Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) during the course of lung cancer. A case report

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ABSTRACT
Introduction. Hyponatremia is a frequently observed electrolyte disorder among patients with cancer. In 1957, Schwartz et al. reported the first case of a patient with hyponatremia due to SIADH, secondary to lung cancer. From that moment on, there has been data published that indicates patients with SIADH are less responsive to chemotherapy, have greater predisposition to central nervous system metastases and are often characterized by an advanced stage of cancer during time of diagnosis. Hyponatremia has many possible causes, and the differential diagnosis can pose a challenge.

Aim. The aim of the study was to consider the occurrence of secondary hyponatremia in the course of cancer and the significance of this disorder in the prognosis of the disease.


Results. A 66-year old patient with hyponatremia was admitted to the Department of Endocrinology, and lung cancer was determined as the cause of the aforementioned electrolyte disorder.

Conclusion. SIADH secondary to cancers should be included in a differential diagnosis of every case of hyponatremia of undetermined etiology.

Keywords. hyponatremia, SIADH, lung cancer

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

Hyponatremia is defined as a serum sodium level <135 mEq/l.1 Hyponatremia is due to impaired renal function and failure to secrete and retain water. Antidiuretic hormone (ADH) affects localized V2 receptors at the basolateral aspect of the collecting duct cells and leads to increased aquaporin expression on the luminal aspect of the collecting duct cells which increases water absorption and diminishes thirst. Normally, thirst and secretion of an antidiuretic hormone depend on plasma osmolality. Hyponatremia occurs if there is persistent ADH stimulation resulting in increased water retention and plasma dilution.2 Symptoms of hyponatremia depend on the severity of plasma sodium deficiency and the time period in which hyponatremia has established.3 Acute hyponatremia has a duration of less than 48 hours. In patients with acute hyponatremia, neurological symptoms are observed as a result of the water moving to the brain tissue, according to the concentration gradient, and resulting brain edema.2 Seizures, speech impairment and even coma or death can also be observed. If hyponatremia persists over 48 hours, it is recognized as chronic. It occurs much more often than acute hyponatremia. The sodium concentration is typically above 120 mEq/L. Chronic hyponatremia is often asymptomatic, since there is enough time for an osmolyte shift (including sodium, potassium and chloride) from the brain cells to the cerebrospinal fluid, which prevents cerebral edema.3,4 Nonetheless chronic hyponatremia can cause symptoms such as nausea, vomiting and neurological symptoms including fatigue, headaches, confusion, epileptic seizures, especially in the case of sudden serum sodium level decrease. Coma is also probable1 and there may be subtle neurological abnormalities. Elderly people may experience frequent falls or gait disturbances.6 Hyponatremia is also observed in the following endocrine disorders: adrenocortical insufficiency and hypothyroidism.7 It occurs in patients with a decrease in blood volume - for example due to hemorrhage or in chronic diseases characterized by edema, such as in liver cirrhosis or heart failure.2 The syndrome characterized by excessive secretion of antidiuretic hormone, and is known as a syndrome of inappropriate antidiuretic hormone secretion (SIADH) which was initially described by Leaf and Mamby.8 SIADH is characterized by hyponatremia, inadequately elevated urine osmolality, significant urine sodium excretion and decline of serum osmolality usually in an euvoletic patient. Peripheral edema is usually absent. The diagnosis requires exclusion of diuretic treatment, and normal cardiac, renal, adrenal, hepatic and thyroid function.9 Hyponatremia accompanies approximately 30% of hospitalizations and SIADH is the most common cause of hyponatremia.8,9,10 SIADH can be caused by various diseases, such as central nervous system disturbances, malignancies like lung tumors, especially small cell carcinoma which produce ADH ectopically, cancers of the pancreas, duodenum, head and neck.9 Many drugs used in the cancer treatment can also cause SIADH.8 However, not only drugs used to treat cancer can cause hyponatremia, it is very often caused by thi- azides and antidepressants.11 Pulmonary diseases such as pneumonia or bronchial asthma, atelectasis, acute respiratory failure and pneumothorax can cause SIADH.9 It can also be observed in tuberculosis.12 Surgical procedures, such as abdominal and chest surgeries, can cause excessive secretion of ADH, probably by the mechanism of pain receptors stimulation.8 Also, neurosurgical interventions, especially those performed in the area of the pituitary gland, may result in the development of SIADH syndrome.9 It was also described in the process of two genetic syndromes: nephrogenic syndrome and hypothalamic syndrome. Nephrogenic syndrome is caused by a gain-of-function mutation in the gene for V2 receptor, which is located on the X chromosome.13 Hypothalamic syndrome is caused by a mutation in the transient receptor potential vanilloid type 4 (TRPV4), which encodes the central osmolality sensing mechanism.14 Both HIV and AIDS are associated with excessive secretion of the antidiuretic hormone and SIADH syndrome due to existing adrenocortical insufficiency, opportunistic infections and cancer associated with HIV infection.9 There are studies indicating the importance of hyponatremia as a HIV-disease severity index.15 Hyponatremia often occurs in older patients with diabetes and during the course of many infections.11 It is important also to mention idiopathic SIADH, the causes of which remain unknown.9 As mentioned above, there is a relationship between lung cancer and the occurrence of SIADH due to ectopic ADH secretion. Hyponatremia is a frequent electrolyte disorder among patients hospitalized for cancer diagnosis or treatment.18 Depending on the type of tumor and the clinical condition of the patient, the incidence of hyponatremia varies.17 The frequency of hyponatremia is estimated between less than 1% to more than 40% due to reports from general hospitals.18 Large group of patients have showed that SIADH occurs in in 15% of cases of small-cell lung cancer.19 2% -4% refer to patients with non-small cell lung cancer.20,21 A common cause is abnormal, ectopic release of antidiuretic hormone (SIADH), independent of tonicity maintained by non-osmotic factors.20 In 1957, Schwartz et al. described the first case of a patient with hyponatremia due to SIADH, secondary to lung cancer.22 Chute et al. stated that the patient with SIADH is less responsive to chemotherapy, has greater predisposition to central nervous system metastases and is often characterized by advanced stage of cancer at the time of diagnosis.23 To illustrate this data, we would like to present a case of a patient with hyponatremia, in whom lung cancer was
detected in the course of the differential diagnosis of the etiology of low serum sodium level.

