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Case Report of a Severe Hyponatriemia in a Patient with Renal Cell Carcinoma

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Abstract

Introduction: Around 14% of all cases of hyponatriemia in hospitalized patients is due to underlying tumor-related conditions, with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and depletional states as two major pathophisiological **mechanisms.**

Case report: A 69-year-old man was commited to our hospital for contituing treatment of mRCC. Phyisical examination at the admission showed sings of extreme malaise, along with confusion, desorientation and weakness. No sings of nephrotic syndrome, cardiac failure, gastrointestinal solute loss or third spacing were found. Hypothyreosis with TSH 112 μIU/ml and T3 1.05 nmol/l was diagnosed and levothyroxine therapy was started with gradual dose increasment. Laboratory tests confirmed stable renal insufficiency with normal kaliemia and severe hyponatriemia refractory to intensive sodium supstitution. Despite the intensive therapy, patient developed cardiorespiratory insufficiency with the lethal outcome on the 13th day of hospitalization. Autopsy was conducted and hypothyroidism was stated as the predominant cause of death.

Conclusion: We suggest early detection of endocrine disfunction in patient with mRCC and sunitinib therapy in course.

Keywords: Renal cell carcinoma; Hyponatriemia; Hypothyroidism

Introduction

Renal cell carcinoma (RCC), one of the most lethal urologic malignancies, accounts for approximately 3% of all adult malignancies and 90% of all adult renal neoplasms [1]. It is twice as common in men and most often occurs in patients from 50 to 70 years old [2]. Although significant improvements have been made in 5-year survival and recurrence-free survival, around 30% of patients still expirience metastatic form of RCC (mRCC) in only 12 months from diagnosis with a 5-year survival rate less than 20% [2].

Hyponatriemia, defined as serum sodium concentration less than 135mmol/l, is one of the most serious electrolyte disorders occuring in up to 22% of hospitalized patients and is related to a serious neurological complications that are dependent both on the severity and the rapidity of onset of change in plasma sodium concentrations [3]. Hyponatriemia depends on the amount of both plasma sodium and water and does not neccesserily imply sodium depletion. Around 14% of all cases of hyponatriemia in hospitalized patients is due to underlying tumor-related conditions, with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and depletional states as two major pathophisiological mechanisms [3,4].

Case report

A 69-year-old man was commited to our hospital for contituing treatment of mRCC. One year earlier the right nephrectomy was conducted due to the non-metastatic light cell RCC with predominant eosinophilic cell morphology of 40%. After the nephrectomy 5 cycle sunitinib therapy followed as the first-line treatment on a standard schedule with no side effects recorded including thyroid

disfunction (routine monitoring of thyroid function was performed every 3 months). Comorbidities included hypertension and chronic insufficiency grade III of the remaining left kidney.

Phyisical examination at the admission showed sings of extreme malaise, along with confusion, desorientation and weakness. No sings of nephrotic syndrome, cardiac failure, gastrointestinal solute loss or third spacing were found. Body temperature ranged from 36.2 to 36.8 ºC with diuresis from 1 to 1.8l per day, normal urin osmolarity and high urinary sodium excretion ranging from 26 to 29 mEq/d. During the hospitalization arterial blood pressure was normal and no episodes of hypotension were recorded. Hypothyreosis with TSH 112 μIU/ml and T3 1.05 nmol/l was diagnosed and levothyroxine therapy was started with gradual dose increasment. Laboratory tests confirmed stable renal insufficiency with normal kaliemia and severe hyponatriemia refractory to intensive sodium supstitution (Table 1).

Laboratory parameter	At the admission	At the end of the hospitalization
Na (mmol/l)	**108**	**124**
K (mmol/l)	**5.3**	**4.7**
Cl (mmol/l)	**77**	**93**
Ca (mmol/l)	**1.99**	**2.05**
Hb (g/l)	**137**	**118**
BUN (mmol/l)	**5.3**	**11.1**
s-creatinine (μmol/l)	139	126
s-albumine (g/l)	31	31
Systolic blood pressure	140	110
Diastolic blood pressure	80	70
Serum total protein (g/l)	61	47
s-glucose (mmol/l)	4.4	5.8
glicosuria	none	none

BUN: Blood Urea Nitrogen

Table 1: Laboratory and clinical parameters

Chest radiography showed billateral pleural effusion, with diffuse secundary deposits of various dimensions. Abdominal ehosonography revealed left renal stasis and secondary liver deposits.

During the 10th day of hospitalization derangement of coordination, weakness of the muscles of the lower extremities and inability to walk, along with somnolence, desorientation and disartria, occured. Neurologist suspected central pontine myelinolysis and indicated cerebral computed tomography scan that revealed only subarachnoid reductive lesions of the cerebral cortex above the base and convexity of the brain, after which additional nuclear magnetic resonance was planned.

Despite the intensive therapy, consisted of 20ml/kg of 0.9% sodium chloride solute along with 80 to 100 ml of 10% sodium chloride per day, serum sodium concentration only slightly rised and no improvement in neurological status occured. Patient developed cardiorespiratory insufficiency with the lethal outcome on the 13th day of hospitalization. Autopsy was conducted and hypothyroidism was stated as the predominant cause of death.

Discussion

Hypothyroidism, adrenal insufficiency, ectopic vasopressin secretion within the SIADH and primary polydipsia are long known to be the reasons of euvolemic hyponatriemia. Our patient expirienced severe primary hypothyreosis with euvolemic hyponatriemia and myxedema coma, that lead to death. It is well known that hyponatriemia in hypothyroidism is caused by both decrease in the delivery of water to the distal nephron, as well as excess vasopresin secretion, but, it is also suggested that only myxedema coma causes significant reductions in glomerular perfusion leading to clinically significant hyponatriemia [5].

The majority of cases of hyponatriemia in hypothyroidism is seen in hospitalized patients with comorbidities which may be additional contributing factor, rather than hypothyroidism alone. Since it is known that SIADH with the consequent hyponatriemia is seen in a broad spectrum of malignant tumors such as small cell lung cancers and carcinoids, other forms of lung cancers, head and neck cancers, genitourinary, gastrointestinal and ovarian cancers, it is possible that our patient with mRCC developed SIADH as well [6]. Taking into the account that vasopressin level is not done routinely, we suggest serial measurments of urine and serum osmolarity along with other laboratory parameters in order to conclude whether there is ectopic vasopressin secretion or not.

One of the possible causes of severe hypothyroidism in our patient could be side effect of thyrosin kinase inhibitor (TKI) therapy. Sunitinib is TKI with a various side effects, among others endocrine toxicity and impaired thyroid function with the frequency reported to be 36 to 85% [7,8]. The most probable mechanism for this could be vascular endothelial growth factor receptor

(VEGFR) blockade inducing tissue ischaemia and consequent thyroid insufficiency [9]. Another recent study revealed that sunitinib specifically binds to three retinoid receptors and suggested the possibility that sunitinib competes with thyroid hormone receptors for binding with retinoic acid receptors which finally results in hormonal dysregulation [10]. Although there are trials reporting better outcome in patients treated with TKI and consequent hypothyroidism, this complications remains a serious and potentially leathal one [11,12].

Although we can not associate with certainty hyponatriemia in our case with sunitinib therapy, due to the fact that this is often a tumor-related phenomenon, still we suggest early detection of endocrine disfunction in patient with mRCC and sunitinib therapy in course, as well as the timely start of substitution therapy if needed, in order to avoid potentialy lethal complications such as myxedema as well as TKI interruptions or dose reductions.

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