

[CASE REPORT]

Syndrome of Inappropriate Antidiuretic Hormone Secretion in a Patient with Mucosa-associated Lymphoid Tissue Lymphoma

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Abstract:

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) may develop in association with several malignancies. However, as an immunohistochemical analysis is not performed in the majority cases, its true cause is often uncertain. We herein report a case of SIADH following chemotherapy due to tumor-derived ADH production in a patient with mucosa-associated lymphoid tissue (MALT) lymphoma. A retrospective immunohistochemical analysis demonstrated ADH expression by lymphoma cells. These findings highlight the importance of using an immunohistochemical analysis to determine ADH production by tumor cells in patients with SIADH. Such analyses play an important role in elucidating the pathogenesis of SIADH and determining the most appropriate treatment.

Key words: syndrome of inappropriate antidiuretic hormone secretion (SIADH), antidiuretic hormone (ADH), mucosa-associated lymphoid tissue (MALT) lymphoma

(Intern Med 56: 3225-3229, 2017)

(DOI: 10.2169/internalmedicine.9048-17)

Introduction

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is caused by the excessive release of antidiuretic hormone (ADH). It has been reported in association with a variety of medical conditions, including drug therapy, central nervous system disorders, infections, and paraneoplastic syndromes accompanying several types of malignancies (1, 2).

Mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell malignancy, and patients at an advanced stage are usually treated with R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) (3). A recent retrospective analysis suggested that Asians may be at an increased risk of developing SIADH during vincristine (VCR) treatment (4). However, there have been several reports of tumor-derived SIADH in patients with malignant lymphoma (5-7), as well associated with the use of anti-cancer drugs (4, 8).

We herein report the first case of tumor-derived hyponatremia following R-CHOP treatment in a patient with MALT lymphoma who was diagnosed with SIADH. After switching from VCR to vindesine sulfate (VDS), she achieved complete remission and did not show recurrence of SIADH. A retrospective immunohistochemical analysis demonstrated ADH expression by lymphoma cells.

Case Report

A 73-year-old Japanese woman attended our hospital in February 2016 with painless bilateral parotid gland swelling. A pathological examination of a needle biopsy of the left parotid gland showed infiltration of CD20-positive lymphocytes and the destruction of the parotid gland's duct, and she was diagnosed with MALT lymphoma (Fig. 1A and B). Fluorodeoxyglucose positron emission tomography revealed bilateral accumulation in the parotid glands, with a maximum standardized uptake value of 14.6 in the neck, multiple

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Received: February 14, 2017; Accepted: April 10, 2017; Advance Publication by J-STAGE: October 11, 2017

