

[CASE REPORT]

Gefitinib Treatment Was Unsuccessful for Central Diabetes Insipidus Due to Pituitary Metastasis of Lung Adenocarcinoma

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Abstract:

We herein report a rare case of advanced lung adenocarcinoma with central diabetes insipidus due to pituitary metastasis. Although treatment with gefitinib was dramatically effective, the symptoms of diabetes insipidus did not improve. Radiotherapy for pituitary metastasis was effective to control diabetes insipidus; however, we could not cease the administration of 1-deamino-8-D-arginine vasopressin (DDAVP). It is important for physicians to positively consider radiotherapy for pituitary metastases even if favorable tumor control is achieved with chemotherapy when diabetes insipidus becomes clinically overt. Furthermore, continuous DDAVP administration may be needed to treat central diabetes insipidus.

Key words: lung cancer, central diabetes insipidus, pituitary metastasis, radiotherapy, 1-deamino-8-D-arginine vasopressin

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Introduction

The incidence of pituitary metastasis of lung cancer in autopsy cases is rare (1, 2). Central diabetes insipidus, a disorder characterized by decreased release of antidiuretic hormone (ADH), is the most common clinical presentation of pituitary metastasis in symptomatic patients (2).

We herein report a case of lung adenocarcinoma with central diabetes insipidus due to pituitary metastasis.

Case Report

A woman in her 80s was admitted to our hospital because of general malaise, thirst, and polydipsia which initiated 3 weeks before admission. Her urine volume was 5 L daily with a similar volume of oral water intake. She had no smoking history and had previously been in good health. Her height was 153 cm and weight was 53 kg, and her vital signs were as follows: body temperature, 36.2°C; blood

pressure, 160/88 mmHg; pulse rate, 63 beats/min with a regular rhythm; respiratory rate, 18 breaths/min; and oxygen saturation, 97% while breathing ambient air. Her Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 4. A physical examination revealed no abnormalities. On neurological examination, there were no focal deficits, and her ocular motion and visual field were normal.

Her serum sodium level was high (159 mEq/L) and serum osmolality (313 mOsm/kg-H₂O) was higher than her urine osmolality (67 mOsm/kg-H₂O); however, her serum ADH level was low (0.5 pg/mL). Her anterior pituitary gland function was within the normal range. Two hours following intranasal 1-deamino-8-D-arginine vasopressin (DDAVP) administration, her urine osmolality increased from 67 to 237 mOsm/kg-H₂O, and her urine volume for two hours decreased from 875 to 80 mL. A chest X-ray showed diffuse micronodular shadows in both lung fields and a mass in the left lower lung field (Fig. 1). Computed tomography (CT) showed diffuse micronodular shadows in both lungs, a mass that measured 40 mm in diameter in the left lower lobe

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(Fig. 2A), and multiple metastases in the liver and adrenal gland. Brain magnetic resonance imaging (MRI) showed multiple gadolinium-enhanced nodules and a heterogeneous enhanced nodule that measured 8 mm in diameter in the sellar region (Fig. 3). On T1-weighted MRI, the posterior pituitary lobe exhibited an isointense signal, suggesting an ADH deficiency. Transbronchial lung biopsy was performed, and she was diagnosed with lung adenocarcinoma (cT2bN3M1c, stage IVB). The tumor was epidermal growth factor receptor (EGFR) exon 19 deletion mutation-positive, anaplastic lymphoma kinase rearrangements-negative, c-ros oncogene 1 rearrangements-negative, and programmed death-ligand 1 -negative. We concluded that the central diabetes insipidus had been caused by pituitary metastasis of the lung cancer.

We initiated first-line treatment with the EGFR tyrosine kinase inhibitor, gefitinib (250 mg daily), because osimertinib had not yet been approved as a first-line treatment at that time. Three weeks after treatment with gefitinib, chest CT showed shrinkage of the primary tumor and multiple metastases (Fig. 2B), and her ECOG PS improved from 4 to 2. Although we initiated the nasal administration of DDAVP



Figure 1. A chest X-ray on admission showed diffuse micronodular shadows in both lung fields and a mass in the left lower lung field.

for the treatment of diabetes insipidus, her urine volume remained unstable. Therefore, we initiated radiotherapy (30 Gy in 10 fractions) for pituitary metastasis. A few days after the completion of radiotherapy, her urine volume decreased to 2 to 3 L daily, and she was discharged.

