Case Report

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Tumor-to-tumor metastasis: lung adenocarcinoma into a clinically non-functioning gonadotroph pituitary adenoma: A rare case

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Abstract

We report a rare case of a metastatic lung adenocarcinoma to a clinically non-functioning pituitary gonadotroph adenoma in a 66-year-old male experiencing progressive headaches and diminished vision. Magnetic resonance imaging revealed a large tumor containing cystic cavity and acute hemorrhagic areas in the sella turcica and extending into the suprasellar cistern. Pathologic examination was consistent with a metastasizing lung adenocarcinoma to a clinically non-functioning pituitary adenoma. Immunohistochemistry revealed both pituitary adenoma and metastatic adenocarcinoma containing FSH and LH immunoreactive cells in the pituitary adenoma whereas napsin A, TTF-1, cytokeratin7, Pancytokeratin and galectin-3 immunopositivity were evidenced by adenocarcinoma cells within sinusoids and around blood vessels. The patient underwent a transthoracic fine needle biopsy that was positive for adenocarcinoma (Napsin-A positive, p63 negative). It was therefore concluded that the primary site for the sellar metastasis was in the lung. Primary metastasis to pituitary gland is rare with the most common primary sites include lung, breast, kidney and the gastrointestinal tract. Although rare, any case with progressive local pressure symptoms and endocrinologic stigmata with or without other signs of malignancy requires further examination to rule out pituitary metastasis.

Keywords: FSH/LH cell adenoma, gonadotroph cell adenoma, immunohistochemistry, metastatic lung adenocarcinoma, pathology, tumor-to-tumor metastasis

INTRODUCTION

Metastases to the pituitary have been previously reported in the literature (1). Pituitary metastases occur more frequently in patients with widespread cancer and mainly involve the posterior lobe. As indicated in the literature pituitary gland but some tumors originating from the nervous system have been affected by various metastasizing malignant tumors. To date, 23 cases of metastatic carcinoma to a pituitary adenoma (PA) have been reported. Pituitary metastases can be the cause of a rapid enlargement of the gland associated with local pressure effects on adjacent tissues giving rise to related symptoms.

Herein, we present the morphologic and immunohistochemical findings of a metastatic adenocarcinoma to a clinically non-functioning gonadotroph cell (FSH/LH) PA. The review of the literature is also discussed and compared to our case to provide the opportunity to shed light on pathologic differential diagnosis including primary and metastatic pituitary tumors.

CASE PRESENTATION

A 66-year-old Caucasian male presented with progressive headache and gradual loss of vision for the last 2 weeks was admitted to the Neurosurgery outpatient clinic. His past medical history revealed no remarkable health issues. His chest x-ray demonstrated a pulmonary mass in his right lower lobe. An endo-bronchial ultrasound assisted fine needle aspiration biopsy was interpreted as non-small cell lung carcinoma (NSCLC). Immunohistochemical analysis of the biopsy revealed p40 negative and napsin-A positive cells mostly likely supporting lung adenocar-

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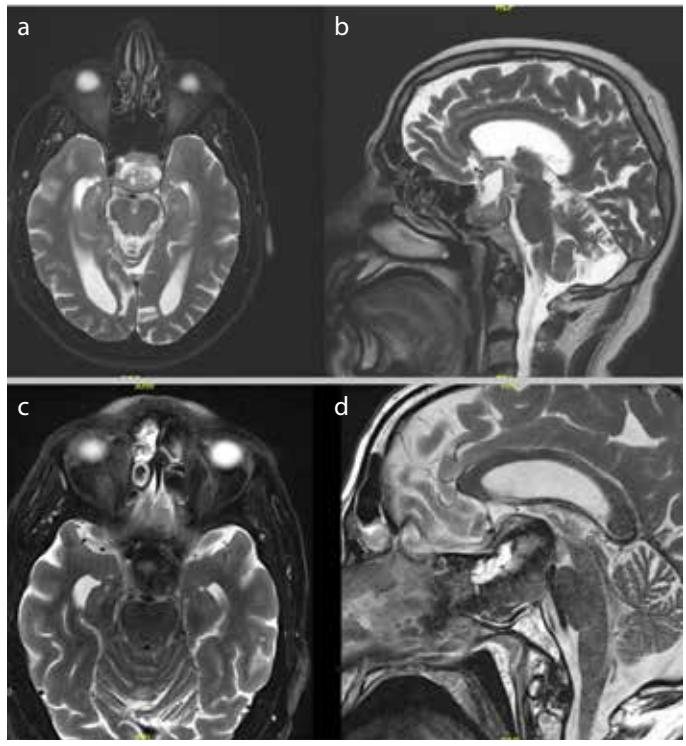
Table 1. Initial hormonal evaluation

