Syndrome of Inappropriate Antidiuretic Hormone Secretion Complicated with Stem Cell Transplantation

Ryoji Kobayashi M.D., Ph.D.
Department of Pediatrics, Sapporo Hokuyu Hospital

SUMMARY

Hyponatremia is a common electrolyte disorders in hospitalized patients. However, reports about hyponatremia complicated with stem cell transplantation (SCT) were very rare. As single center analysis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after stem cell transplantation were reported. SIADH were observed 13.2% of 197 patients after stem cell transplantation. Risk factors for SIADH were younger in age, transplantation from HLA mismatched or unrelated donor, cord blood transplantation, and GVHD prophylaxis with methyl prednisolone. Multivariate analysis showed transplantation from alternative donor was independent of other factors for SIADH. Patients with SIADH had significantly higher probability of overall survival (66.4% versus 50.8%) and event free survival (68.8% versus 43.3%) compared with no SIADH. The median onset of SIADH following cord blood transplantation (CBT) and bone marrow transplantation (BMT) / peripheral blood stem cell transplantation (PBSCT) was 19.5 and 46 days after SCT, respectively, and the median numbers of WBC were 1.1 and 3.3 x 10^9 /l, respectively. Furthermore, severe symptoms such as seizures, somnolence, and rigidity of limbs were observed only in patients with CBSCT (8/16 versus 0/10). These differences were statistically significant ($P<0.01$). SIADH is common complication with SCT, especially in patients transplanted from alternative donor. Although the precise basis for SIADH following SCT remains still unknown, the different features of SIADH observed following CBSCT and BMT/PBSCT suggest that the mechanisms responsible for SIADH are different.

Key words: *hyponatremia, SIADH, CBT, stem cell transplantation*

INTRODUCTION

Stem cell transplantation (SCT) improved survival rates in patients with hematological disorders, malignant disorders, immunodeficiencies and metabolic disorders. Many complications were observed and safety achievement

Correspondence: Ryoji Kobayashi M.D., Ph.D., Department of Pediatrics, Sapporo Hokuyu Hospital,
Higashi-Sapporo 6-6, Shiroishiku Sapporo, 003-0006, Japan
Tel: +81-11-865-0111, Fax: +81-11-865-9719, E-mail: r-koba@jacls.jp

of transplantation was always required. Hyponatremia is a common electrolyte disturbance affecting up to 15% of hospitalized patients and has been extensively reviewed.[1-3] However, reports about hyponatremia complicated with stem cell transplantation were very rare.[4, 5] We previously reported hyponatremia, especially syndrome of inappropriate secretion of antidiuretic hormone (SIADH), complicated with stem cell transplantation.[6] In addition, we previously analyzed detailed data on a larger number of patients with SIADH following SCT, and found different SIADH clinical features following CBT and BMT/PBSCT.[7] In this paper, I analyzed patients with SIADH following SCT using new data and speculate the mechanism of SIADH complicated SCT.

PATIENTS AND METHODS

Between February 1988 and March 2007, a total of 197 patients with different hematological malignancies, metabolic abnormally and immunodeficiency received SCT in Hokkaido university hospital. One hundred twenty five patients were boy and seventy-two patients were girls. Sixty-two patients had acute lymphoblastic leukemia (ALL): 30 of them were in their first complete remission (CR), 21 were in a second CR and 11 were over a third CR. Thirty-three patients were acute myelogenous leukemia (AML): 17 were in their first CR, 11 were in their second CR and 5 were over a third CR. One hundred two patients had other diseases: 29 were aplastic anemia (AA), 12 were neuroblastoma, 10 were non-Hodgkin's lymphoma (NHL), 8 were myelodysplastic syndrome (MDS), 8 were juvenile myelomonocytic leukemia (JMML), 7 were rhabdomyosarcoma, 6 were chronic myelogenous leukemia (CML), 5 were Wiskott Aldrich syndrome (WAS), 3 were severe combined immunodeficiency, 3 were Kostmann syndrome, 2 were Hurler syndrome, 2 were chronic granulomatous disease, 1 was yolk sac tumor, hepatoblastoma, Hunter syndrome, X linked hyper IgM syndrome, primitive neuroectodermal tumor (PNET) chronic active Epstein-Barr virus infection (CAEBV) and Hurler Scheie syndrome, respectively.

