Cent. Eur. J. Med. • 6(4) • 2011 • 475-479
DOI: 10.2478/s11536-011-0040-2

VERSITA

Central European Journal of **Medicine**

Diabetes insipidus due to pituitary metastasis in a woman with lung adenocarcinoma: a case report

Case Report

Chen-Hao Hsiao[1*], Chung-Yih Wang[2], Ming-Teng Chung[3], Ming-Sung Yang[4]

[1] *Department of Surgery, Cheng Hsin General Hospital, 11220 Taipei, Taiwan*

[2] *Department of Radiation Oncology, Cheng Hsin General Hospital, 11220 Taipei, Taiwan*

[3] *Department of Pathology, Cheng Hsin General Hospital, 11220 Taipei, Taiwan*

[4] *Department of Surgery, Cheng Hsin General Hospital, 11220 Taipei, Taiwan*

Received 22 June 2010; Accepted 6 April 2011

Abstract: Metastatic tumors of the pituitary are uncommon and usually asymptomatic. They are often incidental findings from imaging workups for other medical issues or from the assessment of primary tumors in other locations. Diabetes insipidus is the most common symptom resulting from pituitary tumors, including pituitary metastases. A 56-year-old woman with primary lung adenocarcinoma underwent video-assisted thoracic bilobectomy. Regular follow-up was unremarkable until 15 months after surgery, when she presented with polyuria and polydipsia suggestive of diabetes insipidus. A pituitary mass was found on brain magnetic resonance imaging; the diagnosis of lung adenocarcinoma metastasized to the pituitary was confirmed by trans-sphenoidal surgery and biopsy of the pituitary mass. Diabetes insipidus and hormonal profiles are the key to recognize the existence of pituitary metastases, and patients with primary lung cancers presenting with diabetes insipidus should be evaluated for pituitary metastases.

Keywords: *Pituitary tumor • Metastasis • Lung cancer • Diabetes insipidus*

1. Introduction

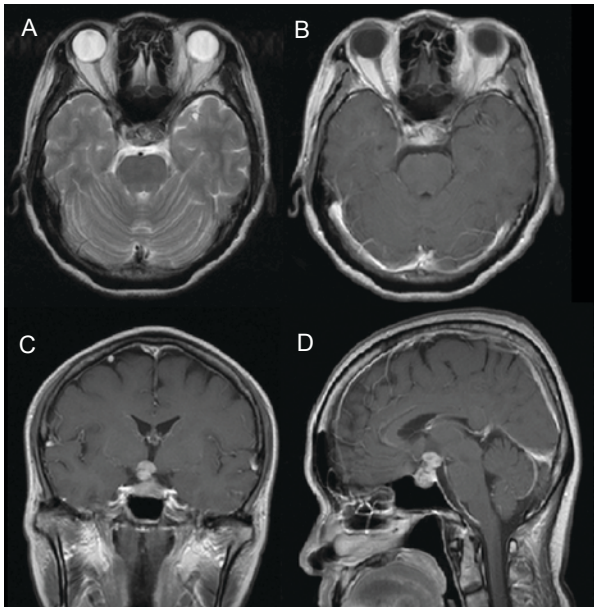
Although tumors metastasized to the pituitary gland are unusual, certain types of primary tumors are associated with spread to the pituitary more frequently [1]. Breast and lung cancers are the most common primary malignant neoplasms that metastasize to the pituitary gland [2]. Most pituitary metastases are asymptomatic and typically detected incidentally on imaging [3]. However, diabetes insipidus is the most common symptom in the few symptomatic pituitary metastases [4] and can raise suspicion of the existence of metastatic pituitary involvement. The purpose of this report is to describe a rare case of an elderly woman with early stage lung cancer who presented with diabetes insipidus 15 months after removal of the primary tumor.

