

# Diabetes insipidus and adrenal insufficiency in a patient with metastatic breast cancer

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## ABSTRACT

A patient previously treated for bilateral breast cancer with mastectomy, radiation therapy and in remission on hormonal therapy for more than five years presented with abdominal symptoms from breast cancer relapse. She developed inappropriate polyuria and hypernatraemia, which responded to desmopressin. In combination with the absence of a high signal from the posterior lobe of the pituitary on MRI, these data indicated the presence of partial central diabetes insipidus. The anterior pituitary showed partial failure (low follicle-stimulating hormone, luteinising hormone and insulin-like growth factor-1 levels). Furthermore, primary adrenal insufficiency had developed, ascribed to bilateral tumour invasion of the adrenals. This rare combination of endocrinological failures in a patient with metastatic breast cancer is discussed.

## KEYWORDS

Breast cancer, central diabetes insipidus, primary adrenal insufficiency

## INTRODUCTION

Endocrine syndromes can occur as a result of tumour metastases. Diabetes insipidus has been described in patients with advanced breast cancer, although in general clinical manifestations of metastases due to involvement of the hypothalamic-pituitary region are rare.<sup>1</sup> Adrenal metastases occur frequently, but only rarely cause adrenal failure.<sup>2</sup> We present a 57-year-old patient with breast cancer who developed partial central diabetes insipidus (CDI), partial anterior pituitary failure and primary adrenal insufficiency from metastases.

## CASE REPORT

A 57-year-old woman presented in 2004 with a two-month history of abdominal pain, dysphagia and occasional vomiting. Her medical history revealed bilateral breast cancer in 1997, for which radical mastectomy and bilateral axillary dissection were performed. Histological examination showed bilateral infiltrating ductal carcinoma and bilateral axillary node metastases; a left supraclavicular lymph node also showed tumour infiltration (left breast: pT1N1M1, right breast: pT1N1M0). The oestrogen receptor was weakly positive for both tumours and the progesterone receptor was weakly positive for the left and positive for the right breast. In addition, she was treated with bilateral locoregional radiotherapy including the left supraclavicular lymph node metastasis and started on systemic adjuvant endocrine therapy with tamoxifen. In 1998 she developed lymphangitis of the chest wall. Subsequently, the hormonal therapy was switched to anastrozole and she attained a complete remission for five and a half years.

Evaluation of her abdomen by a computed tomography (CT) scan showed bilateral hydronephrosis and extensive retroperitoneal, mesenterial and para-aortal lymphadenopathy, as well as bilateral large adrenal glands (right: 41 x 21, left: 44 x 24 mm). Double J stents were inserted. Biopsy from one of the adrenal masses revealed infiltrative ductal carcinoma (oestrogen receptor positive with weak expression of progesterone receptor). Overexpression of HER2 could not be detected on the biopsy specimen nor on either of the primary tumours. She started palliative chemotherapy consisting of cyclophosphamide and doxorubicin. Six days later, she was admitted to our hospital with dysphagia and vomiting, but was still able to drink. She had lost three kilograms in weight. On physical examination a tired looking woman was seen with a body weight of 67 kg. Blood pressure was 100/60 mmHg, pulse rate 68 beats/min and body temperature 37.4 °C. Apart from scars from

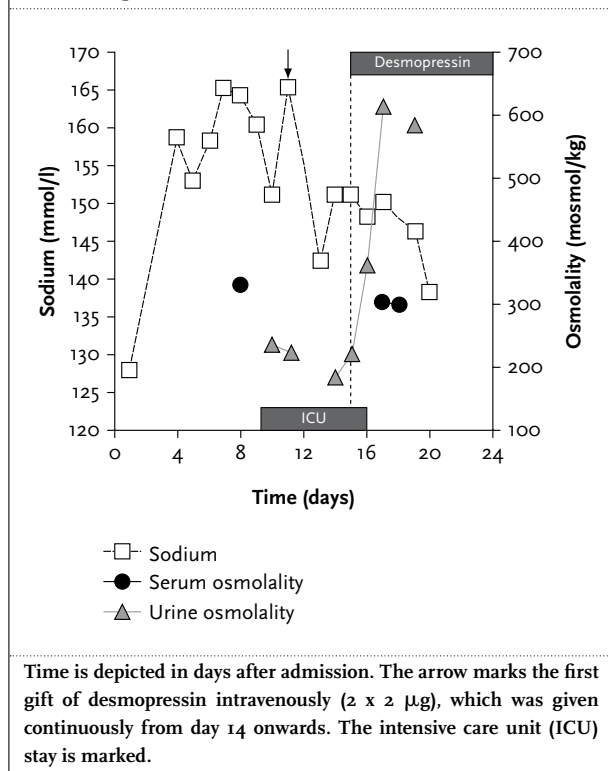
the bilateral mastectomy there were no abnormalities on physical examination. Laboratory investigations showed the following results: haemoglobin 7.0 mmol/l (7.5-10.0), mean cell volume 89 fl (80-100), leucocytes  $1.6 \times 10^9/l$  (4.5-10) with 81.3% neutrophils, thrombocytes  $221 \times 10^9/l$  (150-450), sodium 128 mmol/l (136-144), potassium 3.7 (3.6-4.8), urea 10.0 mmol/l (2.5-7.5), creatinine 106  $\mu\text{mol/l}$  (<80), albumin 39 g/l (40-50), and calcium 2.45 mmol/l (2.25-2.55 mmol/l).