A case report

66 year old patient was admitted to the Endocrinology Department due to electrolyte disorders in the form of chronic hyponatremia of unknown etiology. Patient's medical history included post-operative hypothyroidism, hypertension, ischemic heart disease and primary Sjögren's syndrome. She was admitted to the Department of Endocrinology for further evaluation of the causes of hyponatremia, after previous hospitalization in the Department of Gastroenterology, in the time of which the thyroid function disorders and adrenal insufficiency were ruled out as potential causes of electrolyte disorder. During fifteen days of hospitalization, a number of laboratory tests were carried out. It was found that hyponatremia still persisted at a moderate level; hypothyroidism (due to inadequate substitution dose of L-thyroxine) and adrenocortical insufficiency were again excluded. The results of the study also showed normal diuresis, decreased plasma osmolality, normal urine osmolality, sodium excretion in the daily urine collection higher than 30mmol/l, and decreased urea and uric acid levels.

This clinical and laboratory presentation is very characteristic of SIADH syndrome. As mentioned above, SIADH often has a paraneoplastic etiology, therefore it was decided to extend diagnostics procedures accordingly. In course of the previous hospital stay, the patient had a chest x-ray, which did not show any pathology. At the time of hospitalization in the Clinic of Endocrinology, a CT scan of the neck, chest and abdomen were performed. The thyroid ultrasound visualized a bundle of cervical lymph nodes with central vascularization on the right side, however CT did not confirm the presence of enlarged lymph nodes in the neck. The CT scan however, did show mediastinal lymph node infiltrates with present necrosis and associated mass in the upper lobe of the right lung, as well as involvement of supraclavicular and subclavian lymph nodes. The CT of the abdomen also showed the bilateral presence of focal lesions of the adrenal glands of benign phenotype, with high lipid content, suggestive of adenomas. Hormonal evaluation was performed that revealed no pituitary-adrenal axis disturbances. Due to the the cause of observed SIADH syndrome the patient was referred to the Pulmonology Department for a more extensive evaluation (to determine the type of neoplasm and staging). In process of further patient hospitalization, endobronchial ultrasound (EBUS), the material for histopathological examination was collected. The histopathological evaluation of the material collected from the outbreak and the lymph nodes found in the imaging studies revealed small-cell lung cancer. After the diagnosis, appropriate treatment was initiated.

