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CASE REPORT

Natural killer/T-cell lymphoma with concomitant syndrome of inappropriate antidiuretic hormone secretion: A case report and review of literature

Quan-Bo Liu, Rui Zheng

Quan-Bo Liu, Rui Zheng, Department of Respiratory Medicine, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

ORCID number: Quan-Bo Liu (0000-0002-0668-2829); Rui Zheng (0000-0001-5906-0081).

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Correspondence to: Rui Zheng, MD, PhD, Doctor, Professor, Teacher, Department of Respiratory Medicine, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Heping District, Shenyang 110004, Liaoning Province, China. zhengr@sj-hospital.org
Telephone: +86-2496-61521211
Fax: +86-2496-61572116

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Abstract

We report a case of natural killer (NK)/T-cell lymphoma with concomitant syndrome of inappropriate antidiuretic hormone secretion (SIADH). The patient was a 64-year-old woman with a history of nasopharyngeal carcinoma of over 30 years. She was admitted with a chief complaint of intermittent fever for 2 mo. Palpation after admission indicated a swollen lymph node below the left jaw. Multiple imaging examinations on admission indicated multiple enlarged lymph nodes throughout the body. We performed a left submandibular lymph node biopsy, and the results revealed NK/T-cell lymphoma. A biochemical examination indicated Epstein-Barr virus positivity. At the same time, the patient developed hyponatremia. Based on her laboratory examination and clinical manifestation, decreased plasma osmolality, urine osmolality greater than plasma osmolality, lack of skin swelling, normal blood pressure, normal renal function, no adrenal function detected on serology, and no abnormalities in imaging examination of the adrenal glands, the likelihood of SIADH in the patient was high. After fluid restriction and administration of sodium chloride, the patient's blood sodium level gradually increased. Subsequently, the immune function of the patient declined, there were severe symptoms of infection, and she died of respiratory failure. NK/T-cell lymphoma associated with SIADH has not, to our

knowledge, been previously reported in PubMed. This case emphasizes the importance of monitoring serum ion levels, especially serum sodium, in patients with NK/T-cell lymphoma.

Key words: Epstein-Barr virus; Case report; Literature review; Syndrome of inappropriate antidiuretic hormone secretion; Natural killer/T-cell lymphoma

Core tip: Lymphoma is known to be a cause of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Moreover, Epstein-Barr virus (EBV) has a high infection rate, and in very rare cases, it can lead to extranodal natural killer (NK)/T-cell lymphoma. A very limited number of patients with lymphoma accompanied by SIADH have been reported, but NK/T-cell lymphoma with concomitant SIADH has not yet been reported in PubMed. Here, we present a case of NK/T-cell lymphoma in a 64-year-old woman with EBV infection accompanied by SIADH, suggesting the importance of monitoring serum ions, especially serum sodium, in patients with NK/T-cell lymphoma.

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INTRODUCTION

Epstein-Barr virus (EBV) is a well-recognized carcinogen that has been implicated in the etiology of several malignancies, including nasopharyngeal carcinoma[1]. The viral tropism of EBV is toward the B lymphocyte, but in very rare cases it can infect ectopic T and/or natural killer (NK) cells, leading to extranodal NK/T-cell lymphoma. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatremia[2], but the symptoms of SIADH are nonspecific, which make it hard to detect and treat promptly. Untreated acute hyponatremia can cause substantial morbidity and mortality[3]. Many cancers can lead to SIADH[4], including lymphoma. According to the 2016 revision of the World Health Organization classification of lymphoid neoplasms[5], lymphomas are classified as either Hodgkin or non-Hodgkin lymphomas, and NK-cell lymphomas are in the latter class. Although non-Hodgkin lymphoma with concomitant SIADH has been reported internationally, NK/T-cell lymphoma with concomitant SIADH has not been reported in PubMed. Herein, we present a case of NK/T-cell lymphoma in a 64-year-old woman with EBV infection accompanied by SIADH, and suggest that monitoring serum ions, especially serum sodium, is vital in patients with NK/T-cell lymphoma.

