Napsin A, TTF-1 and Cytokeratin 7 positive. Immunohistochemical analysis for PRL showed positive results in glandular cells, except for other pituitary hormones (growth hormone, ACTH, TSH, FSH, and LH). Furthermore, dopamine receptor D5 (DRD5) staining was strongly positive, but dopamine receptor D2 (DRD2) was negative. Western

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TABLE 1. Basal Endocrinological Evaluation

Hormone	Level measured (preoperation)	Level measured (postoperation)	Normal levels
T3	1.19 nmol/l	1.20 nmol/l	0.89-2.44 nmol/l
T4	72.67 nmol/l	72.68 nmol/l	62.67-150.84 nmol/l
TSH	0.0345 mIU/l	0.0346 mIU/l	0.35-4.94 mIU/l
FSH	2.11 mIU/ml	4.15 mIU/ml	2.6-16.7 mIU/ml
LH	0.39 mIU/ml	1.26 mIU/ml	1.8-11.8 mIU/ml
Testosterone	<.08 ng/ml	0.33 ng/ml	2.7-10.7 ng/ml
ACTH	2.43 pg/ml	64.44 pg/ml	7.0-65.0 pg/ml
Cortisol	1.38 μg/dl	>60 μg/dl	6.7-22.6 μg/dl
GH	0.561 ng/ml	0.278 ng/ml	<0.97 ng/ml
IGF-I	209 ng/ml	153 ng/ml	69-200 ng/ml
PRL	1022 ng/ml	716 ng/ml	<20 ng/ml

blotting (Figure 3) identified strong PRL signal in the metastatic tissue. In addition, WES confirmed somatic mutations in KRAS, PIK3CA, ALK, EPHA3, RRM1, SMO, CTNNB1, ITK, KTN1, KMT2D, NACA, OLIG2, PTPRD, and BAP1 (Table 2).

The PRL level remained high at 716 ng/mL postoperatively (Table 1). The symptom of headache was relieved, but ptosis of the left eye persisted. The patient refused an additional fine-needle aspiration biopsy and accepted to undergo radiotherapy on the outpatient basis after discharge. He was suggested to take cabergoline, cisplatin, and paclitaxel for chemotherapy. The patient died of deterioration of the lung disease 3 mo after the initial diagnosis due to deterioration of the lung disease. The family refused to do an autopsy. The patient agreed before his death to publication of the case report.

DISCUSSION

Pituitary metastases (PMs) are infrequent clinical problems. In autopsy case series, these metastases were revealed in about 5% patients with widely disseminated disease.[1] In surgical case series, PMs were detected in less than 1% patients with sellar or parasellar tumors.[1,4] It was reported that lung cancer was the second most common frequent primary tumor of PMs, following breast cancer.[1]

It is generally believed that a combination of a radiology-identified sellar mass and a serum PRL level above 200 ng/mL establishes the diagnosis of prolactinoma with an almost 100% certainty.[5] However, hyperprolactinemia (HPRL) is not always due to prolactinoma and other causes like pituitary stalk compression should also be considered.[6] The highest PRL level due to stalk compression was 662 ng/mL as reported in a case of nonfunctioning pituitary adenoma.[7] Komninos et al[1] reported an interesting case about pituitary mass with the PRL level rising to 438.6 ng/mL; however, it was finally confirmed as a metastatic hepatocellular carcinoma, in which pituitary stalk compression was the most likely explanation for HPRL. Gernez-Lestradet et al[8] encountered a similar diagnostic dilemma in a patient with an occult lung cancer whose PRL level was as high as 500 ng/mL. Nevertheless, the infiltration of a preexisting prolactinoma by metastatic deposits may also occur, three of cases in the literature showed the tumor-to-prolactinoma metastasis with PRL level exceeding 200 ng/mL. However, metastatic tumors themselves do not produce PRL.[9-11] In our case, the massive and symptomatic HPRL was strongly suggestive of a prolactinoma. However, the tumor was diagnosed as a metastatic lung adenocarcinoma that hardly produced PRL. Thus, the cause of HPRL is production of PRL by a malignant cancer mimicking a prolactinoma, which has not been reported previously in the literature.

Although studies have demonstrated that several extrapituitary tissues and peripheral organs can synthetize and secrete PRL, PRL production by a solid extrapituitary tumor is rare.[12,13] In our study, WES was performed and the WES analysis bolsters the argument that the tumor was a metastatic adenocarcinoma rather than a de novo pituitary adenoma that secreted PRL. PRL up-regulation was associated with none of these genes, except for CTNNB1, as reported in the literature.[14] The mutation site of β-catenin^{N387K} is located in the fifth armadillo repeat domain binding to APC, which is required for β-catenin phosphorylation and degradation via the ubiquitin-proteasome pathway.[15,16] It is therefore hypothesized that aberrantly activated β-catenin modulate PRL transcription.