Origins of stem cell were 122 patients with bone marrow transplantation (BMT), 25 patients with peripheral blood stem cell transplantation (PBSCT), 4 patients with BMT and PBSCT and 46 patients with cord blood stem cell transplantation (CBT). Donor of transplantation were 61 with HLA matched siblings, 3 with 1 locus mismatched sibling, 2 with 3 loci mismatched sibling, 12 with HLA matched or mismatched parents, 48 with HLA matched unrelated donors, 34 with HLA 1 locus mismatched unrelated donors, 4 with 2 loci mismatched unrelated donor and 33 with auto transplantation. The conditioning regimen used in 69 patients for busulfan (BU) containing regimens, 93 with total body irradiation (TBI) containing regimens, 57 with melphalan containing regimens, 125 with cyclophosphamide (CY) containing regimens and 43 with anti lymphocyte globulin (ALG) containing regimens. Prophylaxis for graft versus host disease (GVHD) were 71 patients with cyclosporin A and short term methotrexate, 3 patients with cyclospolin A alone, 42 patients with cyclosporin A and methyl prednisolone, 32 patients with tacrolimus and short term methotrexate, 10 patients with methotrexate alone and 1 patient with tacrolimus and methyl prednisolone. Data was analyzed as of April 1, 2008.

EVALUATION OF HYPONATREMIA

Value of serum sodium was measured with an automated counter. A morning count was taken daily from every SCT patient until day 40 after SCT. We define hyponatremia as cases with detection less than 130 mmol per liter of serum sodium in consecutive days. Furthermore, we define as severe hyponatremia as cases with detection less than 125 mmol per liter of serum sodium in consecutive days.

DIAGNOSIS OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

SIADH was diagnosed with criteria reported by Bartter and Schwartz,[8] which require the presence of all of the following: 1) hyponatremia with hypotonicity of plasma; 2) urine osmolality in excess of plasma osmolality; 3) increased renal sodium excretion; 4) absence of edema or volume depletion; 5) normal renal and adrenal function.

STATISTICAL ANALYSIS

A *t* test or chi squire test was used to compare patients with SIADH and no SIADH. Analyses of overall survival and event free survival were performed using the Kaplan and Meier method with differences compared by the log-rank test. Multivariate analysis stepwise regression was performed to explore the independent effect of variables that show a significant influence found by univariate analysis. Statistical analyses were performed using Dr. SPSS II for windows (release 11.0.1J, SPSS JAPAN Inc.).

RESULTS

SIADH was occurred 26 (13.2%) out of 197 patients. Profile of patients revealed Table 1. CBT was undergone in 16 patients, and transplantation from mismatched

Table 1 Profile of patients with SIADH.

