

# Hiccups as the first presentation of secondary adrenal insufficiency associated with advanced cervical cancer

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## Summary

Hiccups are a common symptom characterized by intermittent spasmodic contraction of the diaphragm. Most hiccups are transient, but some are refractory. Patients with intractable hiccups often have abnormalities of the diaphragm, medulla oblongata, and lesions affecting nerve fibers connecting them. Moreover, electrolyte abnormalities, including hyponatremia, are frequently observed in patients with intractable hiccups. Adrenal insufficiency (AI) is one of the causes of hyponatremia. However, hiccups are not commonly the first presentation. Herein, we describe a case of a 45-year-old woman complaining of refractory hiccups. The patient was initially diagnosed with hiccups associated with cervical cancer metastasis to the liver and peritoneum. The administration of chlorpromazine did not have a beneficial effect on her hiccup. Fasting hypoglycemia and hyponatremia were later found. Her serum cortisol level was low without an elevation of adrenocorticotropic hormone level. MRI of the pituitary gland showed metastatic lesion in the pituitary gland and stalk. Thus, the patient was diagnosed with secondary AI due to cervical cancer metastasis to the pituitary gland and stalk. Administration of hydrocortisone improved her hiccups with the normalization of serum sodium level. Therefore, differential diagnosis in advanced cancer patients with hiccups should include AI-induced hyponatremia.

## Learning points:

- Hiccups could be the first manifestation of adrenal insufficiency (AI).
- Hiccups in patients with AI are often mediated by hyponatremia.
- Hyponatremia is less frequent in secondary AI than in primary AI. However, hyponatremia can result from increased antidiuretic hormone due to loss of cortisol.
- The differential diagnosis should include AI-induced hyponatremia if hiccups occur in patients with advanced cancer, as metastasis to adrenal gland or pituitary gland could cause AI.

## Background

Hiccups are a symptom characterized by intermittent spasmodic contraction of the diaphragm. Most hiccups are transient, but some are refractory. Refractory hiccups can be caused by several conditions, including gastroesophageal conditions, central nervous disorders, malignancy of the

liver and peritoneum, electrolyte abnormalities, alcohol, psychogenic disorders, and some medications.

Most conditions that result in hiccups are common, and patients with advanced cancer often have some of them. Therefore, the prevalence of hiccups in patients



with advanced cancer is high at 3.9–4.8% (1). However, in some patients with advanced cancer, hiccups may improve by removing some of the many causes, even if they have multiple causes. Herein, we described a case of a Japanese woman with advanced cervical cancer, with complaints of refractory hiccups. The patient was initially diagnosed with hiccups associated with cervical cancer metastasis to the liver and peritoneum, which was known to cause hiccups. However, secondary adrenal insufficiency (AI) due to cervical cancer metastasis to the pituitary gland and stalk was diagnosed, and her hiccups resolved immediately after steroid replacement therapy.

## Case presentation

A 45-year-old Japanese woman was admitted to our hospital with a 4-week complaint of refractory hiccups causing a loss of appetite and difficulty sleeping. The patient had been diagnosed with stage 2 cervical cancer 35 months previously and underwent an extensive total hysterectomy and bilateral adnexal resection. The patient then received adjuvant systemic chemotherapy and radiation therapy. However, recurrence was observed in the liver, peritoneum, and cerebellum. The patient had then been treated with combined systemic chemotherapy and gamma-knife radiosurgery. These metastatic lesions had not enlarged on examination 3 months prior. The patient had no family history or drinking or smoking history.

Four weeks before hospitalization, the patient complained of frequent hiccups. CT of the abdomen showed a known liver and peritoneal metastasis of cervical cancer. No abnormality was found on upper gastrointestinal endoscopy and chest CT examination. Therefore, the patient was diagnosed with hiccups associated with liver and peritoneal metastatic lesions. Chlorpromazine (75 mg/day) was administered, but no beneficial effect was observed. Her hiccups worsened, and she experienced severe fatigue to the extent of loss of appetite, which prompted her admission.

On admission, her body weight and BMI were 46.8 kg and 18.7 kg/m<sup>2</sup>, respectively. Her blood pressure was 102/76 mmHg, heart rate was 97 beats/min, temperature was 36.9°C, and oxygen saturation was 98% in room air. No abnormalities were observed on examination of the chest and abdomen.