Hormone (unit)	Preoperative	Postoperative	Reference
GH (ng/mL)	0.078	0.067	0.05-3.00
PRL, direct (mg/mL)	5.9	6.2	4.0-15.2
ACTH (pg/mL)	1	1	7-69
Cortisol (mg/dL)	9	8,9	7 -25
TSH (uIU/mL)	0.45	0,48	0.27 – 4.27
t3 (ng/dL)	63	68	8- 200
t4 free (ng/dL)	1.06	1.00	0.6 – 1.7
IGF-1 (mg/dL)	41.2	43	69 – 200
Testosterone, total (ng/dL)	27.3	25.1	280 – 800
FSH (mIU/mL)	9.6	10.2	1.5 – 12.4
HbA1c (%)	6.0%	5.9	4-5.7
Creatinine, serum (mg/dL)	1	1	0.8-1.3
Mean glucose level (mg/dL)	125.5	131	70-110

ACTH: adrenocorticotropic hormone; Cortisol: cortisol; Creatinine, serum: serum creatinine; FSH: follicle stimulating hormone; GH: growth hormone; HbA1c: Hemoglobin A1c; IGF-1: somatomedin C; Mean glucose level: blood sugar; Prolactin, direct: prolactin; T+: Thyroxin (sT4), free; T3: triiodothyronine; Testosterone, total: testosterone; TSH: thyroid stimulating hormone

Figure 1. a-d. Preoperative and postoperative MRI scans. Preoperative MR (axial) showed tumor filling inside the sella extends suprasellar cistern (a). Diameters of the tumor (sagittal) are 26x29x40 mm (b). Pituitary macroadenoma shows bleeding areas. Signal characteristics are consistent with acute bleeding. Postoperative MR scans (axial) (c), (sagittal) (d) revealed empty tumor bed filled with fat tissue and hemostatic agents bearing a relatively small hematoma.



cinoma while immunohistochemical analysis of the pituitary hormones failed to reveal any abnormalities.

Radiologic Findings

Magnetic resonance imaging (MRI) demonstrated a large tumor, 26x29x40 mm in dimension containing cystic cavity and acute hemorrhagic areas, hyperintense small areas on T2-weighted images involving the sella turcica and extending to the suprasellar cistern (Figure 1a, b). Pre-operative and post-operative serologic endocrine markers showed no remarkable difference; only testosterone and ACTH levels were below normal limits. Blood analysis consisting of creatinine, glucose and HbA1C were within normal range (Table 1).

Intraoperative and Postoperative Findings and Clinical Course

During surgery, a dilated sella turcica was identified. Intra-operative inspection revealed a suprasellar mass enlarging the sella and invading the suprasellar cistern. The soft gray mass contained scattered necrotic cystic foci and hemorrhagic foci. Intra-operative pathology consultation was consistent with a malignant tumor. At that time, evidence of origin was unknown. Post-operative MRI revealed an empty tumor lodge filled with fat tissue and hemostatic agents containing trace amounts of blood (Figure 1c, d). The post-operative period was uneventful. No evidence of electrolyte imbalance or hormonal changes were indicated, and the patient's vision remained the same as before surgery. Post-operative treatment for metastatic lung carcinoma accompanied by metastasizing deposits to pituitary adenoma was determined. The treatment included multi-modal chemoradiotherapy, consisting of pemetrekset disodium (Alimta) 500 mg/m^2, Carboplatin AUC 6 and bevazisumab (Altuzan) 15 mg/kg. After the chemotherapy program, local radiotherapy was initiated. At the time of this report, 3 months following initial diagnosis of the metastasis, he was alive and without any significant morbidity.