Three days after admission she developed fever with neutropenia. One blood culture revealed *Escherichia coli*, whereas urine cultures were negative. Ultrasound examination of the abdomen showed persistent hydronephrosis of the right kidney. The right double J stent was therefore exchanged. After four days she developed hypernatraemia with a highest value of 165 mmol/l (figure 1) and hypokalaemia (2.5 mmol/l). She admitted being thirsty. One week after admission, she became polyuric (3.5-5.5 litres/day) and somnolent and the suspicion of diabetes insipidus arose. Her medical condition deteriorated and she had to be transferred to the intensive care unit because of haemodynamic instability and fear of respiratory arrest. During her stay in intensive care, she required mechanical ventilation for four days and was persistently polyuric and hypernatraemic (figure 1) in the presence of inappropriately low urine osmolality.

Desmopressin resulted in a reduction in the polyuria associated with an increase in urine osmolality (figure 1). Because of persistently low blood pressures, an adrenocorticotrophic hormone (ACTH) stimulation test was performed. This test showed a basal cortisol level of 0.29  $\mu\text{mol/l}$  with a maximal increase of cortisol to only 0.41  $\mu\text{mol/l}$  on ACTH administration (0.25 mg, table 1), indicating primary adrenal failure. Therefore hydrocortisone was started (100 mg three times daily).

After returning to the oncology ward, she gradually recovered from her somnolent state. She then told us that she had been drinking about four litres of fluid a day since 1997, also during the night time. Magnetic resonance imaging (MRI) of the brain with gadolinium enhancement revealed no visible tumours. However, the posterior lobe of the pituitary did not reveal the usual enhanced signal, suggesting tumour infiltration. Hormonal evaluation of other pituitary axes showed low levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), despite her postmenopausal status (table 2). The ACTH stimulation test was repeated as the first test was carried out under high stress conditions (after cessation of hydrocortisone), and showed a normal basal cortisol level in the presence of elevated basal ACTH (584 ng/l) and an absent cortisol response (table 1). Insulin-like growth factor-1 (IGF-1) levels were low compared with age- and

**Figure 1.** Time course of serum sodium levels and osmolality in serum and urine



**Table 1.** Results from ACTH stimulation tests

	Cortisol ( $\mu\text{mol/l}$ )			ACTH (<75 ng/l)
	t = 0	t = 30	t = 60	t = 0
Day 12	0.29	0.41	0.38	
Day 35	0.51	0.53	0.52	584

Days are counted from admission. t = time in minutes after administration of 0.25 mg ACTH. Normal ACTH values are given in parentheses.

**Table 2.** Laboratory results from anterior pituitary hormones

	Day 18	Day 27	Day 41	N
FT4	7.7	14.4		10-24 pmol/l
TSH	2.36	5.62		0.3-4.8 mU/l
LH	0.9	6.8	7.2	11-75 U/l
FSH	6.3	17	14	>30 U/l
Prolactin	13	25		<30 $\mu\text{g/l}$
GH	0.75			0-5 mU/l
IGF-1	7.8	5.3		11.6-48.4 nmol/l

Days are counted from admission. N = normal values; FT4 = free thyroxin; TSH = thyroid stimulating hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor-1; GH = growth hormone.

gender-matched values. This could be explained by her clinical condition and/or growth hormone (GH) deficiency. Because of the contraindications for GH replacement (i.e. presence of cancer), we did not perform a GH stimulation test to confirm a diagnosis of GH deficiency.

Firstly, it was concluded from the clinical symptoms, laboratory results and MRI that she had a partial central diabetes insipidus, possibly present for several years, most likely caused by breast cancer metastases. In addition, she had partial anterior pituitary failure, reflected in low FSH, LH and IGF-1 (*table 2*). Secondly, she had bilateral adrenal gland metastases leading to primary adrenal insufficiency under stressful clinical conditions. She was treated with hydrocortisone in a substitution dose (20-10-10 mg daily) and desmopressin nasal spray 10 µg twice daily, after which the sodium levels returned to normal and the polyuria diminished.