2. Case Report

A 56-year-old postmenopausal woman presented with progressive polydipsia and polyuria occurring for the past three months. She had no history of diabetes mellitus or hypertension, and was a nonsmoker. Fifteen months previously, the patient underwent video-assisted thoracic bilobectomy of the right middle lobe and right lower lobe to remove primary lung adenocarcinomas. Two months before the current admission, she developed insomnia

* *E-mail: oodaoda@gmail.com*

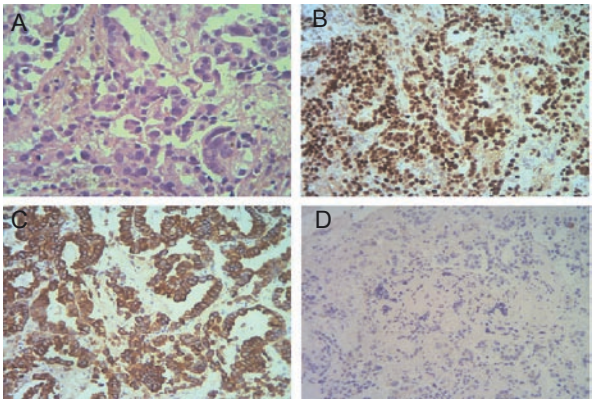
Figure 1. A, Pre-contrast axial MRI T1WI. B, Post-contrast axial MRI T1WI. C, Post-contrast coronal MRI T1WI. D, Post-contrast sagittal MRI T1WI showing heterogeneous enhancing pituitary mass with suprasellar extension.



associated with nocturia. Her daily volume of urine ranged from four to six liters, and she reported being thirsty regardless of markedly increased fluid intake.

The patient was 155 cm in height and 40 kg in weight upon presentation at the clinic, with body temperature of 37 degrees Celsius, blood pressure reading of 117/83 mmHg, and pulse rate 92/min with a regular rhythm. The findings on physical examination were unremarkable, including respiratory and neurological examinations. Initial evaluation of complete blood count revealed white blood cell count 4,800 /µl, hemoglobin 13 g/dl, and platelet count 18.4 x 10^4/µl. Serum electrolytes, liver function tests, and renal function tests were normal. Carcinoembryonic antigen values were 5.21 ng/ml. Notably, the urine specific gravity was 1.004 g/ml (normal 1.01–1.03 g/ml). Central diabetes insipidus was diagnosed by a water deprivation test. Hormonal profiles revealed serum prolactin 97.95 ng/ml (normal 4.79 – 23.3 ng/ml), growth hormone 0.684 ng/ml (normal 0.01 – 3.61 ng/ml), follicle-stimulating hormone 2.94 mIU/ml (normal in postmenopausal 25.8 – 134.8 mIU/ml), luteinizing hormone 0.1 mIU/ml (normal in postmenopausal 7.7 – 58.5 mIU/ml), estradiol 15 pg/ml (normal in postmenopausal < 54.7 pg/ml), adrenocorticotrophic hormone 9.9 pg/ml (normal 9 – 46 pg/ml), free T4 0.55 ng/dl (normal 0.93 – 1.7 ng/dl), T3 0.53 ng/ml (normal 0.8 – 2 ng/ml), and thyroid-stimulating hormone 3.64 uIU/ml (normal 0.27 – 4.2 uIU/ml).

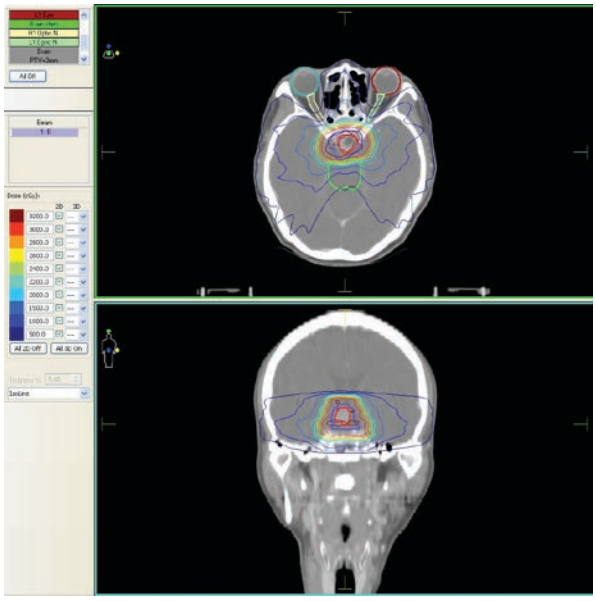
Figure 2. Photomicrographs showing the histological features of adenocarcinoma composed of pleomorphic and hyperchromatic tumor cells arranging in glandular pattern with an infiltrative growth (A, hematoxylin-eosin stain, x400). These tumor cells were strongly immunoreactive for thyroid transcription factor-1 (B, x200) and cytokeratin 7 (C, x200), but negative for cytokeratin 20 (D, x200).



