

Pituitary metastasis of lung neuroendocrine carcinoma: case report and literature review

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SUMMARY

Metastasis to the pituitary gland is an unusual situation in clinical practice, but the frequency thereof is increasing due to the increased survival of cancer patients, and greater availability of imaging. In most cases, they are found between the sixth and seventh decades of life, as determined in image examination of patients with known malignant neoplasm, but, generally, asymptomatic with respect to pituitary involvement. The most common primary sites are breast in women and lung in men. We present the case of a 64-year-old patient with clinical visual changes, polyuria, polydipsia, and decreased level of consciousness whose tests showed pan-hypopituitarism, hypernatremia and low urine specific gravity, and extensive mass in sellar region. *Diabetes insipidus* was confirmed and treated, corticotrophic and thyroid deficits were corrected and then the patient underwent resection by transsphenoidal surgery. The histopathological and immunohistochemistry analysis revealed pituitary metastasis of lung neuroendocrine tumor. Subsequently, a chest CT scan showed pulmonary mass consistent with primary neoplasm. Despite the water and electrolyte correction and intravenous glucocorticoid replacement, the patient continued to show decreased level of consciousness due to compression of the brain stem by the pituitary mass, evolving to death. The purpose is to call attention to the differential diagnosis of invasive lesions of the sellar region, mainly in individuals over 50 years and/or when associated with diabetes insipidus, as it may be a case of metastasis, although there is no known primary neoplasm. Arch Endocrinol Metab. 2015;59(6):548-53

INTRODUCTION

Metastasis to the pituitary gland is an uncommon situation in clinical practice (1-5). Pituitary metastases are estimated to correspond to approximately 1% of pituitary tumors (2,6-8), having been found in 3.6% of consecutive autopsies of patients with metastatic malignant disease (9). However, in recent years, the frequency of pituitary metastases is increasing due to the increased survival of cancer patients, and greater availability of imaging (1,4). Pituitary metastases occur most commonly in the elderly, especially in the sixth and seventh decades of life, with no difference between genders (3,4,10).

Most of the cases of pituitary metastasis are discovered by imaging in patients with malignant neoplasm (2,3,11), but asymptomatic in relation to the pituitary involvement (1,2). Among patients with advanced neoplasm and finding of pituitary mass, the probability of pituitary metastasis is approximately twice that of adenoma (11).

The aim of this paper is to report the case of a 64-year-old patient whose presentation of a lung neuroen-

docrine cancer was visual change, pan-hypopituitarism and *diabetes insipidus* secondary to pituitary metastasis, as well as review the literature on this topic which importance is growing.

CASE REPORT

A female patient, 64, admitted to the emergency service of HSP in August 2013, with a history of apathy, asthenia, somnolence, polyuria and nocturia for about three months. She also experienced diplopia and blurred vision with rapid progression to bilateral amaurosis. Twenty days before admission, the patient developed worsening of general condition, loss of appetite, nausea and vomiting, as well as holocranial headache and cognitive impairment with periods of mental confusion and disorientation. History of longstanding hypertension and former smoker (smoking history of 30 packs per year), quitting 16 years ago.

The general physical examination revealed normal vital signs and mild/moderate dehydration. During neurological examination, the patient was drowsy, di-

oriented in time and space, responding to verbal call with slowed speech. Visual acuity was bilaterally impaired, with perception of light only, without deficit of strength in limbs and deep reflexes decreased globally.

Initial laboratory tests showed normal blood count, blood glucose: 81 mg/dL, Na: 153 mmol/l (RV: 135-145), K: 3.6 mmol/l (RV: 3.5-5.0), creatinine: 1.06 mg/dL (RV: 0.5-0.9) and urine specific gravity: 1,005 (RV: 1,010-1,045). Hormonal evaluation revealed panhypopituitarism (Table 1) and magnetic resonance imaging of the sella turcica showed a large mass in the sellar and suprasellar region (Figure 1).