CASE REPORT

A 64-year-old woman was admitted with a chief complaint of intermittent fever for 2 mo. Two months previously, the patient had a sinus infection resulting from a cold, accompanied by intermittent fevers in the afternoon, with body temperature reaching as high as 38.9 ℃. The patient had a history of nasopharyngeal carcinoma of over 30 years, which was controlled with chemotherapy; there was no recurrence to this point. One year prior, she had traveled to Europe, where she ate local food including sausage and fish.

Physical examination after admission indicated a body temperature of 37.1 ℃, heart rate of 80 bpm, respiratory rate of 18 breaths per minute, and blood pressure of 14.7/9.3 kPa. A 2.5 cm × 1 cm swollen, hard, unfixed, and painless lymph node was palpated below the left jaw. No blood congestion was found in the throat area. The left abdomen was soft with tender. No other obvious abnormalities were observed.

Laboratory tests indicated the following biochemical results: serum sodium, 137.6 mmol/L; white blood cell (WBC) count, 2.4 × 10^9/L; neutrophil count, 4.9 × 10^9/L; C-reactive protein, 11.7 mg/L; EBV quantitative DNA test, 2.19E × 10^4 copies/mL; EBV NA-IgG antibodies, positive (+) (> 600); EBV VCA-IgG antibodies, positive (+) (> 750); and EBV-IgM antibodies, negative. No abnormalities were found in the remaining tests.

An imaging examination was performed on admission. Computed tomography of the lungs indicated that the bilateral axillary and mediastinal lymph nodes were slightly enlarged; enhanced computed tomography of the whole abdomen indicated swollen lymph nodes in the hepatic portal region and retroperitoneum, which did not rule out lymphoma; and bilateral ultrasound of the submandibular glands indicated several visible bilateral swollen lymph nodes. To determine the characteristics of the lymph nodes, whether lymphoma was present, and the margins of the lesion, we performed positron emission tomography-computed tomography, bone marrow biopsy, and left submandibular lymph node biopsy. Positron emission tomography-computed tomography indicated multiple swollen lymph nodes throughout the body accompanied by increased fluorodeoxyglucose metabolism, consistent with lymphoma (Figure 1). Bone marrow biopsy and immunotyping showed a myelogram with hyperplastic activity and a small number of abnormal lymphocytes, accounting for 4.80% of the visible cells other than NK lymphocytes. Biopsy of the left submandibular lymph nodes confirmed NK/T-cell lymphoma, and *in situ* hybridization showed multiple cells with strongly positive signal for EBV-encoded small RNA (Figure 2).

At day 10 after admission, the patient developed

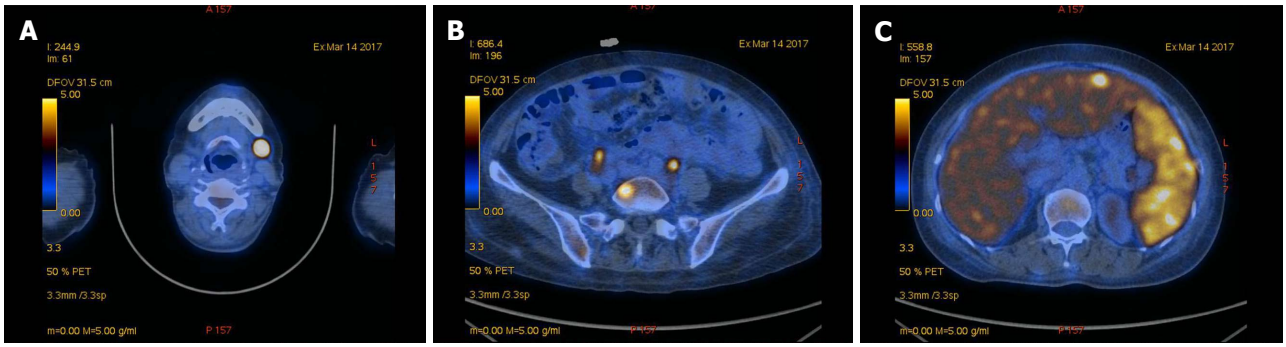

Figure 1 **^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography.** A: A swollen lymph node in the left submandibular region accompanied by increased fluorodeoxyglucose metabolism; B: Multiple lesions in the skeleton and the abdominal cavity with abnormally high metabolic activity; C: Swelling of the liver and spleen with increased metabolic activity accompanied by nodes with high metabolic activity in the parenchyma.

