

# Central Diabetes Insipidus in A Patient with Breast Carcinoma Metastatic to the Pituitary Gland

Wei-Yu Chen<sup>1</sup>, and Chien-Yu Chen<sup>2</sup>

<sup>1</sup>*Division of Hematology and Oncology, Department of Internal Medicine,*

<sup>2</sup>*Department of Radiology, Chi-Mei Medical Center, Yong-Kang Campus, Tainan, Taiwan*

## Abstract

Pituitary metastatic disease is rare, accounting for 1% of all excised pituitary tumors and generally involving the posterior pituitary. Neoplasms that more often originated pituitary metastases are breast and lung cancer. We describe a case of a 50-year-old woman, diagnosed with breast cancer with liver and bone metastases, who underwent chemotherapy. During hospitalization, she developed polydipsia, polyuria, and nocturia. She had a large volume of 24-hour urine production (8-10L/day) with a very low urine osmolality (109 mosm/kg) compared to that of the plasma (334 mosm/kg). Further biochemical and hormonal workups were normal except for hypernatremia and hyperprolactinemia. Pituitary MRI showed a contrast-enhanced nodular lesion in the pituitary stalk, suggesting a metastatic lesion. The patient was treated with DDAVP and local radiotherapy, which led to the patient's clinical improvement. Twelve months after her diagnosis of diabetes insipidus, she died of the metastatic disease. (J Intern Med Taiwan 2017; 28: 252-257)

**Key Words:** Breast cancer, Pituitary metastasis, Diabetes insipidus

## Introduction

The pituitary gland and infundibulum can be involved in a variety of medical conditions, including infiltrative diseases, fungal infections, tuberculosis, and primary and metastatic tumors. Metastases to the pituitary gland (MP) are absolutely rare, and they are often related to primary breast or lung cancers. Pituitary metastases more commonly affect the posterior lobe and the infundibulum rather than the anterior lobe. The most common sign of this metastatic involvement is diabetes insipidus. A case report of a 50-year-old woman who had metastatic breast cancer, and she presented with polyuria,

polydipsia, and a persistent thirst. She had no electrolyte imbalance (such as hyperglycemia, hypokalemia, or hypercalcemia) except hypernatremia. But a pituitary stalk metastasis was found on magnetic resonance imaging (MRI) of the brain. A clinical response to nasal vasopressin was achieved and laboratory results revealed central diabetes insipidus. As a result, the urinary output decreased accordingly. Supplements of DDAVP combined with local radiotherapy completely resolved the clinical symptoms of DI of this patient.

## Case Report

A 50-year-old premenopausal woman was

diagnosed with carcinoma of the breast (stage IV pT4N3M1b, positive estrogen and progesterone receptors, and negative human epidermal growth factor receptor-2 (HER-2)). She was treated with the first course of chemotherapy with epirubicin and docetaxel on Jun 19 2012. But neutropenic fever developed in Jun 26 2012. She had been alert and well oriented. An empiric antibiotic was given for neutropenic fever. She had a large volume of 24-hour urine production (8-10L/day). Tracing back her history, she had a 2weeks history of polydipsia, polyuria, and loss of body weight before the admission. She did not have a headaches or visual complaints. Physical examination revealed no neurological or visual field deficits. The results of laboratory tests revealed a very low urine-osmolality (109 mOsm/kg) compared to that of the plasma (334 mOsm/kg), and a plasma sodium of 159 mEq/L, a glucose of 115 mg/dL, and a calcium of 8.0 mg/dL. An Endocrinological evaluation showed normal cortisol hormone, plasma growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and adrenocorticotrophic hormone, except

mild hyperprolactinemia. Owing to high clinical suspicion and neutropenic fever, water deprivation/vasopressin tests were not undertaken.

Magnetic resonance imaging (MRI) of the brain revealed poor contrast-enhanced lesion 5mm in the right pituitary gland. This could be of pituitary microadenoma or intrasellar metastasis as well as a contrast-enhanced nodular lesion in the pituitary stalk, suggesting metastasis. (Figure. 1a, b). Based upon the clinical symptoms, laboratory results, and radiological findings, the diagnosis of diabetes insipidus without compromising anterior pituitary function was caused by a metastasis in the dorsal part of the pituitary gland. She was then treated with nasal spray l-desamino-8-D-arginine vasopressin (DDAVP) 20mcg twice daily. The symptoms of polyuria and polydipsia resolved completely under the treatment and local radiotherapy. Several attempts were made to discontinue DDAVP; however, the patient experienced a relapse polyuria each time. Twelve months after the diagnosis diabetes insipidus, she died of the metastatic disease. Her family declined autopsy.

