Table 3. Results of multivariate analysis of overall survival according to disease status at transplantation

	First complete remission			Second or after complete remission			More advanced		
Overall survival	n	RR (95% CI)	P	n	RR (95% CI)	P	n	RR (95% CI)	P
AML									
UBMT	130	1.00		82	1.00		95	1.00	
UCBT	50	2.92 (1.38-6.18)	.005	39	1.24 (0.51-3.04)	.63	81	1.29 (0.84-1.98)	.25
ALL									
UBMT	130	1.00		48	1.00		42	1.00	
UCBT	63	1.60 (0.84-3.05)	.16	21	0.62 (0.22-1.74)	.36	30	0.80 (0.38-1.69)	.57

RR indicates relative risk; CI, confidence interval; UBMT, unrelated bone marrow transplantation; and UCBT, unrelated cord blood transplantation.

The unadjusted cumulative incidence of platelet recovery greater than 50 000/μL at 4 months was significantly lower among CB recipients for both AML (59% vs 85%) and ALL (61% vs 83%) compared with that of BM recipients ($P < .001$ for both). The difference was also significant on multivariate analyses for both AML (RR = 0.3, 95% CI = 0.3-0.4, $P < .001$) and ALL (RR = 0.4, 95% CI = 0.3-0.6, $P < .001$; Table 2).

Acute GVHD. The unadjusted cumulative incidence of grade 2 to 4 acute GVHD was lower among CB recipients compared with that among BM recipients (32% vs 35% in AML, 28% vs 42% in ALL); the difference was significant in patients with ALL ($P = .39$ in AML, $P = .008$ in ALL). The difference was also significant on multivariate analyses in ALL (RR = 0.6, 95% CI = 0.4-1.0, $P = .028$). There was no significant difference in patients with AML (RR = 0.8, 95% CI = 0.6-1.2, $P = .23$; Table 2).

Chronic GVHD. The unadjusted cumulative incidence of chronic GVHD at 1 year after transplantation did not significantly differ between CB recipients and BM recipients in both AML (28% vs 32%, $P = .46$) and ALL (27% vs 30%, $P = .50$). The cumulative incidence of extensive-type chronic GVHD was significantly lower among CB recipients compared with that among BM recipients in both AML (8% vs 20%, $P < .001$) and ALL (10% vs 17%, $P = .034$). On multivariate analyses, the risk of developing chronic GVHD was similar in CB recipients and BM recipients in both AML (RR = 0.9, 95% CI = 0.6-1.4, $P = .79$) and ALL (RR = 1.1, 95% CI = 0.7-1.8, $P = .77$). The risk of developing extensive chronic GVHD was lower in CB recipients compared with BM recipients (RR = 0.4, 95% CI = 0.2-0.7, $P = .004$ in AML, and RR = 0.6, 95% CI, 0.3-1.2, $P = .14$ in ALL) and was significantly different in patients with AML (Table 2).

Discussion

The objective of our study was to investigate the outcomes of HLA-A, -B, low-resolution, and -DRB1 high-resolution 0 to 2 mismatched single-unit unrelated CBT in adult patients with acute leukemia compared with those of HLA-A, -B, -C, and -DRB1 (8 of 8) allele-matched unrelated BMT. Although AML and ALL are different diseases, previous comparisons of unrelated BMT and

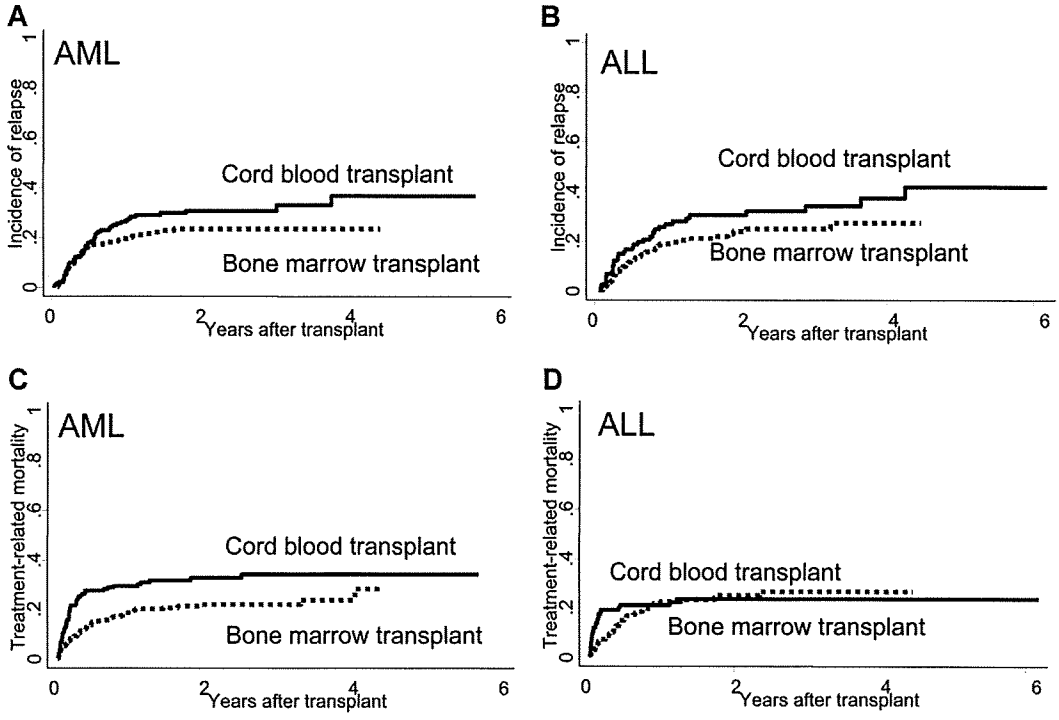

Figure 2. Cumulative incidence of relapse or TRM of recipients of CB or BM among patients with AML or ALL. For patients with AML, the cumulative incidence of (A) relapse (CB vs BM = 31% vs 24% at 2 years, $P = .068$) and (C) TRM (CB vs BM = 33% vs 22% at 2 years, $P = .004$) was higher in CB recipients. For patients with ALL, the cumulative incidence of relapse (B) was higher in CB recipients with marginal significance (CB vs BM = 31% vs 24% at 2 years, $P = .085$), but the incidence of TRM (D) was similar in CB and BM recipients (CB vs BM = 24% vs 25% at 2 years, $P = .83$).

Table 4. Causes of death after transplantation of unrelated cord blood or unrelated bone marrow among patients with acute myeloid leukemia or acute lymphoblastic leukemia

	Acute myeloid leukemia		Acute lymphoblastic leukemia	
Cause of death	UCBT	UBMT	UCBT	UBMT
Recurrence of disease	35 (37)	34 (33)	18 (36)	34 (41)
Graft failure/rejection	3 (3)	4 (4)	0 (0)	3 (4)
Graft-versus-host disease	6 (6)	7 (7)	3 (6)	5 (6)
Infection	22 (23)	19 (18)	13 (26)	11 (13)
Idiopathic pneumonia	4 (4)	4 (4)	2 (4)	6 (7)
Organ failure	17 (18)	17 (16)	8 (16)	10 (12)
Secondary cancer	0 (0)	1 (1)	0 (0)	0 (0)
Other causes	5 (5)	5 (5)	2 (4)	4 (5)
Unknown/data missing	2 (2)	13 (13)	4 (8)	10 (12)
Total	94 (100)	104 (100)	50 (100)	83 (100)

Data are presented as n (%).

UCBT indicates unrelated cord blood transplantation; and UBMT, unrelated bone marrow transplantation.

unrelated CBT did not separate these 2 diseases. Our report is the first to show the result of disease-specific analyses with a sufficient number of patients.

For AML patients, the recipients of CB were more likely to have advanced leukemia at the time of transplantation, as reported previously, suggesting that CB was used as an alternative stem cell source in the later phase of unrelated donor searches, especially in adults.[11,12,14] A larger proportion of CB recipients with ALL had the Philadelphia chromosome abnormality, which correlates with highly aggressive ALL and usually requires urgent transplantation, in which CB has an advantage over BM.[21]

Different outcomes of mortality were found between AML and ALL in a controlled comparison using multivariate analyses. Whereas significantly lower OS and LFS rates were observed in CB recipients with AML, rates of overall mortality and treatment failure were similar between CB and BM recipients with ALL. The relapse rate was not different between CBT and BMT in patients with both AML and ALL, which was consistent with previous reports.[11-13] In adult patients with ALL, a previous report showed no difference in the outcome of related compared with unrelated BM or peripheral blood transplantation in 1CR.[22] Favorable disease status at transplantation could be a more important factor affecting outcome rather than the type of stem cell source or donor type in patients with ALL. It is notable that TRM in HLA allele-matched unrelated BM recipients with AML was quite low in our study. This is probably associated with the low incidence of acute and chronic GVHD in the Japanese population, which is thought to be the result of genetic homogeneity.[23-26] Among patients with AML, although the difference was not statistically significant, a higher trend of TRM observed in CB recipients might be associated with higher overall and TRM rates in CB recipients. Reasons for higher TRM could include the graft source and delayed neutrophil recovery. Better supportive care is required after CBT for patients going through a prolonged neutropenic period. Development of better graft engineering or better conditioning regimens would help to decrease the TRM rate in CB recipients. Because relapse was the major cause of death in all groups, any attempt to decrease TRM should preserve the antileukemia effect to improve OS and LFS. Another reason for the higher TRM could be a higher risk patient population, higher risk for both disease status and comorbid conditions, requiring rapid transplantation. Searching for unrelated donors earlier and providing transplantation earlier in the disease course could help to decrease TRM in CB recipients.