**Fig. 1.** Computed tomography (CT) of the patient’s chest.

**Discussion**

Hyponatremia is the most frequent electrolyte disorder in oncological patients. Such a condition can be the result of tumor antiuretic hormone (ADH) production. Also treatment with such agents as vincristine, vinblastine and cyclophosphamide used in the treatment of lung cancer can also be the cause of hyponatremia. Cylophosphamide enhances the action of ADH at the renal tubule level. Stimulation of ADH secretion can also be stimulated by phenothiazines used as antiemetics medicaments, antidepressants- such as tricyclic drugs and selective serotonin reuptake inhibitors (SSRI), and

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<th>Table 1. The results of basic tests</th>
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<td>WBC</td>
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<td>3.99 × 10³/μL</td>
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<td>pCO₂</td>
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<td>36.4 mmHg</td>
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<th>Table 2. Laboratory results of tests performed to diagnose SIADH</th>
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<td>Sodium concentration in serum</td>
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<td>128 mmol/L</td>
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opioid analgesics. Nausea and vomiting after chemotherapy can also result in hyponatremia. Congestive heart failure seems to be associated with hypovolemic hyponatremia, which complicates the treatment of oncological patients using anthracyclines. This electrolyte disorder can also be observed in patients suffering from paraneoplastic syndrome, like nephrotic syndrome or renal minimal change disease. Hyponatremia may also be a final result of cancer metastases to the central nervous system or adrenal cortex, leading to adrenal insufficiency. Hyponatremia, as mentioned above, can serve as a marker for the disease severity. Hyponatremia has been shown to be an independent prognostic marker in oncological patients. Among patients with lung cancer, hyponatremia is a negative prognostic factor at the time of hospital stay and in patients with erlotinib-based treatment regiments. It should be taken into account that the prognostic value of hyponatremia may vary depending on such factors as: the type of tumor, the severity of the disease and the initial treatment of hyponatremia. The worst prognosis concerns the following cancers: small cell lung cancer (SCLC), mesothelioma, gastrointestinal cancer, renal cell carcinoma and lymphoma. Rapid correction of serum sodium correlates with longer overall survival and improvement of clinical condition. Patients were selected based on the histologically confirmed diagnosis of SCLC and SIADH. Patients started chemotherapy treatment at the same time. Then were treated with tolvaptan which led to performance status improvement and sodium level correction. The treatment was conducted according to the diagnostic and therapeutic algorithm. It led to effective correction of both clinical problems and sodium level in peripheral blood plasma. Patients started chemotherapy treatment at the same time. Then were treated with tolvaptan which led to performance status improvement based on the ECOG score. All patients benefited from the effective treatment of SIADH, avoiding long-term hospitalization. It has been shown that the serum sodium normalization failure after the chemotherapy initiation is a negative prognostic factor. Hyponatremia seems to be in negative correlation with the treatment efficacy. The management of any cancer patient should always take into account an evaluation of sodium level.

Summary

The possibility of SIADH as a paraneoplastic syndrome should be considered in patients with hyponatremia of undetermined etiology. In the case of abnormal sodium concentrations, extensive differential diagnosis should be performed. SIADH can be caused by ectopic neoplastic ADH production, be connected to ADH secretion stimulation or even the result of AVP (the antidiuretic hormone arginine vasopressin) due to anticancer therapy or palliative treatment. Studies have shown that hyponatremia has a prognostic value in groups of patients diagnosed with lung cancer. It is crucial to gradually and effectively correct the hyponatremia, keeping in mind that the process should be spread out over time.

Conclusion

SIADH secondary to different types of malignant neoplasm should be included in a differential diagnosis of every case of hyponatremia of undetermined etiology. Imaging studies and tumor markers evaluation are an important part of diagnostic procedures. Correction of the serum sodium level improves the patient condition.

References


