SYNDROME OF INAPPROPRIATE SECRETION OF ANTI DIURETIC HORMONE (SIADH) WITH THE COEXISTENCE OF SJÖGREN'S SYNDROME AND SMALL CELL LUNG CANCER: A CASE REPORT OF INTRACTABLE HYPONATREMIA

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ABSTRACT

Syndrome of inappropriate secretion of Anti Diuretic Hormone (SIADH) resulting from a variety of disorders with multifactorial etiology, complex pathophysiologic changes and multitude manifestation, is quite common but intractable in clinic.

56-year-old female was admitted with complaints of weakness, nausea, inapetence and vomit. The patient was absent of hypovolemia during hospitalization, without cough, muscle or joint pain, but showed slight dry mouth. Serum sodium level fluctuated within, and plasma osmolality ranged from 241.2 to 257.2 mOsm/L. Yet hyponatremia didn't respond to the treatment of natrium supplementation 0.23-0.26mmol/d through intravenous infusion. Then the patient was diagnosed with SIADH associated with Sjögren's syndrome (SS). The weakness and nausea, inapetence of the patient gradually returned to a normal baseline after fluid restriction and prednisone tablets were administered. After 4-week's application of prednisone tablets (30mg/d), weakness and nausea, inapetence gradually returned to the normal baseline.

Prednisone administration decreased to 25mg/d during the 5th week and cut 5mg per month regularly. Emerging respiratory signs made the patient hospitalized again. Multi-slice spiral computed tomography (CT) examination of lung revealed a nodule located in the right main bronchial, eventually she was diagnosed with small cell lung cancer (SCLC) by the following fiber bronchoscope and biopsy. After 1st round of chemotherapy, the signs and symptoms above began to remit. SIADH is constantly correlated with a malignant tumor; meanwhile the patients with autoimmune disorders (such as SS) are exposed to the increasing risk of carcinoma.

It is concluded that the symptoms of SIADH were obvious because she had both SS and SCLC.

Keywords: *Hyponatremia, inappropriate ADH syndrome, Sjögren's syndrome, small cell lung cancer.* **Nobel Med 2018; 14(1): 49-54**

KÜÇÜK HÜCRELİ AKCİĞER KANSERİ VE SJÖGREN'S SENDROMUNUN EŞLİK ETTİĞİ UYGUNSUZ ANTİDİÜRETİK HORMON SALINIMI SENDROMU: İNATÇI BİR HİPONATREMİ OLGU SUNUMU

ÖZET

Uygunsuz antidiüretik hormon salınımı sendromu (UADHSS); kompleks patofizyolojik değişikliklerin ve çok sayıda belirtilerin bulunduğu multifaktöryel etiyoljili rahatsızlıkların sonuçlarının görüldüğü, oldukça yaygın ama inatçı kliniği olan bir sendromdur.

56 yaşında kadın halsizlik, bulantı, kusma ve iştahsızlık şikayetleri ile başvurmuştur. Kas ve eklem ağrıları ve öksürük olmayan hasta yatırıldığında hipovolemisi yoktu, sadece hafif bir ağız kuruluğu görülmüştü. Serum sodyum seviyesi 113-123mmol/l aralığında dalgalanıyordu ve plazma ozmolalitesi 241,2 ile 257,2 mOsm/L arasındaydı. İntravenöz infüzyon ile 0,23-0,26 mmol/d sodyum destek tedavisi hiponatremiyi düzeltmedi. Hastaya Sjögren's Sendromu (SS) ile birlikte UADHSS tanısı kondu. Hastadaki halsizlik, bulantı ve iştahsızlık sınırlı sıvı desteği (600-700 ml/d) ve prednizon tablet uygulaması ile hızla normal seviyeye döndü. Dört haftalık 30 mg/d prednizon tablet uygulamasıyla halsizlik, bulantı ve iştahsızlık hızla normal seviyeye döndü. Beşinci haftadan itibaren prednizon uygulaması 25 mg/d'ye düşürüldü ve ayda 5 mg olmak üzere kontrollü olarak azaltıldı. Acil solunum problemleri ile hasta hastaneye tekrar yatırıldı. Akciğerlerin multi-slice spiral CT incelemesinde sağ ana bronşta bir nodül tesbit edildi. Son olarak fiberoptik bronkoskop ile yapılan inceleme ve alınan biopside hastaya Küçük Hücreli Akciğer Kanseri (KHAK) tanısı kondu. Hastadaki bulgu ve belirtiler ilk kür kemoterapi ile hafiflemeye başladı. UADHSS bir malign tümor ile birliktedir. Bununla birlikte SS gibi otoimmün rahatsızlığı olan hastalarda karsinoma riskinin arttığı gösterilmiştir.

Sonuç olarak hastada hem SS hem KHAK bir arada olduğu için UADHSS semptomları aşikardı.

