Syndrome of inappropriate antidiuretic hormone release as the initial presentation of adenocarcinoma of the colon

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Abstract

Syndrome of inappropriate antidiuretic hormone release (SIADH) is a condition defined by the unsuppressed release of antidiuretic hormone (ADH) from the pituitary gland or nonpituitary sources or its continued action on vasopressin receptors. Of the many causes of SIADH, an important one includes tumours that secrete ADH. We describe a rare case of a patient with colonic adenocarcinoma presenting initially as SIADH. A 60-year-old man presented with confusion and vomiting. Over the previous month he had fatigue and loss of weight. Baseline investigations showed a low serum sodium level of 108mmol/l. He was euvolaemic on examination and fulfilled the criteria for SIADH. Further evaluation and imaging tests revealed that the patient had adenocarcinoma of the colon. It is remarkable that our patient did not present with any of the cardinal symptoms/signs suggestive of colorectal carcinoma including haematochezia, change in bowel habits or iron-deficiency anaemia. Initial therapy with hypertonic saline, fluid restriction and salt diet for management of SIADH was unsuccessful. Tolvaptan was added to the treatment regimen and the patient improved dramatically. Oncology consultation was initiated, and chemotherapy for the carcinoma was planned.

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Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatraemia in cancer patients[1–3] and is associated with significant morbidity and mortality. Cancer patients have many possible aetiologies for SIADH which include chemotherapeutic drugs, infections acquired in the course of treatment and due to malignancy.[2] However, hyponatraemia as a presenting feature of malignancy is rarely quoted in literature. We describe a unique case of adenocarcinoma of the colon presenting as recurrent hyponatraemia due to SIADH without lower gastrointestinal bleeding, anaemia or altered bowel habits.

Case presentation

A 60-year-old man presented to the emergency triage with fatigue for three weeks and confusion for two days. He also experienced six episodes of vomiting small quantities on the day he was brought to the hospital. There was no history of fever, headache or diarrhoea. However, he had significant weight loss of five kilograms with loss of appetite in the last month.

Prior to this admission he was hospitalised on three occasions in the previous month with similar symptoms and documented hyponatraemia which was treated at a local hospital. The patient was asymptomatic between these episodes. The patient was a known case of type 2 diabetes mellitus (on metformin), hypertension (on amlodipine), ischaemic heart disease status post coronary artery bypass graft (on aspirin and atorvastatin) and rheumatoid arthritis (on methotrexate).

The patient's vitals were stable and general examination was normal. His central nervous system examination was normal except for his confused state. There were no signs of dehydration or volume overload. He had no joint swelling and tenderness. Remarkably, on abdominal examination, a vague mass was palpable in the right iliac fossa.

Baseline investigations (Table 1) showed a low serum sodium level of 108 mmol/l, with normal renal parameters (potassium, urea, creatinine). Blood glucose levels were normal. Further investigations revealed a low serum osmolality (231 mosmol/kg N: 280–290 mosmol/kg) with increased

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Table 1 Baseline Investigations

Investigation	Patient's value	Normal value
Serum sodium	108 mmol/l	135–145 mmol/l
Serum osmolality	231 mosmol/kg	280–290 mosmol/kg
Urine sodium	83 mEq/l	<40 mEq/l
Urine osmolality	430 mosmol/kg	40–100 mosmol/kg
Serum cortisol	25.380 micrograms/dl	4.82–19.5 micrograms/dl
TSH	1.940 mIU/ml	0.27–4.20 mIU/ml
Serum potassium	5.3 mmol/l	3.5–5.1 mmol/l
Serum urea	17 mg/dl	16.6–48.5 mg/dl
Serum creatinine	0.5 mg/dl	0.7–1.2 mg/dl

urine sodium (83 mEq/l, N <40) and urine osmolality (430 mosmol/kg N: 40–100 mosmol/kg). Serum cortisol and thyroid stimulating hormone levels were normal. Liver function tests, serum calcium and phosphorus levels were also within normal range. With the above investigations, we found that the patient fulfilled the Schwartz and Bartter criteria for SIADH.

Chest X-ray was normal. A contrast-enhanced computed tomography scan of the abdomen showed an irregular enhancing lesion involving the caecum and distal ileum causing stenosis of the ileocaecal junction as well as mesenteric, omental and peritoneal soft tissue masses as shown in Figure 1. Colonoscopy could not be done due to extrinsic compression and difficulty manoeuvring the scope. An ultrasound-guided biopsy of the omental deposits confirmed the diagnosis of metastatic adenocarcinoma as shown in Figure 2. Serum carcinoembryonic antigen level was 99.7 ng/ml.

