IJBCS
ISSN: 2147-1428

Case Report
International Journal of Basic and Clinical Studies (IJBCS)
2013;1(1): 31-40. Celik MM et al.

A Case Treated for Refractory Hyponatremia: The Syndrome of Inappropriate Antidiuretic Hormone Secretion Associated with Small Cell Lung Cancer

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Abstract

Hyponatremia is the most common electrolyte imbalance observed in hospitalized patients and it is associated with an increased morbidity and mortality. The management of hyponatremia is based on the underlying cause. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia. Hyponatremia observed in patients hospitalized due to medical causes is usually related to an underlying tumor. SIADH cases are often reported to be caused by cancers, where the majority is linked to small cell lung carcinoma. In this report, we presented a SIADH case which developed in a patient with small cell lung cancer.

Key Words: Hyponatremia, Inappropriate ADH secretion syndrome, small cell lung cancer

Introduction

Hyponatremia is the most common electrolyte imbalance in hospitalized patients. It is defined as an excess of water in relation to sodium in the extracellular fluid (1,2). Normal serum sodium levels vary between 135 and 145 mEq/L. Hyponatremia is generally defined as a serum sodium concentration lessthan135 mEq/L, while it is considered as severe hyponatremia when the serum sodium concentration decreases below125 mEq/L. However; these values can display small variations among clinical laboratories (3,4,1). Hyponatremia is an important electrolyte imbalance with its potential morbidity and mortality. It is commonly encountered inpatient and ambulatory settings (5). Mild hyponatremia (serum sodium level<135 mmol/L) occurs in 15-22% of all hospitalized patients. The incidence of moderate to severe hyponatremia is lower, which occurs in 1-7% of the hospitalized patients (6). It is known that severe hyponatremia is actually acquired in hospital in approximately half of those with a serum sodium <125 mmol/L (1). In this condition, mortality rates of 50% or higher have been reported for patients with serum sodium concentrations less than 120 mEq/L (7-9). The common causes of hyponatremia include drugs and SIADH (10). SIADH is the most frequent cause of hyponatremia (11). SIADH is a syndrome characterized by abnormal response to ADH in renal collecting ducts and/or high levels of ADH associated with excessive secretion from the posterior pituitary (12). The most common form of hyponatremia is hypotonic, normovolemic hyponatremia, which often develops due to non-osmotic stimulation of ADH secretion. In inpatient settings, the hypotonic, normovolemic hyponatremia caused by SIADH is the most common cause of hyponatremia (11,13).

Case Report

A 75-years old man presented to our general internal medicine outpatient clinic with the complaints of nausea, fatigue, appetite loss, muscle weakness, and irritability. He had no history of any chronic disease and surgical operation. The patient cited that he didn't take any medication with potential hyponatremic effect during this period. There was no alcohol or illicit drug use in his history, but he had a smoking history of 32 pack-years. On physical examination, vital signs found to be normal: blood pressure, 130/80 mmHg; heart rate 78 beats, and normal body temperature. He had no edema and his jugular venous pressure was normal. He had no abnormal finding in the examination of other organ systems.

On the laboratory evaluations, the following results were obtained: hemoglobin, 14 g/dL; leukocyte, 6500/μL; platelet, 251000/μL; plasma sodium, 112-110 mEq/L; potassium, 4.5 mEq/L; chloride, 101 mEq/L; BUN, 12 mg/dL; creatinine, 0.8 mg/dL; glucose, 98 mg/dl; total protein, 7.2 gr/dL; albumin, 4.2 gr/dL; AST, 12 U/L; ALT, 15 U/L; calcium, 9.2 mg/dL; phosphorus, 3.2 mg/dL; magnesium, 1.8 mg/dL; uric acid, 4.4 mg/dL; plasma osmolarity, 240 mOsm/kg; urine osmolarity, 686 mOsm/kg; urine sodium, 52 mmol/L. In addition, the following results were obtained in thyroid function tests: TSH, 2.65 uIU/ml (0.34-5.60); and fT4, 1.01 ng/dl (0.61-1.12). The basal cortisol, vitamin B12, EST and CRP values were found as 14.8 μg/dL, 255 pg/mL (180-914), 24 mm/h and CRP 0.8 mg/dL, respectively. A suspected hilar mass was detected on the posterioanterior (PA) chest radiography (Figure-1a).

