Case report

Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) as an initial presenting sign of non small cell lung cancer-case report and literature review

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Article info

Article history:
Received 10 July 2017
Received in revised form 6 August 2017
Accepted 7 August 2017

Keywords:
Non small cell lung cancer
Syndrome of inappropriate ADH secretion
Hyponatremia

Abstract

Association of SIADH with malignancy was first reported in 1957, when it was described in two patients with bronchogenic carcinoma. While the association with small cell lung cancer (SCLC) is well known, that with non small cell lung cancer (NSCLC) has been rarely reported. We report a case of 70 year old male who was found to have hyponatremia secondary to SIADH. Radiological tests revealed right hilar lung mass with mediastinal adenopathy. Bronchoscopic biopsy revealed non-small cell lung cancer of type squamous cell. Magnetic resonance imaging (MRI) of brain showed metastatic lesions, thereby confirming diagnosis of metastatic lung cancer. Paraneoplastic syndromes occur in 10% of lung cancer cases and they represent a group of disorders related to secretion of functional polypeptides or hormones from tumor cells. SIADH is more commonly described in conjunction with small cell lung cancer but there are a few case reports describing it's occurrence after initiation of therapy for NSCLC such as radiation and chemotherapy. The mechanism for this phenomenon is not known. Unlike infectious causes, hyponatremia as initial presentation is an uncommon feature of malignancy-associated SIADH. In the lung cancer population, hyponatremia has been identified as a negative prognostic factor in hospitalized patients and those with advanced-stage disease. Malignancy should be a consideration in the diagnostic evaluation of SIADH, irrespective of the time of presentation.

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1. Introduction

The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is caused by retention of free water secondary to dysregulated release of anti-diuretic hormone (ADH). It is suggested by hyponatremia, low serum and high urine osmolality and continued excretion of urine sodium in the absence of other causes of hyponatremia. Association of SIADH with malignancy was first noted in 1957, when it was described in two patients with bronchogenic carcinoma. After years of research and countless observations, it has been shown to be a common paraneoplastic phenomenon that approximately occurs in 70% of malignancy-related cases of small cell lung cancer (SCLC). Other cancers that have been shown to be associated with SIADH include Lymphoma, thymoma, mesothelioma, Ewing's sarcoma and squamous cell carcinoma of the head and neck [1]. We present a very unique case in which patient was admitted with hyponatremia secondary SIADH and was found to have non-small cell lung cancer (NSCLC). As per our literature search, over last 20 years there have been three other reported cases of SIADH that occurred in association with NSCLC. This case also reviews possible alternative mechanism of SIADH in patients with NSCLC, as it was the presenting sign of underlying malignancy and resolved prior to initiation of therapy. This is in contrary to the other three cases where resolution of SIADH occurred with removal of tumor and/or with initiation of chemotherapy.

2. Case presentation

This is a 70 year old male with past medical history of hyperlipidemia, benign prostate hypertrophy, Tobacco abuse and recent
diagnosis of right sided lung mass with pleural effusion presented to emergency department with complaints of dizziness for 3 weeks. Dizziness was positional and had been progressively getting worse over the course of past 3 weeks. Patient denied nausea and vomiting but he did report that his appetite was deteriorating and so was his oral intake. He didn’t have any hearing loss or ear fullness. He has occasional palpitations but otherwise history is unremarkable. Past surgical history was significant for left shoulder surgery with intramedullary rod placement. Family history was negative for cancer. Patient smoked 2 packs per day for the past 40 years but denied drinking alcohol or using illicit drugs. He denied any occupational exposure to asbestos or other carcinogenic chemicals. His home medications included Aspirin 81mg oral daily, Tamsuloin 0.4mg oral daily, Ferrous sulfate 325mg oral daily, Atorvastatin 20mg oral daily. On admission, vitals included temperature of 98 F, blood pressure of 102/62 mm Hg with positive orthostatic vital signs, pulse rate of 102 beats/min, respiratory rate of 28/min and oxygen saturation of 100% on room air.