The chest roentgenogram revealed the expected postoperative reduction in volume of the right lung and the elevation of right hemidiaphragm. Computed tomography of the chest revealed no tumor recurrence. Magnetic resonance imaging of the brain showed a heterogeneously enhancing mass in the pituitary gland and an enlarged pituitary stalk with thickened and enhancing of the infundibulum of the third ventricle (Figure 1). 99mTC MDP whole body bone scan revealed no definite evidence of bony metastases.

The patient underwent trans-sphenoidal surgery with pituitary gland tumor biopsy. The biopsy specimen measuring, 7 x 7 x 2 mm in aggregate, was submitted for histopathological examination, which revealed an adenocarcinoma composed of pleomorphic and hyperchromatic tumor cells arranged in glandular pattern with infiltrative growth. These tumor cells were strongly immunoreactive for cytokeratin 7 and thyroid transcription factor-1, but negative for cytokeratin 20 (Figure 2). This finding was consistent with that of metastatic adenocarcinoma originating from lung. After biopsy, the patient was referred for radiation therapy targeting the pituitary metastases. She received whole brain radiation therapy of 3000 cGy in 15 fractions followed by pituitary boost radiation in the form of volumetric-modulated arc therapy (3200 cGy in 16 fractions) as shown in Figure 3. Her condition was stable during follow-up; the patient will receive further cisplatin based chemotherapy.

Figure 3. Dose distribution curves of volumetric-modulated arc therapy.



3. Discussion

The pituitary gland is an uncommon site of metastasis, with incidence of 0.14 to 28.1% of all brain metastases in autopsy series [1,2]. There is no differential frequency in males compared to females, but is detected most often in elderly patients during their sixth or seventh decade of life [2,5]. Widespread metastases (associated with more than five metastatic sites) and bony metastasis are typically seen in patients also having pituitary metastases [5]. Breast cancer in women and lung cancer in men are the most common primary malignancies known to metastasize to the pituitary, respectively [2], representing 39.7% (breast cancer) and 23.7% (lung cancer) of the origins for pituitary metastases [2]. Lung cancer, especially small cell lung cancer, is more common in men, but adenocarcinoma is the most frequent subtype in women [3,6]. In this case, the patient presented with lung adenocarcinoma and received video-assisted thoracic surgery bilobectomy of the right middle and right lower lobe. Metastasis to the pituitary gland was diagnosed one and half a year after operation. Unlike typical cases involving pituitary metastases, this patient did not present with widespread metastasis or bony metastasis.

There are several pathways of metastases to the pituitary: direct systemic hematogenous spreading, spreading from hypothalamohypophyseal or infundibulum through the portal vessels, spreading from juxtasellar sites or the skull base, and meningeal spreading [2]. The location of metastases in the pituitary reviewed by McCormick et al. [1] was found an involvement of the posterior pituitary either alone or in combination with the anterior pituitary in 84.6%, whereas only the anterior pituitary was involved in 15.4%. The posterior ptuitary is a preferential site of origin for metastases as it receives direct systemic arterial blood supplied by hypophyseal arteries; in comparison the anterior pituitary receives blood supplied mainly by the hypophyseal portal systems and is thus less likely to promote pituitary metastasis than the posterior portion [2,7]. In addition, metastasis to the anterior pituitary typically originates via spread from primary tumors in the posterior pituitary. The predilection for metastasis to the anterior pituitary is recognized in certain cancers. Marin et al. [8] found an increased affinity of breast cancers for the anterior pituitary due to a nascent hormonal attraction. An environment rich in hormones (especially prolactin) may provide a preferred environment for hormone-sensitive breast cancer cells that enhances their proliferation [7,8].