Histopathological Findings

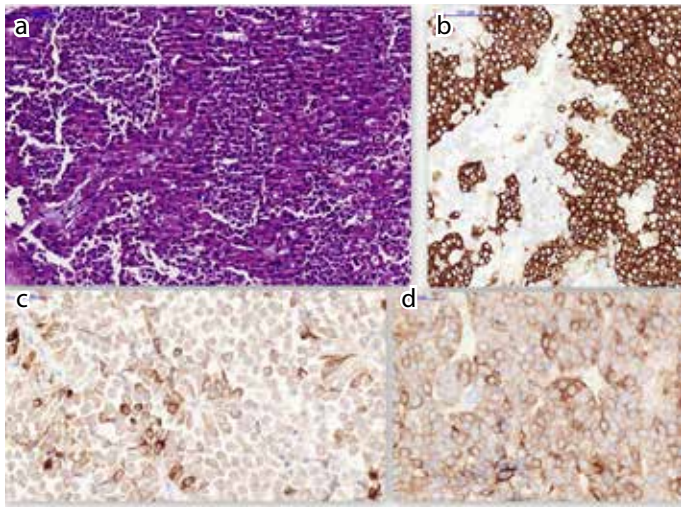
By light microscopy, sections from the surgically resected formalin-fixed paraffin-embedded (FFPE) tissue revealed an admixture of two characteristic neoplasms. The adenomatous component of this double tumor was formed by monotonous cells with acidophilic cytoplasms divided by fibrovascular septa forming micronodules (Figure 2a) Under low power magnification a few hardly visible malignant cells surrounded capillary framework and sinusoids of PA. Careful examination under high power magnification revealed infiltrating adenocarcinoma cells showing nuclear pleomorphism, abundant granular cytoplasm with individual necrosis and apoptotic

Table 2. Summary of immunohistochemical panel in the adenocarcinoma and null cell pituitary adenoma

Antibody	Source	Reactivity of pituitary adenoma	Reactivity of adenocarcinoma
Napsin A	Cellmarque (poly)	-	+++
CK7	Biocare medical (ov-tl 12/30)]	-	++++
CHR	Scytek (5h7)	+++	-
TTF-1	Biocare (8g7g3/1)		++++
GFAP	Leica (ga5)	-	-
SYN	Biocare (27612)	++++	-
MGMT	Novus (mt 23,2)	Methylated: 100%	Methylated: 100%
S-100	Scytek (4c4.9)	-	-
PanCK	Scytek (5d3lp34)	++	++++
Gal-3	Cellmarque (9c4)	+	++++
GH	Genetex (b125,1)	-	-
PRL	Genetex (b109.1)	-	-
ACTH	Genetex (polyclonal)	-	-
LH	Genetex (3 6)	+++	-
FSH	Genetex (polyclonal)	+++	-
TSH	Genetex (qb2/6)	-	-
Ki-67	DAKO (MIB-1)	2%	46%
P53	Scytek (do/7)	-	+++

ACTH: adrenocorticotrope; CHR: chromogranin; CK7: cytokeratin 7; FSH: follicle stimulating hormone; Galectin-3: galectin-3; GFAP: glial fibrillary acidic protein; GH: growth hormone; Ki-67: nuclear antigen; LH: luteinizing hormone; MGMT: methylated guanine methyl thyronine; Napsin A: P53: tumor suppressor gene protein; PanCK (5/6/8/18): pancytokeratin (cocktail of 5, 6, 15, 16, 18); PRL: prolactin; S-100: calcium binding protein; SYN: synaptophysin; TS: thyroid stimulating hormone; TTF-1: thyroid transcription factor
Intensity: +: 0-25%; ++: 25-50%; +++: 50-75%; ++++: >75%

Figure 2. a-d. Hematoxylin-eosin of coexisting tumors and immunohistochemical properties of pituitary adenoma. Lower magnification the admixture of two distinctive neoplasms: pituitary adenoma and adenocarcinoma (H&E, x40, original magnification) (a). Synaptophysin positive pituitary adenoma cells were clearly distinguished from metastatic cells with pleomorphic nuclei nonreactive with synaptophysin (upper right) (b). (Synaptophysin, x40 original magnification). Adenoma cells were FSH positive (FSH, x40 original magnification) (c). Adenoma cells with LH were forming diffuse clusters. (LH, x40 original magnification) (d).



bodies. In some areas metastatic non-cohesive cells were filling sinusoids mimicking that they might easily be interpreted as atypical indigenous cells of a primary pituitary pathology, e.g. atypical adenoma.