On Physical Exam, patient was in no acute distress but appeared clinically dehydrated. Rest of the exam revealed decreased breath sounds over right middle lung zone. On initial evaluation, basal metabolic panel (BMP) revealed sodium of 126 mEq/L, potassium of 3.5 mEq/L, chloride of 84 mEq/L, bicarbonate of 30 mEq/L, blood urea nitrogen of 8mg/dL, creatinine of 0.54 mg/dL, blood glucose of 125 mg/dL and serum lactate of 2.3 mmol/L. Patient’s BMP from one month prior to this admission revealed normal serum sodium levels. Complete blood count showed white blood count of 19.1 Thousand/mL with left shift, hemoglobin of 10.6 g/dL, hematocrit of 32% and platelet count of 385 Thousand/mL. Patient was admitted for dizziness and he was started on intravenous normal saline. This intervention did not improve the serum sodium levels. Further workup for hyponatremia revealed serum osmolality of 268 mOsm/Kg, urine osmolality of 626 mOsm/Kg and urine sodium of 126 mmol/L. Based on these results, a diagnosis of SIADH was made. Intravenous fluids were discontinued and salt tablets were started. On salt tablets, patient’s sodium levels did improve to 134 mEq/L.

CT chest scan showed right hilar lung mass with pleural effusion and mediastinal adenopathy highly suspicious for lung cancer (Figs. 1 and 2).

CT chest did not reveal any evidence of pneumonia, pneumothorax or any other significant lung pathology. CT guided biopsy was done and sample showed necrotic tissue without evidence of malignancy. Since clinical suspicion was high for lung cancer, bronchoscopic biopsy of right hilar mass and mediastinal lymphadenopathy was performed. Histopathology of biopsy specimen revealed clusters of cancer cells that were later positive for CK5/6 staining, consistent with squamous cell carcinoma (Fig. 3).

Patient also underwent Magnetic Resonance Imaging (MRI) of Brain which showed multiple masses with surrounded by vasogenic edema consistent with metastatic lesions (Fig. 4).

Oncology consult was obtained for metastatic squamous cell lung cancer and recommendations were for patient to undergo whole brain radiation, chest radiation and outpatient chemotherapy. Patient’s prognosis was deemed to be poor. While in the hospital, patient received 9 out of 10 fractions of whole brain radiation. Subsequently, patient started complaining of right upper extremity swelling which gradually became worse. Imaging studies revealed superior vena cava thrombosis. But patient was not a good candidate for anticoagulation as he had extensive brain metastasis and there was a significant risk of intracranial hemorrhage.

Due to patient’s poor prognosis, a discussion was initiated regarding his code status and he wanted to be converted to Do Not Resuscitate/Do Not Intubate (DNR/DNI) status. After prolonged hospital course, patient was eventually discharged to a nursing home with instructions to receive chest radiation and palliative chemotherapy. Two weeks later, patient was made hospice and eventually he died in nursing home.

3. Discussion

Paraneoplastic syndromes occur in 10% of lung cancer cases, they represent a group of disorders related to secretion of functional polypeptides or hormones from tumor cells. Recognizing and managing paraneoplastic syndromes is an integral part of cancer management [2]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the paraneoplastic syndrome.

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which has a well-established linkage to small cell lung cancer. It occurs in 7—16% of small cell lung cancer (SCLC) cases and has been linked to worse outcome in patients with SCLC [3,4]. Serum levels of antidiuretic hormone (ADH) are elevated in the majority of cases of SIADH that are associated with SCLC and prior studies have shown that more severe hyponatremia predicts worse prognosis. In these cases, ectopic ADH secretion by malignant cells is the most common mechanism for the development of SIADH. In one study of patients with SCLC, both ADH and atrial natriuretic peptide (ANP) were shown to cause SIADH. It was also noted that the quantity of ADH was more closely associated with the development of hyponatremia [4].