Neutrophil and platelet recovery was slower in CB recipients with either AML or ALL, consistent with the results of previous reports.[11,12,27] Multiple studies have reported lower incidence of acute GVHD in CB recipients.[8-10,12,13] In our study, particularly in patients with ALL, the risk of developing grade 2 to 4 acute GVHD in CB recipients was lower compared with BM recipients, which was reported to be lower compared with the incidence reported from Western countries.[23-25] The risk of developing chronic GVHD was similar between CB and BM recipient with either disease, but the risk of developing extensive-type chronic GVHD was lower in CB recipients; the difference was significant in patients with AML. It is notable that there was no increase in the incidence of acute or chronic GVHD in CB recipients among patients with either AML or ALL, despite HLA disparity.

For differences in outcomes between AML and ALL, one possibility is a difference of treatment before conditioning therapy. Most AML patients received a more intense treatment for induction and consolidation therapy compared with that for ALL. There was no adjustment made for previous treatment, and this could be the reason for higher mortality in CBT, which requires a longer time for neutrophil recovery. Another possible cause of the difference in outcomes is the difference in conditioning regimens. Preparative regimens were similar between CB and BM recipients among ALL patients. However, in patients with AML, the proportion of standard regimens, such as cyclophosphamide and TBI or busulfan and cyclophosphamide, was smaller among CB recipients. These differences in the distribution of preparative regimens were also seen in a previous report.[11] Although the final model was adjusted for conditioning regimens, we cannot rule out the possibility of an effect that larger CB recipients received additional or different chemotherapeutic agents compared with BM recipients among patients with AML. Although the difference was small, the median age of CB recipients with AML was 4 years older than CB recipients with ALL (median age, 38 vs 34 years, $P = .021$), which might have affected the higher mortality rate among CB recipients with AML. It is also possible that some unknown biologic aspects have contributed to these differences, and this would require further evaluation in future studies.

Further subgroup analyses indicated that the superiority of HLA allele-matched BM versus CB for OS was mostly found in patients with AML showing 1CR at conditioning. However, because of the limited numbers of patients in these subgroup analyses and the possibility of an unidentified bias in stem cell source selection, our findings should be verified by further analysis in a larger population.

In conclusion, we found different outcomes between patients with AML and ALL, indicating the importance of disease-specific analyses in alternative donor studies. HLA-A, -B low-resolution, and -DRB1 high-resolution 0 to 2 mismatched single-unit CB is a favorable alternative stem cell source for patients without a suitable related or 8 of 8 matched unrelated BM donor. In the absence of a suitable donor, unrelated CBT should be planned promptly to transplant the patient while in a better disease status and better clinical condition. For patients with AML, decreasing mortality, especially in the early phase of transplantation, is required to improve the outcome for CB recipients.

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Authorship

Contribution: Y.A. and R.S. designed the study and wrote the paper; Y.A. analyzed results and made the figures; S. Kato and Y.M. designed the research; T.-N.I., H.A., and M. Takanashi reviewed and cleaned the Japan Cord Blood Bank Network data and reviewed the results; S. Taniguchi, S. Takahashi, S. Kai, H.S., Y. Kouzai, M.K., and T.F. submitted and cleaned the data; and S.O., M. Tsuchida, K.K., Y.M., and Y. Kodera reviewed and cleaned the Japan Marrow Donor Program data and reviewed the results.

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A complete list of members from the Japan Marrow Donor Program and the Japan Cord Blood Bank Network can be found in the Supplemental Appendix (available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

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LETTER TO THE EDITOR

T-cell post-transplant lymphoproliferative disorder in a patient with chronic idiopathic myelofibrosis following allogeneic PBSC transplantation

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Post-transplant lymphoproliferative disorder (PTLD) is a well-recognized complication after solid organ and hematopoietic SCTs (HSCTs). The majority are of B-cell origin and EBV related.[1] Most of the T-cell PTLD cases have been described as occurring after solid organ transplantations;[2] T-cell PTLD cases following HSCT are exceedingly rare. There are only three reported cases of T-cell PTLD following allogeneic HSCT[3] and four cases following autologous HSCT.[4–7] Here we report a case of T-cell PTLD after allogeneic-PBSC transplantation (allo-PBSCT) in a patient with chronic idiopathic myelofibrosis (CIMF).

A 44-year-old Japanese woman with anemia and fever was diagnosed with CIMF in November 2006. At the time of her diagnosis, her WBC count was 900/μl, Hb 6.9 g/dl, plt count 39 000/μl with no morphologically abnormal cells in her peripheral blood, and an abdominal CT scan showed mild splenomegaly without hepatomegaly, lymphadenopathy or liver tumor. A specimen of her biopsied BM showed diffuse fibrosis and a decreased number of hematopoietic cells. No abnormal cell proliferation was observed. In December 2006, she underwent allo-PBSCT from an HLA-identical brother. Neutrophil engraftment was achieved on day 17 after transplant, and BM analysis showed full hematological recovery with 100% donor-type chimerism assessed by Y chromosome-based FISH analysis. As grade II acute GVHD involving the skin and subsequently an extensive type of chronic GVHD (cGVHD) developed; continued immunosuppressive therapy with cyclosporine and prednisolone was required for several months after the transplant. At 5 months after transplant, a liver tumor, 2 cm in diameter, was detected by an abdominal CT scan. Although PTLD was raised as a differential diagnosis, biopsied liver tissue was inadequate for pathological examination. Immunosuppressive therapy was reduced, resulting in a decrease in liver tumor size to 1.6 cm in 2 months. However, a subsequent flare-up of cGVHD required more intensive immunosuppressive therapy, and the liver tumor's diameter increased twice in size. A liver tumor biopsy performed at this time showed a diffuse proliferation of atypical lymphoid cells (Figure 1a). Immunohistochemically, these tumor cells were positive for LCA, CD3, CD7 and CD8, and negative for CD4, CD5, CD34, CD79a, MPO, CD30, CD56 and TdT (Figure 1b). These pathological findings are compatible with peripheral T-cell lymphoma-unspecified (Figure 1c). EBV infection was not detected by *in situ* hybridization. Y chromosome-based FISH analysis revealed the tumor cells were of recipient origin. She suffered from fever, pancytopenia and decreased liver function, and was hospitalized for further therapy in November 2007. BM examination showed infiltration of 4% abnormal lymphoid cells and the proliferation of macrophage with hemophagocytosis, with no sign of CIMF recurrence. Chromosome analysis of the BM cells showed 44, X, der(X)t(X;7)(q13;q11.2), add(2)(q21), add(4)(p11), add(4)(p16), der(9;17)(q10;q10), −10, −13, add(15)(p11), +mar [2/20]. An abdominal CT scan showed that the liver tumor grew rapidly to a size of $12 \times 6\,cm^2$ (Figure 1d). Serological tests for HIV, HBV, HCV and HTLV-1 were negative, and the EBV VCA IgG was positive but negative for IgM. Analyses by real-time PCR were negative for human herpesvirus-6, VZV, CMV and EBV in her peripheral blood. She was diagnosed with T-cell PTLD with lymphoma-associated hemophagocytic syndrome. CHOP therapy was started, but the disease progressed within 2 weeks after this. She underwent urgent unrelated cord blood transplantation (UCBT) from an HLA two antigen-mismatched donor. Her post-transplant course was complicated by sepsis, renal failure and respiratory failure. She died on day 6 after UCBT. An autopsy was not performed.

To our knowledge, there have been only four cases of T-cell PTLD following allo-SCT, including our case (Table 1). Time to T-cell PTLD diagnosis ranges from 2 to 43 months after a transplant. Although the type of PTLD was not consistent, ranging from precursor to peripheral T-cell neoplasms, none of them were associated with EBV infection. Our case was negative for EBV, and the type was peripheral T-cell lymphoma-unspecified.

There have been a few reports describing myelofibrosis in association with T-cell lymphoma.[8] In these cases, PDGF and tumor growth factor β, which may have been secreted by neoplastic T lymphocytes, had an important role in the development of myelofibrosis. In our case, there was no clinical evidence of T-cell lymphoma at the time of CIMF diagnosis, and no sign of myelofibrosis recurrence at the onset of T-cell lymphoma. Thus, the development of T-cell lymphoma in this case was considered to be independent of the CIMF.

All three patients reported as having T-cell PTLD following allo-SCT had severe GVHD and received a heavy dose of immunosuppressive agents, suggesting some viral agents in an immunosuppressed state may have an important role in the development of T-cell PTLD. However, we were unable to find any evidence of viral

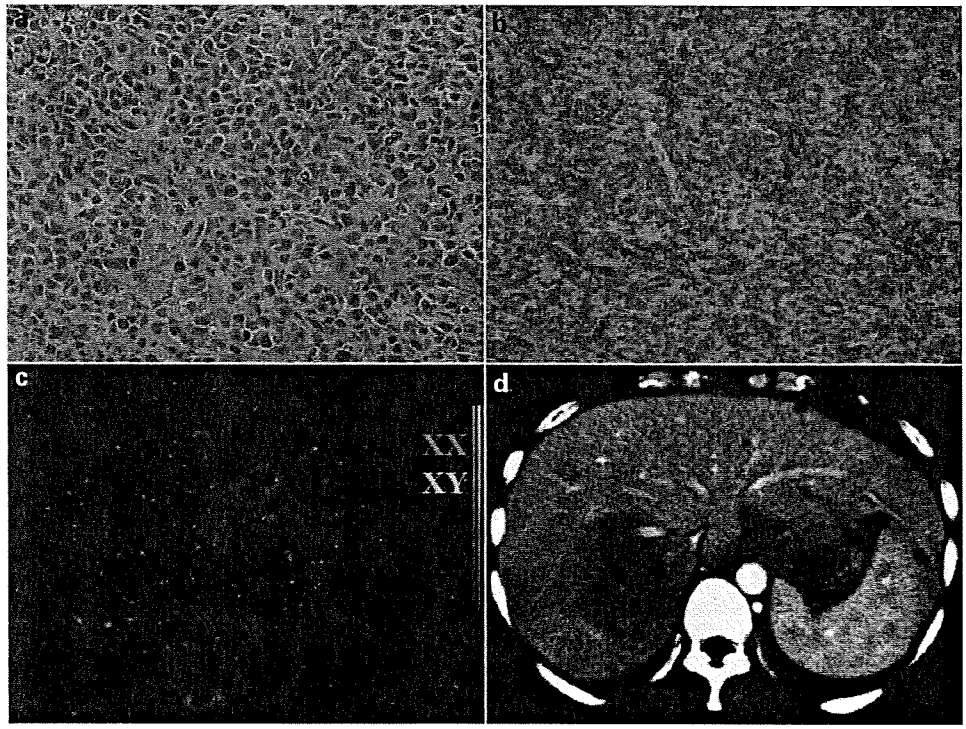

Figure 1 (a) Liver tumor biopsy shows monotonous infiltration of atypical lymphoid cells (H&E stain × 400). (b) Immunostaining for CD3 shows a large number of positive cells within the tumor. (c) Y chromosome-based FISH reveals the tumor cells are of recipient origin (XX signal). (d) Abdominal CT scan shows a low-density area with 12 cm diameter on the right side of the liver.