Table 1. Initial hormonal evaluation

Hormone (unit)	Result	Reference
TSH (μ UI/mL)	0.093	0.27 – 4.2
Free T4 (ng/dL)	0.49	0.93 – 1.7
GH (ng/mL)	0.47	0.13 – 9.9
IGF-1 (ng/mL)	53.2	75 – 212
ACTH (pg/mL)	20	\leq 46
Cortisol (μ g/dL)	4.9	6.2 – 19.4
LH (mUI/mL)	0.9	7.7 – 58.5
FSH (mUI/mL)	< 0.1	26 – 135
Estradiol (pg/mL)	< 5	< 5 – 55
PRL (ng/mL)	27	4.8 – 23

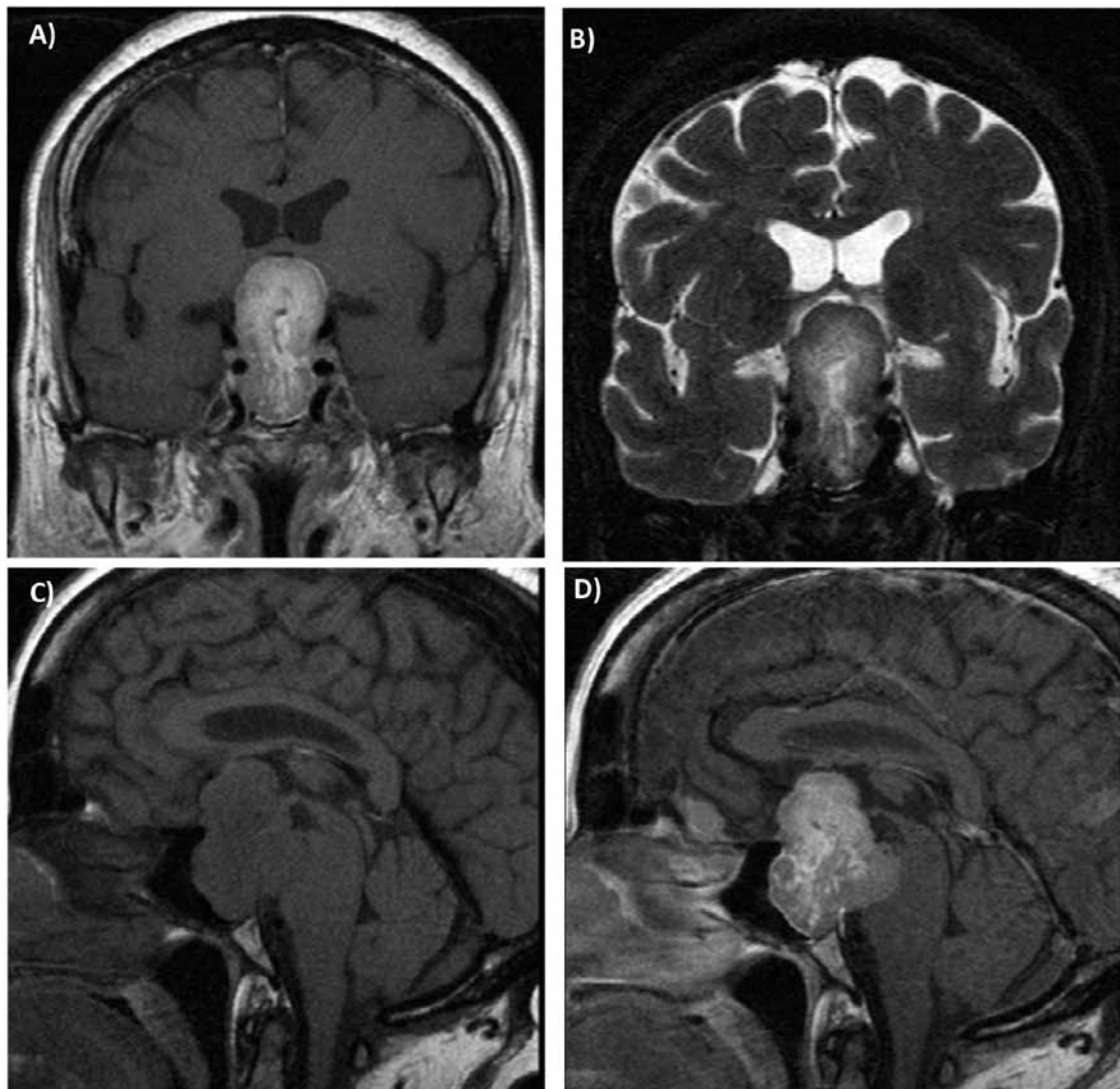


Figure 1. RM sella turcica. RM sella turcica (A) Coronal section in T1: expansive formation in the sellar region, infrasellar and suprasellar with intense enhancement inside after paramagnetic contrast injection, with superior shift of the optic chiasm and in bilateral contact with the internal carotid arteries, with no signs of invasion of the cavernous sinus, measuring about 4.8 x 3.6 cm. (B) Coronal section in T2: mass with heterogeneous hyperintense inside. (C) Sagittal section in T1: mass obliterating suprasellar cisterns and projecting further to the bridge, with isosignal. (D) Sagittal section with contrast indicating compression of the third ventricle floor and the bridge.

