CASE REPORT

Case

A 32-year-old man who had suffered from chronic myelogeneous leukemia (accelerated phase) received allogeneic BMT. CsA (Sandimmun, Novartis, containing polyoxyethylene castor oil and ethanol, 180 mg/body, intravenous infusion, since the day before BMT) and methotrexate (25 mg at day 1 and 17 mg at days 3, 6, and 11) were administered to prevent severe GVHD. Engraftment of the donor's bone marrow cells was observed on day 14. Because of acute GVHD (grade II, skin eruption) on day 20, 60 mg of oral prednisolone was added to the CsA for 30 days and decreased as the GVHD improved in a month. He developed cytomegalovirus cystitis on day 53, and 500 mg of ganciclovir was administered for two weeks and then reduced to 250 mg for a month. Chronic GVHD (quiescent onset type, diarrhea, edema and fever) occurred on day 100. We used 60 mg of prednisolone in addition to 300 mg of CsA for about 10 days and gradually decreased it after the GVHD improved. Although his blood pressure was within normal limits before BMT, it had become constantly higher than 160/100 mmHg at the maximum level of the day since about day seven. He had no past history of hypertension, so this was believed to be cyclosporin-induced. He was administered 24 mg of nicardipine from day eight to day 21, 5 mg of amlodipine starting on day 22, and 5 mg of enalapril besides amlodipine from day 58 to day 115. He also took 20 mg of furosemide from day 135 to day 143 for foot edema probably due to CsA and prednisolone use. After these therapies for hypertension, his blood pressure stabilized at 140/90 mmHg. Changing patterns of blood pressure in a day were also stabilized. Blood pressure monitoring and blood sampling was performed on day 178 after BMT. He orally received 75 mg of CsA twice a day at 9 and 21 o'clock, 20 mg of prednisolone, and 5 mg of amlodipine once a day on day 178. His serum creatinine level was 1.0 mg/dl and creatinine clearance was 50 ml/min at this time.

Blood pressure (Korotkoff- microphone method (KM) and oscillometric method (OS)) and pulse rate were measured as ambulatory blood pressure monitoring every fifteen minutes, from 9 to 21 o'clock by ABPM 630 (Colin Corporation, Japan), and the mean blood pressure and pulse rate were calculated every hour. Blood sampling was performed seven times a day at 9, 10, 11, 13, 15, 17, and 21 o'clock. Whole blood CsA concentrations were quantitated by a fluorescence polarization immunoassay (FPIA) only for parent compound (Dainabot Co.Ltd., Tokyo, Japan). Plasma ET-1 concentrations were quantitated by an enzyme-immunoassay (EIA; Wako Pure Chemical Industries, Ltd., Osaka, Japan). Plasma TM concentrations were measured by an EIA (Mitsubishi Gas Chemical Company, Inc., Tokyo, Japan). Coefficients of variations of CsA and ET-1 were 2.9% and 10% respectively. Normal ranges of CsA, ET-1 and TM were 150−200 ng/ml, <2.3 pg/ml and 9.4−

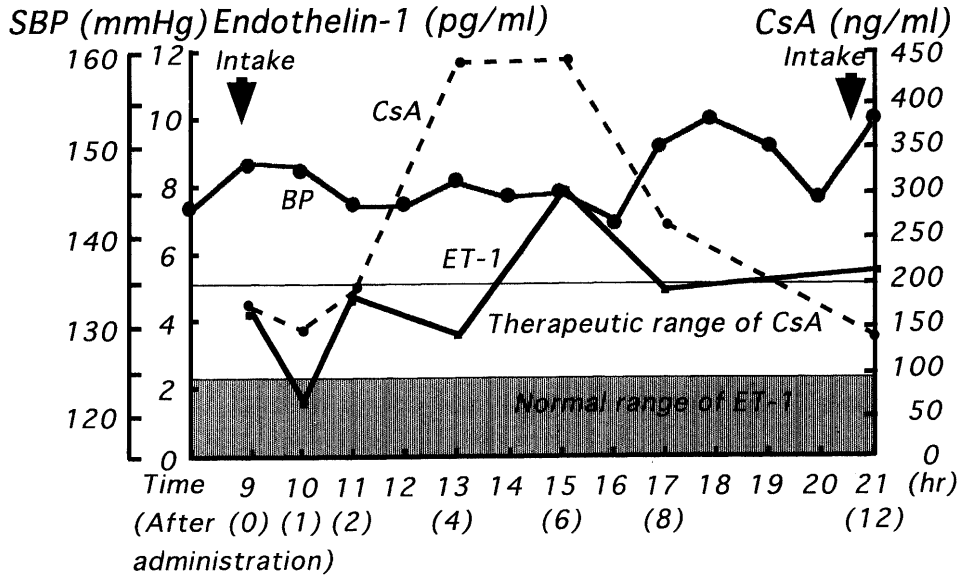

Fig. 1 Changes in cyclosporin A (CsA) and endothelin-1 (ET-1) levels, and blood pressure (BP) in a case with hypertension after BMT.