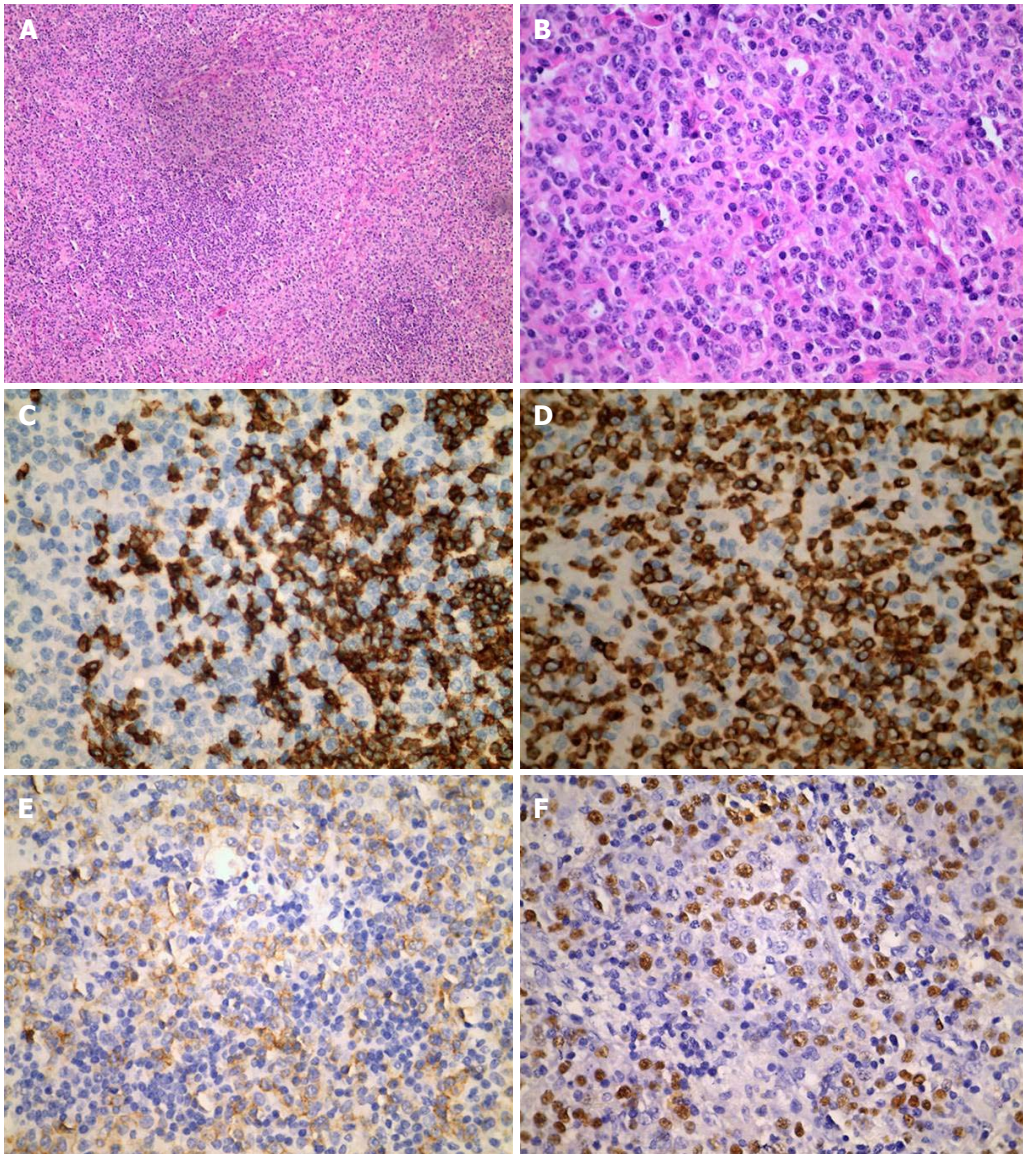

Figure 2 **Histological findings.** A and B: Lymph node biopsy showing diffuse infiltration of malignant lymphoid cells (A: HE, ×100, B: ×400). Immunohistochemical staining for (C) CD20(+), (D) CD3(+), and (E) CD56(+) (× 400). F: *In situ* hybridization showing EBV-encoded small RNA positivity, with most cells showing strongly positive staining (×400). HE: Hematoxylin and eosin; EBV: Epstein-Barr virus.