Although we reduced the dose of gefitinib to an alternative administration because of grade 3 elevations in aspartate aminotransferase and alanine aminotransferase levels, she had achieved a partial response to the treatment. Four months after treatment with gefitinib, brain MRI showed the disappearance of multiple brain metastases (Fig. 3C) and shrinkage of the pituitary metastasis (Fig. 3D). We did not add radiotherapy for brain metastases. No symptoms of diabetes insipidus were noted, and we ceased the treatment with DDAVP. One month after the cessation of DDAVP, the symptoms recurred. After resuming DDAVP, the symptoms improved promptly; therefore, the treatment with DDAVP was continued. The clinical course is summarized in Fig. 4.

Discussion

According to previous postmortem studies, metastasis to the pituitary gland is reported to occur in from 1.8% to 20% of patients with cancer (1, 2). The most common primary sites of pituitary metastasis are the breasts and lungs (3). Only 6.8% of pituitary metastasis cases on autopsy are found to be symptomatic, and diabetes insipidus is the most common clinical presentation of pituitary metastasis in symptomatic patients (2).

The treatments for pituitary metastasis are surgery, chemotherapy, and radiotherapy (4). These treatments are effective for symptoms such as headache and visual field deficits due to compression of the tumor; however, they are mostly ineffective for the symptoms of diabetes insipidus (5). Although some reports have suggested that radiotherapy may be used to treat diabetes insipidus (6-10), chemotherapy alone has not been reported to improve these symptoms. This suggests that radiotherapy is more effective than chemotherapy for brain metastases.

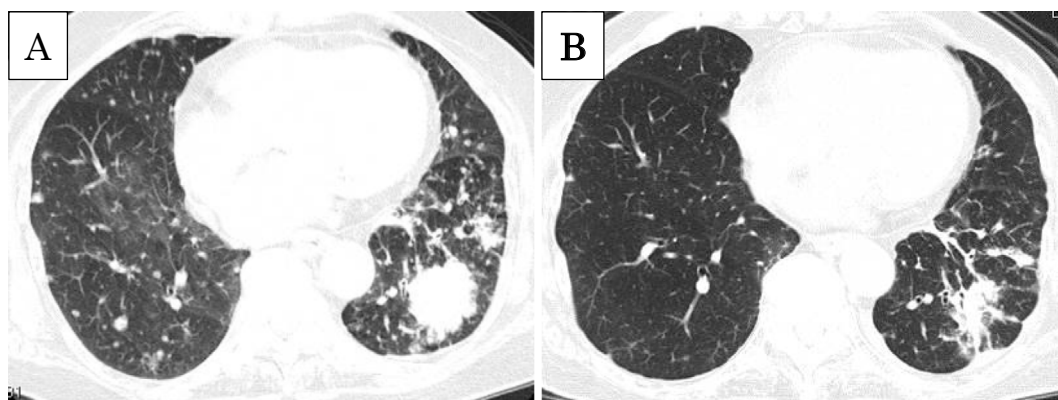


Figure 2. (A) Chest CT on admission showed diffuse micronodular shadows in both lungs, a mass that measured 40 mm in diameter in left lower lobe. (B) Chest CT 3 weeks after treatment with gefitinib showed shrinkage of the primary tumor and multiple metastases.

