Syndrome of Inappropriate Anti-Diuretic Hormone Secondary to Non-Cirrhotic Primary Hepatocellular Carcinoma

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Conflict of interest: None declared

Patient: Male, 71
Final Diagnosis: SIADH
Symptoms: Cachexia • confusion
Medication: —
Clinical Procedure: Percutaneous liver biopsy
Specialty: Oncology

Objective: Rare disease
Background: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is usually seen in pulmonary malignancies, central nervous system disorders, and secondary to medications. SIADH has very rarely been encountered in primary hepatocellular carcinoma. Two cases were reported in Japan and 1 case in Spain after extensive investigation of the medical records.

Case Report: We report a case of a 71-year-old man who presented with confusion, cachexia, and abdominal symptoms in the form of vomiting and abdominal discomfort. On the initial work-up, SIADH diagnosis was made. After an extensive work-up, the reason for SIADH turned out to be a newly diagnosed hepatocellular carcinoma. The precipitating factor for the cancer was not identified by history or by work-up. No metastasis was identified. Liver functions were preserved but patient was severely malnourished.

Conclusions: SIADH can occur as a para-malignant feature of the malignancy. In our case, it was related to the hepatocellular carcinoma, which is a malignancy very rare to cause SIADH.

MeSH Keywords: Inappropriate ADH Syndrome • Liver Neoplasms • Paraneoplastic Syndromes

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Background

Syndrome of inappropriate ADH secretion (SIADH) is a disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH) [1]. ADH secretion primarily arises from the posterior pituitary gland, but it can be secreted by other sources. Although SIADH has been described in the setting of central nervous system disorders, secondary to medications, and in some malignancies [mainly small cell lung cancer, head and neck cancer, olfactory neuroblastoma (esthesioneuroblastoma), and blood malignancies] [2–4], it is very rarely associated with primary hepatocellular carcinoma. There have only been 3 previous remotely reported cases of this association based on our comprehensive and extensive review of the literature [5–7]. We report a case of a Guatemalan man diagnosed with SIADH in the setting of primary hepatocellular carcinoma.

Case Report

Patient information

We report on a 71-year-old Guatemalan man with no reported past medical history.

Family history was not significant for any known malignancy. Social history was significant for long-term heavy smoking history but he quit 1 year before presentation. Alcohol drinking was heavy but limited to weekends and no complications from alcohol overuse were known by history.

Objectives for case reporting

SIADH can be secondary to some malignancies but is rarely reported secondary to hepatocellular carcinoma. Adding this case report to the 3 previously reported cases in the medical history records indicates SIADH as a rare complication secondary to hepatocellular carcinoma.

Main medical problem

SIADH.

Coexisting diseases

Hepatocellular carcinoma. Newly discovered uncontrolled hypertension.

Case presentation

Our patient presented with persistent nausea, non-bilious vomiting, and vague abdominal discomfort, which commenced a few days prior to admission. The patient was cachectic and confused. He had elevated blood pressure. Laboratory findings showed an initial serum sodium level of 115 mmol/L, chloride of 77 mmol/L, and serum osmolarity of 246 mOsm/L. Urine osmolarity was 514 mOsm/L and urine sodium was 152 mmol/L. BUN was elevated at 8.6 mmol/L but serum creatinine and uric acid levels were normal at 80.4 umol/L and 232 umol/L, respectively. No acid-base disturbance was detected. LDH level was normal in blood. Chest x-ray did not reveal any suspected lung mass or pathology. CT of the chest demonstrated a 2-mm calcified nodule in the left upper lobe, likely a consequence of prior granulomatous infection, and scattered foci of emphysema bilateral lungs in a predominantly centri-lobular distribution. CT of the abdomen and pelvis demonstrated a large, heterogeneous hepatic mass lesion present within the right hepatic lobe, measuring approximately 11.8×13.8×10.2 cm with marked compression of the IVC and concomitant dilatation of the main pancreatic duct at the level of the pancreatic body, measuring up to 3 mm in maximal diameter (Figure 1). MRI of the abdomen and pelvis with gadolinium was done and confirmed the previous liver findings.