As the patient presented severe polyuria (8-12 liters/day), hypernatremia and low urine specific gravity, corrected after desmopressin administration, there was no need for additional tests to confirm the diagnosis of central *diabetes insipidus*. She was maintained with desmopressin 1.0 µg, subcutaneous, once a day and, after hydrocortisone replacement (initial dose: 100 mg intravenous 8/8h) and levothyroxine 200 µg/day showed progressive improvement, in a few days, of drowsiness, anorexia, nausea and vomiting, although she still showed periods of mental confusion.

Subsequently, the patient underwent transsphenoidal surgery with partial resection only of the mass due to heavy bleeding lesion. After surgery, she showed a slight visual improvement, but kept fluctuating consciousness.

Intraoperative frozen biopsy showed a solid tumor with high-grade nuclear atypia. Anatomopathological analysis showed neuroendocrine tumor metastasis of lung primary site with positive immunohistochemistry for CK (cytokeratin) 8/18, CA (antigen carbohydrate) 19.9, TTF-1 (thyroid transcription factor 1), NSE (neu-

ron specific enolase), chromogranin and synaptophysin. The Ki-67 showed high cell proliferation rate (Figure 2).

After histological diagnosis of sellar mass indicated the origin of the lesion, we performed CT scan of the chest, which showed a solid mass in the right lower lobe consistent with the primary neoplasm (Figure 3).

As the risk of lung mass biopsy was considered high (elevated pulmonary artery pressure) and given the certainty of the anatomopathological diagnosis of pituitary mass, we decided to start radiation therapy of the central nervous system followed by systemic chemotherapy. During this hospitalization, the patient also had severe sepsis (urinary infection), delaying the start of the treatment plan. After 64 days, she was discharged to then start radiotherapy. The patient underwent only two sessions of radiotherapy, evolved with reduction of consciousness and was hospitalized again. She was admitted in a coma (Glasgow 6), hypotensive (70 x 40 mmHg), with poorly reactive mydriatic pupils and hypernatremia (Na = 160 mmol/l). Despite the water and electrolyte correction and intravenous administra-