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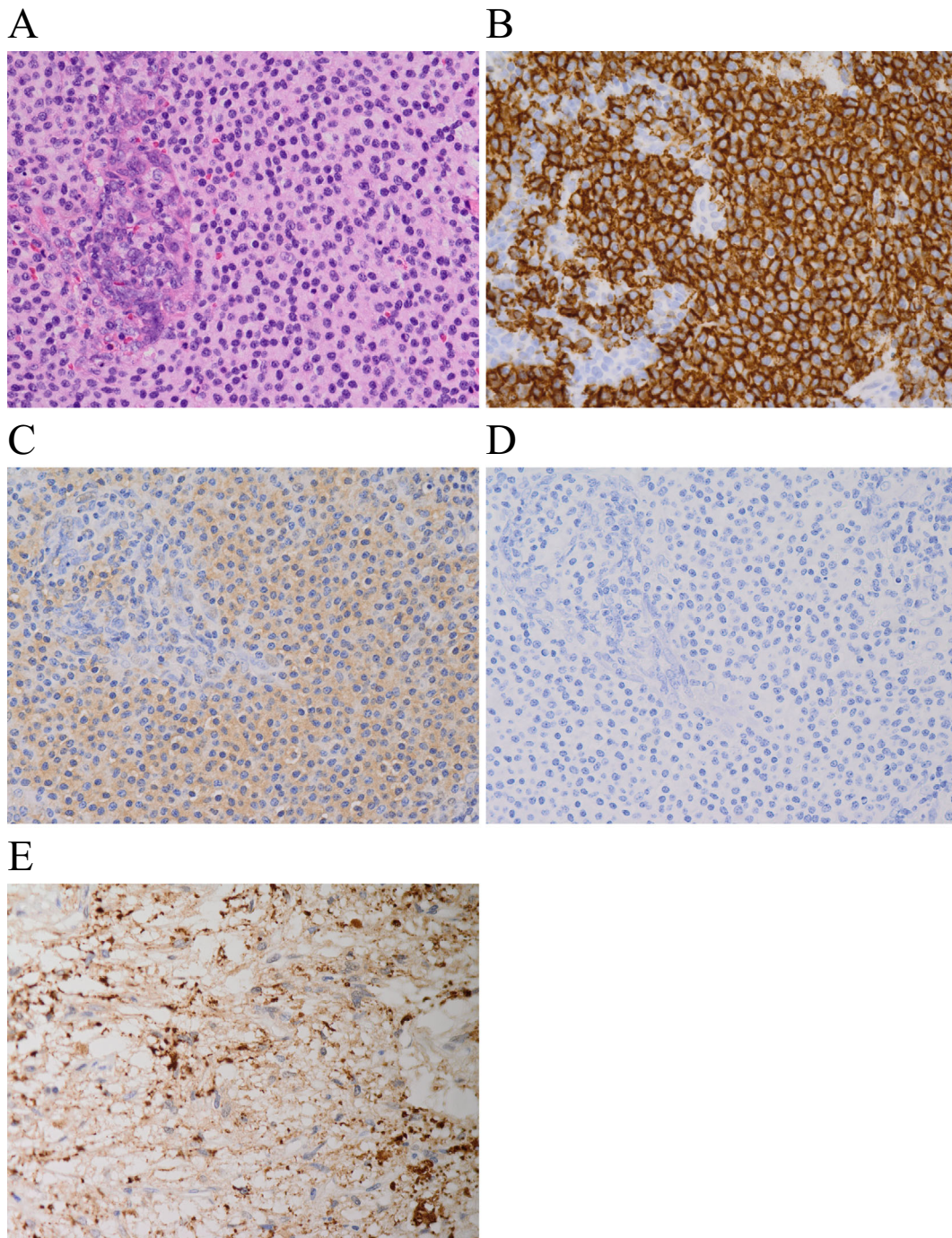


Figure 1. A: Histologic sections of swollen left parotid gland, demonstrating mucosa-associated lymphoid tissue lymphoma. Hematoxylin and Eosin staining. B: Lymphoma cells expressing CD20. C: Lymphoma cells positive for anti-diuretic hormone. D: Negative control slide for anti-diuretic hormone. E: Positive control slide for anti-diuretic hormone in human pituitary gland.

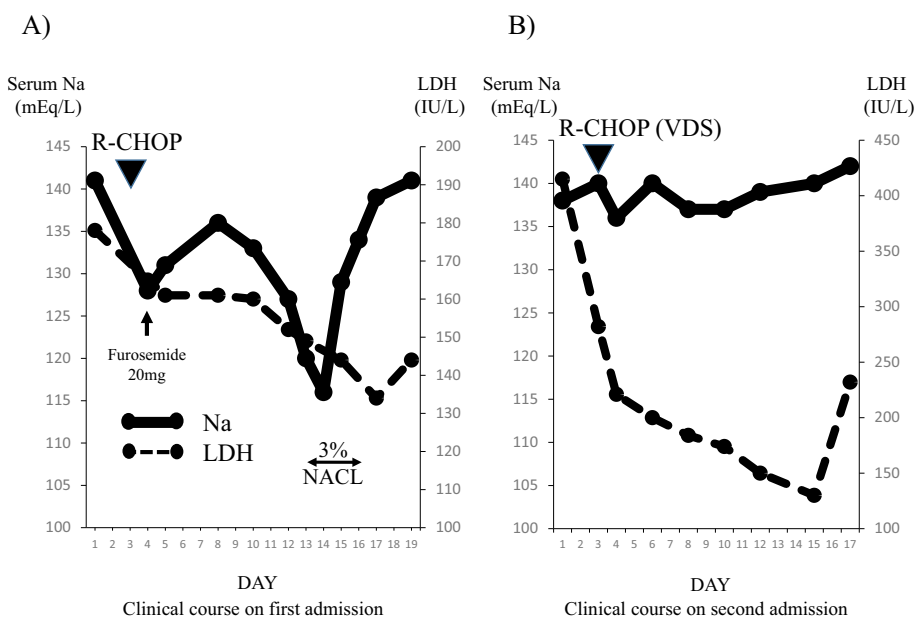
subcutaneous tumors, and multiple small consolidations in the lung. Accordingly, she was diagnosed with MALT lymphoma at clinical stage IVA.