21.1 U/ml, respectively. Recommended therapeutic concentration of CsA is 150−200 ng/ml as trough.

Changes in CsA levels, ET-1 levels, and systolic blood pressure (KM) are shown in Fig. 1. CsA level was the lowest one hour after the administration of CsA and reached a maximum 4−6 hours after administration of CsA. ET-1 levels showed similar phases of peaks to that of CsA (least squares method: r= 0.454, not significant, r; correlation coefficient between ET-1 level and CsA level). Systolic blood pressure was over 140 mmHg throughout the day, and tended to rise further 3−4 hours after ET-1 levels rose. Immediate changes in systolic blood pressure associated with ET-1 change were not seen in this study (r=0.152, not significant; between ET-1 level and blood pressure at same time); however, the ET-1 levels significantly correlated with the blood pressure observed 3 hours later (r=0.709, $p<0.05$; between ET-1 level and blood pressure 3 hours later). No changes except a low grade continuous elevation of TM levels, which indicate vascular endothelial cell damage, were observed (26.0 ± 1.4 U/ml).

In contrast, even after BMT, another 33-year-old male patient with normal blood pressure was suffering from myelodysplastic syndrome (refractory anemia), and had normal ET-1 levels and low concentration levels of CsA (Fig. 2). This series of blood pressure monitoring and blood sampling was performed on day 90 after BMT.

DISCUSSION

Increased efferent sympathetic nerve activity[3], an increase of plasma ET-1, and sodium retention have been reported[2,3,11] as possible causes of cyclosporin-induced hypertension. CsA induces increases in messenger RNA concentrations of ET-1[12] and ET-1 released from endothelial cells to prevent vessel relaxation. However, previous studies in normal volunteers[13] have suggested rapid and non-direct mechanisms for a rise in blood pressure; that is, a rise in blood pressure followed by renal hypofiltration or antinatriuresis approximately 6 hours after CsA peaks in the blood. Cyclosporin-induced sodium retention is thought to be one of the major factors causing cyclosporin-induced hypertension. The significant correlation between the ET-1 level and the blood pressure observations 3 hours later in this case possibly indicate that these states concern the onset of hypertension besides immediate direct effect of ET-1.

Prednisolone and amlodipine were also administered to the patient on the day of this study. Although the effect of testosterone on ET-1 levels is reported to increase[14], the effect of prednisolone on it is still unclear. A high dose combination of the angiotensin converting enzyme (ACE) inhibitor benazeprilat and amlodipine is reported to be the most effective in inhibiting contractions to ET-1, and amlodipine suppresses the weak contractions at low concentrations of ET-1 in porcine ciliary arteries[15]. The effect of

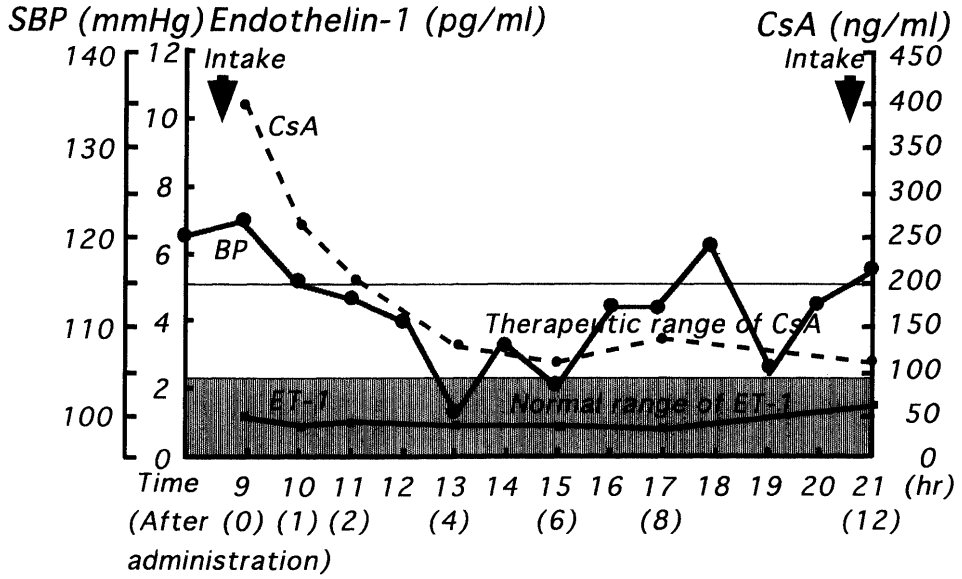

Fig. 2 Changes in cyclosporin A (CsA) and endothelin-1 (ET-1) levels, and blood pressure (BP) in a case without hypertension after BMT.

amlodipine in itself on ET-1 levels is also still unclear. Therefore, the high levels of ET-1 in this case can most probably be considered as a cyclosporin-induced increase of plasma ET-1. In contrast, another patient who had normal blood pressure after BMT showed low concentration levels of CsA even after its intake and also showed normal ET-1 levels (Fig. 2).

In the present study, changes in plasma ET-1 levels almost paralleled CsA concentration changes, and the basal ET-1 levels were higher than normal levels in the hypertension case. However, an immediate rise in blood pressure in association with rises in CsA and ET-1 was not found, and blood pressure peaked approximately 5 hours after CsA peaked in the blood concentration. It is possible but by no means certain that only the elevation in ET-1 levels can account for the hypertension; however, the results in this study confirm that ET-1 is released from endothelial cells, against the background of high concentrations of cyclosporin A, and may contribute to cyclosporin-induced hypertension together with indirect effects of CsA after BMT.

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