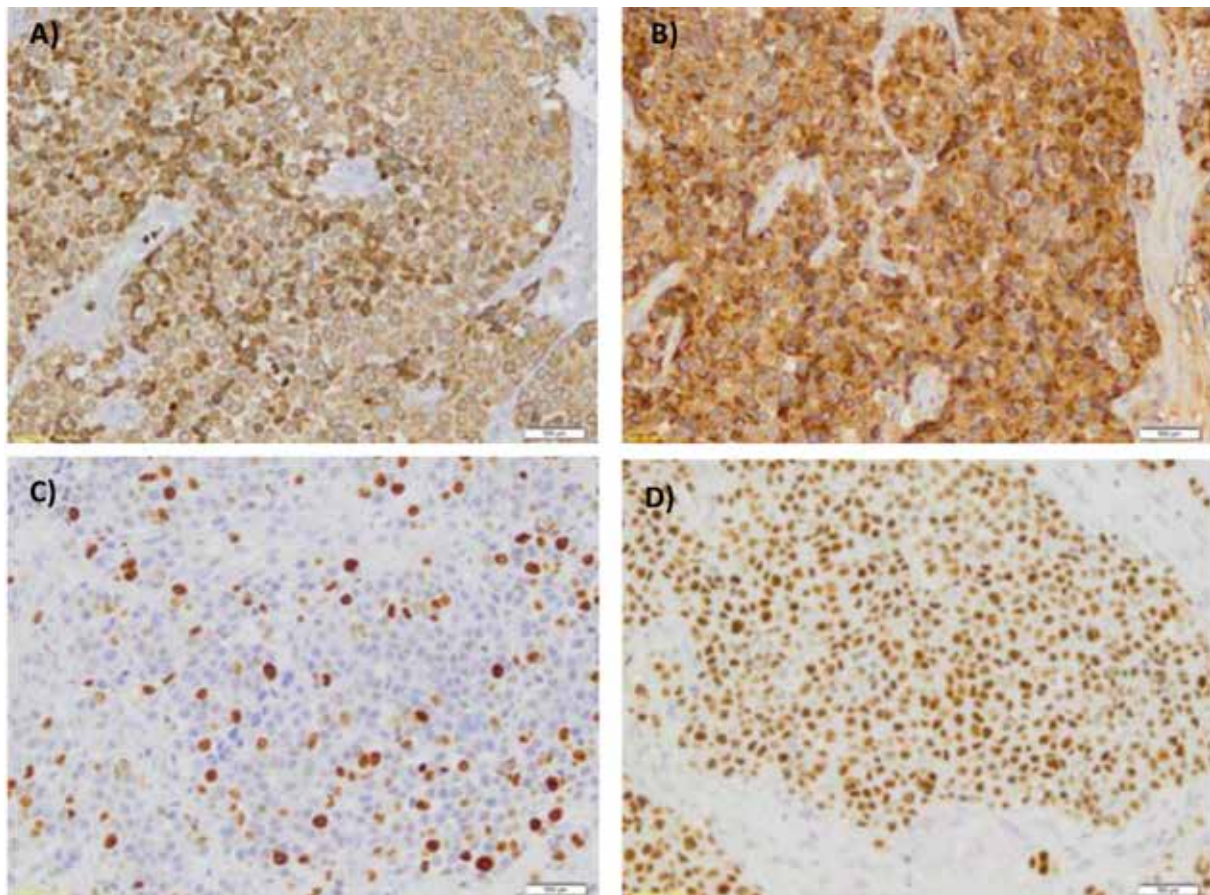


Figure 2. Histopathological and immunohistochemical analysis (A) Cytokeratin stained slides, proving that it was a carcinoma. (B) IHC-positive for chromogranin, proving endocrine origin. (C) IHC-positive for TTF-1 indicating pulmonary origin. (D) Ki-67 showing high cell proliferation index.

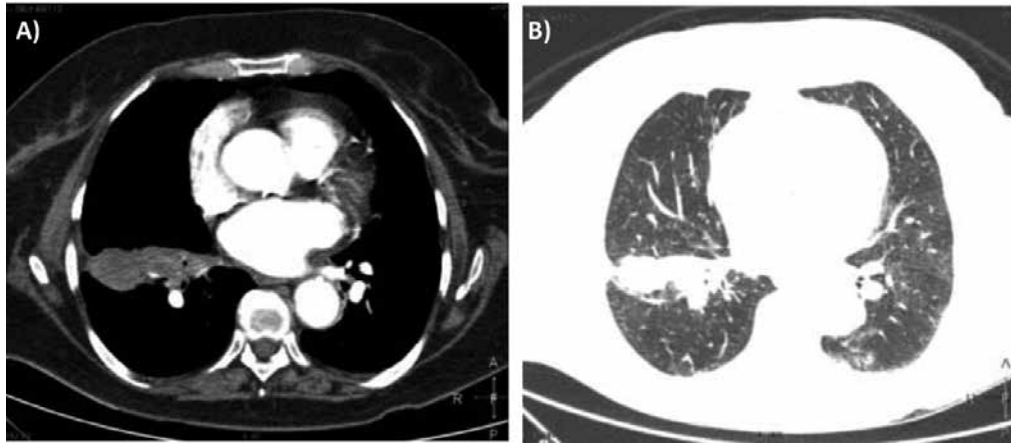


Figure 3. Chest CT. High resolution chest CT in mediastinal window with contrast (A) and lung window (B), showing consolidation in the basal segment behind the right lower lobe of nearly 6.5 x 4.7 cm, indicating the primary neoplastic lesion.

tion of glucocorticoids, the patient continued to show decreased level of consciousness requiring ventilatory support. Through images (CT and MRI) and electroencephalogram, the diagnostic possibilities of ischemia or central nervous system bleeding and nonconvulsive status epilepticus, respectively, were ruled out. Thus, the lowering of consciousness was attributed the very brainstem compression by the metastasis that could already be observed in the initial image (Figure 1). Faced with the severity of the condition, it was decided, together with family members, for palliative care. After 72 days of the second hospitalization, the patient died.

DISCUSSION

Pituitary metastases are usually detected in patients with advanced malignant disease, but they most often remain silent, because other metastases, usually coexisting, shorten the time of life (12). More rarely, they are discovered due to signs and/or symptoms of impairment of the pituitary region, preceding the diagnosis of the primary tumor (8,13), as in the case reported here.

The most common primary sites of pituitary metastases are breast in women and lung in men (1,2,3,7,9), and these two sites account for about two-thirds of the cases (Table 2). In cases of lung cancer, small cell and non-small cell cancer cause metastasis to the pituitary gland with the same frequency (9).