lethargy, and had a serum Na^+ level of 116.9 mmol/L. Once daily concentrated sodium chloride solution of 20 mL + 250 mL 0.9% normal saline was administered intravenously. One day later, the serum Na^+ level decreased rapidly to 109.3 mmol/L. The serum K^+ level was 3.36 mmol/L, urea level was 2.99 mmol/L, serum creatinine was 47.8 μmol/L, blood glucose level was 7.08 mmol/L, plasma osmolality was 235.39 mOsm/kg, and urine osmolality was 494 mOsm/kg. The patient's blood pressure was normal during that time. The fluid intake of the patient was immediately restricted, and three times daily, two salt capsules and 10 mL of concentrated sodium chloride were administered orally. After 2 d, the patient's blood Na^+ level gradually increased to 126.5 mmol/L (8.6 mmol/L per day). Her mental state returned to normal, and the endocrinology department was consulted. Based on the patient's decreased plasma osmolality, urine osmolality greater than plasma osmolality, lack of skin swelling, normal blood pressure, normal renal function, no adrenal function detected on serology, and no abnormalities in imaging examination of the adrenal glands, as well as the effect of treatment, the likelihood of SIADH in the patient was high. The supplemental infusion of intravenous concentrated sodium chloride solution was discontinued, and renal sodium secretion was assayed. The hematology department was also consulted, and the patient was administered with epirubicin, vinorelbine sulfate, flumethasone, cyclophosphamide, and asparaginase chemotherapy, along with supportive treatment. We believed that the patient might be involved in stage 4B NK/T-cell lymphoma with concomitant SIADH, although with slightly lower renal sodium levels (20 mmol/L).

On day 30 after admission, the patient's white blood cell (WBC) count gradually decreased to 0.1×10^9/L, and the neutrophil count rapidly decreased to 0/L. The immune function of the patient declined, there were severe symptoms of infection, and respiratory function further deteriorated. On day 31 after admission, the WBC count gradually decreased to 0, various vital signs declined, and the patient died after failed resuscitation.

DISCUSSION

SIADH has a hidden onset and is a syndrome caused by excessive antidiuretic hormone (ADH) secretion by the posterior pituitary[6]. It has a high mortality rate[3]. SIADH has many causes, and many cancers can lead to SIADH. It has been reported that lymphoma cells secrete ADH, and this prolonged ADH production results in SIADH[7-9]. SIADH secondary to lymphoma is relatively rare, and SIADH secondary to NK/T-cell lymphoma has not yet been reported.

The symptoms of SIADH are nonspecific, and are primarily based on diagnostic standards published by Bartter *et al*[10] in 1967: (1) decreased plasma osmolality; (2) urine osmolality greater than plasma osmolality; (3) increased renal sodium secretion; (4) no skin swelling and normal blood pressure; and (5) normal renal and adrenal function. Recent studies showed that a fractional excretion of uric acid > 12% has a high sensitivity and specificity for diagnosing SIADH[11] and can serve as a new basis for confirming an SIADH diagnosis. The first-line treatment for SIADH is restriction of fluid intake. If urine osmolality is higher than 500 mOsm/kg H_2O and fluid restriction is ineffective, demethylchlortetracycline, urea, tolvaptan, and other drugs are instead used for treatment[12-14]. Intravenous infusion of 20-40 mg furosemide is used to manage volume overload, and 3% hypertonic saline solution by mouth or continuous intravenous infusion can be used as necessary for correcting hyponatremia[10,15]. During sodium solution infusion, the focus should be on changes in blood sodium rather than the rate of sodium solution infusion. In the first 24-48 h, changes in blood sodium should be closely monitored, and treatment should be adjusted accordingly to rapidly correct blood sodium to within the safe range; otherwise, correction to normal ranges will not be achieved.

Studies have shown that drugs and malignant tumors are the most common causes of SIADH[16], and the prognosis for SIADH secondary to malignant tumors is poorer than that caused by drugs[4]. To reduce the development of SIADH, regular examinations of blood sodium should be performed when malignant tumors are discovered as well as when beginning to administer drugs that are known to cause SIADH; this can help facilitate the immediate discovery of decreased blood sodium and thus immediately manage symptoms and improve prognosis.