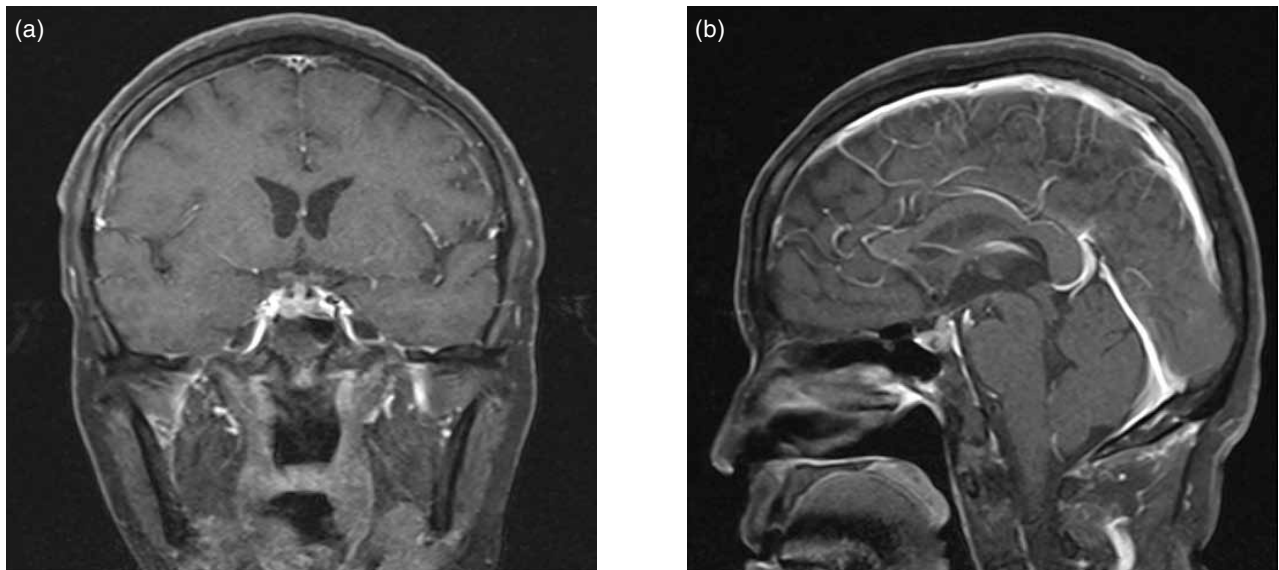


Figure 1. MRI image of the patient: (a) Coronal image of the Gadolinium-enhanced T1-weighted magnetic resonance imaging scan of the brain showed: contrast-enhanced nodular lesion in the pituitary stalk, suggesting metastasis. (b) Sagittal image of the Gadolinium-enhanced T1-weighted magnetic resonance imaging scan of the brain showed: contrast-enhanced nodular lesion in the pituitary stalk, suggesting metastasis.

## Discussion

Diabetes insipidus (DI) is a result of a deficiency of vasopressin (ADH) due to a hypothalamic-pituitary disorder (central DI [CDI]) or from a resistance of the kidneys to vasopressin (nephrogenic DI [NDI]). Polyuria and polydipsia develop. CDI must be differentiated from other causes of polyuria, particularly psychogenic polydipsia and NDI. All tests for CDI (and for NDI) are based on the principle that increasing the plasma osmolality in normal people will lead to a decreased excretion of urine with increased urine osmolality. The water deprivation test is the simplest and most reliable method for diagnosing CDI. However it should be done only while the patient is under constant supervision. A normal response produces maximum urine osmolality after dehydration (often  $> 1.020$  specific gravity or  $>700$  mOsm/L), exceeding the plasma osmolality; osmolality does not increase more than an additional 5% after injections of vasopressin. Patients with CDI are generally unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality by  $> 50$  to  $>100\%$  after exogenous vasopressin administration. Patients with partial CDI are often able to concentrate urine to above the plasma osmolality but show a rise in urine osmolality of 15 to 50% after vasopressin administration. Patients with NDI are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration. Owing to high clinical suspicion and neutropenic fever, water deprivation/vasopressin tests were not undertaken.