Neuroendocrine neoplasms may also show an aggressive behavior, and pituitary involvement is extremely rare (14). In a recent review, about 15 cases of pituitary metastases by neuroendocrine neoplasia were compiled, and small cell pulmonary carcinoma to neuroendocrine neoplasm were more frequent (15).

Table 2. Origin of the primary neoplasm in cases of pituitary metastasis

Primary site	%	Primary site	%
Breast	39.7	Pancreas	1.3
Lung	23.7	Pharynx	1.3
Prostate	5.0	Endometrium	1.3
Kidney	2.6	Leukemia	1.3
Skin (melanoma)	2.4	Bladder	1.1
Colon	2.4	Liver	1.1
Thyroid	2.1	Cervix	1.1
Stomach	1.8	Undetermined	3.1

Adapted from reference 4.

As already mentioned, in most cases pituitary metastases are silent, however, such possibility should be raised in patients with pituitary mass and *diabetes insipidus*, since such condition is seen in less than 1% of patients with pituitary adenomas (7). In symptomatic patients, up to 70% of cases (11) present *diabetes insipidus*, which is a more commonly reported condition (3,4,7,9,11). Deficiency of anterior pituitary hormones is less common and occurs alone in nearly 23% (4). Such difference is due to the intense vascularization of pituitary posterior lobe, with direct arterial supply from systemic circulation, while the anterior lobe is deprived of direct blood supply (5,6,12,16). Corticotrophic and thyrotrophin deficits are the most commonly followed by panhypopituitarism (3). A rare case of acute adrenal crisis due pituitary metastases was recently described (17).

Hyperprolactinemia is seen at 6.3% of pituitary metastases due to compression of pituitary stalk (2) and although prolactin values greater than 250 ng/mL are indicative of prolactinomas (18), in a described case of pituitary metastases originating from hepatocellular car-

cinoma, prolactin value was 438.6 ng/mL (4), which can make diagnosis difficult and delay treatment. Interestingly, the case of a patient with a bronchogenic non-small cell carcinoma who developed pituitary metastases to the inside of a prolactinoma was published (5). In the case reported, we observed mild hyperprolactinemia.

Other manifestations of pituitary metastases include: visual field deficiencies due compression of the optic chiasm (more often hemianopsia bitemporal), cranial nerve palsies by infiltration of the adjacent cavernous sinus (mostly oculomotor nerve) and headache due to distension of sellar diaphragm (3,4,11). Seizure associated with pituitary metastases was already described (19) and an unusual case of pituitary apoplexy associated with pituitary metastases was reported (20). Rare cases of primary neuroendocrine tumors (lung and pancreas) secreting ACTH or GHRH have already been reported with functioning pituitary metastases leading to Cushing's syndrome and acromegaly (22,23). In the case reported, it was observed, at admission, *diabetes insipidus* and panhypopituitarism with no evidence of underlying disease, besides less commonly reported symptoms such as altered consciousness, nausea, vomiting and cognitive decline (4).

Radiological findings of pituitary metastases are not specific (4,16). In general, in MRI is observed isointense or hypointense sellar mass on T1 and hyperintense on T2 with homogeneous enhancement after gadolinium (4). Invasion of cavernous sinus is common and extension to the sphenoid sinus and other central nervous system lesions can occur concomitantly (9). However, that should mostly raise suspicion of pituitary metastases is the evolution with rapid and invasive growth, with *diabetes insipidus* and/or changes of cranial nerves especially in patients over 50 years of age (4,6,11), as observed in the case reported.

The treatment of pituitary metastases should be targeted to the treatment of the underlying disease and control of symptoms (16). Although radiotherapy and chemotherapy are the methods of choice, surgical intervention should be considered for relief of symptoms, especially headache and visual field deficits (4), as demonstrated in this case. Survival was not different between groups with approach to pituitary mass and groups for which such approach was not performed (1,10). The prognosis is poor with survival around six months (9) depending on the aggressiveness of the primary tumor and staging of disease (4,13). A case of metastatic neuroendocrine neoplasm and for the pitui-

tary gland and liver was recently published, with immunohistochemistry demonstrating higher expression for somatostatin receptor, with good response to treatment with radiolabeled somatostatin analogue (14).

Therefore, metastasis to the pituitary region is a rare condition, and it is even more unusual in case of neuroendocrine neoplasms, but it must be a differential diagnosis of invasive lesions in the sellar region, mainly in patients over 50 years of age and/or associated with *diabetes insipidus*.

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