	age	gender	SCT	disease	conditioning	regimen	GVHD prophylaxis	at the time of SIADH Sodium	day	WBC	symptom
1.	4	M	U-BMT	(matched)	JMML(CP)	TBI+VP16+CY	CsA+shortMTX	122	40	2.8	nausea
2.	10	M	R-BMT	(1 locus mismatched)	AML(CR1)	TBI+VP16+CY+ATG	CsA+shortMTX	121	60	2.5	nausea
3.	1	M	U-CBT	(matched)	WAS	BU+CY	CsA+shortMTX	110	32	1.6	seizure
4.	7	F	U-CBT	(1 locus mismatched)	AML(CR2)	BU+L-PAM	CsA+mPSL	118	41	4.2	none
5.	1	M	U-CBT	(1 locus mismatched)	NHL(CR3)	TBI+VP16+CY	CsA+mPSL	120	15	1.0	nausea
6.	5	F	U-CBT	(1 locus mismatched)	AML(CR2)	BU+L-PAM	CsA+mPSL	121	18	1.0	nausea
7.	1	M	R-BMT	(1 locus mismatched)	aplastic anemia	TLI+ATG+CY	CsA+shortMTX	106	74	3.3	nausea
8.	3	F	U-BMT	(matched)	aplastic anemia	TBI+ATG+CY	FK506+shortMTX	115	27	4.2	nausea
9.	7	F	R-PBSCT	(1 locus mismatched)	ALL(CR1)	ATG+CY	FK506+shortMTX	115	54	0.2	nausea
10.	3	M	R-BMT	(matched)	ALL(CR1)	TBI+VP16+CY	CsA+shortMTX	121	52	2.9	nausea
11.	9	F	U-CBT	(2 loci mismatched)	neuroblastoma(CR1)	CBDCA+VP16+L-PAM	CsA+mPSL	117	19	0.1	nausea
12.	0	M	U-CBT	(matched)	WAS	BU+CY+ATG	CsA+mPSL	122	19	0.9	nausea
13.	10	F	U-BMT	(matched)	ALL(CR1)	TBI+VP16+CY	FK506+shortMTX	123	31	6.4	nausea
14.	12	M	R-BMT	(1 locus mismatched)	AML(CR2)	BU+L-PAM	FK506+shortMTX	122	18	13.3	nausea
15.	2	M	R-BMT	(1 locus mismatched)	Hurler Scheie	BU+CY+ATG	FK506+shortMTX	123	35	2.7	nausea
16.	3	M	U-CBT	(1 locus mismatched)	JMML(CP)	TBI+Ara-C+CY	CsA+mPSL	123	34	0.6	seizure
17.	1	F	U-CBT	(matched)	Hurler syndrome	BU+CY+ATG	CsA+mPSL	128	21	1.9	nausea
18.	6	M	U-CBT	(1 locus mismatched)	ALL(CR2)	TBI+VP16+CY	CsA+mPSL	115	28	0.5	somnolence
19.	14	F	U-CBT	(2 loci mismatched)	CAEBV	Flu+VP16+TBI	CsA+mPSL	118	22	1.6	seizure
20.	11	F	U-CBT	(1 locus mismatched)	ALL(CR1)	TBI+VP16+CY	CsA+mPSL	117	15	1.2	somnolence
21.	7	M	U-CBT	(1 locus mismatched)	ALL(nonCR)	TBI+VP16+CY	CsA+mPSL	120	17	2.4	nausea
22.	4	M	U-CBT	(1 locus mismatched)	aplastic anemia	Flu+L-PAM+TBI	CsA+mPSL	120	20	0.4	seizure
23.	5	M	U-CBT	(1 locus mismatched)	AML(CR3)	BU+L-PAM	CsA+mPSL	120	15	2.5	rigidity
24.	3	M	U-CBT	(1 locus mismatched)	neuroblastoma(CR1)	TBI+VP16+CY	CsA+mPSL	115	17	0.2	seizure
25.	15	M	U-BMT	(1 locus mismatched)	ALL(CR3)	BU+L-PAM	FK506+shortMTX	122	72	5.6	nausea
26.	11	M	U-CBT	(2 loci mismatched)	ALL(CR3)	TBI+VP16+CY	CsA+mPSL	123	21	2.3	none

SIADH:syndrome of inappropriate antidiuretic hormone, SCT:stem cell transplantation, BMT:bone marrow transplantation, CBT:cord blood stem cell transplantation, PBSCT:peripheral blood stem cell transplantation, HLA:human leukocyte antigen, JMML:juvenile myelomonocytic leukemia, AML:acute myelogenous leukemia, WAS:Wiskott–Aldrich syndrome, NHL:non-Hodgkin's lymphoma, ALL:acute lymphoblastic leukemia, CAEBV:chronic active Epstein-Barr virus infection, TBI:total body irradiation, VP16:etoposide, CY:cyclophosphamide, ATG:antithymocyte globulin, BU:busulfan, L-PAM:melphalan, TLI:total lymphoid irradiation, CBDCA:carboplatine, Ara-C:cytarabine, Flu:fludarabine, GVHD:graft-versus-host disease, CsA:cyclosporin A, MTX:methotrexate