Most pituitary metastases are clinically silent; only 7% of pituitary metastases are symptomatic [9]. The most common symptom of patients with pituitary metastasis is diabetes insipidus, reflecting the predominance of metastasis to the posterior pituitary [2,4]. Diabetes insipidus is also a critical indicator for differentiation of pituitary metastases from pituitary adenomas, as only 1% patients with for the anterior pituitary adenomas present with it [2,3,7]. Komninos et al. [2] found that 45% of the symptomatic patients of pituitary metastases presented with diabetes insipidus; 27.9% with cranial nerve II deficit; 23.6% with anterior pituitary insufficiency (partial or total); 21.6% with cranial nerve III, IV or VI palsy; 15.8% with headaches/postocular pain; 7.9% with fatigue/general malaise; and 6.3% with hyperprolactinemia. Metastasis to the posterior pituitary is recognized to cause diabetes insipidus. In contrast, metastasis to the anterior pituitary is recognized to cause anterior pituitary insufficiency. The incidences of these differentiating symptoms correspond to the prevalence of the different metastatic locations (anterior vs. posterior pituitary). Branch and Laws [10] proposed that if a patient presents with the clinical triad of headache, extraocular nerve palsy, and diabetes insipidus, metastasis to the sella should be strongly suspected. Our case presented with one element of the clinical triad, diabetes insipidus, and partial anterior pituitary insufficiency of gonadotrophs (low levels of follicle-stimulating hormone and luteinizing hormone). Based on these symptoms, metastasis to the posterior pituitary with the anterior pituitary involvement was suspected. Hyperprolactinemia was encountered in 6.3% of pituitary metastases, attributed to stalk compression [2]. When the hyperprolactinemia involved

values above 200 ng/ml, a prolactinoma should be suspected; pituitary metastases typically are associated with prolactin values no higher than 149.2 ng/ml [2]. As noted for this patient, prolactin was elevated (97.95 ng/ml, normal range: 4.79 to 23.3 ng/ml) but did not exceed the value that would allow differentiation between pituitary metastasis versus pituitary adenoma. The diagnosis of pituitary metastasis of the primary lung adenocarcinoma was confirmed after trans-sphenoid pituitary gland tumor biopsy. Magnetic resonance imaging of the brain also demonstrated a heterogeneously enhancing mass in the pituitary gland and enlarged stalk consistent with the histopathology findings.

Pituitary hormones are important clues to estimate the location of pituitary metastases. The anterior pituitary secretes multiple hormones (adrenocorticotrophic hormone, growth hormone, thyroid-stimulating hormone, prolactin, follicle-stimulating hormone, and luteinizing hormone). The posterior pituitary lobes secrete two hormones involved in control of water and electrolyte function: anti-diuretic hormone and oxytocin. Pituitary metastases in anterior lobes may lead to anterior pituitary insufficiencies [2,3,7]. In symptomatic pituitary metastases, hypothyroidism and hypocorticolism are most frequent followed by panhypopituitarism [7]. Hypogonadism and hyperprolactinemia are least frequencies [2,7]. However, few cases have been reported involving hyperfunction in anterior pituitary hormones (e.g. Cushing's syndrome or acromegaly) due to ectopic secretion of adrenocorticotrophic hormone in small cell lung cancers and growth hormone in growth hormone releasing hormone producing tumors, respectively [2,11,12]. A few cases of pituitary metastases, accompanied by coticotrophic or somatotrophic adenoma, have been reported to present with Cushing's syndrome or acromegaly [2]. Pituitary metastasis in the posterior lobes and stalks could lead to diabetes insipidus [1-7]. Rarely, diabetes insipidus may be concealed due to regeneration of neurohypophyseal fibers or anterior pituitary insufficiency of corticotrophs [2,7]. In the analysis of our patient's hormonal profiles, growth hormone and adrenocorticotrophic hormone were within normal limits. However, she had hypothyroidism indicated by low free T4 and T3, hypogonadism indicated by low follicle-stimulating hormone and luteinizing hormone, and hyperprolactinemia. According to her hormonal analysis and the presence of diabetes insipidus, we suspected that pituitary metastasis in this patient involved both the anterior and posterior pituitary. This prediction was confirmed by magnetic resonance imaging (Figure 1). The excised pituitary metastasis stained positive on immunihistochemistry for thyroid transcription factor-1and cytokeratin 7, but was negative for cytokeratin 20. These immunohistochemical staining techniques are very useful in the differential diagnosis of primary lung adenocarcinomas [13]. Thyroid transcription factor-1 is a very sensitive and specific marker of primary lung adenocarcinomas if a thyroid origin is excluded. Cytokeratin 7 is also a common marker of primary lung adenocarcinomas. However, cytokeratin 20 is negative in primary lung adenocarcinomas and positive in colon adenocarcinomas. In pituitary adenomas, the pattern of immunohistochemical expression of cytokeratin 7 and 20 was indicative of the primary tumor origin in lung adenocarcinoma [14]. In about 90% of pituitary adenomas, cytokeratin 7 is either negative or reactive in only a few scattered cells. Cytokeratin 20 is also always negative in pituitary adenomas. But rare pituitary adenomas like corticotrophs and sparsely granulated growth hormone-positive adenomas are consistently cytokeratin 20 positive and cytokeratin 7 negative [14]. In our patient, the tumor cells were strongly positive for thyroid transcription factor-1 and cytokeratin 7, but negative for cytokeratin 20; growth hormone level was within normal limits. The immunohistochemical profile of the excised pituitary mass was consistent with the differential diagnosis of pituitary metastatic adenocarcinoma of lung origin.