To correct an assumed hypovolemic hyponatremia, we administered normal saline infusion at 100 ml/hour as a total of 1 liter total in 6 hours. Overnight, the sodium level was noted to have dropped to 110 mmol/L, with serum osmolarity decreasing to 234 mOsm/L. Thereafter, water restriction was instituted with initiation of hypertonic saline infusion in place of the normal saline. The patient was admitted directly to the intensive care unit. A CT of the brain was unremarkable. Tumor markers CEA, AFP, and CA-9-19 all returned within normal limits. TSH and cortisol levels were normal, as were the B-natriuretic peptide, ammonia level, and basic coagulation studies. Liver function tests showed normal hepatic synthetic function and only a marginal elevation of liver enzymes and bilirubin level. Hepatitis viral panel showed no reactivity. Blood count only

Figure 1. CT of the abdomen and pelvis showing liver mass (presented by the arrow).
showed mild anemia, with normal white cell count and platelet count. There was negative occult blood test in stool.

The sodium level rose in response to water restriction and hypertonic saline. The latter was stopped after the sodium level reached 120 mmol/L. The patient’s confusion was improving slightly. To promote free water excretion, the ADH V2 receptor antagonist, Tolvaptan, was initiated 24 hours later and was continued for 3 consecutive days. Sodium levels were monitored several times daily. Return to normal sodium levels was observed after 3 days of Tolvaptan therapy. A diagnosis of SIADH was made, given the clinical course, laboratory

Figure 2. Graph of the serum sodium levels during the hospital course before and after intervention by the managing physicians. Red arrow indicates the day that hypertonic saline infusion was given. Black arrows indicate the days on which tolvaptan was given.

Figure 3. Histopathologic specimen from the liver biopsy. 10×: A well-differentiated hepatocellular carcinoma with cells in a trabecular pattern and forming pseudo glands. 40×: Malignant hepatocytes with prominent nucleoli and some intracytoplasmic bile. The arrow highlights endothelial wrapping of the tumor cells, which is a feature of HCC.
findings, and response to appropriate management. ADH level was not requested in blood or urine because the laboratory findings before and after hypertonic saline and Tolvaptan administration (Figure 2) were satisfactory for SIADH diagnosis. However, ADH level measurement is time consuming, expensive, and of less importance for confirmation of SIADH. The patient was transferred to the regular medical floor after his sodium level was more than 130 mmol/L. Serum osmolarity at that time increased to 267 mmol/L. The patient’s blood pressure was elevated during the hospital course and he was given nicardipine infusion, which was later shifted to oral amlo- dipine and metoprolol. An ultrasound-guided liver biopsy was done when the patient was deemed medically stable.

Later in the hospital course, dextrose 5% with normal saline was given at 70 ml/hour because the patient was not eating due to poor appetite and some residual confusion. Daily sodium levels following the infusion of the above fluid revealed mild reduction but remained above 130 mmol/L. Workup for dementia was done, including HIV, ANA, RPR, vitamin B12, and folate levels. Results returned unremarkable. Liver biopsy revealed a diagnosis of primary hepatocellular carcinoma (Figure 3). An oncology consult was obtained and therapeutic options were discussed. However, prognosis was poor given the age, persistent confusion, and significant malnutrition. The family expressed desire to bring the patient back to his country of origin. He was thus discharged at his family’s request.

**Discussion**

SIADH is associated with clinical hyponatremia in the setting of several underlying medical conditions. In the setting of malignancy, it is primarily associated with small-cell carcinoma of the lungs, and much less with other lung tumors. Schwartz’s hypothesis suggested that small-cell carcinoma produced some quantity of antidiuretic hormone, which was later found to consist of arginine vasopressin (AVP) by Bleich HL in 1976. Bleich also discovered the AVP-regulated water channels in the kidneys, which were later termed “aquaporins”. Schwartz’s hypothesis was proven by detecting ectopic AVP in small-cell carcinoma [8–10]. This hypothesis was further confirmed by expression analysis of the AVP-NP II gene, which controls the production of AVP, in small-cell carcinoma cells. These findings established the well accepted mechanism of action of SIADH caused by small-cell carcinoma [11–13]. Many researchers have found the AVP gene not only in small-cell carcinoma but also in undifferentiated carcinoma [14] and anaplastic carcinoma [15]. However, they have failed to find the AVP gene in squamous cell carcinoma [15,16].