donor was undergone in 19 patients. Transplantation from HLA matched sibling donor was only 1 (3.8%) out of 26 patients. Symptoms of hyponatremia were 5 patients with seizure, 2patients with somnolence, 1 patient with rigidity of limbs and 16 patients with nausea and vomiting. Compared with patients of SIADH and no SIADH, risk factors of SIADH were younger in age, transplantation from HLA mismatched or unrelated donor, cord blood transplantation, and GVHD prophylaxis with methyl prednisolone ($p<0.05$) (Table 2). Drugs containing with conditioning regimen were not associated with SIADH. Multivariate analysis revealed transplantation from alternative donor is risk factors of SIADH (Table 3). In all patients undergone SCT, survival rate was superior in patients with SIADH than no SIADH (Figure 1) and both were statistically significant ($p=0.0204$). Comparison between 150 patients having malignant disease with SIADH and no SIADH revealed statically significant in event free survival ($p=0.0478$). The median of minimum serum sodium level was 120 mmol/l. The median onset of SIADH was 24.5 days after SCT and the median number of white blood cell (WBC) at the onset of SIADH was 2.1×10^9 /l. In the patients with SIADH, we compared the above-mentioned factors between patients with CBT and those with BMT/PBSCT (Table4). Gender, age,

Table 2 Comparison between patients with SIADH and non SIADH.

factor		total	SIADH (n=26)	no SIADH (n=171)	P
gender	male	126	17	109	1.000
	female	71	9	62	
age			5.96±4.35	8.52±5.16	0.019
disease	malignant	150	18	132	0.317
	non malignant	47	8	39	
donor	autologous	33	0	33	<0.001
	matched related	62	1	61	
	mismatched related	16	4	11	
	matched unrelated	48	6	42	
	mismatched unrelated	38	15	23	
SCT	BM	122	9	113	<0.001
	BM+PB	4	0	4	
	PB	25	1	24	
	CB	46	16	30	
conditioning					
	TBI	93	14	79	0.980
	BU	67	9	58	
	CY	118	18	100	
	L-PAM	57	7	50	
	VP16	93	12	81	
	ATG	43	7	36	
acute GVHD(>grade2)	33	7	26	0.154	
GVHD prophylaxis					
	CsA	119	20	99	<0.001
	MTX	113	11	102	
	FK506	33	6	27	
	mPSL	44	15	29	

Table 3 Risk factor of SIADH with multivariate analysis.

Factor		relative risk	p	95% CI
Donor	Alternative	7.703	0.006	2.379-153.363
SCT	CB	1.655	0.198	0.428-59.925
Age	<3y	0.281	0.914	0.470-3.725
GVHD Prophylaxis	mPSL	0.152	0.697	0.052-7.199

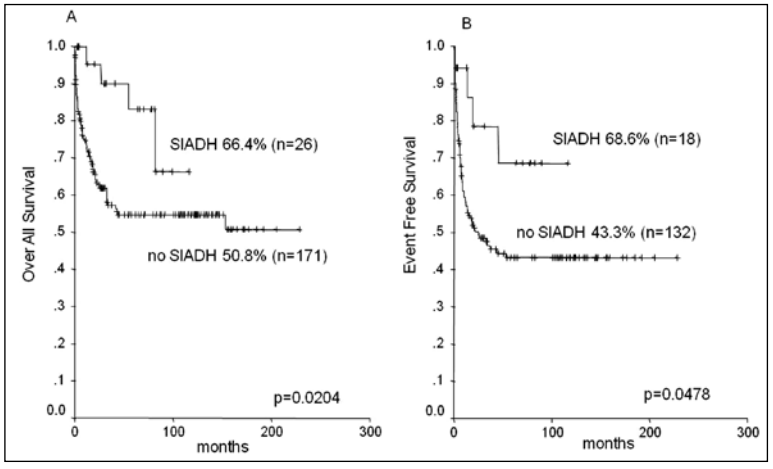

Figure 1 A. Overall survival curve with and without SIADH. B. Event free survival curve with and without SIADH in patients with malignant disease.
Patients with SIADH had significantly higher probability of overall survival (66.4% versus 50.8%) and event free survival (68.6% versus 43.3%) compared with no SIADH.