Primary diabetes insipidus, due to a defect inherent in the gland itself (no organic lesion), may be familial, occurring as a dominant trait; or, more commonly, sporadic or idiopathic. Secondary diabetes insipidus is due to destruction of the functional unit by trauma, infections (eg, encephalitis, tuberculosis, syphilis, CMV, herpes simplex), breast

cancer or lung cancer (common), vascular accidents (rare), and xanthomatosis (eosinophilic granuloma or Hand-Schuller-Christian disease). Nephrogenic diabetes insipidus is due to a defect in the kidney tubules that interferes with water reabsorption and occurs as an X-linked recessive trait. At times this type is acquired, eg, after pyelonephritis, potassium depletion, or amyloidosis. Certain drugs (eg, demeclocycline, lithium) may induce nephrogenic diabetes insipidus.

The most important differentiation is from the "psychogenic" water-drinking habit. Polydipsia and polyuria may also be seen in diabetes mellitus, chronic nephritis, hypokalemia (eg, in primary hyperaldosteronism), and in hypercalcemic states such as hyperparathyroidism.

Pituitary metastases are an uncommon complication of cancer, representing only 1% of the pituitary lesions<sup>1,2</sup> and 0.14% to 28% of all brain metastases in reported autopsy series<sup>3,4</sup>. They are often related to breast or lung cancers, with other sites of primary tumors being reported less often<sup>1,2,5,6</sup>. According to a recent meta-analysis, it showed breast and lung cancer account for 37.2% and 24.2% of the pituitary metastatic lesions, respectively<sup>7</sup>. Pituitary metastases are symptomatic in 2.5-18.2% of cases<sup>1,2</sup>, with the most important signs being diabetes insipidus, cranial nerve II deficit, and an anterior pituitary insufficiency<sup>1</sup>. The tumor mass may also cause headaches, and ophthalmoplegia<sup>1,2,5,6</sup>. Studies, including a recent meta-analysis indicate that DI is the most common clinical manifestation in patients who have pituitary metastasis<sup>7</sup>. No gender predominance has been reported<sup>2</sup>. At diagnosis, most patients are elderly in the sixth or seventh decade of life, and have widespread diseases with multiple sites of metastases<sup>8,9</sup>. Pituitary metastases may also be the first presentation of an occult primary cancer or may be the only site of metastasis<sup>4,10-12</sup>. They rarely occur in early adulthood<sup>13</sup>. Metastatic lesion is one of the differential diagnoses. Other causes of

thickened pituitary stalk (TPS) include Langerhans cell histiocytosis, granulomatous disease, germ cell tumor, lymphoma, etc<sup>14</sup>. Isolated pituitary stalk metastasis accounts for only 2% of pituitary gland metastasis<sup>15</sup>. An antemortem diagnosis of pituitary stalk metastasis of breast cancer was usually made by MRI without histological confirmation<sup>16</sup>.

The hematogenous spread (from portal vessels to the pituitary parenchyma or diaphragm sellae) is the most important mechanism for the development of these metastases. Alternative hypotheses for the spread are extension from juxtaseellar and skull base metastasis, or a meningeal spread through the suprasellar cistern<sup>1,8,11</sup>.

Mc Cormick *et al*<sup>3</sup> reviewed the location of MP in 201 cases and found an involvement of the posterior lobe either alone or in combination with the anterior lobe in 84.6%, whereas the anterior lobe affected only in 15.4%. The predilection for metastasis to the posterior lobe is mainly attributed to the lack of direct arterial blood supply of the anterior lobe<sup>3,4,9-11,14,15</sup>. The posterior lobe is more affected than the anterior lobe, mainly because of the lack of a direct arterial blood supply to the anterior lobe as well as a larger area of contact between the posterior lobe and the adjacent *dura madre*<sup>3,15</sup>. For this reason, the most common sign of this metastatic involvement is diabetes insipidus<sup>1,2,4,14</sup>.