Table 1 T-cell post-transplant lymphoproliferative disorder after allogeneic stem cell transplantation

Authors	*Age/sex*	*Initial Dx*	*HSCT*	*Type of PTLD Dx (months after HSCT)*	*Origin*	*EBV*	*GVHD*	*Outcome (months after Dx)*
Zutter *et al.*[3]	14/M	AML	HLA-identical BM graft	T-lymphoblastic lymphoma (43)	Recipient	Neg	Mild aGVHD(S,L,Gut) Severe cGVHD(S,L,Gut)	Death (28)
	9/M	ALL	HLA-identical BM graft	T-lymphoblastic lymphoma (21)	Donor	Neg	Mild aGVHD(S) Severe cGVHD(S,L)	Death (6)
	2/F	ALL	HLA-2 mismatched BM graft	Polymorphic T-cell lymphoma (2)	Donor?	Neg	Severe aGVHD(S,L)	Death (0)
Present case	44/F	CIMF	HLA-identical allogeneic PBSC	PTCL-u (5)	Recipient	Neg	aGVHDII(S3,L0,Gut0) Extensive cGVHD(S,L)	Death (2)

Abbreviations: aGVHD = acute GVHD; cGVHD = chronic GVHD; CIMF = chronic idiopathic myelofibrosis; Dx = diagnosis; F = female; Gut = gastrointestinal tract; HSCT = hematopoietic stem cell transplantation; L = liver; M = male; neg = negative; PTCL-u = peripheral T-cell lymphoma-unspecified; PTLD = post-transplant lymphoproliferative disorder; S = skin.

infection and reactivation in our case and previously reported cases. It has been reported that only 15 of 76 cases of T-cell PTLD after solid organ transplantation were EBV positive,[9] and any other viral involvement has not been clearly demonstrated. These findings suggest that not only viral infection but also other factors, such as chronic antigenic stimulation, impaired immunoregulation and genetic factors, may be associated with the development of T-cell PTLD.[10]

The outcomes of reported T-cell PTLD so far are poor. All patients died because of the progression of the disease. In our patient, a transient response was observed by reducing immunosuppression, suggesting a graft-versus-lymphoma effect, which was necessitated to increase the immunosuppression. Standard cytotoxic chemotherapy led to a poor response in our patient, similar to the other cases previously described. More intensive chemotherapy, donor lymphocyte infusion or second HSCT should be considered at an early stage of the disease.

In conclusion, T-cell PTLD rarely occurs after allo-HSCT. Further research, however, is needed to fully characterize the clinicopathological features of this condition and to investigate the optimal therapy.

Conflict of interest

The authors declare no conflict of interest.

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SPECIAL REPORT

Hematopoietic SCT activity in Asia: a report from the Asia-Pacific Blood and Marrow Transplantation Group

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The hematopoietic SCT (HSCT) activity in nine Asian countries/regions was surveyed to overview the current situation. Data of 58 113 HSCTs (allogeneic: 63% vs autologous: 37%) performed between 1986 and 2006 by 432 transplant teams were collected. The number of HSCTs has been increasing in the past two decades in most countries/regions. The increase in allogeneic HSCTs is greater than in autologous HSCTs. The proportion of unrelated donors among allogeneic HSCTs in 2006 varied widely from <1% (Iran and Vietnam) to 62% (Japan). The use of each stem cell source, that is, BM, PBSC, cord blood and others (including co-infusion of BM and PBSC), also varied widely (36, 58, 0.1 and 6% in HSCT from related donors, respectively, and 53, 11, 35 and 1% in HSCT from unrelated donors, respectively). HSCTs have been continuously increasing for all indications except for chronic myelogenous leukemia and solid tumors. Hemoglobinopathy is a common indication among non-malignant diseases in many Asian countries/regions except for China, Japan and Korea. This survey clearly shows the recent progress of HSCTs in Asia and also some differences in donor and stem cell selection and disease application among countries/regions.
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Introduction

Hematopoietic SCT (HSCT) is now an established treatment procedure for many patients suffering from various malignant and non-malignant diseases.[1–3] Over the past two decades, its use has expanded rapidly, and many changes and progress have occurred in technology, stem cell sources and infrastructure. The activity and the trends of HSCTs are different among countries, reflecting the different disease prevalences, economic situations and availability of donor programs.[4] HSCT is still a challenge for several countries with low incomes because of its high cost of establishment and maintenance of HSCT system. Recent reports on HSCT from Asian countries suggest the progress of HSCT in this region.[5–21] However, no comprehensive picture of the current state of HSCT in Asia has been obtained. The Asia-Pacific region consists of countries with various ethnic, economical and social backgrounds. The Asia-Pacific Blood and Marrow Transplantation Group (APBMT) was established in 1990 to promote HSCT in Asia (http://www.apbmt.org). In 2006, its data center was established to develop the APBMT Registry to collect data on HSCT in this region. As a first step, we performed a retrospective transplant activity survey to provide an overview of the current state of HSCT in nine Asian countries.

Materials and methods

Data collection

The data on transplants performed between 1986 and 2006 in nine Asian countries/regions (mainland China, Hong Kong, Iran, Japan, Korea, Malaysia, Singapore, Taiwan

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Table 1 Baseline data of each country/region

Country/region	Population (×1000) [a]	Category of income [b]	Donor program	CB bank	First HSCT in this study
China	1 330 000	Lower middle	Yes	Yes	1987
Hong Kong	7019	High	Yes	Yes	1990
Iran	65 875	Lower middle	Yes	Yes	1991
Japan	127 288	High	Yes	Yes	Before 1986
Korea	48 379	High	Yes	Yes	Before 1986
Malaysia	25 274	Upper middle	Yes	Yes	1987
Singapore	4608	High	Yes	Yes	Before 1986
Taiwan	22 921	Lower middle	Yes	Yes	Before 1986
Vietnam	86 117	Low	No	Yes	1995
Total	1 717 481				

[a]Data obtained from the US census office (http://www.census.gov), updated June 2008.
[b]The World Bank's definition (http://www.worldbank.org).

and Vietnam) were collected according to each disease indication, donor type and stem cell source, using a simple survey sheet. The data were submitted to the APBMT data center through the national/regional registries in Japan, Korea, Malaysia and Taiwan. In Japan, the data were collected by paper forms or using a new electronic registration system, *TRUMP* (Transplant Registry Unified Management Program), as previously reported.[3,22] In Hong Kong, Iran, Singapore and Vietnam, the APBMT data center contacted the major transplant centers in each country/region. It was estimated by each APBMT regional coordinator that 80–100% of all transplants performed between 1986 and 2006 were captured in each country/region except for mainland China. In mainland China, where there are more than 50 transplant centers,[5] data from only 12 centers could be collected. The information on population and the World Bank's income category based on the Gross National Income per capita were collected from the following websites (http://www.census.gov and http://www.worldbank.org, respectively). According to the criteria set by the World Bank, each country's economic status was classified as low income, middle income (subdivided into lower middle and upper middle) or high income (Table 1). The list of the participating centers is shown in the Appendix according to the countries/regions.

Results

Number of transplants

Transplant data of 58 113 HSCTs from 432 teams in nine countries/regions were submitted to the APBMT Data Center. The number of participating transplant teams, the reported numbers of HSCTs between 1986 and 2006 and the reported numbers of performed HSCTs in 2006 are shown in Table 2. The information on population, the World Bank's income category and the availability of donor programs and cord blood (CB) banks in each country/region are also shown in Table 1. The largest number of transplants was performed in Japan with a total of 38 523 transplants, followed by Korea with 9570.

Allogeneic vs autologous HSCTs

The total reported number of HSCTs in the study period is increasing in all countries/regions, except for Vietnam. As shown in Table 2, the number of HSCTs performed per 10 million people was higher in the countries/regions with higher incomes (Japan, Korea, Singapore and Hong Kong) than in those with middle/low incomes. The number of HSCTs performed in the nine countries/regions in 2006 was 6418, which has doubled in the past 10 years ($n=2734$ in 1996). The number of allogeneic HSCT has been consistently increasing in this study period, but the increase in autologous HSCT has slowed down since 1998 (Figure 1a). Of 6418 HSCTs performed in 2006, 3992 (62%) were allogeneic and 2416 (38%) were autologous. In most countries/regions, the number of allogeneic HSCT was larger than autologous HSCT (Figure 1b).

Related vs unrelated donors

As shown in Figure 1a, the total number of HSCTs from unrelated donors in the nine countries/regions has been increasing in the study period and exceeded the number of HSCTs from related donors in 2006. The number of related HSCTs has stabilized since 2002. However, the proportion of related and unrelated HSCTs differed among countries/regions. Recently, the number of unrelated HSCTs was higher than or equal to that of related HSCTs in Japan, Korea and Singapore (Figure 1b). In other countries/regions the proportion of related HSCTs was higher. In Iran and Vietnam, only a few unrelated HSCTs were performed.