Anahtar kelimeler: Hiponatremi, uygunsuz ADH sendromu, Sjögren's sendromu, küçük hücreli akciğer kanseri. **Nobel Med 2018; 14(1): 49-54**

INTRODUCTION

Syndrome of inappropriate secretion of ADH (SIADH) is not only a common clinical syndrome, but an abstruse, complicated and serious complication resulting from rheumatic autoimmune disease, such as Sjögren's syndrome (SS), and its potential related malignancy.[1] We provide this case of a woman presenting severe hyponatremia and SIADH strongly associated with both of SS and small cell lung cancer (SCLC).

CASE

A 56-year-old female was sent to the department of gastroenterology for nausea, decreasing energy, inapetence and vomit. No hypovolemia symptoms were detected. It had been found no familiar disorders in her family. Raynaud's phenomenon was found six years ago but that went unscrutinized. Gastritis and gastric carcinoma were all ruled out. The initial laboratory tests (in the Table below) showed the normal renal and hepatic function, and routine imaging tests (e.g., X-ray, computed tomography) also found no pathologic cardiopulmonary changes, except for sodium (113-123 mmol/L). Dramatically, the low plasma osmolality ranging from 241.2 to 257.2 mOsm/L was accompanied by high urinary osmolality (225- 378 mOsm/L) (Figure 1).

In view of rampant teeth (Figure 2), we exerted autoimmune antibody detection and linked examination on this patient. SS was diagnosed according to criteria of PSS included the 2002 international classification of SS for the classification of SS, based on the following clinical items: 1) repeated dry mouth for more than 2 years; 2) constantly drinking water was essential when dry and solid comestible was swallowed; 3) the biopsy revealed glandularis cheilitis and its inflammatory damages attributed to lymphocytes clustering; 4) positive anti-SSA antibody/Ro52Kd.[2]

Yet hyponatremia didn't respond to the treatment of natrium supplementation 0.23-0.26 mmol/d through intravenous infusion. So we adjusted supplement of sodium with fluid restriction (600-700 ml/d) together with application of prednisone tablets (30 mg/d) since the 5th day. Four-week later, weakness and nausea, inapetence gradually returned to a normal baseline, together with the remission of Raynaud's phenomenon. Prednisone administration decreased to 25 mg/d during the 5th week and cut 5 mg per month regularly. Two months later, emerging respiratory

Table. Laboratory examination during hospitalization

Exam/day	2013.12.31	2014.1.1	2014.1.2	2014.1.5	2014.1.9	2014.1.16	2014.1.16
Serum Na (mmol/l)	113	114	118	118	122	123	121
Serum K (mmol/l)	3.6	4.2	3.8	4.2	4.6	4.1	3,7
Serum Cl (mmol/l)	83	80	86	90	86	87	89
Serum Ca (mmol/l)	2.19	2.41	2.43	2.52	2.41	2.67	2.52
Urinary Na (mmol/l)	59		66			53	
Urinary K (mmol/l)	19		16			20	
Creatine (µmol/l)	55	31		51	39	42	
BUN (mmol/l)	2.61	2.23	2.4	2.37	2.08	2.21	
Uric acid (µmol/l)	65	29	48	58	33		
AST (u/l)	19						
ALT (u/l)	23						
pH	7.41						
pCO_2 (mmHg)	33						
pO_2 (mmHg)	95						
TSH (mIU/l)	2.3						

BUN: Blood urea nitrogen, **TSH:** thyroid stimulating hormone.

signs made the patient hospitalized again. Multi-slice spiral CT reexamination of lung revealed a nodule located in the right main bronchial; eventually she was diagnosed with SCLC by the following fiber bronchoscope (Figure 3a) and biopsy (Figure 3b).

After the 1st round of chemotherapy, the signs and symptoms above began to remit. This patient is still under regular follow-up.

DISCUSSION

Intractable hyponatremia arising from two patients with lung cancer led to the 1st description of SIADH by Schwartz in 1957, and SIADH had been regarded as the most common cause of hyponatremia after several decades of research.[3-5] Hypoosmolality is initially combined with a diversity of manifestations, such as nonspecific symptoms (headache, nausea, etc) and obvious symptoms (disorientation, confusion, seizures, etc). This nervous disturbance has been defined as hyponatremic encephalopathy which prompts osmotic water to the brain because of low plasma osmolality. Significant neurologic symptoms usually do not emerge until serum sodium falls below 125 mmol/L, but the clinical situation varied in different patients. There hasn't been a fixed correlation on the level of serum sodium and nervous symptoms for any single patient.