Immunohistochemical Analysis

For the IHC analysis of the resected tumor, two sets of wide spectrum immunostaining panels for PA and metastatic neoplasms were selected for distinguishing metastatic cells from indigenous PA. Immunohistochemical batteries targeted for pituitary markers and metastatic panel were used. The IHC panel for PA was comprised of neuroendocrine biomarkers including growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and S-100 protein, Glial Acidic Fibrillary Protein (GFAP) for folliculostellate cells, Synaptophysin (SYN), S-100 protein, O-6-methylguanine-DNA methyltransferase (MGMT), galectin-3, and Ki-67/MIB-1 for cell proliferative index and tumor suppressor protein p53. The PA was SYN positive. Acini forming pituitary adenoma cells with delicate fibrovascular septa were immunoreactive for FSH (Figure 2c) and LH (Figure 2d) whereas remaining endocrine markers were non-reactive. Most of the non-functioning,

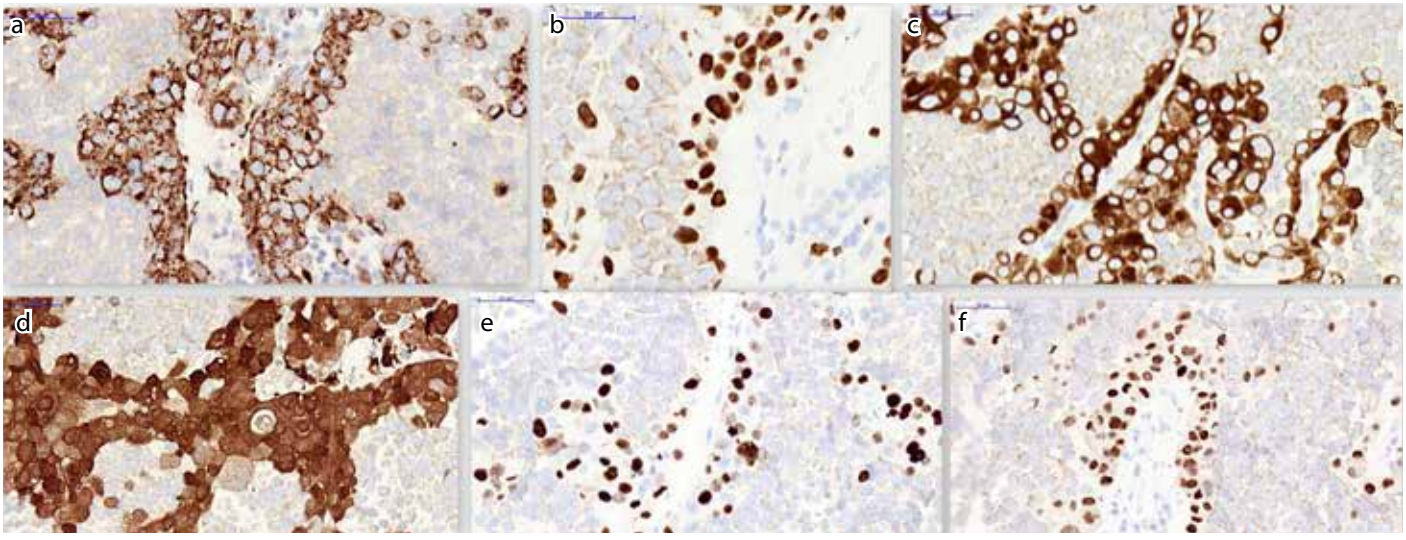
Table 3. Summary of reported cases of metastases to pituitary adenoma (in chronological order)