Trends of HSCTs in each country/region

The trends of autologous and allogeneic HSCTs in each country/region are shown in Figure 2. Autologous transplant was increasing in all Asian countries (Figure 2a). An increase in the number of related HSCTs has been observed in China and Iran since 2000, although it was only recently stabilized in other countries (Figure 2b). Unrelated HSCTs were increasing in most of the countries except for Iran and Vietnam in the study period (Figure 2c).

Table 2 Numbers of institutes and transplants in each country/region

Country/region	*Institutes*		*No. of reported HSCTs*				
	No.	*Per 100 million population*	*2006*	*Per 10 million population*	*Ratio of 2006/1996*	*Total from 1986 to 2006*	*Median no. of HSCTs/year*
China	12	1[a]	352	3[a]	9.8	2220	39.5
Hong Kong	3	43	142	202	1.7	1684	100
Iran	2	3	325	49	10.2	1699	45.5
Japan	355	279	3834	301	1.9	38 523	1992
Korea	37	76	1338	277	3.4	9570	388
Malaysia	9	36	124	49	4.4	1174	31.5
Singapore	3	65	73	158	1.6	839	42
Taiwan	9	39	225	98	1.8	2351	114
Vietnam	2	2	5	1	—	53	4
Total	432	25 (108)[b]	6418	37 (157)[b]	2.3	58 113	

Abbreviations: HSCT = hematopoietic SCT; NE = not evaluable.
[a]Among more than 50 institutes in China, data from 12 institutes were included in this study.
[b]Numbers in parentheses are those excluding China.

Stem cell source

The stem cell source of autologous HSCT has changed from BM to PBSC, and 95% of autologous HSCTs were PBSC transplantations (PBSCTs) in 2006. For related HSCT, a shift of stem cell source from BM to PBSC was also observed, and the number of PBSCTs has exceeded that of BMTs since 2001 (Figure 3a). In 2006, the number of PBSCTs was higher than that of BMTs in most countries/regions, except for China, Hong Kong and Japan (Figure 3b). In China, transplants of both BM and PBSC from a haplo-identical familial donor, which was designated as other stem cell source in this survey, were recently performed in large numbers.[23] In Hong Kong and Japan, the numbers of BMTs and PBSCTs were almost equal in 2006.

For unrelated HSCTs, all types of stem cell sources (BM, PBSC and CB) have been continuously increasing in the study period (Figure 3a). In 2006, the annual number of unrelated BMTs, unrelated PBSCTs and cord blood transplantations (CBTs) were 1087, 229 and 701, respectively. However, as shown in Figure 3b, the proportion of each stem cell source varied among countries/regions. In China and Taiwan, a large proportion of the unrelated HSCTs performed were PBSCTs. In contrast, almost no unrelated PBSCTs were performed in Japan. In Iran and Vietnam, where only a few unrelated HSCTs have been performed, all unrelated HSCTs were CBTs. The recent increase in CBT was most prominent in Japan, where 593 CBTs were performed in 2006.

Disease indication

The diseases requiring HSCTs in each country/region between 1986 and 2006 are depicted in Figure 4. The most common indication for HSCT was hematological malignancy in all countries/regions (72–94% of all HSCTs). The proportions of solid tumors ranged between 0% in Vietnam to 11% in Japan. Among non-malignant diseases, hemoglobinopathy was one of the most common diseases in Asian countries/regions, except for China, Korea and Japan, where no or very few transplants for this disorder were reported.

The number of HSCTs for most types of hematological malignancies, including acute myeloid leukemia, acute lymphoblastic leukemia and malignant lymphoma, has been increasing in most Asian countries/regions in the study period. However, CML showed a different trend (Figure 5). The number of transplants for CML has decreased since 2000, excluding China and Iran. The proportion of CML out of the total HSCTs was almost stable in Iran and Malaysia from 10 to 20%. The ratio was decreasing in Hong Kong, Japan, Korea, Singapore and Taiwan. HSCTs for solid tumors also showed a unique trend. In Japan, the number had been increasing until 1998 ($n = 169$ in 1998) and then it decreased ($n = 41$ in 2006).[24] In Korea, it also decreased after 1999. In other countries/regions, the number of HSCTs for solid tumors was low and stable.

Discussion

This survey showed that the number of HSCTs performed has been increasing in most Asian countries/regions over the past two decades, although several differences exist in donor selection, transplant procedures and disease indications among countries/regions. HSCT is expensive for all countries. The significant effect of the economic strength of individual countries on HSCT activity was reported by Gratwohl *et al.*[25] Our results are consistent with their findings. The most significant increases in the past 10 years were observed in Iran and China, which have middle incomes. Even in countries/regions of the high-income group (Hong Kong, Japan, Korea and Singapore) the number of HSCTs performed has been consistently increasing in the study period and is not likely to reach a plateau any time soon. This suggests that the demand for HSCTs has not been fulfilled in any of these countries. The improving likelihood of finding an HLA matched donor because of expanding donor pools; the development of reduced-intensity conditioning regimens, which has broadened the indication of HSCT to older patients; and the increased list of disease

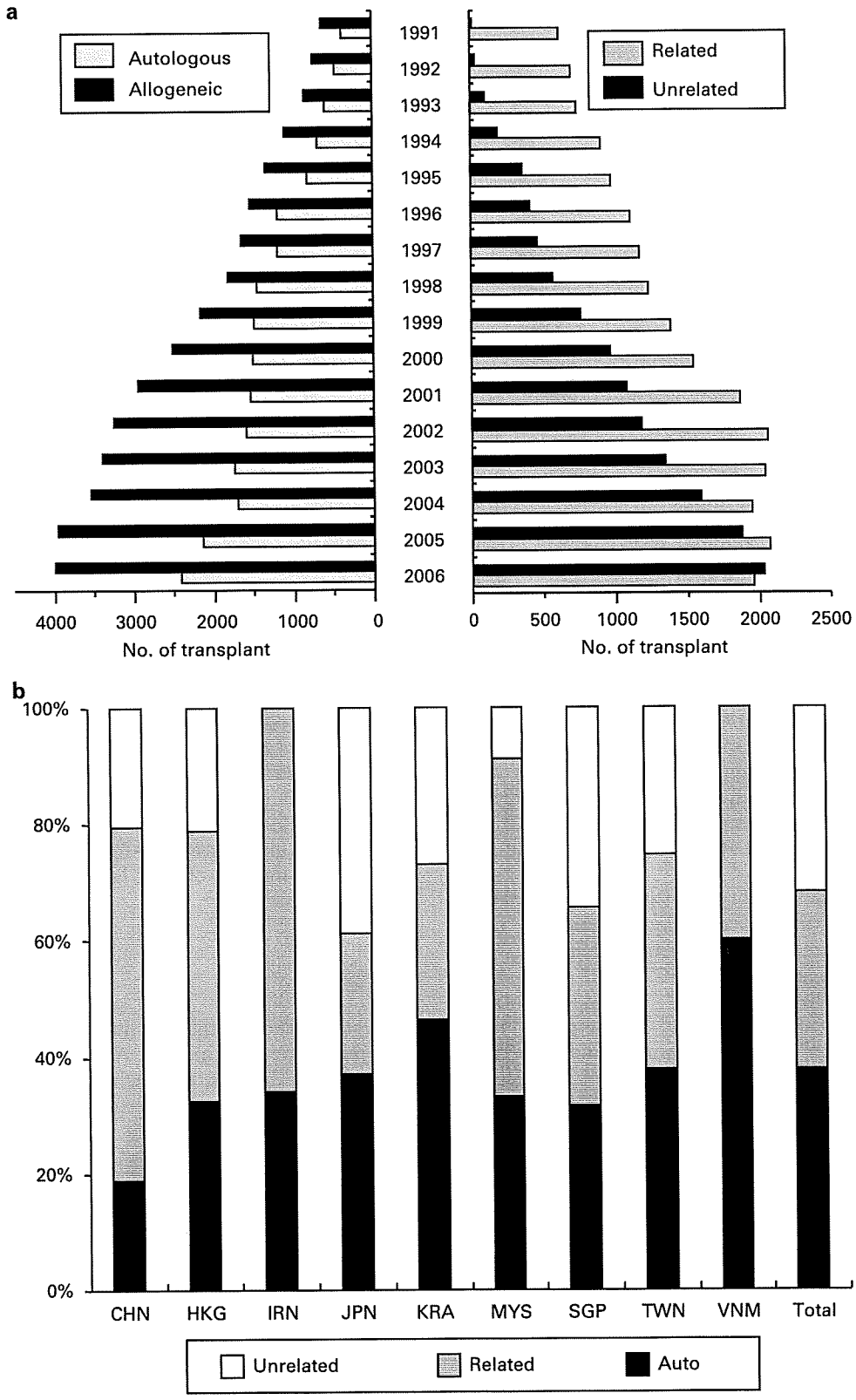

Figure 1 Activity of hematopoietic SCT (HSCT) in nine Asian countries/regions. (**a**) Trends of the total numbers of autologous HSCTs and allogeneic HSCTs from related and unrelated donors in nine countries/regions are shown. (**b**) The proportions of autologous and allogeneic HSCTs from related and unrelated donors in 2006 in each country/region are shown. CHN, mainland China; HKG, Hong Kong; IRN, Iran; JPN, Japan; KRA, Korea; SGP, Singapore; TWN, Taiwan; VNM, Vietnam.