According to the 2016 revision of the World Health Organization classification of lymphoid neoplasms[5], lymphomas are classified as either Hodgkin or non-Hodgkin lymphomas. Non-Hodgkin lymphomas are classified as either mature B cell lymphomas or mature T-cell lymphomas, and NK-cell lymphomas are the latter. Currently, 34 cases of non-Hodgkin lymphoma with concomitant SIADH have been reported internationally[7,8,17-34] (Table 1).

The male/female ratio of these 34 cases was 19:15, mean age was 69 years (range 23-84 years), and patients aged between 60 and 90 years accounted for 85% (29/34) of the patients. The clinical manifestations of SIADH in these cases were nonspecific, and large B-cell lymphoma made up 47% (16/34) of all the pathological types. Based on the known treatment data, the main treatment was fluid restriction, which was administered to 80% (16/20). The ratio of outcomes died/cured/unknown was 17:10:7, and the mortality rate of known outcomes was 63% (17/27). The clinical characteristics of known cases may be useful for clinicians to remain aware for these characteristics in patients who may be at risk for SIADH.

The pathogenesis of SIADH secondary to lymphoma

Table 1 Published cases of non-Hodgkin lymphoma with concomitant syndrome of inappropriate antidiuretic hormone secretion

Classification	Ref.	Country	Gender	Age	EBV status	Lymphoma classification	Symptoms	Treatment	Outcome
T-cell lymphoma	Chubachi *et al*[18] 1995	Japan	M/ F	53/78 yr	Infected	Nasal T-cell lymphoma	Fever following adjuvant chemotherapy	Fluid restriction	Died
	Demirkan *et al*[19] 2001	Turkey	M	23 yr	Unknown	Anaplastic large cell lymphoma	Weight loss Night sweats Fever	Fluid restriction	Died
	Hirata *et al*[8] 2012	Japan	F	40 yr	Unknown	Primary cutaneous anaplastic large cell lymphoma	Erythema Right shoulder ulceration	Fluid restriction Isotonic saline	Died
	Nishiwaki *et al*[30] 2014	Japan	F	70 yr	Unknown	Acute adult T-cell leukemia/lymphoma	Rash	Fluid restriction Isotonic saline	Cured
	Sun *et al*[34] 2018	China	M	71 yr	Uninfected	Extranodal nasal type natural killer (NK) /T cell lymphoma	Testicular enlargement Multiple rashes with eschar Obstinate hyponatremia	Fluid restriction Sodium chloride for oral Hypertonic saline infusion Hydrocortisone infusion	Died
	Phan *et al*[25] 1998	Indonesia	M	53 yr	Unknown	Burkitt's lymphoma	Left maxillary swelling	Plasma exchanges Methotrexate Cytarabine Hydrocortisone	Died
B-cell lymphoma	Sica *et al*[22] 1999	Italy	F	41 yr	Unknown	Primary central nervous system lymphoma	None	Fluid restriction Normal saline Diuretics	Cured
	Watabe *et al*[23] 2000	Japan	M	70 yr	Infected	Angiotropic B-cell lymphoma	Anemia High LDH	Fluid restriction	Died
	Ohara *et al*[27] 2007	Japan	F	65 yr	Unknown	Diffuse large B-cell lymphoma	Abdominal pain	Fluid restriction Acyclovir infusion	Cured
	Morimoto *et al*[20] 2007	Japan	M	75 yr	Unknown	Intravascular large B-cell lymphoma	Nothing	Fluid restriction Hypertonic saline infusion Furosemide Fludrocortisone acetate	Died
	Brodmann *et al*[26] 2007	Switzerland	F	76 yr	Unknown	Mantle cell lymphoma	Unknown	Fluid restriction Sodium chloride Potassium chloride	Cured
	Kobayashi *et al*[7] 2008	Japan	F	84 yr	Unknown	Diffuse large B-cell lymphoma	Left cervical tumor increased	Fluid restriction Isotonic saline	Cured
	Polprasert *et al*[21] 2011	Thailand	F	64 yr	Unknown	Follicular lymphoma	Watery diarrhea	Ganciclovir Rituximab Cyclophosphamide Vincristine Prednisolone	Cured
	Onishi *et al*[28] 2011	Japan	F/ M/ M M	73/80/83 yr 69/83 yr	Unknown	Asian variant of intravascular large B cell lymphoma	Unknown	Unknown	Unknown Died
	Onishi *et al*[28] 2011	Japan	M/M/F F/M	75/60/83 yr 84/64 yr	Unknown	Diffuse large B-cell lymphoma	Unknown	Unknown	Unknown Died
	Onishi *et al*[28] 2011	Japan	M/M/F/ M	74/69/75/75 yr	Unknown	Plasmablastic lymphoma/ Primary central nervous system lymphoma/ Mantle cell lymphoma/ Lymphoplasmacytic lymphoma	Unknown	Unknown	Died/ Died/ Unknown/ Died
	Bockorny *et al*[29] 2012	America	M	70 yr	Unknown	Marginal zone lymphoma	Fatigue Confusion Skin lesions	Fluid restriction Demeclocycline Rituximab	Cured
	Zhu *et al*[24] 2013	China	F	70 yr	Unknown	Diffuse large B-cell lymphoma	Nausea Vomiting Left leg radiating pain	Fluid restriction CHOP	Cured