The essential standards for the diagnosis of SIADH are: 1) Low osmolality of the extracellular fluid (plasma osmolality<275 mOsm/L); 2) high urinary concentration (urinary osmolality>100 mOsm/L, with a normal renal function); 3) increased urinary sodium excretion; 4) absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism and diuretic use.[6] As for the difficulty in detecting the concentration of arginine vasopressin (AVP), serum sodium level and plasma-urinary osmotality usually serve as the diagnostic indicators. The expansion of blood volume contributes to the

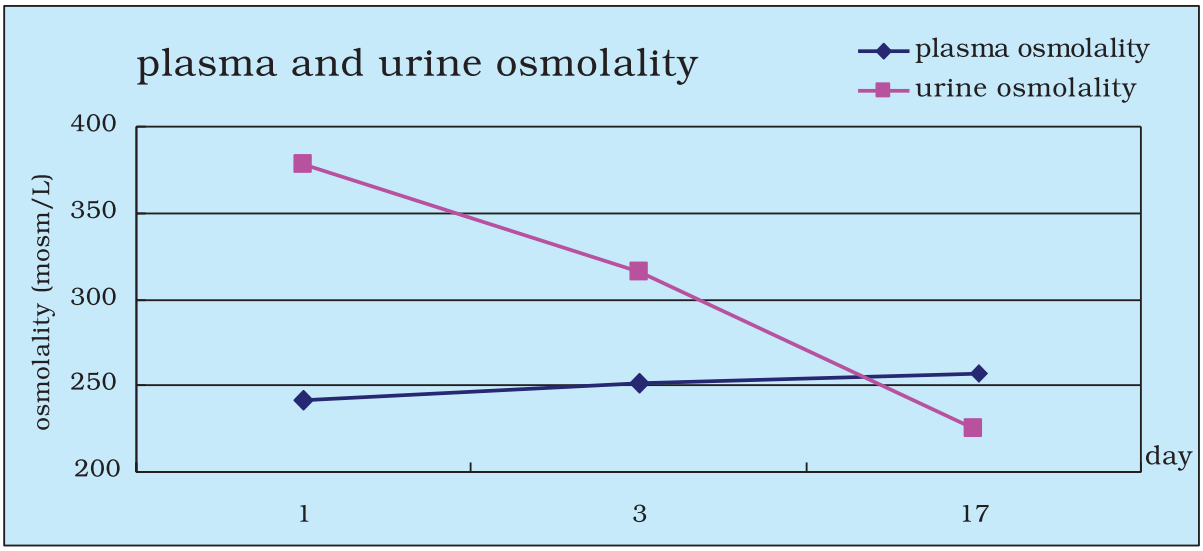

Figure 1. Osmotality value of plasma and urine at different points during hospitalization.

inhibition of renin angiotensin aldosterone system, with the increasing elimination of uric acid and urea nitrogen.[6] Therefore SIAHD should be taken into account when hyponatremia emerges together with hypouricemia and low urea nitrogen. The patient was diagnosed with SIADH specifically with the accordance to the diagnostic criteria.

Meanwhile, many studies have reported that rheumatic diseases (such as systemic lupus erythematosus, rheumatoid arthritis, SS, adult Still disease) can lead to SIADH.[7-10] The mechanisms that rheumatic diseases cause SIADH are not yet fully elucidated. Recent literatures revealed several possible mechanisms: 1) pleurisy and interstitial pneumonitis resulting from rheumatic lung lesion; 2) therapeutic management (such as tacrolimus, cyclophosphamide, azathioprine, non-steroid anti-inflammatory drugs) leading to SIADH; 3) intracranial vasculitis involving hypothalamus.[11,12]

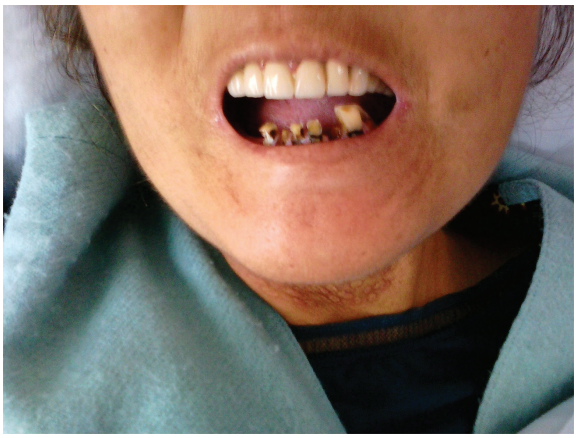

Figure 2. Rampant teeth (maxillary denture and mandibular rampant teeth)

A recent study by Zarouf et al suggested that SIADH displayed substantial relation with high level of IL-6, IL-1b, neutrophil count, and C-reactive protein. In particular, IL-6, a significant inflammatory mediator, in cerebrospinal fluid is likely to stimulate more release of ADH from posterior pituitary.[13] The previous interpretation indicated that inflammation may contribute to the pathogenisis, but the exact mechanism of SS-induced SIADH remains unclear.