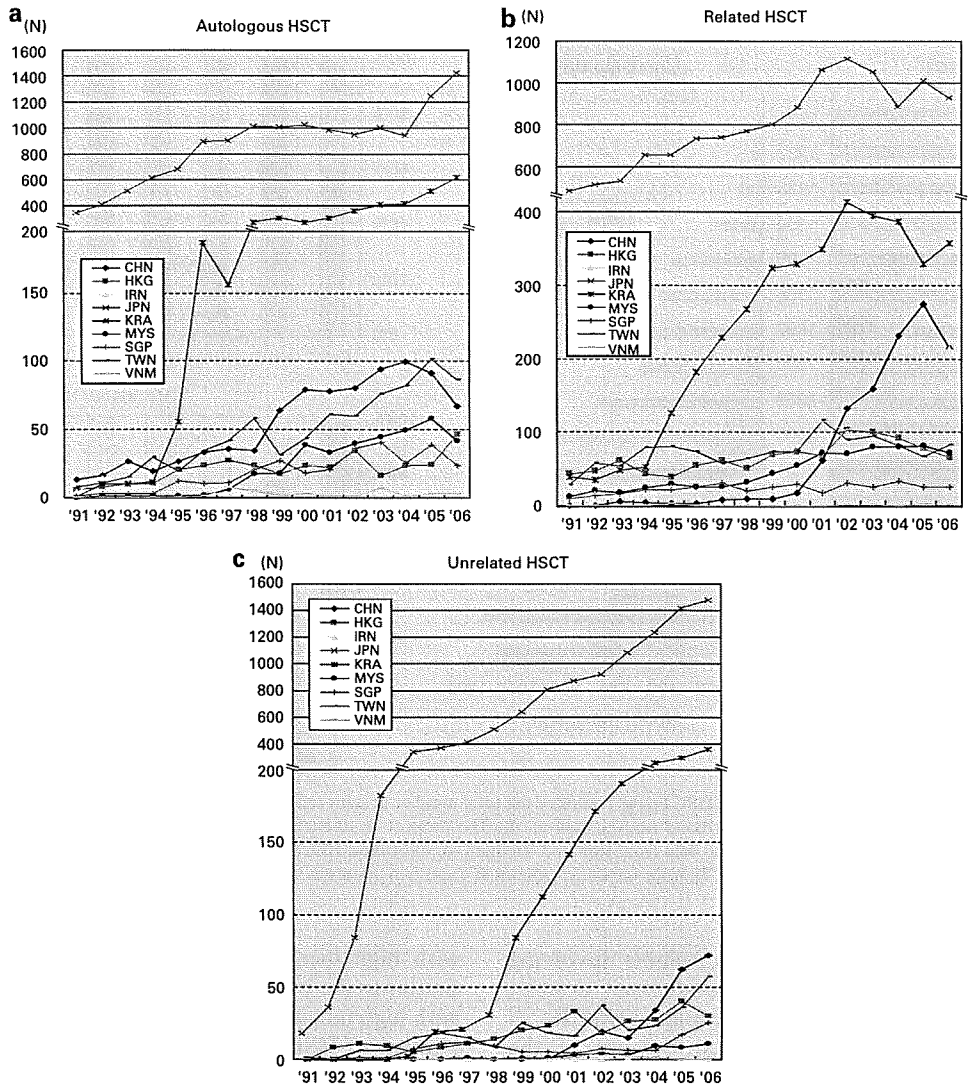

Figure 2 Trends of hematopoietic SCT (HSCT). Numbers of autologous (**a**) and allogeneic HSCTs from related (**b**) and unrelated donors (**c**) in each year are plotted. See legend to Figure 1 for abbreviations.

indications for HSCT may lead to further increases in the numbers of HSCTs performed.

The high proportion of allogeneic HSCTs compared with autologous HSCTs in most Asian countries/regions (62% in 2006) was in contrast to a report from Europe (39% in 2006).[26] However, our results need careful interpretation because of possible reporting bias. The capture rate of autologous HSCTs might be lower than that of allogeneic HSCTs, because some smaller centers, which perform only autologous HSCTs, could not be sufficiently included in this survey.

A notable finding in this study was that there were marked differences in donor and stem cell selections among Asian countries/regions. First of all, the proportion of unrelated HSCTs among allogeneic HSCTs was quite different (62% to <1%). In most of the countries/regions, except for Iran and Vietnam, the number of unrelated HSCTs has been increasing in the study period. This might partially depend on the size of donor pools and the activity of each donor program. A dramatic increase in the number of unrelated HSCTs performed in China was observed after the China Marrow Donor Program started servicing the public in 2001, resulting in the rapid expansion of the donor pool, which is currently the largest among the nine Asian countries/regions (more than 0.7 million donors).[5] Unrelated HSCT activity is associated with economic strength.[27] Because of the cost of searching for donors, coordination and shipment of the product, unrelated HSCT is more expensive than related HSCT. In this report, the number of unrelated HSCTs was higher in countries with higher incomes, which is consistent with a report from Europe.[27] The high use of unrelated HSCTs in Japan was, in part, dependent on the limited HLA diversity of Japanese population because of the historical isolation of island country, and low incidence of GVHD.[28]

Another interesting finding in this study is the difference of stem cell source for both unrelated and related HSCTs. For related HSCTs in 2006, the proportion of PBSCTs was higher than that of BMTs in many countries/regions, which was consistent with reports from Europe.[4,26] However,

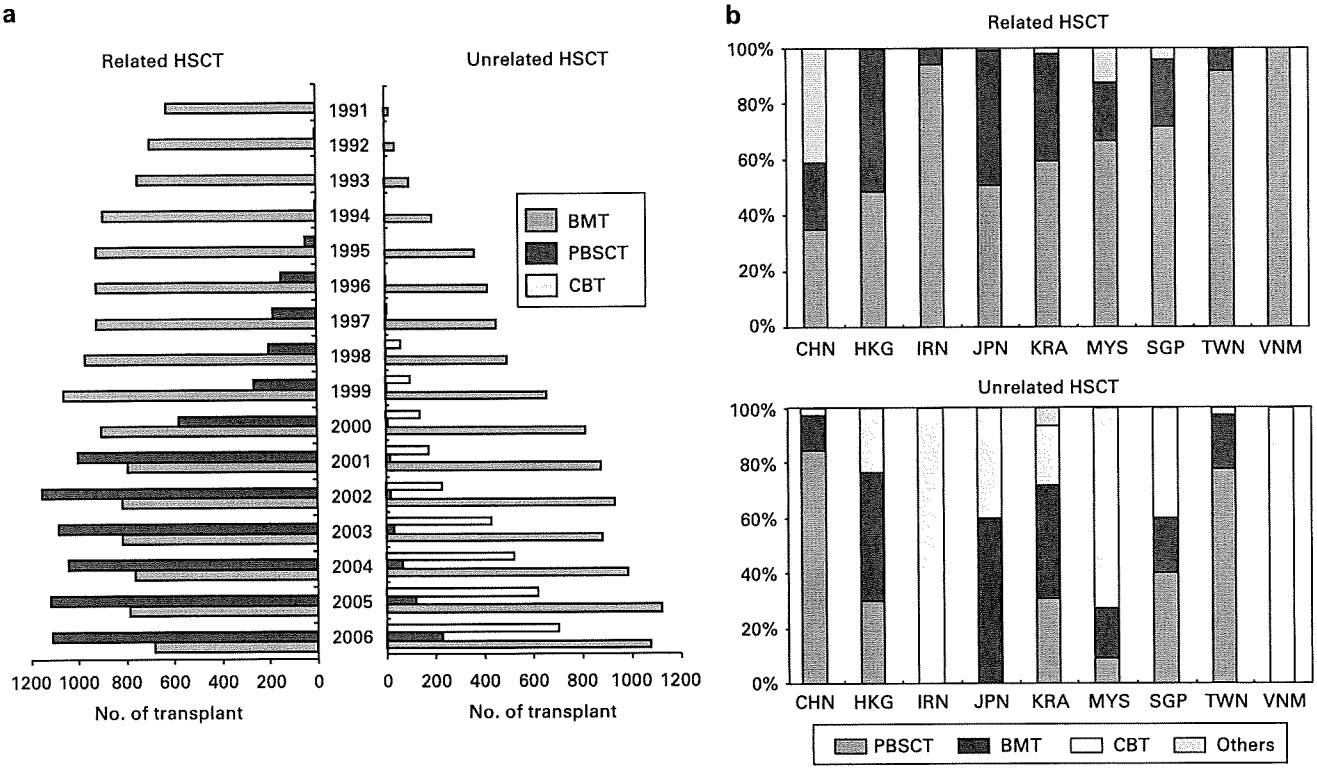

Figure 3 Stem cell sources of hematopoietic SCT (HSCT). **(a)** Trends of the total number of stem cell sources for allogeneic HSCTs from related and unrelated donors in nine Asian countries/regions. CBT, cord blood transplantation. **(b)** The proportion of each stem cell source for allogeneic HSCT from related and unrelated donors in 2006 in each country/region. The data from Iran and Vietnam for allogeneic HSCTs from unrelated donors indicate all transplants between 1986 and 2006 because of the low numbers of HSCTs from unrelated donors in these two countries. See legend to Figure 1 for abbreviations.

China showed the unique use of transplants involving combined BM and PBSC from haplo-identical donors, which made up a large proportion of the related HSCTs.[5,23] This procedure was intensively studied because of the decreasing family size in China.[5] The stem cell source of unrelated HSCTs largely depended on the policy of the donor program of each country. The Japan Marrow Donor Program provided only BM, but the China Marrow Donor Program provided only PBSCs. It is noteworthy that CBT made up 35% of unrelated HSCTs in 2006, which was larger than that reported by the European Group for Blood and Marrow Transplantation (EBMT).[27] CB banks have been established, and unrelated CBT has been performed in all countries/regions. CB seems to be an important stem cell source in Asian countries/regions.