The patient was treated with calculated amount of hypertonic saline (3% NaCl) as per sodium deficit, fluid restriction and extra salt diet, but his sodium levels failed to show improvement. Tablet tolvaptan 15 mg/day was added to the treatment regimen and improvement was seen. Serum sodium level was frequently monitored and gradually increased to 125 mmol/l over 4–5 days. His sensorium normalised when serum sodium levels increased to 120 mmol/l. Oncology consultation was obtained for metastatic colonic adenocarcinoma and it was recommended to start chemotherapy. At the time of discharge, he was advised to continue water restriction and oral salt *ad libitum*. The patient's serum sodium concentration was 125 mmol/l. A daily dose of tolvaptan 15 mg/day was continued. However, the patient was lost to follow-up.

Figure 1 CT scan of the abdomen, axial view (A) and coronal view (B) showing the irregular enhancing lesion involving the ileocaecal junction (yellow arrows).

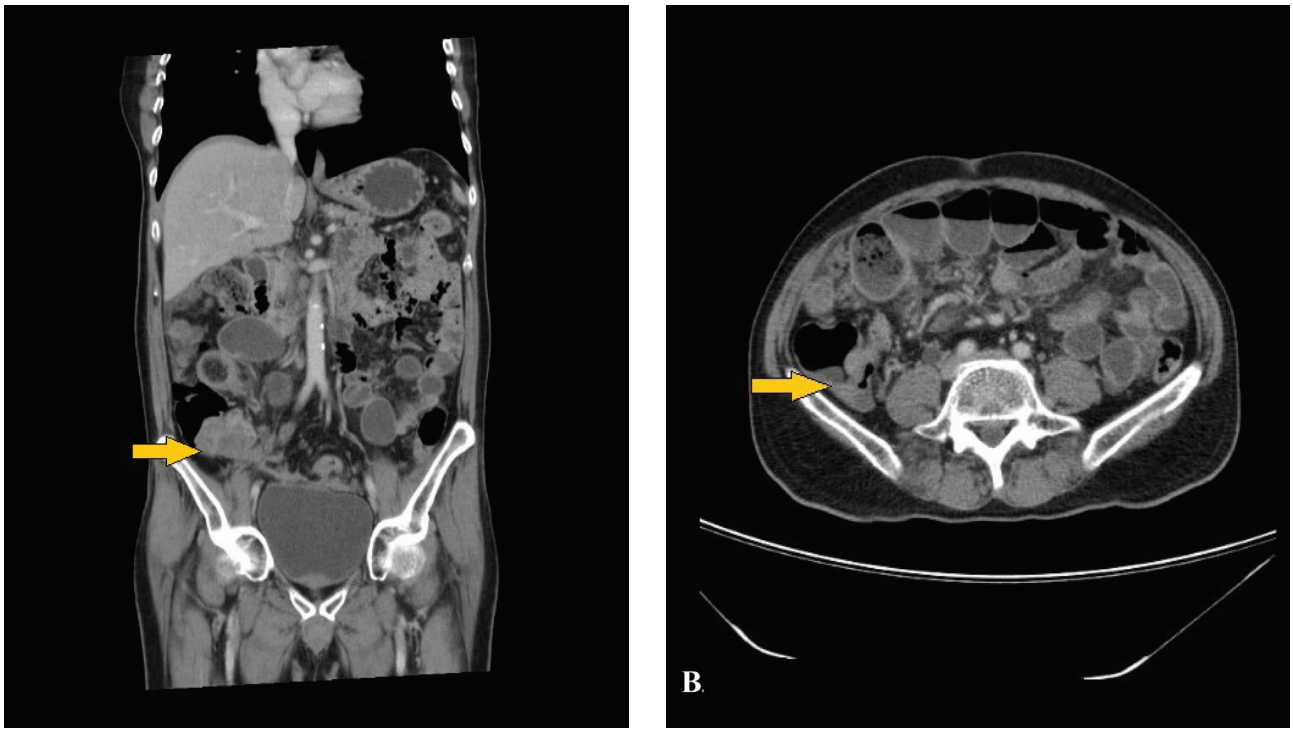
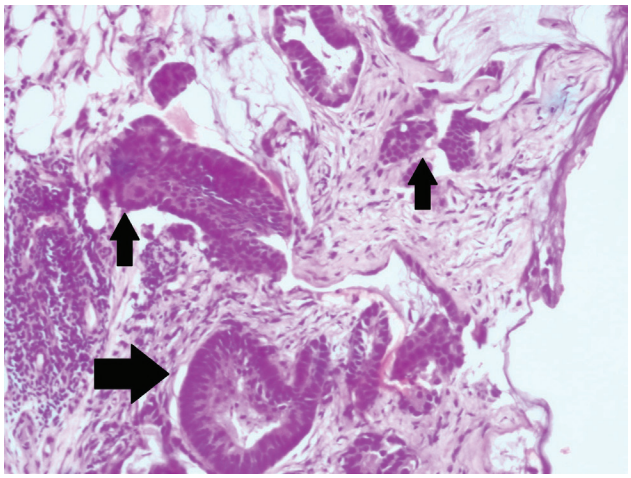


Figure 2 Omental biopsy showing tumour deposits (black arrows); metastasis from adenocarcinoma of the colon.