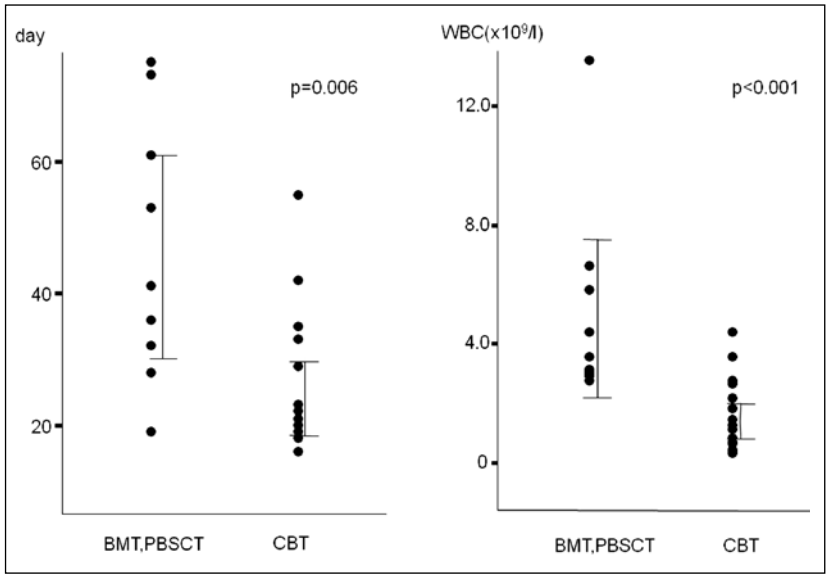

Figure 2 A Onset day of SIADH in BMT/PBSCT and CBT. B. WBC counts of SIADH in BMT/PBSCT and CBT.
SIADH developed earlier in patients with CBT than in those with BMT, and the median numbers of WBC at the onset of SIADH were lower in patients with CBT than in those with BMT.

and minimum serum sodium level were not different between them. However, severe symptoms such as seizure, somnolence, and rigidity of limbs were observed in 8 (50.0%) of the 16 patients with CBT, whereas in none of the 10 patients with BMT/PBSCT. This difference was statistically significant (p=0.007). Additionally, SIADH developed earlier in patients with CBT (median onset, 19.5 days after SCT; range, 15 to 54 days) than in those with BMT (median onset, 46 days after SCT; range, 18 to 74 days), and the median numbers of WBC at the onset of SIADH were lower in patients with CBT (median, 1.1 x 10^9 /l; range, 0.1 to 4.2 x 10^9 /l) than in those with BMT (median, 3.1 x 10^9/l; range, 2.5 to 13.3 x 10^9 /l) (Figure 2). These differences were statistically significant ($P < 0.01$).

Table 4

		BMT, PBSCT (n=10)	CBT (n=16)
Gender	male	7	10
	female	3	6
Age (median, years old)		5.5	5
Minimum value of sodium (median, mmol/l)		121.5	120
Onset of SIADH (median, day)		46	19.5
WBC at onset of SIADH (median, $\times 10^9$ /l)		3.1	1.1
Severe symptom at SIADH		0	6
Neurological sequelae		1	4

DISCUSSION

Hyponatremia is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter. Hyponatremia is a common electrolyte disturbance in clinical practice. Causes of hyponatremia are manifold.[9, 10] The most frequent causes of hyponatremia are extrarenal sodium loss due to vomiting or diarrhea, hepatic cirrhosis, drug induced hyponatremia and the SIADH. Hypovolemic disorders due to extrarenal or renal sodium loss are principal cause of hyponatremia. If the hyponatremia is progressive, headache, nausea, vomiting, muscle crumps, lethtargy, restlessness, disorientation, and depressed reflexes can be observed. Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain stem herniation, and death. The consequences of acute hyponatremia are more serious in young children and premenopausal women.[11]