There was a marked difference in disease indications for HSCTs among APBMT countries/regions. Disease prevalence might be one of the factors that influence the activity of HSCT. Thalassemia is common in South and Southeast Asia, but rare in Northeast Asia. A high proportion of HSCTs for this disorder was noted in the former region. The numbers of HSCTs performed for most diseases are increasing in the study period, but those for CML and solid tumors were exceptions. Gratwohl *et al.*[29] also reported marked differences in the trends of HSCTs for CML among European countries, reflecting the economic strength of each country. The dramatic decrease of HSCTs for CML since 1999 after the introduction of imatinib, which was observed in Asian countries/regions with high incomes and some with middle incomes, was similar to the phenomenon observed in European countries with high incomes.[29] Interestingly, a marked increase in the number of HSCTs for CML has been observed even after 2004 in mainland China and Iran. Imatinib is an expensive agent, which needs to be given to patients for a long period. The consideration of cost effectiveness between these two highly expensive treatments, imatinib and HSCT, by health-care providers in each country may have a great effect on the trends among countries/regions.[30] The number of HSCTs for solid tumors has remained low in most Asian countries/regions. In Japan, there was an increase in the number of autologous HSCTs performed for solid tumors, especially for breast cancer, in the 1990s because of expectations of its positive effectiveness on the outcome of patients. However, the disappointing results of several randomized clinical trials called into question its benefits and resulted in decreases in the number of HSCTs performed for breast cancer as well as other solid tumors.[31–34] This trend is similar to that observed in European countries.[35]

Although this simple survey was able to provide reasonably comprehensive information about the current state of HSCT in Asia, further efforts should be made to establish a registry system to obtain information from all centers and Asian countries/regions that are missing from this study. It is also important to be aware that there are some countries where very few HSCTs are currently performed because of several factors, such as financial restrictions, lack of a

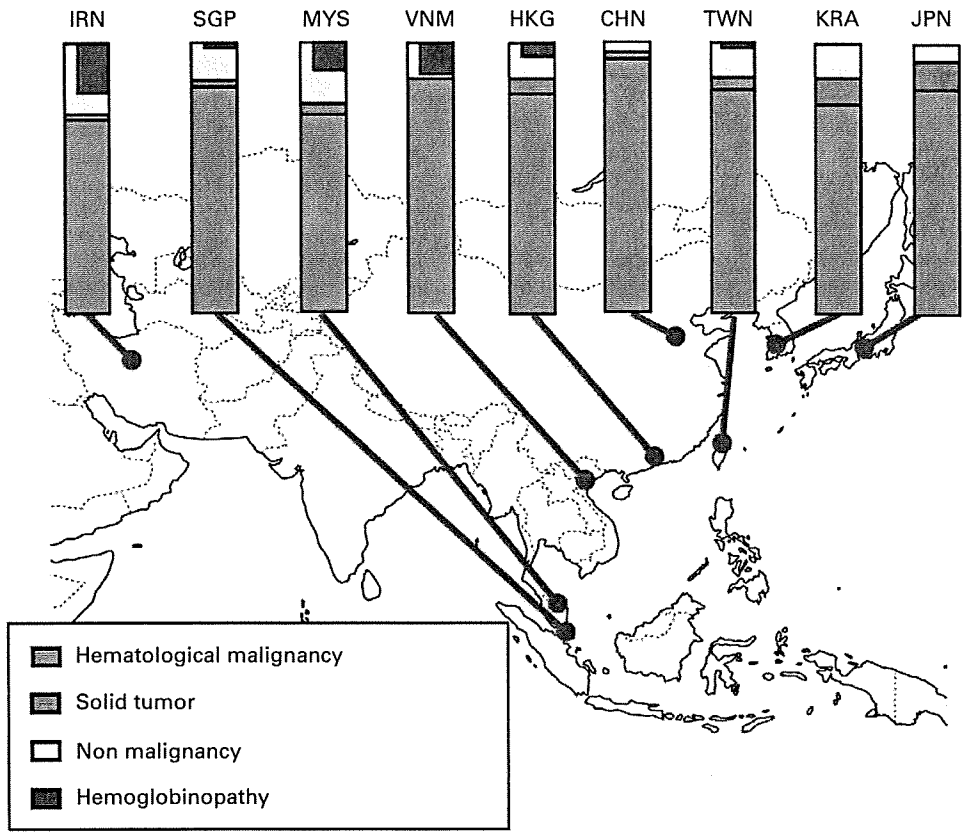

Figure 4 Disease indications of hematopoietic SCT (HSCT). Proportions of each category of disease indication in each country/region are shown.

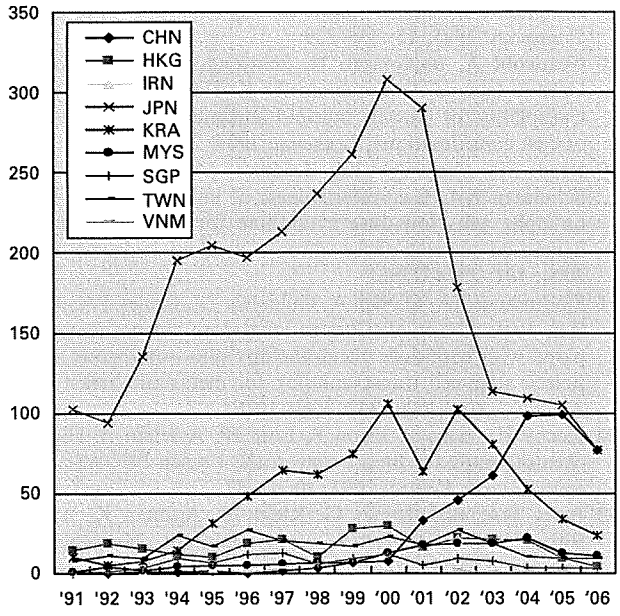

Figure 5 Trends of HSCTs for chronic myelogenous leukemia (CML) in each country/region. The number of transplants for CML has decreased since 2000, excluding China and Iran. See legend to Figure 1 for abbreviations.

national health insurance system and governmental support and an inability to develop local transplant centers.[7,11]

A similar survey has been annually reported by the EBMT since 1990 to illustrate the trends of HSCT in European countries in an elegant way.[4,25–27,29,35–37] Although this study elucidated several differences, such as the proportion of allogeneic and autologous HSCTs between Europe and Asia, there were many similarities in the trends of HSCTs in both regions. This suggests that similar clinical decisions have been made globally in the practice of HSCT, probably because of the rapid spread of information about the technology and the outcome of HSCT. A global transplant activity survey has been recently planned by the EBMT, the Centre for International Blood and Marrow Transplant Research and the APBMT, among others, under the umbrella of the Worldwide Network of BMT (http://wbmt.org), which may clarify the global trends of HSCT and provide fundamental information to facilitate international cooperative studies for further improvement of this treatment procedure.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Appendix

Regional coordinators and the contributing centers are listed according to their countries/regions.

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Hong Kong
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Iran
Coordinator: Ardeshir Ghavamzadeh
Centers: Teheran University of Medical Science: Transplant Research Center, Shiraz University of Medical Sciences.