## Investigation

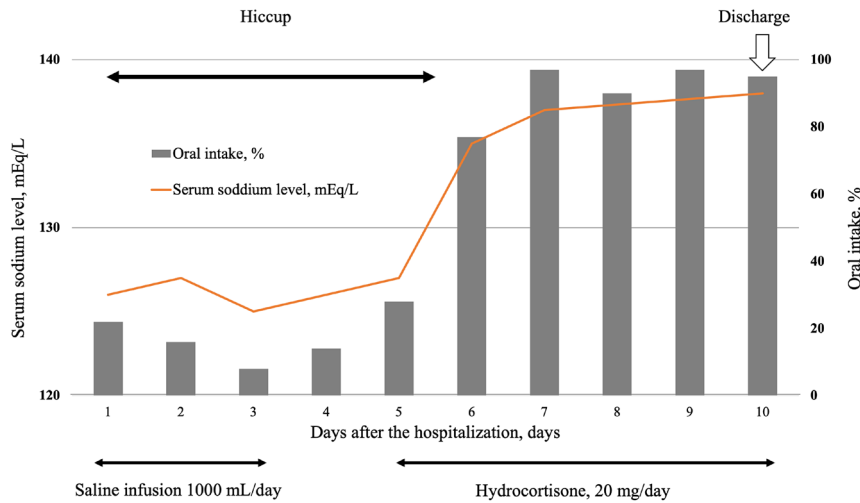
As shown in Table 1, laboratory evaluation revealed hyponatremia (126 mEq/L) with urine sodium excretion

**Table 1** Laboratory findings.

Parameter	Results	Normal range
TP, g/dL	5.5	6.7–8.3
Alb, g/dL	3.3	4.0–5.0
BUN, mg/dL	12	8.0–22.0
Cr, mg/dL	1.03	0.60–1.0
AST, U/L	36	13–33
ALT, U/L	15	8–42
γGTP, U/L	25	10–47
Na, mEq/L	127	135–249
K, mEq/L	4.6	3.5–4.9
Cl, mEq/L	96	96–108
Ca, mg/dL	9.2	8.0–10.5
P, mg/dL	3.8	2.5–4.5
FPG, mg/dL	44	69–109
Serum osmolarity, mOsm/L	235	275–290
TSH, pg/mL	0.58	0.34–3.88
FT4, pg/mL	0.86	0.95–1.74
ACTH, pg/mL	15.2	7.2–63.3
Cortisol, μg/mL	2.89	7.07–19.6
LH, mIU/mL	2.23	11–50
FSH, mIU/mL	17.29	26–120
GH ng/mL	1.14	0.13–9.88
IGF-1, ng/mL	27	87–172
PRL, ng/mL	193	3.12–29.32
E2, pg/mL	<5.0	<47.0
ADH, pg/mL	1.5	<2.8

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; E2, estradiol; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FT4, free thyroxine; γGTP, γ-glutamyl transpeptidase; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; PRL, prolactin; TP, total protein; TSH, thyroid-stimulating hormone.

of 47 mEq/L, urine osmolarity of 354 mOsm/L, and fractional excretion of sodium of 3.37%. No abnormalities in other electrolytes such as potassium and calcium were observed. Her clinical course is shown in Fig. 1. The patient was treated with intravenous saline infusion. However, serum sodium levels did not improve, and hiccups persisted. After hospitalization, fasting hypoglycemia (46 mg/dL) was observed. The patient's adrenocorticotropic hormone (ACTH), cortisol, prolactin, and antidiuretic hormone (ADH) levels were 15.2 pg/mL, 2.89 μg/dL, 193 ng/mL, and 1.5 pg/mL, respectively. Her urine-free cortisol level was 9.2 μg/day. ACTH levels after corticotropin-releasing hormone loading were 11.5 and 159 pg/mL, respectively, which indicated an overreaction of ACTH. Contrarily, serum ACTH and cortisol levels did not increase after hypoglycemia. MRI of the pituitary gland showed metastatic lesions in the pituitary gland and stalk (Fig. 2). Therefore, the patient was diagnosed with secondary AI due to cervical cancer metastasis to the pituitary gland and stalk.



**Figure 1**  
Clinical course of this patient. After hospitalization, saline infusion was administered. However, the patient's hiccups, loss of appetite, and hyponatremia did not improve. Oral hydrocortisone was administered on day 5. The patient's symptoms improved within a day.

## Treatment

Administration of hydrocortisone 20 mg/day normalized the serum sodium level, and the hiccups quickly resolved within the day. In addition, her appetite improved and her fatigue disappeared. The patient was discharged 5 days after the administration of hydrocortisone, as her hiccups, fatigue, and loss of appetite improved.

## Outcome and follow-up

After her discharge, her hiccups did not recur. After discharge, she continued gamma-knife radiosurgery for brain metastases and systemic chemotherapy. But her tumor continued to grow. Two months after discharge, she was hospitalized with a bowel obstruction due to peritoneal lesions. Fortunately, she was discharged from the hospital, but her treatment plan was changed to best supported care.