Akhtar *et al*[17] 2013	United Kingdom	M	75 yr	Unknown	Intravascular large B-cell lymphoma	Weight loss Clammy Incontinent hypoxic	Fluid restriction Demeclocycline Fludrocortisone	Died
Sumiyoshi *et al*[31] 2014	Japan	F	61 yr	Unknown	Follicular lymphoma	Epigastralgia Peritoneal irritation Intestinal pseudo-obstruction	Aciclovir	Cured
Itaya *et al*[32] 2015	Japan	M	81 yr	Unknown	Diffuse large B-cell lymphoma	Fever Fatigue Anorexia	Hypertonic saline Hydrocortisone sodium succinate	Died
Shimizu *et al*[33] 2017	Japan	F	73 yr	Unknown	Mucosa-associated lymphoid tissue lymphoma	Unknown	Fluid restriction Hypertonic saline	Cured

F: Female; M: Male; EBV: Epstein-Barr virus; LDH: Lactate dehydrogenase; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone.

is complex. One potential cause is abnormal secretion of ADH by lymphocytes[7,10,30]. In our case, because of the death of the patient, whether hyponatremia was recurrent could not be determined, and abnormal secretion of ADH by lymphocytes could not be ruled out. Central nervous system injury secondary to non-Hodgkin lymphomas may also play an important role in the pathogenesis of SIADH[10]. Hyponatremia can also lead to nervous system symptoms[10], but the likelihood of central nervous system injury in our patient was low. The use of chemotherapy drugs such as vinca alkaloids and cyclophosphamide can also induce SIADH[35]. However, before SIADH was discovered in our patient, no chemotherapy drugs had been administered, so this did not apply in our case.

Hypercytokinemia is another important factor in the development of SIADH secondary to lymphoma. Studies have shown that the levels of epidermal growth factor (EGF), granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-5, IL-6, IL-12, IP-10, sIL-2Rα, membrane immunoglobulin (MIG), IL-1RA, and other cytokines are significantly elevated in T-cell lymphomas[36,37]. In extranodal nasal type NK/T-cell lymphomas, sIL-2Rα, IL-6, and IL-10 are significantly elevated[38]. Increased IL-2, sIL-2R, IL-6, IL-1β, and tumor necrosis factor (TNF)-α can lead to abnormal secretion of ADH[39]. Watabe *et al*[23] found that patients with high levels of the cytokine IL-6 are more likely to develop SIADH. We did not examine the levels of cytokines in our patient; however, it cannot be ruled out that SIADH in our patient was associated with abnormal secretion of ADH by lymphocytes or that the lymphoma regulated ADH secretion through cytokines.