Case No	Year	Age/Gender	Presentation	Source of Metastasis	Adenoma–Hormone Secreting
1	1971	70/F	Severe headache, left hemiparesis	Breast adenocarcinoma	Unknown
2	1971	73/F	Vision loss	Breast adenocarcinoma	No
3	1973	78/M	Fever, nausea, dehydration, diarrhea	Renal pelvis and ureter transitional cell carcinoma	No
4	1984	75/M	Visual field deficit, bitemporal hemianopsia	Renal cell carcinoma	Yes: PRL
5	1985	71/M	Decreased visual acuity, incomplete bitemporal hemianopsia	Lung small cell carcinoma	Unknown
6	1985	66/F	Headache, nausea, somnolence, sudden blindness left eye	Gastroesophageal adenocarcinoma	Yes: PRL
7	1987	56/F	Headache, double vision, bilateral CVI nerve palsies	Breast adenocarcinoma	No: studies not performed
8	1988	67/M	Incidental finding at autopsy	Prostate adenocarcinoma	Unknown
9	1988	50/F	Exophthalmia, obesity	Pancreatic poorly differentiated endocrine carcinoma	Yes: ACTH
10	1988	61/F	Decreased visual acuity, bitemporal hemianopsia	Unknown	Unknown
11	1988	77/M	Headache, total anopsia, complete ophthalmoplegia	Lung carcinoma	No
12	1992	76/M	Decreased visual acuity, bitemporal hemianopsia 13superior quadrantanopsia	Adenocarcinoma of unknown origin	Yes: GH
13	1997	46/F	Blurred vision, headache, bitemporal hemianopsia	Anterior mediastinal malignant carcinoid	Yes: PRL
14	1999	42/F	Secondary amenorrhea, galactorrhoea (6 months' duration)	Lung adenocarcinoma	Yes: PRL
15	2001	60/M	Progressive blurred vision, incomplete homonymous hemianopsia	Presumed colorectal adenocarcinoma	No
16	2001	75/ F	Bilateral visual decline	Breast (3y)	Yes: FSH/LH PA
17	2001	87/M	Bilateral visual decline, optical atrophy	Unknown	Yes: FSH/LH PA
18	2003	62/ F	Headache, visual loss (4m)	Kidney (4y)	No: non-functioning PA
19	2006	44/ F	Bitemporal anopsia	Lung (7y) (GHRH producing atypical carcinoid)	Yes: GH cell hyperplasia/ PA
20	2009	71/M	Loss of vision, CIII palsy (2w)	Lung (6 mo)(small cell carcinoma)	No: non-functioning PA
21	2012	55/F	Leg pain	Unknown (neuroendocrine carcinoma)	Yes: GH PA
22	2013	66/M	Headache	Lung (Autopsy) (non- small cell carcinoma)	Yes: PRL PA
23	2014	76 /F	Diplopia, progressive vision loss, ptosis	Clear cell Renal cell carcinoma	Yes: FSH/LH PA
24	2016	66/M	Progressive headache, bilateral visual decline	Lung adenocarcinoma	Yes: FSH/LH PA

ACTH: adrenocorticotropic hormone; FSH/LH: follicle stimulating hormone/luteinizing hormone; GH: growth hormone; PA: pituitary adenoma

non-hormone producing PA considered to belong to the family of FSH/LH/alpha-subunit tumors, i.e. gonadotroph cell adenoma. This case was tested immunopositive for FSH/LH consistent with gonadotroph cell adenoma. Furthermore, the carcinoma cells were Pancytokeratin, CK7, galectin-3, TTF-1 and napsin-A immunopositive. Although adenocarcinoma cells were barely visible by H&E, but their immunopositivity with napsin-A (Figure 3a). TTF-1 (Figure 3b) Pancytokeratin, CK7 (Figure 3c), and galectin-3 (Figure 3d) deciphered their presence. The remaining antibodies were negative. MIB-1 labeling index was calculated as 2% for the PA and 48% (Figure 3e) for the carcinoma whereas p53 nuclear protein was focal and mildly reactive in the PA and positive in carcinoma cells (Figure 3f) In both tissues MGMT reactivity was intensely positive. Tissue for ultrastructural study was not available (Table 2).