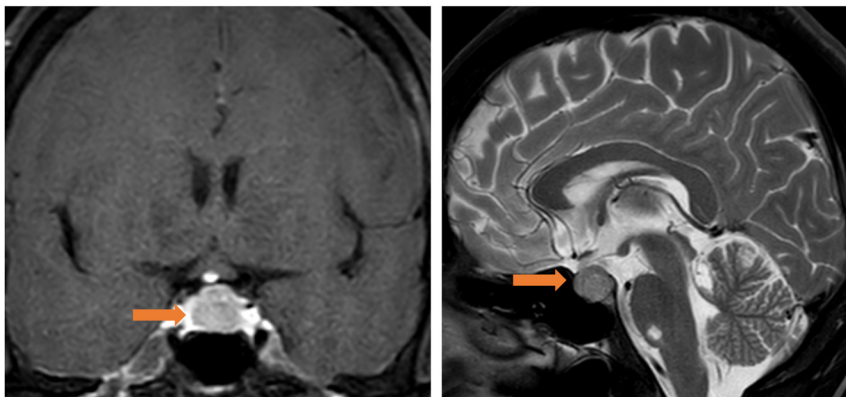
## Discussion

To our knowledge, this is the first case of a patient presenting with hiccups as the first symptom of secondary

AI. The patient was initially diagnosed with hiccups associated with the liver and peritoneal metastasis of cervical cancer. However, the patient was later diagnosed with secondary AI and her hiccups resolved immediately after steroid replacement therapy.

AI is characterized by cortisol deficiency and can be classified as primary AI and secondary AI. Primary AI occurs when a pathology affects the adrenal glands. Secondary AI results from a decrease in ACTH levels in the pituitary gland. The most common symptoms of AI are unintentional weight loss, anorexia, hypotension, fatigue, muscle pain, and abdominal pain (2). Conversely, it is not widely known that hiccups are one of the symptoms associated with AI.

Hiccup is defined as an intermittent spasmodic contraction of the diaphragm. Afferent fibers from the diaphragm are vagal and diaphragmatic nerves. Stimulation from the diaphragm is transmitted via these nerves to the medulla oblongata. The centrifugal tract from the medulla oblongata is the diaphragmatic nerve, which transmits the stimulus to the diaphragm and causes hiccups. Pathological hiccups occur when one of these pathways is compromised,



**Figure 2**  
Enhanced T1-weighted image of pituitary MRI. MRI of pituitary gland shows metastasis in the pituitary gland and stalk.



and they can be divided into four categories depending on the causative lesion. The first is lesions that directly irritates the diaphragm. These lesions include malignant tumors and inflammatory lesions in liver, peritoneum, and lung. The second is lesions that stimulate the afferent and/or centrifugal tract between the diaphragm and medulla oblongata. These lesions include gastroesophageal lesions and lung disease. The third is intracranial lesions that stimulate medulla oblongata directly. The presence of a brainstem lesion or inflammation or compression that stimulates the brainstem can cause hiccups. Finally, electrolyte abnormalities, primarily hyponatremia, and some medications are listed as the cause of pathological hiccups. There is no known mechanism for hyponatremia-induced hiccups. However, George *et al.* reported that every 10 mEq/L reduction in serum sodium level increases the risk of developing hiccups 17 times (3).

In our case, hyponatremia and metastatic lesions of the liver and peritoneum were seen as the cause of hiccups and steroid replacement therapy improved hiccups. Although metastasis of cervical cancer to the liver and peritoneum was observed in our case, these lesions were unlikely improved by hydrocortisone. This is because there are no reports in which steroid treatment for cervical cancer results in tumor shrinkage. Considering the correlation between the course of serum sodium level and the course of hiccups in our case, hiccups were considered caused by hyponatremia associated with AI.

As shown in Table 2, only five cases of AI-induced hiccups have been reported (4, 5, 6, 7). These reported cases were similar to ours in that hyponatremia was present, and the hiccups resolved promptly with steroid replacement therapy and normalization of serum sodium levels. However, there are some differences between these reported cases and ours. The first is the category of AI.

All these reported cases were diagnosed with primary AI. However, our patient was diagnosed with a secondary AI. In primary AI, aldosterone secretion from the adrenal glands is impaired. Conversely, aldosterone secretion from the adrenal glands is preserved in secondary AI. Therefore, hyponatremia is more likely to occur in primary AI than in secondary AI. However, in secondary AI, the loss of cortisol increases ADH levels and induces hyponatremia (8). Therefore, hyponatremia was observed in our case, despite the case being secondary AI. The second difference was the coexisting disease. Our case showed metastatic lesions in the liver and peritoneum, which could cause hiccups. Of the five reported cases, four had no evidence of malignancy. Pathmanathan *et al.* reported a case of AI associated with malignant lymphoma (6). However, the lesion of malignant lymphoma was limited in the bilateral adrenal gland, which could not directly stimulate the diaphragm. In our case, the coexisting disease itself could also cause hiccups, which made the initial diagnosis difficult.