After admission in May 2016, she was treated with R-CHOP, a chemotherapy that includes rituximab. On the day following treatment, she developed nausea and appetite loss, and her serum sodium level declined to 128 mEq/L. She was treated with intravenous furosemide 20 mg once for excess fluid volume due to the chemotherapy. Her serum sodium level improved, but the nausea and appetite loss con-

tinued. On day 12 after treatment, her serum sodium levels had again decreased to 127 mEq/L, with a serum chloride level of 90 mEq/L, plasma osmolality of 263 mOsm/kg, and serum lactate dehydrogenase level of 152 IU/L. A urinalysis demonstrated an increased sodium level of 53 mEq/L, a chloride level of 24 mEq/L, and osmolality of 665 mOsm/kg. Her serum ADH level was 1.7 pg/mL (Table). Her thyroid and adrenal function were normal. Accordingly, she was diagnosed with SIADH and treated with 1,000 mL/day of intravenous 3% saline and fluid restriction from day 13 to

Table. Laboratory Data When Syndrome of Inappropriate Antidiuretic Hormone Secretion Developed.

Hematology		Biochemistry		Endocrinology	
WBC	3,000/ μ L	CRP	0.02 mg/dL	ACTH	15.5 pg/mL
RBC	537 \times 10 ⁴ / μ L	TP	6.6 g/dL	CS	21.5 μ g/dL
Hb	15.0 g/dL	Alb	3.7 g/dL	PAC	122 pg/mL
Ht	41.8%	AST	18 IU/L	PRA	1.5 ng/mL/h
Plt	21.7 \times 10 ⁴ / μ L	ALT	15 IU/L	ADH	1.7 pg/mL
Seg	76.5%	LDH	152 IU/L		
Lymp	20.7%	ALP	152 IU/L	Urinalysis	
Mono	1.9%	γ GTP	30 IU/L	Na	53 mEq/L
Eosino	0.6%	T-BIL	0.8 mg/dL	K	76.9 mEq/L
Baso	0.3%	BUN	10.6 mg/dL	Cl	24 mEq/L
		Cre	0.58 mg/dL	Uosm	665 mOsm/kg
		Na	127 mEq/L		
		K	4.4 mEq/L		
		Cl	90 mEq/L		
		BS	161 mg/dL		
		Posm	263 mOsm/L		

**Figure 2. A: Clinical course during initial R-CHOP therapy. B: Clinical course during the second round of R-CHOP therapy with vindesine sulfate.**

day 16 after treatment. On day 20 after admission, her condition improved with normalization of the sodium level, and she was discharged (Fig. 2A).

We speculated that SIADH might have developed due to the administration of VCR, so we replaced this with VDS. The SIADH resolved during subsequent chemotherapy (Fig. 2B), and the patient achieved complete remission after the sixth chemotherapy session. A retrospective immunohistochemistry analysis of the original sample showed the lymphoma cells to be positive for ADH expression (Fig. 1C) compared with a negative control (Fig. 1D). An immunohistochemical analysis of ADH in lymphoma cells was performed using rabbit anti-vasopressin antibody (dilution at 1:2,000; EMD Millipore, Temecula, USA) with a Ventana

iVIEW DAB Universal Kit (Roche Diagnostics, Tokyo, Japan). The specimen was incubated with the primary antibody for 30 minutes at 37 °C. Normal rabbit immunoglobulin fraction was used for negative control with same lymph node sample (Fig. 1D). For a positive control, normal human pituitary gland was stained with rabbit anti-vasopressin antibody as described above (Fig. 1E).

Discussion

We herein reported the first case of SIADH following R-CHOP therapy for MALT lymphoma. After switching from VCR to VDS, the patient's SIADH resolved, and she achieved complete remission after the completion of her

treatment. A retrospective immunohistochemical analysis of her lymphoma cells demonstrated ADH protein expression (Fig. 1C). SIADH appeared to have developed in the present case due to tumor lysis in response to chemotherapy.