Knowing that PMs are intricate and complex with a high mortality[17] and PRL expression is significantly associated with poorer overall survival,[18,19] it would be best to develop a comprehensive strategy that can both control the local tumor and cure the systemic disease. Although the surgical eradication of the pituitary lesion may not significantly benefit the overall survival, it could be used for relief of the visual deficit, ophthalmoplegia, and pain.[1] Conventional radiotherapy and gamma knife stereotactic radiosurgery have also been utilized for symptom relief and local tumor control for patients who are not surgical candidates, or as a postoperative adjuvant therapy.[17] Standard cytotoxic chemotherapy is indicated for multiple-organ involvement.[20] Considering our previous study, cabergoline could be used to

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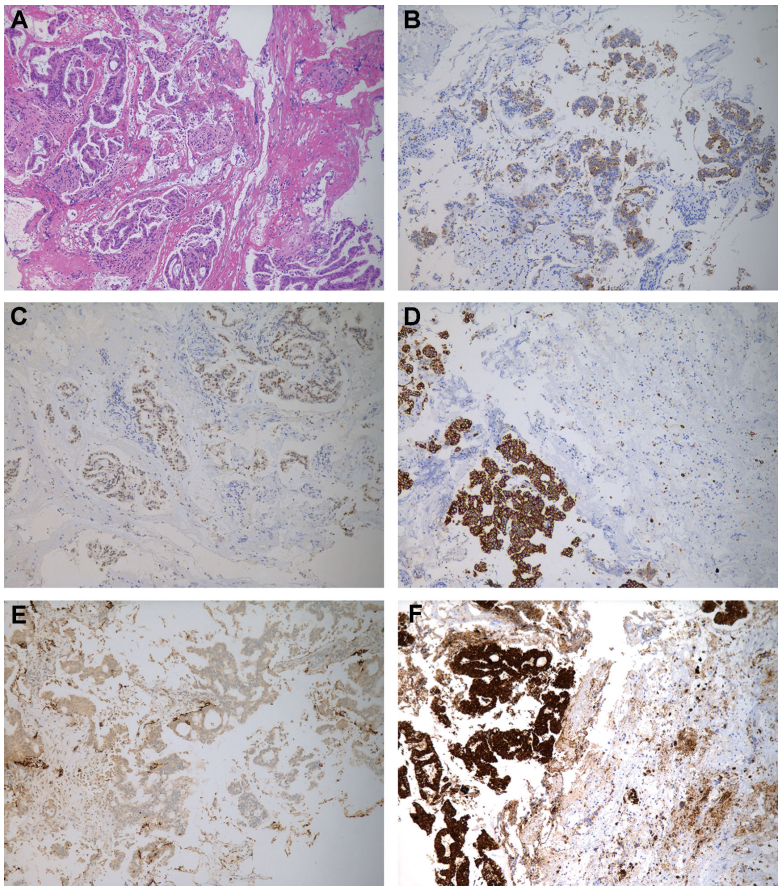

FIGURE 2. *Histopathology of lung adenocarcinoma metastasizing to the pituitary.* **A**, *Hematoxylin-eosin staining staining shows a generally adenoid pattern infiltrating the pituitary parenchyma containing irregularly shaped cells with hyperchromatic nuclei.* **B-D**, *The tumor is positive for Napsin A, TTF-1, and Cytokeratin 7, consistent with lung adenocarcinoma.* **E**, *In addition, it is positive for PRL, and* **F**, *strongly immune reactive for DRD5. Magnification, ×50.*

control cancer progression and HPRL by DRD5 activation, knowing that the tumor highly expresses DRD5 rather DRD2 in such cases.[21] Given the activating mutations of KRAS and PIK3CA, the use of everolimus could be considered, and crizotinib is also recommended in the case of ALK mutation.[22]

CONCLUSION

In conclusion, this is the first case of PRL-producing lung cancer metastasizing to the pituitary mimicking a prolactinoma. Extrapituitary PRL expression is likely driven by distinct gene mutation. Given the poor prognosis, a comprehensive strategy is required to control tumor progression.

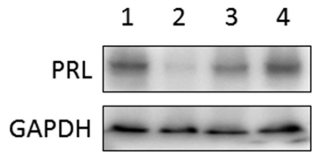

FIGURE 3. *Western blotting. A strong PRL signal is identified in the metastatic lung adenocarcinoma tissue from the patient (lane 1), and there is no PRL signal in the control sample from lung adenocarcinoma (lane 2). PRL is also identified in 2 known PRL-secreting pituitary tumors (lane 3 and 4). GAPDH, glyceraldehyde 3-phosphate dehydrogenase (lower panel).*

Disclosures

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TABLE 2. Mutations Identified With WES