Follow-up in the outpatient department showed a regression of the lymphadenopathy and reduction in the volume of adrenal gland metastasis on abdominal CT scan after six cycles of cyclophosphamide and doxorubicin.

## DISCUSSION

Diabetes insipidus is a syndrome characterised by hypotonic polyuria and polydipsia, either as a result of inadequate antidiuretic hormone (ADH) secretion (central diabetes insipidus (CDI)), inadequate renal response to ADH (nephrogenic diabetes insipidus) or primary polydipsia. Causes of CDI are congenital or acquired lesions that disrupt the neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus axis. These lesions are malformations, damage resulting from surgery or trauma, tumours, haemorrhage, thrombosis, infarction or granulomatous disease. Some 30 to 50% of cases are idiopathic.<sup>3,4</sup> Primary tumours are craniopharyngioma, meningioma or germinoma, but secondary tumours can also occur. Metastases in the posterior pituitary lobe are more common than in the anterior lobe, possibly caused by the direct blood supply of the posterior lobe from the systemic circulation. Metastases in the hypothalamic-pituitary region at autopsy are relatively common in breast cancer, varying from 5.3 to 28%.<sup>15</sup> However, clinical symptoms of CDI in patients with metastatic breast cancer are rare.

On MRI the posterior pituitary is identified by hyperintensity, probably caused by phospholipids or secretory granules in pituicytes.<sup>6</sup> A lack of this hyperintensity on sagittal T1-weighted images, as was observed in our patient, is the hallmark of hypothalamic-posterior pituitary disorders and may represent an early stage of tumour infiltration.<sup>4,7</sup> A thickened pituitary stalk could be another indicative finding.

Our patient developed hypernatraemia and hyperosmolality while producing many litres of urine of a low osmolality (*figure 1*), probably triggered by insufficient water intake. There was no glucosuria or other causes of osmotic diuresis. A water deprivation test was not performed because of the high clinical suspicion of central diabetes insipidus, the instable condition of the patient and the good response to desmopressin, which indicates insufficient endogenous ADH secretion. Our patient stated that she had been drinking many litres a day for years, suggesting that she had pituitary metastases while being in complete remission for five years on anastrozole.

All anterior pituitary gland hormones could be involved in the metastatic process. In our patient serum gonadotropin levels were inappropriately low for a postmenopausal woman. In contrast to tamoxifen, which reduces gonadotropin levels by its weak oestrogen agonistic effect, anastrozole, an aromatase inhibitor, is expected to increase FSH and LH.<sup>8</sup> Furthermore, IGF-1 levels, controlled by GH, were also low. These findings are in accordance with the diagnosis of partial pituitary insufficiency. The abnormalities found in free thyroxin and thyroid-stimulating hormone could be ascribed to nonthyroidal illness, as these levels returned to normal values.

Primary adrenal insufficiency is usually caused by autoimmune disease. Other causes are infections or haemorrhagic infarction of the adrenals. Infiltration of the adrenal glands by metastases (lung, breast, melanoma, lymphoma) is common, but this rarely leads to adrenal insufficiency, probably because not all cortex tissue is destroyed.<sup>2,9</sup> However, there are reports that patients with bilateral adrenal gland metastases are prone to develop partial adrenal insufficiency, requiring corticosteroid replacement therapy.<sup>10,11</sup>

During critical illness and stress situations, such as in intensive care units, relative adrenal insufficiency can be caused by maximal endogenous cortisol stimulation. An increase in cortisol after exogenously administered ACTH can then be absent, as was found in the first ACTH test in our patient.<sup>12</sup> The second test showed a higher basal cortisol level, but in the presence of increased ACTH levels and no response to exogenous ACTH administration, indicating primary hypoadrenalism.<sup>13,14</sup> Probably the combination of illness together with adrenal gland tumour invasion led to (subclinical) adrenal insufficiency.

The serum electrolyte abnormalities known to be caused by adrenal insufficiency are in contrast to those found in our patient. This can be caused by diminished glucocorticoid production rather than mineralocorticoid deficiency and by the simultaneously occurring hypernatraemic CDI. The hyponatraemia associated with adrenal insufficiency is caused by volume contraction and inappropriate ADH

secretion<sup>15</sup> and upregulation of aquaporin-2 (the water channels regulated by ADH).<sup>16</sup> As ADH production could not be increased, hyponatraemia did not occur in our patient. Another interaction between ADH and the hypothalamus-pituitary-adrenal gland axis is the association of CDI with higher ACTH and cortisol levels by as yet unclear mechanisms.<sup>17,18</sup> On the other hand, secondary adrenal insufficiency results in higher ADH levels.<sup>19</sup> Mineralocorticoid treatment was not started because of the good clinical response to hydrocortisone alone and the possibility of electrolyte disturbances from the simultaneously occurring CDI and hypokalaemia.