Hyponatremia, which is one of the causes of hiccups, is seen in 47% of patients with advanced cancer (9). AI is one of the main causes of hyponatremia in patients with advanced cancers. Adrenal metastases are found in 14–16% of patients with recurrent cervical cancer (10). Moreover, the metastasis to the hypothalamus and/or pituitary gland can also induce secondary AI, although there are no detailed reports on the prevalence of secondary AI in patients with advanced cancer. Therefore, patients with advanced cancer may experience AI-induced hyponatremia and hiccups. Thus, the search for AI should be performed in patients with advanced cancer and hiccups, even if lesions which directly stimulate the diaphragm and could cause hiccups are present.

**Table 2** Summary of adrenal insufficiency cases complicated by hiccups.

Author	Age/sex	Serum sodium level	Types of AI	Etiology of AI	Response to steroid
Sawamura <i>et al.</i> (this case).	45/Female	127	Secondary	Metastasis to pituitary gland and stalk	Cure
Hardo <i>et al.</i> (4)	49/Male	N/A	Primary	Autoimmune Addison disease	Cure
Hardo <i>et al.</i> (4)	60/Male	134	Primary	Autoimmune Addison disease	Cure
Giwa <i>et al.</i> (5)	26/Male	111	Primary	N/A	Cure
Pathmanathan <i>et al.</i> (6)	65/Male	122	Primary	Malignant lymphoma of bilateral adrenal gland	Cure
Srirangalingam <i>et al.</i> (7)	Elderly man	127	Primary	Histoplasmosis of bilateral adrenal gland	Cure

AI, adrenal insufficiency.



We should discuss about the direct effects of hydrocortisone to the diaphragm too. This is because glucocorticoid receptor (GR) and  $11\beta$ -hydroxysteroid dehydrogenase type 1 ( $11\beta$ -HSD1) is expressed in the diaphragm. The activation of GR in the skeletal muscle induced the upregulation of Kruppel-like factor 15 and its downstream pathway, leading to the inhibition of the uptake and utilization of glucose in the skeletal muscle and the catabolism of muscle. In critically ill mice, the expression of  $11\beta$ -HSD1 and GR was normal or upregulated very slightly. However, glucocorticoid-induced leucine zipper, which is the marker of the action of GR is reported to be upregulated in the diaphragm. Thus, the steroid excess could cause the abnormalities of the diaphragm (11). On the other hand, there are little reports in which the lack of steroid in diaphragm are discussed. However, the administration of methylprednisolone protected diaphragm function through the inhibition of the calpain system in rat with ventilation. Therefore, the administration of steroid might protect the diaphragm function under certain circumstances. There are no reports in which the function of GR and its downstream signals in the diaphragm during AI. At this time, hyponatremia is the most likely cause of hiccups in patients with AI, but further investigation is needed including the direct effects of steroid to diaphragm (12).

To the best of our knowledge, this is the first case of secondary AI with a complaint of hiccups. This patient had advanced cervical cancer and was initially diagnosed with hiccups associated with cancer metastasis. If hiccups occur in patients with advanced cancer, the differential diagnosis should include hyponatremia. Moreover, AI is one of the important causes of hyponatremia in patients with advanced cancer.

#### Patient's perspective

When I continued to suffer from hiccup, my doctor first told me that it was a symptom of peritoneal metastasis and would not go away. My hiccups increased in frequency, I lost my appetite and could not do anything I wanted to do. When I was hospitalized, I had already given up hope of leaving the hospital. However, I was diagnosed with AI and treatment for the disease could lead me to leave the hospital and spend time with my family. I understand that cancer itself cannot be completely cured, but I am happy that I can still have my happy time thanks to the diagnosis and treatment of AI. I would like to thank my doctor and the hospital staff.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

#### Author contribution statement

T S was the attending physician of this patient. A O and K S worked with the attending physician to provide medical care for this patient during her hospitalization. T S wrote the manuscript. S K supervised manuscript writing. D A, M K, and T Y were medical advisers of the Endocrine and Diabetes Unit of Kanazawa University Hospital, and Y T was the medical adviser of the Internal medicine Unit of Asanogawa General Hospital in the care of this patient. All authors have read and agreed to the published version of the manuscript.

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