Japan (National Registry)
Coordinators: Ayami Yoshimi, Yoshiko Atsuta, Ritsuro Suzuki, and Yoshihisa Kodera, supported by the Japan Society for Hematopoietic Cell Transplantation, the Japan Society of Pediatric Hematology, Japan Marrow Donor Program, and Japan Cord Blood Bank Network
Centers: National Hospital Organization Nishigunma National Hospital, Aichi Cancer Center Hospital, Aichi Medical University Hospital, Aiseikai Yamashina Hospital, Akashi Municipal Hospital, Akita University School of Medicine, Anjo Kosei Hospital, Aomori Prefectural Central Hospital, Asahikawa City Hospital 1, Asahikawa Medical College Hospital, Asahikawa Red Cross Hospital, Chiba Aoba Municipal Hospital, Chiba Children's Hospital, Chiba University Hospital, Children's Medical Center, Osaka City General Hospital, Chugoku Rosai General Hospital, Dokkyo Medical University School of Medicine, Ehime Prefectural Central Hospital, Ehime University Graduate School of Medicine, Faculty of Medicine Hospital Tokyo Medical and Dental University, Faculty of Medicine, Saga University, Faculty of Medicine, Kagawa University, Fuchu Hospital, Fujita Health University School of Medicine, Fukaya Red Cross Hospital, Fukuoka University School of Medicine, Fukushima Medical University School of Medicine, Gifu Municipal Hospital, Gifu University Graduate School of Medicine, Gunma Children's Medical Center, Gunma University Graduate School of Medicine, Hakodate Municipal Hospital, Hamamatsu Medical Center, Hamamatsu University School of Medicine, Hamanomachi Hospital, Higashi Sapporo Hospital, Hirosaki University Hospital, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima University Hospital, Hirosima-Nishi Medical Center, Hitachi General Hospital, Hokkaido Medical Center for Child Health and Rehabilitation, Hokkaido University Hospital, Hyogo Cancer Center, Hyogo Children's Hospital, Hyogo College of Medicine, Ibaraki Children's Hospital, Iizuka Hospital, Imamura Bun-in Hospital, International Medical Center of Japan, Ishikawa Prefectural Central Hospital, Iwaki Kyoritsu General Hospital, Iwate Medical University, Iwate Medical University School of Medicine, Iwate Prefectural Kitakami Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, Japanese Red Cross Nagoya First Hospital, Japanese Red Cross Narita Hospital, Japanese Red Cross Society Wakayama Medical Center, Japanese Red Cross Medical Center, Jichi Medical University Hospital, Jikei University school of Medicine, Jikei University Kashiwa Hospital, Juntendo University School of Medicine, Kagawa National Children's Hospital, Kagawa University, Kagoshima City Hospital, Kagoshima University Medical and Dental Hospital, Kameda General Hospital, Kanagawa Cancer Center, Kanagawa Children's Medical Center, Kanazawa Medical University, Kanazawa University Hospital, Kansai Medical University, Kansai Medical University Hirakata Hospital, Kawasaki Medical School, Keio University School of Medicine, Kin-ikyo Sapporo Hospital, Kinki University School of Medicine, Kishiwada City Hospital, Kita-Fukushima Medical Center, KKR Suifu Hospital, Kobe Central Hospital of Insurance, Kobe City Medical Center General Hospital, Kobe University Graduate School of Medicine, Kochi Health Sciences Center, Kochi Medical School, Kochi University, Kochi University, Kokura Memorial Hospital, Komaki City Hospital, Konan Kosei Hospital, Kouseiren Takaoka Hospital, Kumamoto University School of Medicine, Kurashiki Central Hospital, Kurobe City Hospital, Kurume University School of Medicine, Kyorin University School of Medicine, Kyoto City Hospital, Kyoto First Red Cross Hospital, Kyoto Katsura Hospital, Kyoto Prefectural University of Medicine, Kyoto University Hospital, Kyushu Kosei-Nenkin Hospital, Kyushu University Hospital, Kyushu University Hospital at Beppu, Maebashi Red Cross Hospital, Matsudo City Hospital, Matsushita Memorial Hospital, Matsuyama Red Cross Hospital, Matsuzaka General Hospital, Meitetsu Hospital, Mie University Hospital, Mitoyo General Hospital, Miyagi Cancer Center, Miyagi Children's Hospital, Miyazaki prefectural Miyazaki Hospital, Nagano Children's Hospital, Nagano Red Cross Hospital, Nagaoka Red Cross Hospital, Nagasaki University Graduate School of Biomedical Sciences, Nagoya City University Hospital, Nagoya Daini Red Cross Hospital, Nagoya University Graduate School of Medicine, Nagoya Memorial Hospital, Nakadoori General Hospital, Nara Medical University, National Cancer Center Hospital, National Cancer Center Hospital East, National Center for Child Health and Development, National Defense Medical College Hospital, National Hospital Organization Kyusyu Medical Center, National Hospital Organization Okayama Medical Center, National Hospital Organization Hokkaido Cancer Center, National Hospital Organization Kure Medical Center, National Hospital Organization Mito Medical Center, National Hospital Organization Okayama Medical Center, National Hospital Organization Osaka Minami Medical Center, National Hospital Organization Osaka National Hospital, National Hospital Organization Tokyo Medical Center, National Hospital Organization, Kagoshima Medical Center, National Hospital Organization Nagoya Medical Center, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kumamoto Medical Center, National Hospital Organization Minami-Okayama Medical Center, National Hospital Organization Nagasaki Medical Center, National Kyushu Cancer Center, Nihon University Itabashi Hospital, Niigata Cancer Center, Niigata University Medical and Dental Hospital, Nippon Medical School, NTT Kanto Medical Center, NTT West Osaka Hospital, Oita Prefectural Hospital, Oita University Faculty of Medicine, Oita University Hospital, Oita Kouseiren Tsurumi Hospital, Okayama Rosai Hospital, Okayama University Hospital, Okazaki City Hospital, Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Osaka City General Hospital, Osaka City

University Graduate School of Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka Medical Center For Cancer and Cardiovascular Diseases, Osaka Medical College Hospital, Osaka Red Cross Hospital, Osaka University Hospital, Our Lady of Snow Medical Juridical Corporation St Mary's Hospital, The Institute of Medical Science: The University of Tokyo, Rinku General Medical Center Izumisano Municipal Hospital, Ryukyu University Hospital, Saga Prefectural Hospital Koseikan, Saga University, Saiseikai Maebashi Hospital, Saitama Children's Medical Center, Saitama Medical Center: Saitama Medical University, Saitama Medical Center: Jichi Medical University, Saitama Medical University Hospital, Saitama Medical University Hospital, Saitama Medical University International Medical Center, Sakai Hospital Kinki University School of Medicine, Saku Central Hospital, Sapporo City General Hospital, Sapporo Hokuyu Hospital, Sapporo Medical University Hospital, Sasebo City General Hospital, Seirei Hamamatsu General Hospital, Shiga Medical Center for Children, Shiga University of Medical Science, Shimane Prefectural Central Hospital, Shimane University Faculty of Medicine, Shimonoseki Kosei General Hospital, Shinshu University School of Medicine, Shizuoka Children's Hospital, Shizuoka City Hospital, Shizuoka General Hospital, Shizuoka Red Cross Hospital, Shizuoka Saiseikai General Hospital, Showa University Fujigaoka Hospital, Showa University School of Medicine, Social Insurance Chukyo Hospital, Social Insurance Kyoto Hospital, St Marianna University School of Medicine Yokohama City Seibu Hospital, St Luke's International Hospital, St Mariannna University School of Medicine, Sumitomo Hospital, Suzuka General Hospital, Suzuka Kaisei Hospital, Takamatsu Red Cross Hospital, Takanohara Central Hospital, Teikyo University School of Medicine, Teikyo University School of Medicine Mizonokuchi Hospital, Teine Keijinkai Hospital, Tenri Hospital, The Institute of Medical Science: The University of Tokyo, The Tazuke Kofukai Medical Research Institute Kitano Hospital, Tochigi Cancer Center, Toho University Omori Medical Center, Tohoku University Hospital, Tokai University School of Medicine, Tokushima Red Cross Hospital, Tokushima University Hospital, Tokuyama Central Hospital, Tokyo Medical University Hospital, Tokyo Metropolitan Bokutoh Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center-Komagome Hospital, Tokyo Metropolitan Fuchu Hospital, Tokyo Metropolitan Geriatric Hospital, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo Women's Medical University Hospital, Toranomon Hospital, Tottori Prefectural Central Hospital, Tottori University Faculty of Medicine, Toyama Prefectural Central Hospital, Toyohashi Municipal Hospital, Toyota Memorial Hospital, Tsuchiura Kyodo General Hospital, Tsukuba Memorial Hospital, Tsukuba University Hospital, University of Fukui Hospital, University of Miyazaki Hospital, University of Occupational and Environmental Health Japan, University of the Ryukyus Hospital, University of Tokyo Hospital, University of Toyama, University of Tsukuba, University of Yamanashi Faculty of Medicine, Wakayama Medical University, Yamagata University School of Medicine, Yamanashi Prefectural Central Hospital, Yokohama City University Hospital.

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Taiwan (National Registry)
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CASE REPORT

Mikulicz's disease with severe thrombocytopenia following autologous stem cell transplantation in a multiple myeloma patient

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Abstract We report the first case of Mikulicz's disease (MD) occurring 2 years after autologous peripheral blood stem cell transplantation (PBSCT) for multiple myeloma (MM). A 70-year-old man developed bilateral enlargement of parotid and submandibular glands. The patient had previously received 2 courses of autologous PBSCT for IgG-κ type MM, and had been stable for 2 years. This salivary gland enlargement was initially felt to represent a recurrence of MM, since along with gland swelling, IgG was also elevated. However, repeated biopsy of the left submandibular gland revealed chronic sclerosing sialadenitis rather than plasmacytoma. Results of salivary gland scintigraphy, serological testing, and absence of sicca symptoms also supported the diagnosis of MD. Concurrently, the patient developed severe thrombocytopenia ($0.8 \times 10^4/\mu l$). Bone marrow biopsy showed abundant megakaryocytes, suggesting enhanced platelet destruction. After high-dose steroid and immunoglobulin therapy, the platelet count gradually returned to normal with complete resolution of the salivary gland enlargement. No apparent signs of MM recurrence were documented during these clinical events.

Keywords Mikulicz's disease · Thrombocytopenia · Autologous stem cell transplantation · Multiple myeloma

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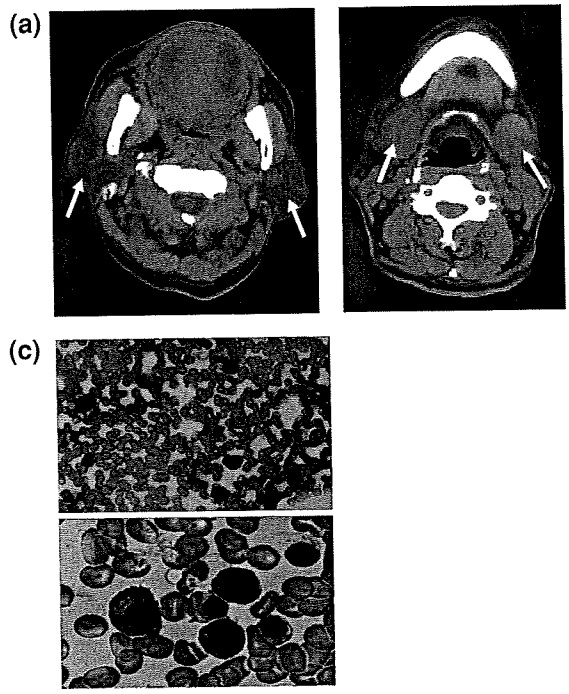
1 Introduction

Although secondary autoimmune disorders can occur following autologous stem cell transplantation, most reported cases are related to immune-mediated cytopenia [1, 2]. Temporarily impaired regulatory T-cell function is considered the underlying mechanism for development of this disease condition.

Mikulicz's disease (MD) is a relatively rare autoimmune disorder characterized by symmetrical swelling of lacrimal and parotid glands. While it has recently been re-categorized as systemic IgG4-related plasmacytic syndrome [3], no case of MD following autologous PBSCT has yet been reported. We report the first case of MD associated with immune-mediated thrombocytopenia occurring 2 years after autologous PBSCT for MM.