Cases of SIADH associated with NSCLC and other malignancies including squamous cell carcinoma (SCC) have been previously reported, but the mechanism by which it occurs has not been clarified. McDonald, Philip, Lane, Colleen et al. presented a patient with biopsy proven NSCLC who developed hyponatremia secondary to SIADH. In their case report, patient developed SIADH only after initiation of radiation therapy. The likely explanation was hypothesized to be secondary to release of ADH due to tumor lysis. This phenomenon was previously only noticed in patients with SCLC [1]. Another case report described a patient with poorly differentiated NSCLC, who was severely hyponatremic (115 mmol/l) on presentation. Interestingly, patient’s hyponatremia improved after initiation of chemotherapy [5]. Chemotherapy with cisplatin has itself shown to cause hyponatremia [6] but in the above mentioned case, hyponatremia onset preceded chemotherapy and got better after initiation of chemotherapy. A previous case report had shown surgical resection of NSCLC to resolve SIADH [7], but this was the first time chemotherapy had been described to successfully treat this condition. In one large case series, 3 out of 427 patients with non-small cell lung cancer were noted to have SIADH but the characteristics or time of onset of SIADH in these patients is unknown [8].

The time during a patient’s hospital course at which SIADH is diagnosed can be highly suggestive of its etiology. Hyponatremia which develops gradually over a long period of time most likely represents stimulation of endogenous ADH secretion rather than production of ectopic hormone. Hyponatremia at presentation is an uncommon feature of malignancy-associated SIADH [8]. In our case, patient presented with hyponatremia secondary to SIADH and this occurred even prior to initiation of radiation or chemotherapy. Hyponatremia in this patient did not gradually develop over long time as his serum sodium levels 1 month prior to this admission, were normal. The hyponatremia improved after starting him on salt tablets. There is no rational explanation for this phenomenon.

Sorenson JB, Andersen MK et al. explained in their study that NSCLC rarely produce polypeptide hormones like ADH and atrial natriuretic peptide (ANP) [8]. In all the previous reported cases of non small cell lung cancer with SIADH, hyponatremia occurred before or after initiation of chemotherapy, radiation or surgical resection. However, our patient presented with SIADH on presentation and even before initiation of treatment, it had resolved with medical management. Also, he did not have any other explanation for SIADH like medications (chemotherapies, opioids, target therapies), lung disease (pneumonia, pneumothorax, COPD etc), central nervous system infections (meningitis, encephalitis or abscess), head injuries (skull fracture, subdural contusion, subarachnoid hemorrhage) or psychosis (schizophrenia, bipolar disease etc). Although brain tumors can cause SIADH, this phenomenon has been explained in literature with primary brain tumors and not metastatic lesions to brain [8,9]. Keeping the above points in mind, we could postulate that SIADH in this patient could have occurred due to ectopic release of anti-diuretic hormone (ADH) or ANP but there is no explanation for why it resolved even before initiation of therapy.

Hyponatremia has been identified as a negative prognostic factor in a number of different malignancies. In the lung cancer population, hyponatremia is a negative prognostic factor in hospitalized patients and those with advanced-stage disease [10]. Furthermore it has been shown to negatively correlate with the performance status as well as tumor status and inflammation in completely resected NSCLC [11]. It is important for physicians to determine and validate prognostic factors in order to optimize and personalize the management of NSCLC. Sodium normalization is an independent prognostic factor for overall survival in patients with advanced lung cancer treated with first-line therapies [12].

In summary, this is a patient who was presented with hyponatremia secondary to SIADH and was diagnosed with metastatic non small cell lung cancer. This case is unique as SIADH was the...
presenting feature of his non small cell lung cancer and it resolved even before initiation of therapy. SIADH is uncommonly associated with NSCLC but it is even more uncommon for it to be the first presentation of malignancy.

Acknowledgments

We would like to thank the Internal Medicine Residency Program at St. Francis Medical Center, NJ and Department of Pulmonary and Critical Care at University of Tennessee Health Science Center for reviewing our case report and giving us their valuable inputs. We would especially like to thank Dr. Muhammad K Zaman-Associate Professor, Department of Pulmonary and Critical Care at University of Tennessee Health Science Center for his valuable guidance in improving the quality of this manuscript.

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