Figure 3. a-f. Immunohistochemical staining properties of metastasizing adenocarcinoma. Adenocarcinoma cell reacting with napsin-A (napsin-A, x40 original magnification) (a). Adenocarcinoma cells reacting with TTF-1. (TTF-1, x40 original magnification) (b). Adenocarcinoma cells reacting diffusely with CK7. (CK7 x40 original magnification) (c). Galectin-3 positive cells of adenocarcinoma. (Galectin-3, x40 original magnification) (d). MIB-1 LI 48% in adenocarcinoma (MIB-1, x40 original magnification) (e). Intense and diffuse p53 reactivity in adenocarcinoma cells (p53, x40 original magnification) (f).



DISCUSSION

Tumors metastasizing to the pituitary are extremely rare (2). As evidenced in the literature 1 to 3.6% of patients with malignant tumors, pituitary metastasis does occur (3). This group represents between 0.14 and 28.1% of the brain metastasis cases (4). In an earlier study, researchers found an incidence rate of metastatic disease to the pituitary gland of 1% (18 out of 1,857) autopsy cancer cases reviewed (1). Relative frequency of metastatic tumors among 18 cases, in decreasing frequency, were breast (n=7) and lung (n= 5) (1).

To date, 23 cases of carcinoma giving rise to metastasis to PA have been reported (5) (Table 3). Data analyzed within the last four decades (1971-2016) has shown that the primary organs that gave rise to metastatic tumors were: lung, breast, kidney gastrointestinal tract, and prostate (Table 3). Of these 23 reported cases, 17 presented with visual problems which included visual loss, visual field deficit, bitemporal hemianopsia, anopsia, double vision, exophthalmus, or sudden blindness, while only 7 presented with headache. Most of the patients were admitted due to symptoms related to local pressure effects of PA. Of 12 cases with functioning PA out of those who displayed metastasis by various malignant neoplasms, 3 were secreting GH, 5 were PRL , 1 case was ACTH and 3 other cases FSH/LH (6-11). Of the 23 PA six were non-functioning pituitary neoplasms unaccompanied by any endocrinologic manifestations (12) (Table 3).

Bret et al. examined two cases where visceral cancers metastasized to pituitary adenomas which were diagnosed as gonadotroph cell adenomas (11). In various adenocarcinoma types indicate cellular configurations, patterns and immunoprofiles differ, depending from which organ they originate. Individual immunohistochemical batteries are critical to distinguish them. Preferred immunostains include CK7 and mammoglobin, GCDFP 15, ER, PR, Her2 for breast, EMA, TTF-1, napsin-A, CK7 for lung non-small cell carcinoma, TTF-1, CK7, chromogranin, synaptophysin, CD56 for NSCLC, CK20 and CDX2 for colon, vimentin and CD10, RCC for renal and PSA and PAP for prostate carcinoma (4).

Although CK7 is recommended for differential diagnosis of metastatic lesions, recent research has documented dispersed CK7 positive anterior pituitary cells, of which include dendritic processes. CK7 immunoreactive cells often displayed a dendritic-type morphology within macroadenomas. These cells contain cytoplasmic extensions resembling folliculostellate cells found in the anterior pituitary may look like a metastatic lesion. Therefore, the distribution pattern of CK7 positive cells is important since a diffuse pattern will most likely favor a metastatic neoplasm (13). No adenomas were ever found to have diffuse, strong CK7 immunoreactivity. In this case, scattered CK positive cells amongst adenoma cells did not possess dendritic extensions. As a result, these discreet cells should most likely be considered as individual cancer cells rather than indigenous sporadic CK7+ cellular component.

Our case is an example of tumor-to-tumor metastasis as documented in various reports in which different visceral organs and nervous system receiving metastases (14). The suggestive mechanisms underlying tumor-to-tumor metastasis have been explained either mechanistic angiogenic variables or due to biological infrastructure of recipient organ that eases metastatic cells to be deposited in an appropriate microenvi-

ronment ("seed and soil"). Former theory proposes rich vascular framework of PA receives its blood directly from systemic vascular system. Consequently, this microvascular configuration authenticates bypassing of cancer cells and reaching the fertile soil, i.e. PA (15). The latter theory presumes high expression of angiogenic factors (CD31, VEFG, VEGF1) by some tumor types incapacitating interaction between stromal cells and vascular endothelium to promote proliferation of extraneous metastasizing malignant cells (16).