In conclusion, a past history of cancer is the most important diagnostic feature for evaluation of pituitary metastases, especially if a patient presents with a history of breast or lung cancers. The prevalence of pituitary metastases of lung origin is not strongly different in men or women but metastases from breast cancers and lung adenocarcinomas tend to be more common among women while metastases from small cell lung cancers tend to be more commonly seen in men. Diabetes insipidus and hormonal profiles are the key diagnostic features needed to narrow down the potential location of pituitary metastases. Degrees of hyperprolactinemia and immunohistochemical expressions are useful clues to differentiate between pituitary adenomas and pituitary metastases. Although pituitary metastases are uncommon, breast cancer and lung cancer patients should always be evaluated when symptoms consistent with metastasis to the pituitary are present.

References

[1] McCormick P.C., Post K.D., Kandji A.D., Hays A.P., Metastatic carcinoma to the pituitary gland, Br J Neurosurg., 1989, 3, 71-80

[2] Komninos J., Vlassopoulou V., Protopapa D., Korfias S., Kontogeorgos G., Sakas D.E., et al., Tumors metastatic to the pituitary gland: case report and literature review, J Clin Endocrinol Metab., 2004, 89, 574-580

[3] Rajput R., Bhansali A., Dutta P., Gupta S.K., Radotra B.D., Bhadada S., Pituitary metastasis masquerading as non-functioning pituitary adenoma in a woman with adenocarcinoma lung, Pituitary., 2006, 9, 155-157

[4] Sioutos P., Yen V., Arbit E., Pituitary gland metastases, Ann Surg Oncol., 1996, 3, 94-99

[5] Nelson P.B., Robinson A.G., Martinez A.J., Metastatic tumor of the pituitary gland, Neurosurgery., 1987, 21, 941-944

[6] Krol T.C., Wood W.S., Bronchogenic carcinoma and diabetes insipidus: case report and review, Cancer., 1982, 49, 596-599

[7] Morita A., Meyer F.B., Laws E.R. Jr., Symptomatic pituitary metastases, J Neurosurg., 1998, 89, 69-73

[8] Marin F., Kovacs K.T., Scheithauer B.W., Young W.F. Jr., The pituitary gland in patients with breast carcinoma: a histologic and immunocytochemical study of 125 cases, Mayo Clin Proc., 1992, 67, 949-956

[9] Teears R.J., Silverman E.M., Clinicopathologic review of 88 cases of carcinoma metastatic to the pituitary gland, Cancer., 1965, 36, 216-220

[10] Branch C.L. Jr., Laws E.R. Jr., Metastatic tumors of the sella tunica masquerading as primary pituitary tumors, J Clin Endocrinol Metab., 1987, 65, 469-474

[11] Chandra V., McDonald L.W., Anderson R.J., Metastatic small cell carcinoma of the lung presenting as pituitary apoplexy and Cushing's syndrome, J Neurooncol., 1984, 2, 59-66

[12] Sanno N., Teramoto A., Osamura R.Y., Genka S., Katakami H., Jin L., et al., A growth hormone-releasing hormone-producing pancreatic islet cell tumor metastasized to the pituitary is associated with pituitary somatotroph hyperplasia and acromegaly, J Clin Endocrinol Metab., 1997, 82, 2731-2737

[13] Jerome Marson V., Mazieres J., Groussard O., Garcia O., Berjaud J., Dahan M., et al., Expression of TTF-1 and cytokeratins in primary and secondary epithelial lung tumours: correlation with histological type and grade, Histopathology., 2004, 45, 125-134

[14] Coons S.W., Estrada S.I., Gamez R., White W.L., Cytokeratin CK 7 and CK 20 expression in pituitary adenomas, Endocr Pathol., 2005, 16, 201-210