However, autoimmune diseases which are accompanied by the activation of T/B lymphocytes and related inflammatory cytokines may increase the risk of some types of malignancies.[14] SS being one of the disorders, was characterized by lymphocytic infiltration of exocrine and dysfunction for immune system. Some clinical studies have revealed the correlation between SS and malignancies, while lymphoma is the most focused disease.[15,16] The factors susceptible to SS include exogenous (EBV, cytomegalovirus, retroviruses, hepatitis C virus or ultraviolet radiation) and endogenous (HLA of B8, DR2, DR3 and DQ types; populations of CD4+T cells, anti-SSA/Ro, anti-SSB/La and anti-muscarinic receptor type 3 antibody, interferon- gamma) sources. In some cases, monoclonal B-cell proliferation occurs and this may lead to lymphomas.[16]

Comparatively speaking, rarely observations report the association between SS and solid tumors, in particular, the lung cancer. Peking Union Hospital have reported the robust analysis from 1990 to 2005 recruited 1,320 patients with SS. The subjects in the retrospective study were followed for a mean of 4.4

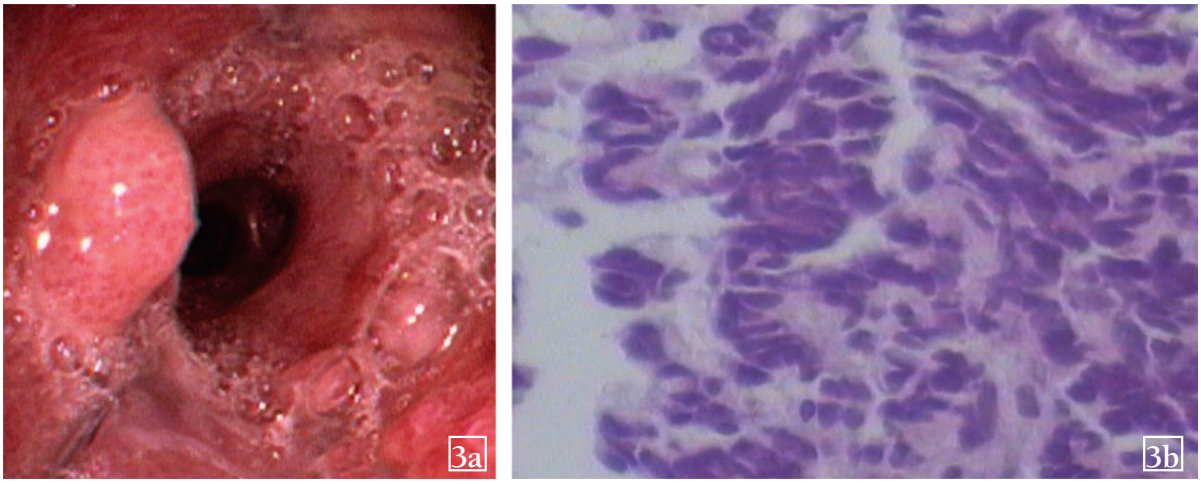

Figure 3. Fiberbronchoscopy scan (3a) and pathological examination (3b).
(3a) Fiber bronchoscope showed a polyp-like nodule located in the right main bronchial.
(3b) The cancer cells were difused, with the characteristics of small size, spindle or oat-like shape, little cytoplasm.

years. 29 patients (2.2%) developed neoplasms during the follow-up. Different types of malignancies were observed among them: 10 lymphoid and hematological malignancies (two myelomas, eight lymphomas) and 19 solid tumors (invasive thymoma, breast cancer, lung cancer, gastrointestinal adenocarcinoma, hepatoma, squamous cell carcinoma of the tongue, cervical cancer, renal cell carcinoma, thyroid carcinoma and mucoepidermoid carcinoma of the parotid gland). Meanwhile it was observed that hyperplasia of the parotid glands, monoclonal immunoglobulins and the presence of hypergammaglobulinemia were regarded as the main risk factors in the pathogenesis of SS.[17]

CONCLUSION

SIADH is often regarded as one of the paraneoplastic syndromes and intractable hyponatremia is common in patients with lung cancer.[18] SIADH may be the hallmark of the advanced stages and progression of SCLC, even some retrospective data indicated that hyponatremia could promise to the poor prognosis in patients with SCLC.[19] So far, we have been aware that both SS and SCLC can lead to refractory hyponatremia, but the relationship between SS and SCLC seems to be a chicken-and-egg conundrum for hyponatremia. With regard to clinic work, it is of great importance to monitor the serum sodium concentration among the patients who was once attacked by severe and obstinate hyponatremia. Hyponatremia, SIADH and its potential causes (in particular malignancy) should be taken into account if a patient suffers from deterioration in clinical condition.

*The authors declare that there are no conflicts of interest.

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