Syndrome of inappropriate secretion of antidiuretic hormone induced by tacrolimus hydrate

<Case Report>

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ABSTRACT

A 24-year-old man with chronic myelocytic leukemia underwent a bone marrow transplant. Tacrolimus hydrate (FK506) was given for the prophylaxis of graft versus host disease (GVHD), but subsequently grade II skin and intestinal GVHD occurred. Increased administration of FK 506 with simultaneous use of prednisolone relieved GVHD; however, hyponatremia occurred. Because renal function was normal and urinary osmolality was higher than serum osmolality, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was diagnosed. When FK506 was replaced by cyclosporine on day 43, the hyponatremia improved rapidly. FK506 is thought to be the agent that caused SIADH in the present case.

Key words : Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Tacrolimus hydrate (FK506), Chronic myelocytic leukemia (CML), Bone marrow transplant (BMT)

INTRODUCTION

Although bone marrow transplant (BMT) is a standard treatment in patients with chronic myelocytic leukemia (CML), a variety of complications including infection, venoocclusive disease, and graft versus host disease (GVHD) may occur. Electrolyte imbalance often occurs in BMT recipients as a result of inappropriate hydration, vomiting, diarrhea, renal dysfunction, or side effects of the drugs prescribed. A recent report has shown that hyponatremia is observed in 40% of pediatric patients receiving BMT and that 11.4% of pediatric recipients suffer from syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[1]. In contrast, judging by the number of reports, cases of SIADH in adult BMT recipients would appear to be few[2].

Tacrolimus hydrate (FK506) is a potent immunosuppressive agent used for organ transplantation and autoimmune diseases. In addition to its strong immunosuppressive action, FK506

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shows many side effects including renal failure, cardiac dysfunction, and encephalopathy[3]. In renal transplant patients, cases of hyponatremia based on sodium-losing nephropathy and distal tubular damage have been reported[4]. Here we describe a case of SIADH induced by the administration of FK506 for GVHD after an allogeneic BMT.

CASE REPORT

A 24-year-old man, who has been in good health, visited our hospital for further examination of leukocytosis found at a blood donation. A physical examination did not reveal any lymph node enlargement or hepatosplenomegaly. The white cell count was 39,400/μl with 6.7% promyelocytes, 4.0% myelocytes, 6.0% metamyelocytes, 15.3% bands, 57.3% segmented neutrophils, 7.7% lymphocytes, 0.7% monocytes, and 2.3% eosinophils. Neutrophil alkaline phosphatase score was 117. The platelet count was 624,000/μl and the hematocrit was 37.9%. The bone marrow was markedly hypercellular with a myeloid to erythroid ratio of 14.9. Chromosomal analysis by the G-banding method revealed that marrow cells contained t(9;22)(q34;q11) and the dual-color fluorescence in situ hybridization method showed that 94.3% of peripheral leukocytes were positive for the *bcr-abl* fusion gene. The results of serum hepatic and renal function tests, including electrolytes level, were normal except for an elevation of lactic dehydrogenase to 962 IU/L. A diagnosis of chronic phase CML was made and hydroxyurea was administrated for 5 months with no cytogenetic response.

The patient then received an allogeneic BMT from a one-locus-mismatched sibling. A combination of busulfan (4 mg/kg *p.o.* in divided doses daily on days −7 to −4) and cyclophosphamide (60 mg/kg once daily *i.v.* on days −3 and −2) was administered for the preparative regimen. FK506 (0.035 mg/kg) and short-term methotrexate was given to prevent GVHD. Engraftment was confirmed 14 days later. On day 10, maculopapular rashes on the patient's extremities spread to the trunk, and he suffered from diarrhea with abdominal pain, which was diagnosed as Grade II GVHD. Methyl prednisolone was administered, and the dose of FK506 was increased to 0.075 mg/kg. Eruption and diarrhea disappeared in 2 weeks. On day 27, the serum sodium level began to decrease and reached 123 mEq/L. Fluid restriction and administration of normal saline had transient effects. The patient's serum sodium concentration remained low, in contrast to the high urine sodium level (88 mEq/L). Urine osmolality (819 mOsm/L) was inappropriately higher than serum osmolality (259 mOsm/L), and the serum antidiuretic hormone level was not lowered. Renal, adrenal, thyroid, and cardiac functions were normal. There was no clinical evidence of volemic imbalances. Brain magnetic resonance imaging and chest film revealed no abnormalities. With several lines of evidence, we diagnosed his state as drug-induced SIADH. On day 43, administration of FK506 was stopped, and cyclosporine A was started on the next day. Serum osmolality and sodium concentration promptly recovered without fluid restriction or administration of saline (Fig. 1). The patient has been in complete remission for 12 months after BMT without chronic GVHD or abnormal electrolyte balance.