Discussion

Hyponatraemia can be classified broadly into hypervolaemic, hypovolaemic and euvolaemic hyponatraemia based on total body fluid status. Time of development of the hyponatraemia is also used to classify it into acute (<48h) and chronic (≥48h) hyponatraemia. The earliest clinical manifestations of acute hyponatraemia include nausea and malaise. With a more severe and acute fall in sodium concentration, headache, lethargy, obtundation, and eventually, seizures can occur. Chronic hyponatraemia allows cerebral adaptation, and the patients remain asymptomatic despite a serum sodium concentration below 120 mmol/l. Non-specific symptoms like nausea, vomiting, gait disturbances, memory and cognitive problems, fatigue, dizziness, confusion, and muscle cramps can occur.[4] Our patient presented with recurrent episodes of confusion, fatigue and vomiting.

Euvolaemic hyponatraemia is commonly caused by secondary adrenal insufficiency, hypothyroidism and SIADH. SIADH is caused by the unsuppressed release of antidiuretic hormone (ADH) from the pituitary gland or non-pituitary sources or its continued action on vasopressin receptors. The condition was first detected in two lung cancer patients by William Schwartz and Frederic Bartter in 1967.[4] Our patient was clinically euvolaemic, investigations showed hypo-osmolar state with raised urine sodium and osmolality. Renal function tests and a random blood sugar test, done to check for hyperglycaemia and uraemia as these are potential causes of non-hypotonic hyponatraemia, were normal. Thyroid and adrenal functions were normal thus fulfilling Schwartz and Bartter criteria for the diagnosis of SIADH.[4]

Causes of SIADH include conditions that dysregulate ADH secretion in the central nervous system like infection and subarachnoid haemorrhage, tumours that secrete ADH, particularly small cell lung cancer, drugs that increase ADH secretion like chlorpropamide, and various pulmonary conditions.[4] Serum ADH levels were not measured in our patient due to non-availability of the test at our centre.

SIADH is one of the common paraneoplastic syndromes frequently diagnosed in cancer patients. A single-centre retrospective study in a tertiary care centre by Goldvaser et al. including 204 patients with active malignancies diagnosed with SIADH, showed that most patients, 149 (73%) had malignancy-associated SIADH, while 55 (27%) had SIADH due to other aetiologies.[5] In this study it was found that the most common malignancy associated with SIADH was lung cancer, followed by colon cancer, lymphoma, breast cancer and pancreatic cancer. Malignancies associated with SIADH are commonly symptomatic for primary disease or on chemotherapy at the time of diagnosis. Hyponatremia/SIADH as presenting symptom without primary features of malignancy are rare. One case report described a patient who presented with hyponatraemia secondary to SIADH and was diagnosed with metastatic non-small cell lung cancer.[6] Our case is interesting because our patient did not present with any of the typical symptoms/signs associated with colorectal carcinoma including haematochezia or melaena, abdominal pain, otherwise unexplained iron deficiency anaemia, and/or a change in bowel habits.

The treatment of hyponatraemia in SIADH has three components, including treatment of the underlying disease (if possible), initial therapy to raise serum sodium which varies with severity of hyponatraemia and presence or absence of symptoms, and prolonged therapy in patients with persistent SIADH. As in our patient, those with symptomatic hyponatraemia must first be treated with hypertonic saline in bolus doses with a maximum of 10 mmol/l increase in sodium concentration in the first 24 hours.[7] Stopping the infusion is recommended after a 5 mmol/l increase in sodium concentration or if the symptoms improve, whichever comes first.[7] Fluid restriction is the mainstay of therapy in most patients with SIADH and the goal fluid intake is estimated based on levels of urinary and plasma electrolytes.[8] Unless the SIADH is reversible (e.g. due to a drug that can be discontinued), patient must be on maintenance therapy after raising the serum sodium levels effectively which includes fluid restriction, oral salt or urea and furosemide if the urine osmolality is twice that of the plasma osmolality.

Our patient did not respond to the hypertonic saline infusion and improvement was seen only after tolvaptan was added to the treatment regimen. Tolvaptan, an oral ADH receptor antagonist causes free water clearance from kidneys and increase in serum sodium. In the Study of Ascending Levels of Tolvaptan in Hyponatremia-1 (SALT-1 and SALT-2 trials), n = 448,[9] tolvaptan (starting dose, 15 mg/day; maximum dose, 60 mg/day) was significantly better at increasing serum sodium levels than placebo in patients with euvolaemic or hypervolaemic hyponatraemia. The long-term safety is uncertain with risk of liver injury on drug usage of more than 30 days.[10] Due to these limitations, tolvaptan should be considered only when the serum sodium concentration cannot be maintained above 120 mmol/l or when there are persistent neurological symptoms thought to be due to chronic hyponatraemia despite treatment with other measures.

Conclusion

This case highlights a rare manifestation of colonic adenocarcinoma as recurrent hyponatraemia at its onset without primary bowel-related complaints. Careful clinical examination is always vital to diagnosis.

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