Data from publications confirms that the majority of non-functioning PA with metastatic deposits are gonadotroph adenomas (FSH/LH), prolactinomas, somatotropinomas, or corticotropinomas (7, 8, 10, 11, 16). The majority of sellar masses have either local pressure symptomatology, and/or endocrine changes. Thus, the distinction of underlying pathology directs treatment and prognosis. Patients with pituitary metastasis have poor prognosis. Previous studies reported that patients with sellar metastasis died within a few weeks to 15 months after surgical intervention. Most of these cases were accompanied by widespread metastases (6, 9, 10, 16). In addition to analysis of morphologic features, influence of specific IHC techniques bear an important role in diagnostic surgical pathology.

Galectin-3 is a multifunctional protein which has been implicated in regulation of cell growth, cell adhesion, cell proliferation, angiogenesis, apoptosis and metastasis (17). It is found in the nuclear, cytoplasmic membranes and extracellular matrix. The major component, lectin performs an anti-apoptotic function and is expressed in many carcinomas, including NSCLC, adenomas, lymphomas and soft tissue tumors. In pituitary neoplasms, galectin-3 is expressed only in prolactinomas and corticotropinomas, with all remaining histotypes being immunonegative. Galectin-3 was also higher in ACTH and PRL cell carcinomas. As in this case, other than a few scattered cells of the PA, the carcinomatous component consisted of galectin-3 immunoreactive tumor cells. The relevant question remained whether the tumor was an ACTH or PRL- cell pituitary carcinoma with galectin-3 reacting cells or a metastatic tumor with diffusely reacting galectin-3. Almost all galectin-3 immunopositive malignant cells around capillaries reacted with napsin-A, TTF-1, CK7 and had a high MIB-1 labeling index. These combined features of the malignant cells favored rather an adenocarcinoma expressing intense galectin-3. Patients with NSCLC and those which express galectin-3 were documented as following a progressive clinical course (17). Other studies validate that increased expression of galectin family members, could correlate with elevated invasiveness. One study demonstrated that in 37 colon cancer patients, galectin-3 expression was significantly higher in patients with metastatic deposits in lymph nodes. In NSCLC, both galectin-3 expressivity in tumor tissue and higher serum level was consistent with increased risk of occult carcinoma. Therefore, galectin-3 could be a possible determinant of histotype of pituitary adenoma/carcinoma that is either PRL or ACTH or as a primary site of metastatic cells from which they take their origin, as documented in this atypical case.

CONCLUSION

In summary, our case documents a rare primary metastatic lung adenocarcinoma that has metastasized in a clinically non-functioning gonadotroph cell adenoma with some unusual morphologic and immunophenotypical features. Despite the fact that the patient had a mass in his left lung which was identified after hospital admission and confirmed to be a NSCLC by endobronchial ultrasound assisted biopsy, his neuroradiological and intraoperative findings were interpreted as a clinically non-functioning PA. The perplexing morphological features of metastatic deposits were their concealment around capillary network, possibly misdiagnosed as a pituitary carcinoma with lung metastases. Selected IHC pituitary and metastatic panels aided in recognition of a metastatic adenocarcinoma expressing napsin-A, TTF-1, CK7, galectin-3, high MIB-1 labeling index and strong p53 nuclear expressivity.

The use of multimodal chemotherapy and local sella radiotherapy is currently used, inevitably although sellar primary metastatic cases have sinister prognosis. Metastasis into PA is very rarely the initial site of disease presentation which may mimic a PA. The most common neurological deficits include headache, vision disturbances, and to lesser extent endocrine symptoms like obesity and amenorrhea. Since metastatic tumors may masquerade as a primary PA, it is important to remain cognizant "the gold standard" for final diagnosis is exclusively based on the histopathologic and immunohistochemical findings.

Ethics Committtee Approval: N/A.

Informed Consent: Written informed consent was not obtained due to the archival investigation nature of the study.

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