Gene	Location	Mutation type	Ref→Seq	Blood variant frequency	Tumor variant frequency	Coding	Amino acid change	PhyloP[a]	SIFT [b]	PPhen-2[c]	COSMIC
KRAS	chr12:25398284	SNV	G→A	0%	27.05%	c.G35A	p.G12D	2.668	0	0.517	COSM521
EPHA3	chr3:89462289	Deletion	2A→T	0%	22.93%	c.1763-1763del		2.276			
RRM1	chr11:4142879	SNV	A→T	0%	32.27%	c.A922T	p.I308F	2.03	0	0.996	
PIK3CA	chr3:178952085	SNV	A→T	0%	24.35%	c.A3140T	p.H1047L	2.333	1	0.01	COSM776
CTNNB1	chr3:41274911	SNV	T→G	1.02%	25.42%	c.T1161G	p.N387K	0.227	0.06	1	
ALK	chr2:29416544	SNV	C→T	0%	23.24%	c.C4409T	p.A1470V	1.274	0.14	0.958	COSM721284
SMO	chr7:128851999	SNV	C→A	0%	25.96%	c.C2071A	p.L691I	2.428	0.42	0.244	
ITK	chr5:156671294	SNV	G→C	0%	24.88%	c.G1255C	p.V419L	2.835	0	0.995	
KTN1	chr14:56146374	SNV	C→T	0%	26.07%	c.C3869T	p.T1290I	1.528	0	0.169	
KMT2D	chr12:49443732	SNV	G→T	0%	28.11%	c.G3639T	p.Q1213H	0.714	0	0.029	
NACA	chr12:57114742	SNV	T→G	0%	12.12%	c.T572G	p.V191G	-0.736	0	0.816	
OLIG2	chr21:34399480	SNV	C→A	0%	22.50%	c.C310A	p.P104T	1.626	0.39	0.668	
PTPRD	chr9:8470997	SNV	G→A	0%	2.14%	c.G2269A	p.E757K	2.711		0.995	
BAP1	chr3:52441252	SNV	A→G	0%	3.29%	c.A518G	p.Y173C	2.323	0	1	

[a] PhyloP score: positive scores—measure conservation, which is slower evolution than expected, at sites that are predicted to be conserved; negative scores—measure acceleration, which is faster evolution than expected, at sites that are predicted to be fast-evolving

[b] SIFT score: 0.0-0.05—deleterious; 0.05-1.0—tolerated

[c] PolyPhen-2 score: 0.0-0.15—variants with scores in this range are predicted to be benign; 0.15-1.0—variants with scores in this range are possibly damaging; 0.85-1.0—variants with scores in this range are more confidently predicted to be damaging

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COMMENTS

Hyperprolactinemia may occur in a variety of physiological or pathological conditions. For neurosurgeons, it is commonly encountered in the setting of a prolactin-secreting pituitary adenoma or as a result of compression of the pituitary stalk from a non-secreting pituitary neoplasm. However, it may also occur in an array of other states and a careful workup is always prudent. For example, elevated serum prolactin levels may occur due to administration of dopamine-antagonists such as certain neuroleptic, anti-psychotic, or anti-depressant medications. Hyperprolactinomia is also reported as a paraneoplastic syndrome related to a variety of hematological or organ-specific malignancies or as a component of complex syndromes such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal proliferative disorders, and skin changes).[1-3] Separately, metastatic involvement of the pituitary gland is also well described.[4,5]

In this anecdote, the authors report the first case of a prolactin-secreting lung adenocarcinoma that metastasized to the pituitary gland. Convincing pathological analysis bolsters the case that this was truly a prolactin-secreting lung adenocarcinoma that metastasized to the pituitary gland rather than an undiagnosed primary prolactin-secreting pituitary neoplasm. The patient was a heavy smoker who presented with subclinical apoplexy, hyperprolactinomia (prolactin level 1022 ng/dl), and a sellar mass. A subtotal, endoscopic transphenoidal resection of the invasive pituitary neoplasm was performed; the histopathology and immunohistochemistry clinched the diagnosis (Prolactin & Dopamine D5 receptor positive/TTF-1 & CK-7 positive). However, the authors supplemented this with a whole exome sequence analysis and both the sella and lung tumors had identical genetic profiles.

Although this is a single case report, it is compelling and an excellent paradigm of the constructive triangulation of various modalities of modern neuropathology. The World Health Organization (WHO) recognizes this and issued an updated classification of brain tumors based on their molecular signatures. It is hence logical that the same investigative capacity will be extended to the identification of metastatic tumors that betray the same genetic proclivities as their parent tumor. One constraint is cost-whole exome sequencing is expensive and it is unlikely that most centers will be able to subject their tissue specimens to an analysis as detailed as described in this manuscript. Nonetheless, this reinforces the need to complement traditional histopathology with molecular genetic analysis for select pituitary tumors as that may affect the management of the patient.

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Autonomous prolactin secretion by tumors that are not composed of lactotroph cells is truly rare. Such isolated cases include patients with gonadoblastoma, ovarian teratoma harboring pituitary tissue, bronchogenic carcinoma, and renal cell carcinoma. The present case is even more unusual in the sense that it describes a patient with lung adenocarcinoma metastatic to the sella, which expressed prolactin and led to substantial hyperprolactinemia. The case report is well documented and expands the differential diagnosis of hyperprolactinemia. Future studies are needed to elucidate whether prolactin expression has any influence on prognosis in these patients.

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