DISCUSSION

We demonstrate a case of hyponatremia occurring after allogeneic bone marrow transplant. Since urine osmolality was inappropriately elevated without suppression of antidiuretic hormone in normal renal, adrenal, thyroid, and cardiac functions, SIADH was the most likely cause of the hyponatremia. Various carcinomas, pulmonary diseases, and cranial lesions may cause SIADH; however, these possibilities were ruled out in this case. Another cause of SIADH is drugs including cyclophosphamide[5] and thiotepa[6]. In the present case, we first suspected cyclophosphamide to be the responsible agent; however, the duration from the administration of cyclophosphamide to the onset of SIADH was too long and hyponatremia continued after the end

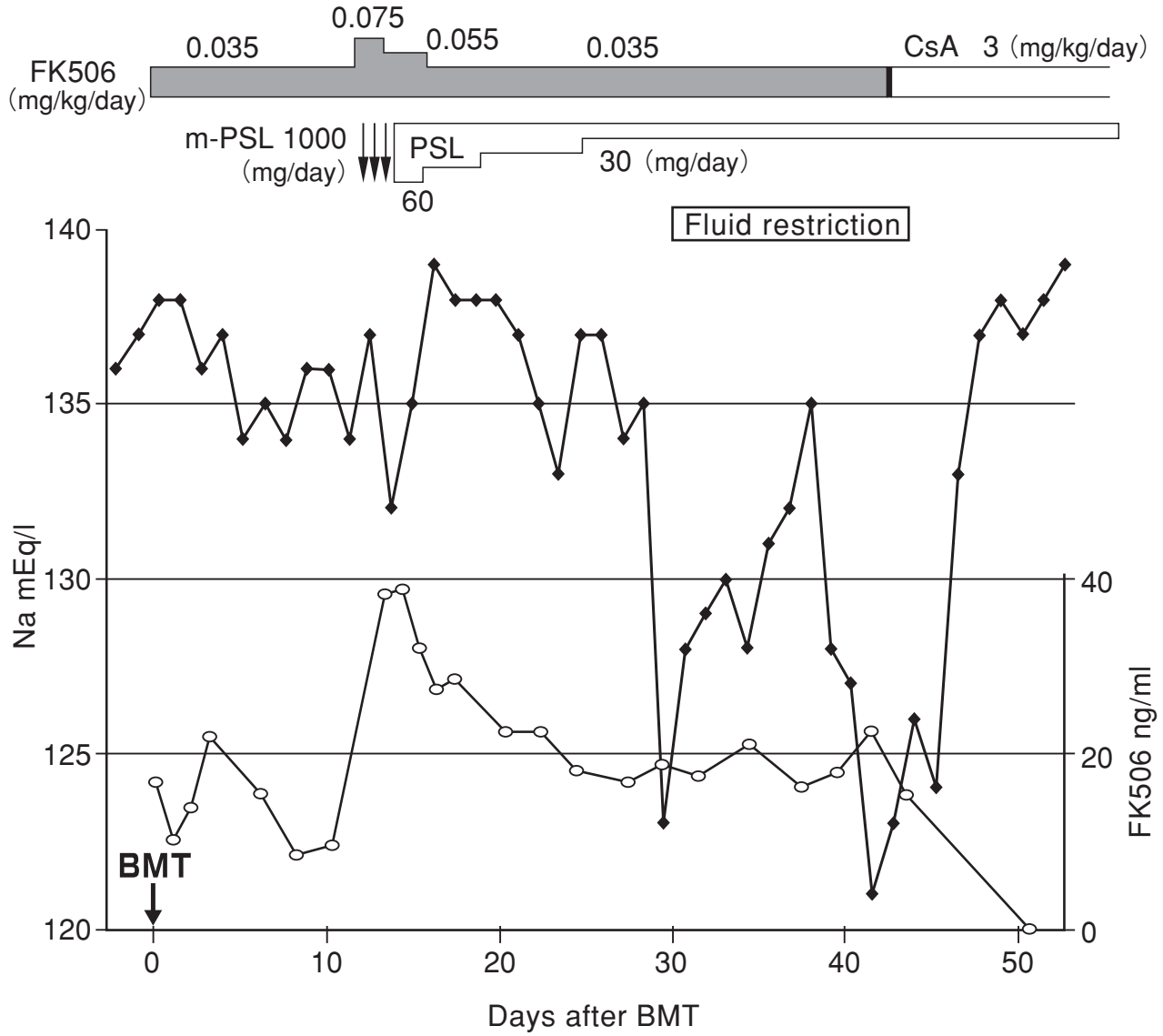

Fig. 1 Sequential serum sodium and FK506 concentration.
Serum FK506 concentration (open circle) reached 37.6 ng/ml after increasing the dosage. Serum sodium concentration (closed square) decreased to 123 mEq/L 27 days after the bone marrow transplant. Fluid restriction and administration of saline were not effective in relieving the symptoms. When FK506 was exchanged for cyclosporine on day 43, the sodium level rapidly recovered to within the normal range.

of cyclophosphamide treatment. We therefore presumed it likely that FK506 was the cause of SIADH, and switched to cyclosporine A. Prompt normalization of serum osmolality and sodium concentration after cessation of FK506 indicated that FK506 was indeed the drug responsible for the SIADH. FK506 induces hyponatremia due to renal tubular damage, especially in renal transplant recipients[4]; however, the results of laboratory examinations showed no renal dysfunction in the present case. SIADH was observed in 11.4% of pediatric patients who received stem cell transplant (SCT), and the incidence was greater in patients with young age, HLA-mismatched sibling or unrelated donor, cord blood transplantation, and methyl prednisolone treat-

ment[1]. Since few adult cases of SIADH after SCT have been reported[2], the frequency and risk factors of SIADH in adult patients remains to be investigated.

The mechanism whereby FK506 causes SIADH is a subject requiring delineation. The present case shows that high serum concentration of FK506 may adversely affect serum sodium level (Figure 1). The concomitant use of prednisolone, which increases serum concentration of FK506 and is itself one of the risk factors for SIADH in pediatric patients, may also decrease sodium concentration.

Most patients with drug-induced SIADH recover soon after cessation of the agent; however, fatal cases have also been reported[5]. When FK506 is administered, frequent examination of electrolytes is needed so as not to delay the diagnosis of SIADH.

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