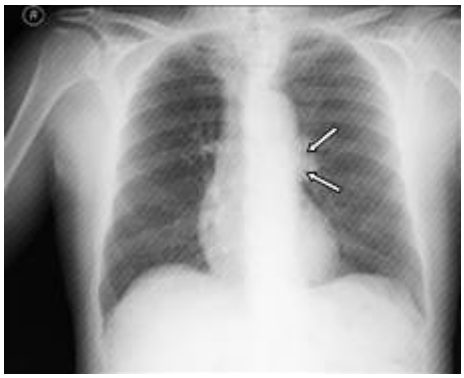

Figure-1a: Two mass lesions with ill-defined border adjacent to left pulmonary hilum on PA chest radiography (white dotted arrows).

Thus, a spiral computerized tomography (CT) chest scan was performed and a hilar mass (2.5x2 cm in size) with conglomerated central lymphadenopathies were seen on the chest CT scan. On the thorax CT scan, paramediastinal pleural-based mass lesions with lobulated contours, which had linear extensions to surrounding pulmonary parencyhma and no contrast enhancement, were detected at anterior segment of superior lobe (2x2 cm in size) and at superior lingula (2.5x2.0 cm in size) at left lung (Figure-1b).

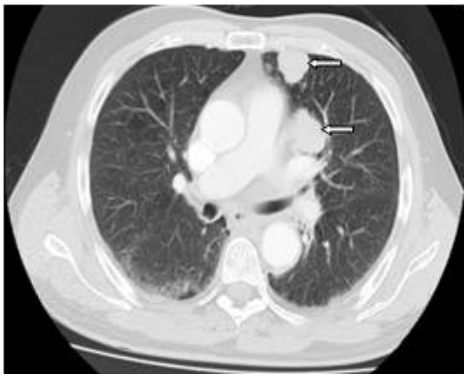

Figure-1b: Parasternal and pleural based localization of mass lesion a left hilum and anterior to hilum on axial thorax CT scan (white dotted arrows).

In the same localizations, multiple pleural-based nodules (as the largest one being 7 mm in size) were seen, while conglomerated lymphadenopathy (5x3 cm in size) was detected at mediastinal region (Figure-1c).

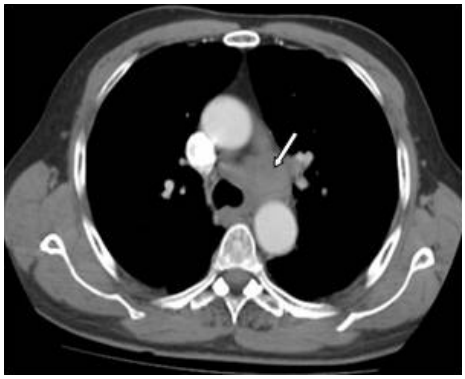

Figure-1c: A paked lymphadenopathy on the aortic-pulmonary window on axial thorax CT scan (white dotted arrows).

The abdominopelvic and cranial MR imaging were normal. A diagnostic endobronchial bronchoscopy was performed, which revealed no definitive conclusion. Therefore, a transthoracic biopsy was planned to sample tumoral lesion in lung. The patient was diagnosed as small cell lung cancer by the pathological evaluation of specimen obtained from tumoral tissue via CT-guided transthoracic biopsy (Figure-2a, 2b, 2c).

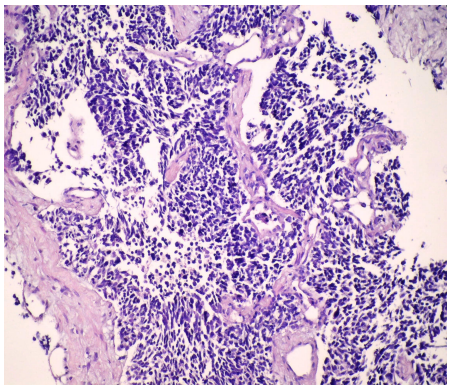

Figure-2a: Tumor consisted of small cells with oval or spindle-like nuclei stained dark and limited cytoplasm or no cytoplasm on the microscopic evaluation

