© Wydawnictwo UR 2018
ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2018.2.14

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2018; 16 (2): 163–167

CASUISTIC PAPER

Agnieszka Radzka [1(ABDFG)], Urszula Fałkowska [2(ABDFG)], Aleksander Sławiński [2(ABDFG)], Aleksander Ryczkowski [2(ABDFG)], Ewa Obel [3(ABDFG)], Marcin Lewicki [4(ABDFG)]

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

[1] Student's Scientific Group at the Clinic of Endocrinology of Medical University of Lublin, Poland
[2] Student's Scientific Group at the Department of Epidemiology and Clinical Research Methodology of Medical University of Lublin, Poland
[3] Department of Endocrinology of Medical University of Lublin, Poland
[4] Department of Epidemiology and Clinical Research Methodology of Medical University of Lublin, Poland

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.

Methods. An analysis of the clinical history of the patient and a review of available literature.

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

Corresponding author: Agnieszka Radzka, e-mail: radzka.agnieszka@gmail.com

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

Received: 25.03.2018 | Accepted: 04.05.2018
Publication date: June 2018

Radzka A, Fałkowska U, Sławiński A et al. *Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) during the course of lung cancer. A case report*. Eur J Clin Exp Med. 2018;16(2):163–167. doi: 10.15584/ejcem.2018.2.14

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.[2] 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 probable[5] 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 euvolemic 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.[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.[9] However, not only drugs used to treat cancer can cause hyponatremia, it is very often caused by thiazides 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.[9] 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.[16] 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 Endrocrinology, 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 Patinet was reffered 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.[24,25] Such a condition can be the result of tumor antidiuretic 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.[26] Cyclophosphamide 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

Table 1. The results of basic tests

WBC	RBC	HCT	PLT	pH	pO_2
$3.99 \times 10^3/\mu L$	$3.8 \times 10^6/\mu L$	33.1%	$305 \times 10^3/\mu L$	7.41	90.6 mmHg

pCO_2	CRP	Cholesterol	Creatinine	TSH	Cortizol
36.4 mmHg	0.964 mg/L	199 mg/dL	0.5 mg/dL	2.118 mIU/L	192.40 µg/24h

Table 2. Laboratory results of tests performed to diagnose SIADH

Sodium concentration in serum	The value of sodium in the daily collection of urine	Serum osmolality	Urine osmolality
128 mmol/L	72 mmol/L	254 mOsm/kg H_2O	375 mOsm/kg H_2O

opioid analgesics.[26] 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.[27] This electrolyte disorder can also be observed in patients suffering from paraneoplastic syndrome, like nephrotic syndrome or renal minimal change disease.[28] 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.[29,30] 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.[31,32] 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.[33,34,35,36,37] Rapid correction of serum sodium correlates with longer overall survival and improvement of clinical condition.[38] Petereit et al. conducted a study in 10 patients diagnosed with SCLC and SIADH. Patients were selected based on the histologically confirmed diagnosis of SCLC and the clinical picture of neurocognitive deficit induced by SIADH- associated hyponatremia. All patient data were monitored for clinical improvement based on ECOG (fitness scale according to the Eastern Cooperative Oncology Group) status, time of chemotherapy initiation and sodium levels 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.[39] Hyponatremia seems to be in negative correlation with the treatment efficacy.[40] 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

1. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation and treatment of hyponatremia: Expert panel recommendations. *Am J Med*. 2013;126(10):1–42.
2. Sahay M, Sahay R. Hyponatremia: A practical approach. *Indian J Endocrinol Metab.* 2014;18(6):760-771.
3. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. *Ann Pharmacother*. 2003;37(11):1694–1702.
4. Adrogué HJ. Consequences of inadequate management of hyponatremia. *Am J Nephrol*. 2005;25(3):240–249.
5. Schwartz E, Fogel RL, Chokas WV, Panariello VA. Unstable osmolar homeostasis with and without renal sodium wastage. *Amer J Med*. 1962;33:39-53.
6. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness and attention deficits. *Am J Med*. 2006;119(1):71.1–8.
7. Liamis G, Milionis HJ, Elisaf M. Endocrine disorders: causes of hyponatremia not to neglect. *Ann Med*. 2011;43(3):179-187.
8. Leaf A, Mamby AR. An antidiuretic mechanism not regulated by extracellular fluid tonicity. *J Clin Invest*.1952;31(1):60–71.
9. Pillai BP, Unnikrishnan AG, Pavithran PV. Syndrome of inappropriate antidiuretic hormone secretion: Revisiting a classical endocrine disorder. *Indian J Endocrinol Metab.* 2011;15(3):208-215.
10. Upadhyay A, Jaber BL, Medias NE. Incidence and prevalence of hyponatremia. *Am J Med.* 2006; 119(1):30–35.
11. Filipinos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. *Clin Interv Aging*. 2017;12:1957-1965.
12. Jonaidi Jafari N, Izadi M, Sarrafzadeh F, Heidari A, Ranjbar R, Saburi A. Hyponatremia Due to Pulmonary Tuberculosis: Review of 200 Cases. *Nephro-urology monthly*. 2013;5(1):687-691.