EBV is a member of the human herpesvirus family and its genome consists of a single double-stranded DNA molecule. It has a high infection rate, with potentially 90% or more of all individuals infected worldwide[40,41]. Humans are the only host for EBV and they become lifelong carriers of the virus after infection. Most hosts can live with EBV for a long period without any serious effects, but in some individuals, EBV is closely associated with the development of malignant tumors[42], including nasopharyngeal carcinoma and lymphomas. The viral tropism of EBV is toward B lymphocytes, but in very rare cases, it can infect ectopic T and/or NK cells, leading to chronic active EBV infection, extranodal NK/T-cell lymphoma, or invasive NK cell leukemia[43].

EBV can be divided into three latency programs. Latency Ⅱ shows expression of EBV nuclear antigen 1 (EBNA1) and latent membrane proteins (LMPs), and is closely associated with the development of peripheral NK/T-cell lymphoma and nasopharyngeal carcinoma in elderly patients[42,44-46]. Our patient had been diagnosed with both nasopharyngeal carcinoma and NK/T-cell lymphoma, and the possibility of long-term latent EBV infection cannot be ruled out.

According to the 2016 revision of the World Health Organization classification of lymphoid neoplasms, NK/T-cell lymphoma is categorized into mature T-cell lymphoma and extranodal nasal type NK/T-cell lymphoma. The latter type is a relatively rare lymphoma characterized by high invasiveness, poor prognosis, and high likelihood of recurrence. According to a 2010 report, extranodal nasal type NK/T-cell lymphoma accounts for 6.9% of non-Hodgkin lymphomas and 28.2% of T-cell and NK cell lymphomas in China[47,48]. Eighty to ninety percent of patients with nasal type NK/T-cell lymphoma report symptoms of nasal congestion, sinus infection, ulceration, and epistaxis[48]. Traditional treatments include chemotherapy, radiotherapy, and multimodal therapy, but even in patients with stage Ⅰ or Ⅱ disease, the 3-year survival rate is only 40%-50%[49-51]. Most published studies related to the efficacy of chemotherapy in extranodal NK/T-cell lymphoma have shown that the recurrence rate is as high as 50%[52]. Our patient was diagnosed with nasopharyngeal carcinoma 30 years earlier without recurrence following control with chemotherapy, but specific pathological examination results were not obtained. In addition, paraffin sections from over 30 years ago cannot be re-stained. Given the limitations of

previous pathological examinations, the possibility that the patient developed extranodal nasal type NK/T-cell lymphoma cannot be ruled out. However, based on its biological characteristics, namely, a high recurrence rate, high invasiveness, and poor prognosis, the likelihood that our patient developed extranodal nasal type NK/T-cell lymphoma 30 years ago is small.

In summary, NK/T-cell lymphoma with concomitant SIADH is relatively rare. Blood sodium must be closely monitored in lymphoma patients as an indicator of the development of SIADH, and immediate treatment by restricting fluid intake and replenishing sodium should be administered based on blood sodium levels. At the same time, actively searching for the cause of the disease and planning adjunctive therapy with drugs as needed will prevent critical patients from developing hyponatremia and hypo-osmolality, thereby improving their prognosis.

ARTICLE HIGHLIGHTS

Case characteristics

A 64-year-old woman was admitted with intermittent fever for 2 mo.

Clinical diagnosis

Stage 4B natural killer (NK)/T-cell lymphoma with concomitant syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Differential diagnosis

Infection, typhia, brucellosis, *etc*.

Laboratory diagnosis

As determined by blood and urine sampling examination, serum Na^+ was 109.3 mmol/L, urea was 2.99 mmol/L, serum creatinine was 47.8 μmol/L, plasma osmolality was 235.39 mOsm/kg, and urine osmolality was 494 mOsm/kg.

Imaging diagnosis

Positron emission tomography-computed tomography indicated multiple swollen lymph nodes throughout the body accompanied by increased fluorodeoxyglucose metabolism, consistent with lymphoma.

Pathological diagnosis

Biopsy of the left submandibular lymph nodes confirmed NK/T-cell lymphoma.

Treatment

Chemotherapy, fluid restriction, and administration of sodium chloride.

Related reports

This is the first known report of NK/T-cell lymphoma with concomitant SIADH in PubMed.

Term explanation

Lymphoma is one of the causes of SIADH; however, NK/T-cell lymphoma with concomitant SIADH has not been reported.

Experiences and lessons

This case report emphasizes the importance of monitoring serum ions and etiological treatment in patients with NK/T-cell lymphoma.

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