In our study, surprisingly, SIADH was observed many patients after SCT, unexpectedly. Hyponatremia, related to SIADH, has been associated with various antineoplastic agents, including vincristine, cyclophosphamide, ifosfamide and thiotepa.[12, 13] Our analysis revealed drugs and radiation containing conditioning regimen were not associated with SIADH. SIADH has been reported to be associated with a few hematologic diseases such as NHL and Hodgkin's disease.[14-17] The common cause of SIADH in NHL is thought to be either vinca alkaloid-containing chemotherapy or direct invasion into the pituitary gland. Chubati et al. have reported three cases of NHL in association with HPS and SIADH and have proposed an attractive hypothesis.[14] One patient with B-cell NHL received no chemotherapy prior to the onset of SIADH. In this patient, some cytokines such as IL-1β and TNF-α may stimulate the hypothalamic synthesis and release of both ADH and corticotropin releasing hormone (CRH). CRH induces the secretion of corticotropin and cortisol, which in turn suppress the secretion of endogenous ADH. After SCT, cytokines such as IL-2 and IFN-γ enhance T-cell expansion, induce cytotoxic T cells and natural killer cell responses, and prime additional mononuclear phagocytes to produce TNF-α and IL-1.[18, 19] From these facts, mechanism of SIADH after SCT may be speculated as action of releasing cytokine.

Alternative donor is risk factors of SIADH in our analysis. SCT from HLA mismatched donor and unrelated donor frequently complicate severe GVHD and it is known that levels of cytokines like TNF-α and IL-6 are high.[20] Occurrences of hyponatremia in patients with SIADH are from 15 to 74 days after SCT. This time agrees the time when acute GVHD develops. These cytokines may induce occurrence of SIADH. Patients with SIADH had higher survival rate than those without SIADH. Multivariate analysis revealed only SIADH as a factor associated with survival time. Although that reason is not clear, cytokines thought to be related with SIADH may improve survival as anti-tumor effect.

Our findings revealed the patients with CBT had an earlier onset, a lower WBC count at the onset, and more severe symptoms than those with BMT/PBSCT. These surprising findings are extremely important to consider when investigating the mechanism of SIADH following SCT. Recently, pre-engraftment immune reactions (PIR), characterized by high-grade fever and weight gain, have been proposed as an early phenotype of post-CBT immune reaction[21, 22] PIR develops at a median of 9 days after CBT, and it is speculated that this results after a cytokine reaction after transplantation. Interestingly, PIR has not been reported after BMT/PBSCT. As previously wrote, interleukin-6 has been reported to be involved in SIADH.[23-25] Thus, one may speculate that SIADH in some CBT cases shows a cytokine reaction after a specific length of latent period, and this reaction may explain in part, the different features of SIADH following CBT and BMT/PBSCT.

In conclusion, SIADH is relatively common complication with SCT, especially in patients transplanted from alternative donor. Furthermore, the different features of SIADH observed following CBT and BMT/PBSCT suggest that the mechanisms responsible for SIADH are different.