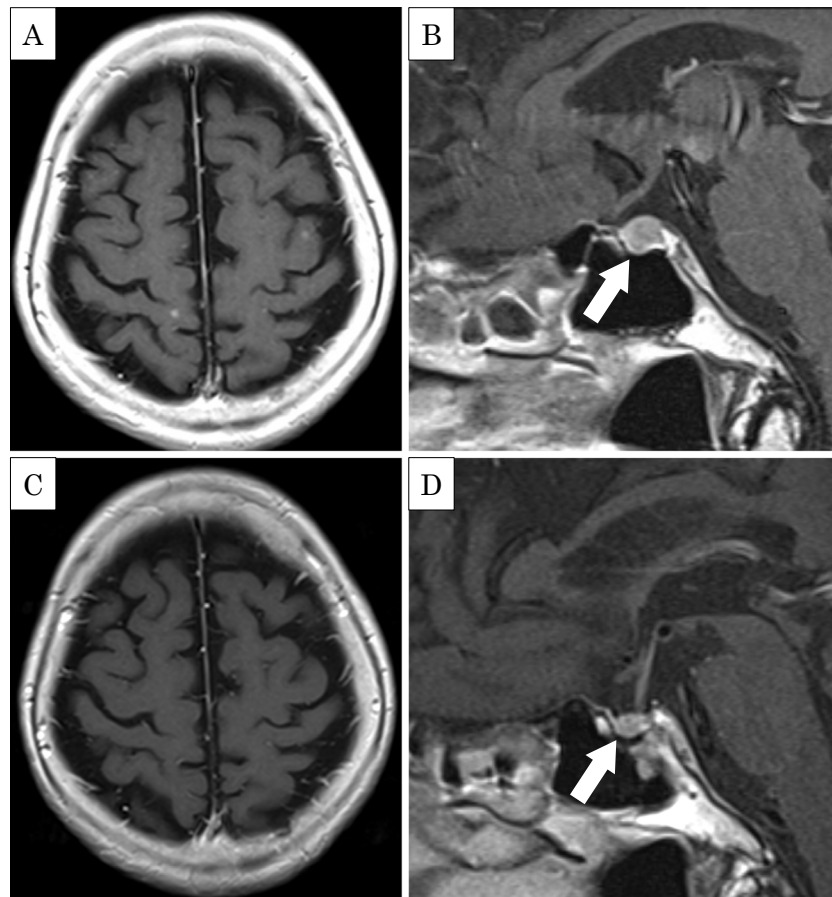


Figure 3. Brain MRI (T1-weighted scan with gadolinium contrast) on admission showed (A. coronal section) multiple gadolinium-enhanced nodules, (B. midsagittal section) a heterogeneous enhanced nodule that measured 8 mm in diameter in the sellar region (arrow). Brain MRI 4 months after treatment with gefitinib showed the disappearance of multiple brain nodules (C) and shrinkage of the pituitary nodule (arrow) (D).

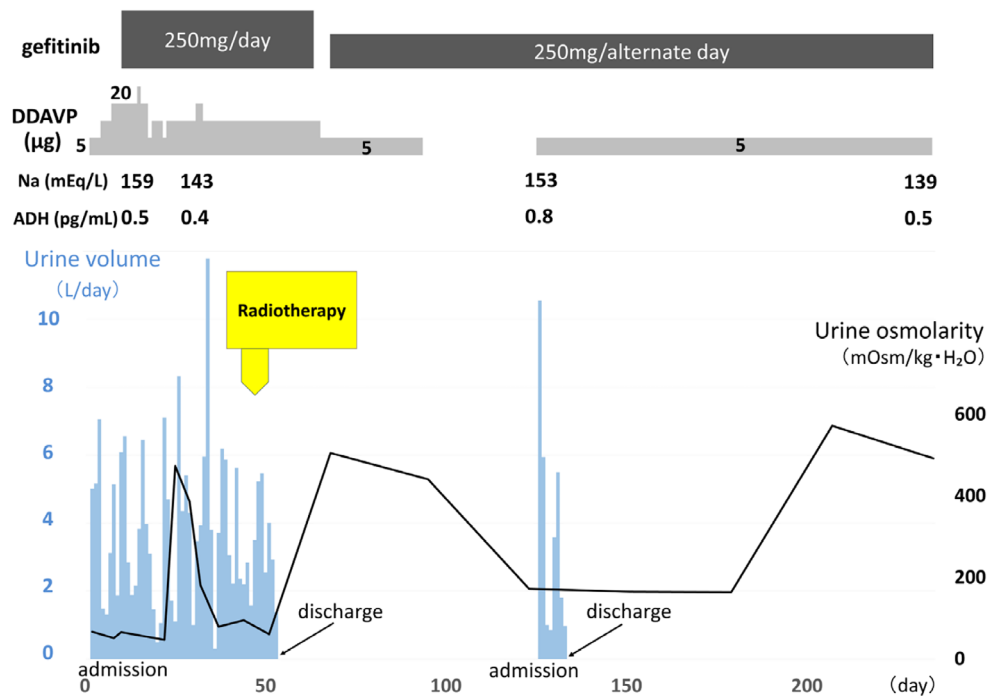


Figure 4. The clinical course after admission. ADH: antidiuretic hormone, DDAVP: 1-deamino-8-D-arginine vasopressin

In the present case, treatment with gefitinib was effective for controlling the lung cancer including brain metastasis. However, it was ineffective for controlling diabetes insipidus within 3 weeks. As reported previously, radiotherapy was promptly effective for diabetes insipidus. However, the continuous administration of DDAVP was needed. This suggests that the ability of hormone secretion was irreversibly destroyed by the tumor. The 5-year incidence of radiation-associated hypopituitarism is approximately 20%, which increases to 80% after 10-15 years (11). In the present case, the patient was super elderly; therefore, we did not consider the long-term complications due to radiotherapy.

In conclusion, we should positively consider radiotherapy for pituitary metastases even in cases of favorable tumor control when diabetes insipidus becomes clinically overt. Furthermore, continuous DDAVP administration may be needed to treat central diabetes insipidus.

The authors state that they have no Conflict of Interest (COI).

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