Our patient needed potassium chloride supplementation during her hospital stay. She received parenteral feeding for several weeks because oral feeding resulted in vomiting and subileus, probably due to the intra-abdominal metastases. The loss of potassium was likely caused by gastric secretions and renal loss from the polyuria. After correction of the potassium, polyuria persisted. Short-lived nephrogenic diabetes insipidus can result from hypokalaemia, but the mild concentrating defect does not cause hyperosmolality and responds to correction. This probably results from downregulation of aquaporin-2 and does not respond to desmopressin.<sup>20</sup>

The combination of failure in the hypothalamic-pituitary area and primary adrenal insufficiency is rarely reported.<sup>21</sup> Trincado *et al.* described a male patient with bronchogenic carcinoma whose first clinical manifestation was diabetes insipidus secondary to metastases to the hypothalamic-pituitary area who developed anterior pituitary failure, as well as primary adrenal insufficiency due to metastases in both adrenals.

In conclusion, we present a patient with breast cancer relapse after having been in remission for more than five years on hormonal therapy, who developed partial CDI, partial anterior pituitary insufficiency and primary adrenal insufficiency.

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#### REFERENCES

1. Huinink DT, Veltman GA, Huizinga TW, Roelfsema F, Keizer HJ. Diabetes insipidus in metastatic cancer: two case reports with review of the literature. *Ann Oncol* 2000;11(7):891-5.
2. Lutz A, Stojkovic M, Schmidt M, Arlt W, Allolio B, Reincke M. Adrenocortical function in patients with macrometastases of the adrenal gland. *Eur J Endocrinol* 2000;143(1):91-7.
3. Verbalis JG. Management of disorders of water metabolism in patients with pituitary tumors. *Pituitary* 2002;5(2):119-32.
4. Maghnie M. Diabetes insipidus. *Horm Res* 2003;59(suppl 1):42-54.
5. Fassett DR, Couldwell WT. Metastases to the pituitary gland. *Neurosurg Focus* 2004;16(4):E8.
6. Shin JH, Lee HK, Choi CG, et al. MR imaging of central diabetes insipidus: a pictorial essay. *Korean J Radiol* 2001;2(4):222-30.
7. Chaudhuri R, Twelves C, Cox TC, Bingham JB. MRI in diabetes insipidus due to metastatic breast carcinoma. *Clin Radiol* 1992;46(3):184-8.
8. Bajetta E, Zilembo N, Bichisao E, Pozzi P, Toffolatti L. Steroidal aromatase inhibitors in elderly patients. *Crit Rev Oncol Hematol* 2000;33(2):137-42.
9. Lam KY, Lo CY. Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. *Clin Endocrinol (Oxf)* 2002;56(1):95-101.
10. Redman BG, Pazdur R, Zingas AP, Lored R. Prospective evaluation of adrenal insufficiency in patients with adrenal metastasis. *Cancer* 1987;60(1):103-7.
11. Seidenwurm DJ, Elmer EB, Kaplan LM, Williams EK, Morris DG, Hoffman AR. Metastases to the adrenal glands and the development of Addison's disease. *Cancer* 1984;54(3):552-7.
12. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003;348(8):727-34.
13. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003;139(3):194-204.
14. Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996;335(16):1206-12.
15. Ahmed AB, George BC, Gonzalez-Auvert C, Dingman JF. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucocorticoids. *J Clin Invest* 1967;46(1):111-23.
16. Saito T, Ishikawa SE, Ando F, Higashiyama M, Nagasaka S, Sasaki S. Vasopressin-dependent upregulation of aquaporin-2 gene expression in glucocorticoid-deficient rats. *Am J Physiol Renal Physiol* 2000;279(3):F502-8.
17. Pivonello R, Faggiano A, Filippella M, et al. Hypothalamus-pituitary-adrenal axis in central diabetes insipidus: ACTH and cortisol responsiveness to CRH administration. *J Endocrinol Invest* 2002;25(11):932-7.
18. Itagaki E, Ozawa S, Yamaguchi S, et al. Increases in plasma ACTH and cortisol after hypertonic saline infusion in patients with central diabetes insipidus. *J Clin Endocrinol Metab* 2001;86(12):5749-54.
19. Yatagai T, Kusaka I, Nakamura T, et al. Close association of severe hyponatremia with exaggerated release of arginine vasopressin in elderly subjects with secondary adrenal insufficiency. *Eur J Endocrinol* 2003;148(2):221-6.
20. Amlal H, Krane CM, Chen Q, Soleimani M. Early polyuria and urinary concentrating defect in potassium deprivation. *Am J Physiol Renal Physiol* 2000;279(4):F655-63.
21. Trincado P, Playan J, Acha J, et al. Adrenal failure due to metastasis both to the hypothalamic-pituitary area and the adrenals. *Tumori* 1996;82(4):401-4.