After exhaustively exploring all the likely etiologies of SIADH in our patient, we have discovered in our literature search that there is no other possible link to SIADH than the patient’s co-existent newly diagnosed primary hepatocellular carcinoma.

Hyponatremia due to syndrome of inappropriate antidiuretic hormone (SIADH) is associated with significant morbidity [17], mortality [18–21], and increased length of hospital stay. With severe hyponatremia (plasma sodium less than 120 mmol/l), there is an exponential increase in mortality, with death rates of 50% reported as plasma sodium concentration falls below 115 mmol/L [22,23]. Although ADH level was not measured in blood or urine in our case, different guidelines for confirmatory laboratory diagnosis of SIADH depend mainly on the serum and urine electrolytes and osmolarity and the changes after administration of hypertonic saline and tolvaptan, with little role of measurement of ADH levels [23–25].

One of the problems that our case confronted was the newly discovered uncontrolled hypertension that was controlled first by intravenous nicardipine that was shifted to PO amlodipine. The patient had a normal B-type NP level and did not exhibit signs of acute diastolic heart failure or any end-organ damage secondary to the uncontrolled hypertensive episode that was controlled adequately. Echocardiogram showed ejection fraction 56.1% with mild concentric left ventricle hypertrophy. A chest X-ray was done and did not show any signs of conges-tive heart failure or pleural effusion. This hypertension was not known to be new- or old-onset because the patient did not have a history of hypertension and was not on any medication, nor was he regularly seeing a primary care physician.

The para-neoplastic syndromes (PNS) that have been usually associated with HCC (hepatocellular carcinoma) include hypercholesterolemia, hypercalcemia, erythrocytosis, hypoglycemia, demyelinating disease, pemphigus, polyarthritis, encephalomyelitis, and thrombocytosis [26–34]. The most common PNS associated with HCC are hypercholesterolemia, hypercalcemia, hypoglycemia, and erythrocytosis [35]. Para-neoplastic erythrocytosis is believed to occur as a result of increased tumor erythropoietin produced by the HCC or as a compensatory response to local hypoxia produced by tumor necrosis [36–39]. ADH secretion from hepatocellular carcinoma can be as a response to the tumor burden and the stress associated with that burden. This can raise the question about the possible mechanism of SIADH in this case in a similar way to other known para-neoplastic syndromes known in hepatocellular carcinoma.

Despite a major association of ectopic ADH secretion with SCLC and head and neck tumors, a broad spectrum of malignant tumors have also been reported to cause SIADH; however, most of these observations have been in case reports of very few patients and include such tumors as olfactory neuroblastomas, small-cell neuroendocrine carcinomas, adenoid cystic carcinomas, undifferentiated carcinoma, and sarcomas that result in
ectopic ADH production [39]. SIADH secondary to gastrointestinal malignancies is uncommon. A 1985 case report presented with SIADH secondary to adenocarcinoma of the colon [40]. Another case report was found with SIADH secondary to gastric carcinoma that was surgically resected and the SIADH resolved after that surgical resection [41]. Another case was a diagnosis of SIADH secondary to esophageal small-cell carcinoma [42].

Conclusions

SIADH can be secondary to unexpected causes. In our case, it was surprising to have it secondary to hepatocellular carcinoma, given that no other causes could be identified. In our reported case, the patient had locally advanced hepatocellular carcinoma with no evidence of liver cirrhosis or distant metastasis. This is a reminder that SIADH is a rare para-neoplastic syndrome secondary to hepatocellular carcinoma. This means that SIADH can always unexpectedly happen in any kind of malignancy.

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Statement

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