The differential diagnosis of metastases in the hypothalamic pituitary region and pituitary adenoma may be difficult<sup>8,14</sup>. In contrast to 3.6% pituitary metastases found in 500 consecutively autopsied patients with cancer, only 1.8% with pituitary adenomas<sup>8</sup>. However, the general clinical manifestations of metastases in the hypothalamic-pituitary region and differ from pituitary adenoma. Metastases present with diabetes insipidus or, less commonly, with extra-ocular nerve palsies<sup>8,14,17</sup>. These symptoms occur in less than 2% of patients with pituitary adenoma<sup>18</sup>. Thus, diabetes insipidus is the most important criterion for the differentia-

tion of MP from adenomas. Other clinical characteristics that raise the suspicion for a pituitary lesion to represent a metastatic lesion rather than a benign adenoma include headaches, visual field deficits due to cranial nerve palsies (especially abducens nerve palsy), presence of skull-bone destruction, demonstration of rapid growth on serial scans, and presence of coexisting focal lesions (metastasis)<sup>19</sup>. Hormonal assay to be most commonly affected is high prolactin levels, which is however the case in both metastatic lesions and macroadenomas; hence does not help distinguish the two<sup>19</sup>.

Management of these patients may also be very difficult because the prognosis depends on the stages of the primary neoplasm. Treatments, being basically palliative, depends on the symptoms and the extent of the systemic disease<sup>1,3,11,20,21</sup>. Reports of the surgery of MPs indicate that the lesions tend to be firm, diffuse, invasive, vascular, and hemorrhagic. To that, therefore the total resection is unlikely<sup>4,9,20,21</sup>. In this setting, local radiation and/or chemotherapy are recommended for the initial treatment, especially in patients with widespread metastases, and in combination with pituitary hormone substitution therapy<sup>3,4,9,20,21</sup>. Surgical exploration and decompression, alone or combined with radiation, is essential if clarification of diagnosis is likely to affect the therapy or if suprasellar extension causes progressive deterioration in vision or pain<sup>3,4,9,12,14,20,21</sup>. Surgery and radiation are well tolerated in noncompromised patients, being associated with low morbidity and minimal complications<sup>11,14</sup>. Tumor debulking is beneficial in alleviating the local symptoms, especially headaches and visual field defect, whereas symptoms such as diplopia, and those related to anterior pituitary failure remain unaffected<sup>11,14,21-22</sup>. The transphenoidal approach, completeness of resection, and aggressive treatment (surgery plus local radiation) are associated with better symptom relief but do not affect the survival rates<sup>11,22</sup>.

In patients reported in the literature, diabetes insipidus was usually irreversible after only and anti-tumour therapy only<sup>16</sup>. The survival of the patients with dural and posterior pituitary metastases is better than parenchymal brain metastases or leptomeningeal carcinomatosis<sup>14</sup>. Prognosis of patients with MPs is still poor, not because of the location *per se* but because of the aggressiveness of the primary cancers<sup>23</sup>. Mean survival length in clinical series is about 6–7 months<sup>5,9,11</sup>. Ntyonga-Pono *et al*<sup>12</sup> reviewed 72 patients from the literature, and found that only 10% of patients survived more than 1 year after the diagnosis, with the longest survival being 3 years. Patients with a single MP may have a better outcome<sup>5,11</sup>. Age over 65 years at presentation, metastasis from small-cell lung carcinoma, and short duration (<1 year) between initial diagnosis of cancer and pituitary invasion have been related to a poorer outcome<sup>11</sup>. In conclusion, patients with cancers who have symptoms such as polyuria, nocturia and polydipsia should be evaluated for not only metabolic complications like hyperglycemia, hypercalcemia, but also for metastasis of the posterior pituitary gland. MRI should be the first choice of imaging for pituitary metastasis. In the context of malignancy, the emergence of CDI should alert the clinician, for the possibility of pituitary's metastasis.

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# 乳癌病人因轉移至腦垂腺所導致尿崩症之個案報告

陳威宇<sup>1</sup> 陳建宇<sup>2</sup>

奇美醫學中心 血液腫瘤科<sup>1</sup> 放射診斷科<sup>2</sup>

## 摘 要

我們在此報告一個乳癌轉移患者，在接受首次化療後，因發燒而注意到病人有多尿以及多渴之情形。在經過一系列檢查之後診斷為尿崩症，核磁共振檢查後發現腦垂腺轉移，在經過藥物治療以及放射線治療之後，病人尿崩症狀完全受到控制。