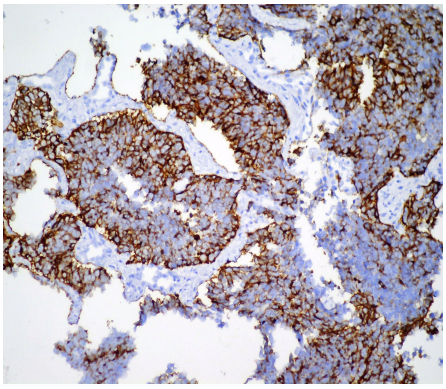

Figure-2b: Tumor consisted of small cells with oval or spindle-like nuclei stained dark and limited cytoplasm or no cytoplasm on the microscopic evaluation

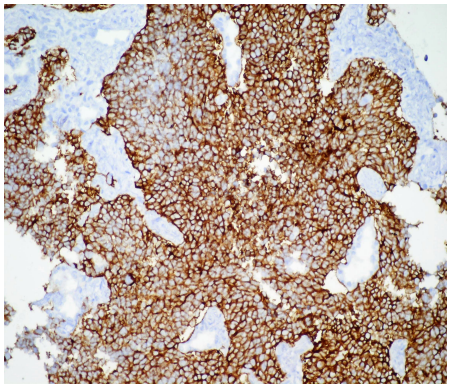

Figure-2c: Synaptophysin positivity on immunohistochemical staining (Synaptophysin, x20)

Renal disease, hypothyroidism and adrenal insufficiency were excluded by the additional work-up for hyponatremia. Therefore, based on clinical euvolemia and biochemical, radiological and pathological data, the diagnosis was established as SIADH secondary to small cell lung cancer. Throughout diagnostic workshop, the regular management of hyponatremia was scheduled. For this purpose, total fluid intake of the patient was limited to 1 liter. Intravenous furosemid (40-60 mg/day) was given with hypertonic saline (3% NaCl). However, plasma sodium levels continued to decrease after short periods of increase. This

was attributed to paraneoplastic ADH secretion. After 2 weeks treatment, plasma sodium level reached to a level of 130 mEq/L.

Therefore, a chemotherapy protocol consisted of carboplatin (100 mg/m^2) and etoposide (AUC 5) was initiated to the patient who had a creatinine level of approximately 1.5 mg/dL. At the end of first cycle, it was found that the plasma sodium levels were in normal range.

Discussion

Hyponatremia is the most common electrolyte imbalance, with a prevalence of 1-3% in hospitalized patients, and it is associated with a greatly increased morbidity and mortality. The SIADH is the most frequent cause of hyponatremia in inpatient settings (14). In 1957, Schwartz et al. presented the first clinical case with ectopic SIADH. Authors described two patients with lung cancer who developed hyponatremia associated with persistent loss of urinary sodium. They postulated that the tumors led to the inappropriate release of ADH which was termed as SIADH (15). This suggestion was later confirmed by the observation of elevated ADH in the plasma of patients with bronchogenic carcinoma (16). SIADH is accounted from approximately one-third of all hyponatremia cases (14). SIADH results from insufficiency of plasma hypotonicity to inhibit ADH secretion. This causes water retention and elevation of extracellular fluid volume. Then, a secondary dilution in plasma sodium and loss of sodium from kidneys occur [17]. SIADH is usually observed in hospitalized patients with prevalence up to 35% (18). SIADH has two types including idiopathic and secondary forms. Malignancies including lungs, duodenum, kidney, bladder, lymphomas, intracranial diseases, infectious diseases, and drugs such as furosemide, thiazide diuretics, carbamazepine, haloperidol, cyclophosphamide, chlorpropamide have been reported to cause SIADH in some

patients (14). In medical inpatients, about 14% of hyponatremia is caused by underlying tumor-related conditions (19). The tumors most commonly resulting in hyponatremia secondary to SIADH include lung, breast and head-neck tumors (20).

SIADH cases are often reported to be caused by cancers, where the majority (approximately 70%) is linked to small cell lung carcinoma. (21,22). Almost all the tumors producing ADH are small cell lung cancers, and much less commonly, non-small cell lung cancers (23). Our case was also admitted to our clinic due to hyponatremia and diagnosed as small cell lung cancer by the evaluations. It was found that the refractory hyponatremia in our case was caused by SIADH secondary to small cell lung cancer. It was seen that the hyponatremia was resolved after treatment targeting primary etiology with the principles of management for normovolemic hypotonic hyponatremia. By this case, it was aimed to emphasize that SIADH secondary to a malignancy should be considered in cases with refractory hyponatremia.

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