SIADH may develop due to a variety of causes. There are many previous reports of drug-induced SIADH, including in response to cytotoxic agents (VCR, VDS, cisplatin, melphalan, and cyclophosphamide) as well as several other drugs (4, 8, 9). Hammond et al. reported that Asian patients might be at an increased risk of SIADH associated with VCR (4). We initially speculated that the development of SIADH in our patient was associated with VCR. However, there has been only one previous report of successful VDS treatment in a patient with SIADH secondary to VCR (10), suggesting that it is extremely rare to be able to avoid SIADH associated with VCR through using VDS.

To date, three previous reports have described SIADH associated with tumor lysis during chemotherapy in malignant lymphoma patients, with an immunohistochemical analysis demonstrating the expression of ADH by lymphoma cells. Kobayashi et al. reported tumor-derived SIADH in a case of diffuse large B-cell lymphoma, with a plasma osmolality of 231 mOsm/kg and a serum ADH level of 4.2 pg/mL on day 28 after chemotherapy (7). Hirata et al. reported two cases of lymphoma; one was a case of anaplastic large cell lymphoma, with a plasma osmolality of 265 mOsm/kg and a serum ADH level of 7.1 pg/mL on day 10 after chemotherapy (6), and the other was a case of peripheral T-cell lymphoma, with a plasma osmolality of 251 mOsm/kg and a serum ADH level of 2.1 pg/mL on day 8 after chemotherapy (5). These three patients had normal sodium levels before chemotherapy and then developed SIADH after the initiation of chemotherapy. Until now, there have been no reports of lymphoma cell-derived SIADH in a case of MALT lymphoma. The present case had a normal sodium level of 141 mEq/L at admission and then developed SIADH after chemotherapy (Fig. 2A). Her serum ADH level on day 12 after treatment was 1.7 pg/mL (the normal range is <4.2 pg/mL).

Smith et al. reported formal criteria for the diagnosis of SIADH in 2,000 (11). The level of ADH is not an essential feature of these criteria. The essential features are (i) plasma osmolality <270 mOsm/kg H₂O, (ii) inappropriate urinary concentration (U_{osm} >100 mOsm/kg), (iii) clinically euvolemic status, (iv) elevated urinary sodium (>40 mmol/L) with normal salt and water intake, and (v) hypothyroidism and glucocorticoid deficiency excluded (11). There was therefore a possibility that the patients in the previous three reports might have developed SIADH early after chemotherapy. Indeed, the sodium level of the present case decreased to 128 mEq/L on the day following chemotherapy. Nausea subsequently persisted, and her drinking intake was less than usual. She was treated with 1,000 mL/day of intravenous 3% saline on day 12 after treatment when her sodium level again decreased to 127 mEq/L. We therefore speculated that the reduction in the serum sodium was delayed due to fluid

restriction, resulting in a delay in the diagnosis of SIADH.

There have been several reports of SIADH at the time of diagnosis in patients with malignant lymphoma (12-14). However, an immunohistochemical analysis of the ADH levels in the lymphoma cells was not performed for these patients, so the involvement of tumor-derived SIADH in these cases is unclear. Another patient of ours, an 81-year-old Japanese man with diffuse large B-cell lymphoma at clinical stage IVB who had developed SIADH at the time of diagnosis, was negative for ADH expression by lymphoma cells (data not shown). In this case, his serum SIADH remained constant after chemotherapy, and treatment for SIADH continued.

During treatment for malignant lymphoma, it is not possible to reexamine the lymph nodes due to tumor shrinkage. It is therefore difficult to evaluate definitively whether or not tumor-derived ADH alone is involved in the pathogenesis of SIADH. However, it is important to examine the tumor ADH production using immunohistochemical analyses in patients who develop SIADH after chemotherapy. Immunohistochemical analyses play an important role in understanding the pathogenesis of SIADH in such patients, in addition to informing the most appropriate treatment options. Indeed, Hirata et al. reported the successful treatment with ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) of a case of tumor-derived SIADH following chemotherapy a patient with malignant lymphoma (5). It may be appropriate for patients with SIADH in malignant lymphoma to be evaluated by endocrinologists during chemotherapy.

In conclusion, this is the first report of tumor-derived SIADH in a patient with MALT lymphoma. Immunohistochemical An immunohistochemical analysis of the ADH production by lymphoma cells has an important role in determining the most appropriate therapeutic options for such cases.

The authors state that they have no Conflict of Interest (COI).

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