13. Gitelman SE, Feldman BJ, Rosenthal SM. Nephrogenic syndrome of inappropriate antidiuresis: A novel disorder in water balance in pediatric patients. *Am J Med*. 2006;119:54–58.
14. Tian W, Fu Y, Garcia-Elias A, et al. A loss-of-function nonsynonymous polymorphism in the osmoregulatory TRPV4 gene is associated with human hyponatremia. *Proc Natl Acad Sci USA*. 2009;106(33):14034-14039.
15. Braconnier P, Delforge M, Garjau M, Wissing KM, De Wit S. Hyponatremia is a marker of disease severity in HIV--infected patients: a retrospective cohort study. *BMC Infectious Diseases*. 2017;17:98.
16. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kidney Dis*. 2012;59(2):222–228.
17. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(21):1581–1589.
18. Berghmans T., Paesmans M., Body J. A prospective study on hyponatremia in medical cancer patients: epidemiology, aetiology and differential diagnosis. *Support Care Cancer*. 2000;8(3):192–197.
19. Sørensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. *J Intern Med*. 1995;238(2):97–110.
20. Petereit C, Zaba O, Teber I, Lüders H, Grohé C. A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan. *BMC Pulmonary Medicine*. 2013;13:55.
21. List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. *J Clin Oncol*. 1986;4(8):1191–1198.
22. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med*. 1957;23(4):529–542.
23. Chute JP, Taylor E, Williams J, Kaye F, Venzon D, Johnson BE. A metabolic study of patients with lung cancer and hyponatremia of malignancy. *Clin Cancer Res*. 2006;1;12(3,1):888-896.
24. Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. *Support Care Cancer*. 2007;15:1341–1347.
25. Onitilo AA, Kio E, Doi SAR. Tumor-Related Hyponatremia. *Clinical Medicine & Research*. 2007;5(4):228-237.
26. Grohé C, Berardi R, Burst V. Hyponatraemia – SIADH in lung cancer diagnostic and treatment algorithms. *Crit Rev Oncol Hematol*. 2015;96(1):1–8.
27. Sawyer DB. Anthracyclines and heart failure. *N Engl J Med*. 2013;368(12):1154–1156.
28. Birkeland SA, Storm HH. Glomerulonephritis and malignancy: a population-based analysis. *Kidney Int*. 2003;63(2):716–721.
29. Gill G, Huda B, Boyd A, et al. Characteristics and mortality of severe hyponatraemia – a hospital-based study. *ClinEndocrinol (Oxf)*. 2006;65(2):246–249.
30. Hansen O, Sorensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. *Lung Cancer*. 2010;68(1):111–114.
31. Svaton M, Fiala O, Pesek M, et al. Predictive and prognostic significance of sodium levels in patients with NSCLC treated by erlotinib. *Anticancer Res*. 2014;34(12):7461–7465.
32. Kobayashi N, Usui S, Yamaoka M, et al. The influence of serum sodium concentration on prognosis in resected non-small cell lung cancer. *Thorac Cardiovasc Surg*. 2014;62(4):338–343.
33. Rawson NS, Peto J. An overview of prognostic factors in small cell lung cancer. A report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. *British Journal of Cancer*. 1990;61(4):597-604.
34. Schutz FAB, Xie W, Donskov F, et al. The Impact of Low Serum Sodium on Treatment Outcome of Targeted Therapy in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Cancer Database Consortium. *European urology*. 2014;65(4):723-730.
35. Berardi R, Caramanti M, Fiordoliva I, et al. Hyponatraemia is a predictor of clinical outcome for malignant pleural mesothelioma. *Support Care Cancer*. 2015;23(3):621–626.
36. Kim HS, Yi SY, Jun HJ, et al. Clinical outcome of gastric cancer patients with bone marrow metastases. *Oncology*. 2007;73(3-4):192–197.
37. Castillo JJ, Glezerman IG, Boklage SH, et al. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients. *BMC Cancer*. 2016;16:564.
38. Balachandran K, Okines A, Gunapala R, Morganstein D, Popat S. Resolution of severe hyponatraemia is associated with improved survival in patients with cancer. *BMC Cancer*. 2015;15:163.
39. Petereit C, Zaba O, Teber I, Groh C. Is hyponatremia a prognostic marker of survival for lung cancer? *Pneumologie*. 2011;65(9):565–571.
40. Sengupta A, Banerjee SN, Biswas NM, et al. The Incidence of Hyponatraemia and Its Effect on the ECOG Performance Status among Lung Cancer Patients. *J Clin Diag Res: JCDR*. 2013;7(8):1678-1682.