REFERENCES

1 Adrogue HJ, Madias NE: Hyponatremia: Review article. New

England Journal of Medicine 342: 1581-1589, 2000
2 Ishikawa SE, Schrier RW: Pathophysiological roles of arginine vasopressin and aquaporin-2 in impaired water excretion. Clinical Endocrinology 58: 1-17, 2003
3 Smith DM, McKenna K, Thompson CJ: Hyponatremia: A review. Clinical Endocrinology 52: 667-678, 2000
4 Abe T, Takaue Y, Okamoto Y, Yamaue T, Nakagawa R, Makimoto A, Sato J, Kawano Y, Kuroda Y: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in children undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Pediatr Hematol Oncol 12:363-369, 1995
5 Festuccia F, Polci R, Pugliese F, Gargiulo A, Cinotti GA, Mene P: Syndome of inappropriate ADH secretion: a late complication of hemopoietic stem cell allograft. G Ital Nefrol 19: 353-360, 2002
6 Kobayashi R, Iguchi A, Nakajima M, Sato T, Yoshida M, Kaneda M, Suzuki Y, Mino E, Kuroki F, Kobayashi K. Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion complicating stem cell transplantation. Bone Marrow Transplant 34: 975-979, 2004
7 Suzuki Y, Kobayashi R, Sato T, Iguchi A, Kaneda M, Kobayashi K, Ariga T. The syndrome of inappropriate secretion of antidiuretic hormone associated with stem cell transplantation; clinical differences following stem cell transplantation using cord blood and bone marrow/peripheral blood. Bone Marrow Transplant in press
8 Bartter FC, Schwarz WB: The syndrome of inappropriate secretion of antidiuretic hormone. American Journal of Medicine 42: 790-806, 1967
9 Peter HB: The syndrome of inappropriate antidiureric hormone secretion. The International Journal of Biochemistry and Cell Biology 35 1495-1499, 2003
10 Coenraad MJ, Meinders AE, Vanderbroucke JP, Frolich M, Taal JCW, Bolk JH: Causes of hyponatremia in the departments of internal medicine and neurosurgery. Eur J Int Med 14: 302-309, 2003
11 Adrogue HJ, Madias NE: Hyponatremia. New England Journal of Medicine 342: 1581-1589, 2000
12 Sorensen JB, Andersen MK, Hansen HH: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med. 238:97-110, 1995
13 Sica S, Cicconi S, Sora F, Chiusolo P, Piccirillo N, Laurenti L, La Barbera EO, Giordano G, Leone G: Inappropriate antidiuretic hormone secretion after high-dose thiotepa. Bone Marrow Transplantation 24:571-572, 1999
14 Chubati A, Miura I, Hatano Y, Ohshima A, Nishinari T, Miura AB: Syndome of appropriate secretion of antidiuretic hormone in patients with lymphoma-associated hemophagocytic syndrome. Ann Hematol 70: 53-55, 1995
15 Ciaudo M, Chauvenet L, Audouin J, Rossert J, Favier R, Horellou MH, Bernadou A, Samama M: Peripheral T-cell lymphoma with hemophagocytic histiocytosis localized to the bone marrow associated with inappropriate secretion of antidiuretic hormone. Leukemia and Lymphoma 19: 511-514, 1995
16 Eliakim R, Vertman E, Shinhar E: Syndrome of inappropriate secretion of antidiuretic hormone in Hodgkin's disease. Am J Med Sci 291: 126-127, 1986
17 Kelton JG, Logue G: Inappropriate antidiuretic hormone complicating histiocytic lymphoma. Arch Intern Med 139: 307-308, 1979
18 Reddy P, Ferrara JL.: Immunobiology of acute graft-versus-host disease Blood Rev 17:187-94, 2003
19 Castenskiold EC, Kelsey SM, Collins PW, Coldwell RD, Allen PD, Side LE, Makin HLJ, Goldstone AH, Newland AC: Functional hyperactivity of monocytes after bone marrow transplantation: possible relevance for the development of post-transplant complications or relapse. Bone Marrow Transplantation 15: 879-884, 1995
20 Nagler A, Bishara A, Brautbar C, Barak V: Dysregulation of inflammatory cytokines in unrelated bone marrow transplantation. Cytokines Cell Mol Ther 4:161-167, 1998
21 Kishi Y, Kami M, Miyakoshi S, Kanda Y, Murashige N, Teshima T et al. Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. Transplantation 80: 34-40, 2005
22 Narimatsu H, Terakura S, Matsuo K, Oba T, Uchida T, Iida H et al. Short-term methotrexate could reduce early immune reactions and improve outcomes in umbilical cord blood transplantation for adults. Bone Marrow Transplant 39: 31-39, 2007
23 Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab 79: 934-939, 1994
24 Gionis D, Ilias I, Moustaki M, Mantzos E, Papadatos I, Koutras DA et al. Hypothalamic-pituitary-adrenal axis and interleukin-6 activity in children with head trauma and syndrome of inappropriate secretion of antidiuretic hormone. J Pediatr Endocrinol Metab 16: 49-54, 2003
25 Ghorbel MT, Sharman G, Leroux M, Barrett T, Donovan DM, Becker KG et al. Microarray analysis reveals interleukin-6 as a novel secretory product of the hypothalamo-neurohypophyseal system. J Biol Chem 278: 19280-19285, 2003