2 Case presentation

A 70-year-old man with MM was admitted to our hospital in July 2007 for evaluation of bilateral enlargement of his parotid and submandibular glands. In January 2003, the patient was admitted to other hospital and received a diagnosis of MM (IgG-κ type, stage IA). The patient was initially followed without any specific treatment, but IgG was rapidly elevated. Therefore, the patient received



(b)

WBC	2800 /μl
RBC	390 X10⁴/μl
Hb	12.5 g/dl
Plt	18.0 X10⁴/μl
TP	8.0 g/dl
Alb	3.4 g/dl
Ca	8.4 mg/dl
BUN	21 mg/dl
Cr	0.9 mg/dl
LDH	173 IU/l
β2-MG	2.8 μg/ml
IgG	3181 mg/dl
IgG4	594 mg/dl (4.8-105)
IgA	131 mg/dl
IgM	64 mg/dl
C3	47 mg/dl (65-135)
C4	1.5 mg/dl (13.0-35.0)
CH50	<10.0 (30.0-47.0)
Anti-nucleotic antibody	X1280 (homogenous)
Anti-dsDNA antibody	5.3 IU/ml (0.0-6.0)
Anti-SS-A antibody	negative
Anti-SS-B antibody	negative
Cortisol	13.0 μg/dl (3.8-18.4)

Fig. 1 CT scan, bone marrow aspiration, and laboratory results at the onset of MD. **a** CT scan of neck reveals swollen bilateral parotid and submandibular glands, as indicated by *arrows*. **b** Laboratory findings at the onset of MD. **c** Upper bone marrow photomicrograph at the onset of MD shows a paucity of myeloma cells. Lower photomicrograph is at higher magnification

chemotherapy, such as MP (melphalan 6 mg/day × 4 days and prednisolone 40 mg/day × 4 days) at monthly intervals. However, serum IgG was elevated up to 4955 mg/dl. Because of the worsening condition, the patient moved into our institution for receiving further treatments in July 2003. The patient received 3 courses of VAD (vincristine 0.4 mg/body/day × 4 days, adriamycin 9 mg/m^2/day × 4 days, and dexamethasone 40 mg/body/day × 4 days). Harvest of peripheral blood progenitor cells (PBPCs) was performed following high-dose etoposide (500 mg/m^2/day × 3 days) and 10 μg/kg/day of filgrastim mobilization. Subsequently the patient received high-dose melphalan (200 mg/m^2/day × 1 day) followed by the first auto PBSCT in November 2003, resulting in only partial remission, and serum IgG level again gradually elevated after the treatment. The second transplant was performed in April 2004. The patient eventually achieved very good partial remission, and then followed without any symptoms for 2 years. However, in August 2006, the patient complained of a painless swelling of his bilateral parotid and submandibular glands, and also had an elevated serum IgG on subsequent laboratory testing. The biopsy of the enlarged gland revealed nonspecific sialadenitis. The patient, therefore, was observed without any specific treatment, but the masses continued to enlarge (Fig. 1a) accompanied by further elevation of serum IgG up to 3181 mg/dl (Fig. 1b). The patient was admitted for further evaluation in July 2007. However, detailed investigation including bone marrow aspiration (Fig. 1c), immunoelectrophoresis of serum protein (Fig. 2), urine test for Bence-Jones protein, and beta 2-microglobulin in serum and urine could not confirm MM recurrence. Serum complement level was decreased (50% hemolytic complement activity; <10 U/ml) and anti-nucleotic antibody (more than 1280×) was positive, both findings strongly suggested involvement of autoimmune disorder.

The patient, therefore, underwent a repeat biopsy of the left submandibular gland, which eventually revealed pathological features compatible with chronic sclerosing sialadenitis with marked involvement of IgG4-positive plasma cells, rather than myeloma cells (Fig. 3). The concentration of serum IgG4 was elevated by 594 mg/dl (normal range: 4.8–105 mg/dl). Salivary gland scintigraphy showed decreased accumulation of radiotracer in the left submandibular gland and weakened reactivity against acid stimulation in all salivary glands. These clinical findings coupled with negative data for SS-A or SS-B antibodies and absence of sicca symptoms strongly suggested the diagnosis of MD rather than Sjögren's syndrome (SS). Since MD belongs to systemic IgG4-related plasmacytic syndrome (SIPS), systemic screening for other endocrine disorders was mandatory. Magnetic resonance cholangiopancreatography and abdominal CT scan disclosed no evidence of autoimmune pancreatitis or retroperitoneal fibrosis. The pituitary and adrenal functional tests were also within normal range (data not shown). We, therefore, concluded that MD was limited to the parotid and submandibular gland. However, 1 month later, the patient developed severe thrombocytopenia (0.8 × 10^4/μl) with active oral mucosal bleeding. The subsequent bone

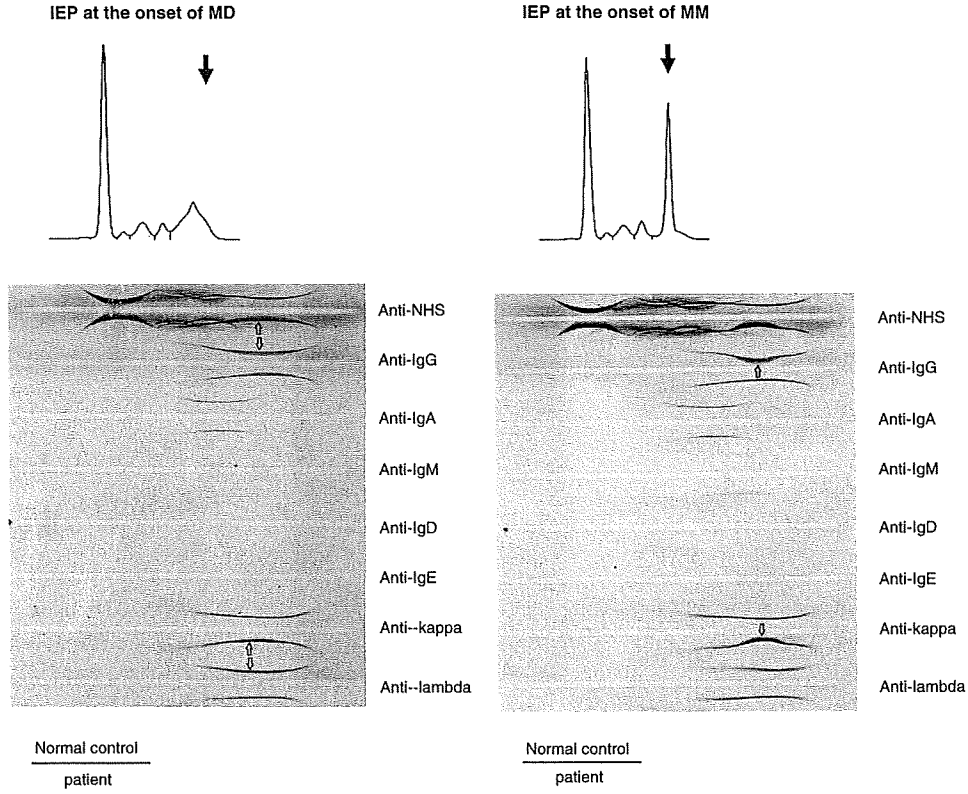


Fig. 2 A pattern of immunoelectrophoresis (IEP) obtained at the onset of MD (*left*) and at the onset of MM (*right*). At the onset of MM, it has steep M-spike (*red arrow*), with M-bow strongly positive for IgG and kappa-light chain, whereas it shows smaller M-spike at the onset of MD, with M-bow positive for IgG, kappa and lambda-light chain, suggesting polyclonal M-protein pattern

marrow biopsy showed abundant morphologically normal megakaryocytes, suggesting enhanced peripheral platelet destruction. Platelet-associated IgG obtained at that time and 1 month later was 49.8 and 268.5 ng/10^7 cells, respectively. Since the patient had no apparent recent history of drug administration, autoimmune-mediated platelet destruction was highly suspected and the patient received intravenous immunoglobulin therapy (5 g/day for 5 days), concurrently with high-dose corticosteroid (methylprednisolone 1 g/day for 3 days) [4]. High-dose corticosteroid was repeated every 2 weeks up to 4 courses, followed by a maintenance dose of 1 mg/kg/day, which was eventually tapered to 4 mg/week (Fig. 4). Throughout these treatments, the platelet counts gradually returned to normal with complete resolution of the salivary gland enlargement. Details of the entire clinical course and treatment are shown in Fig. 3.

3 Discussion

In 1888, Johann von Mikulicz-Radecki reported the first case of MD with bilateral, painless, symmetrical swelling of lacrimal, parotid, and submandibular glands [5]. In 1953, Morgan reported that the pathologic findings of MD and SS were similar [6]. After this report, MD was regarded as a subtype of SS for many years. However, recent studies have disclosed clinical features of MD distinguishing it from SS. These include absence of sicca symptoms, a specific pattern of acinar cell apoptosis, and prominent infiltration of IgG4-positive plasmacytic cells along with elevation of serum IgG4 level. These clinical findings are now used to make the distinction between MD and SS.

More recently, Yamamoto et al. have suggested that MD be regarded as a form of systemic IgG4-related plasmacytic syndrome (SIPS), featuring an autoimmune-mediated multiorgan dysfunction involving lacrimal glands, salivary glands, pancreas, retroperitoneum, prostate, thyroid, and kidney [3].

To our knowledge, this is the first reported case of MD accompanying immune thrombocytopenia. However, autoimmune pancreatitis (AIP), one of IgG4-related plasmacytic syndrome, is occasionally complicated with immune thrombocytopenia. Ohara et al. [7] reviewed 314 cases of autoimmune pancreatitis, with 5 cases complicated by immune thrombocytopenia. Murase et al. [8] reported a case of autoimmune pancreatitis with interstitial pneumonitis and immune thrombocytopenia. The patient also had sclerosing sialadenitis which resembles MD, although it is not histologically confirmed. In our case, it is likely that MD and elevated IgG4 played a certain role in immune thrombocytopenia, but this is just a speculation since we did not confirm binding of IgG4 to platelets.

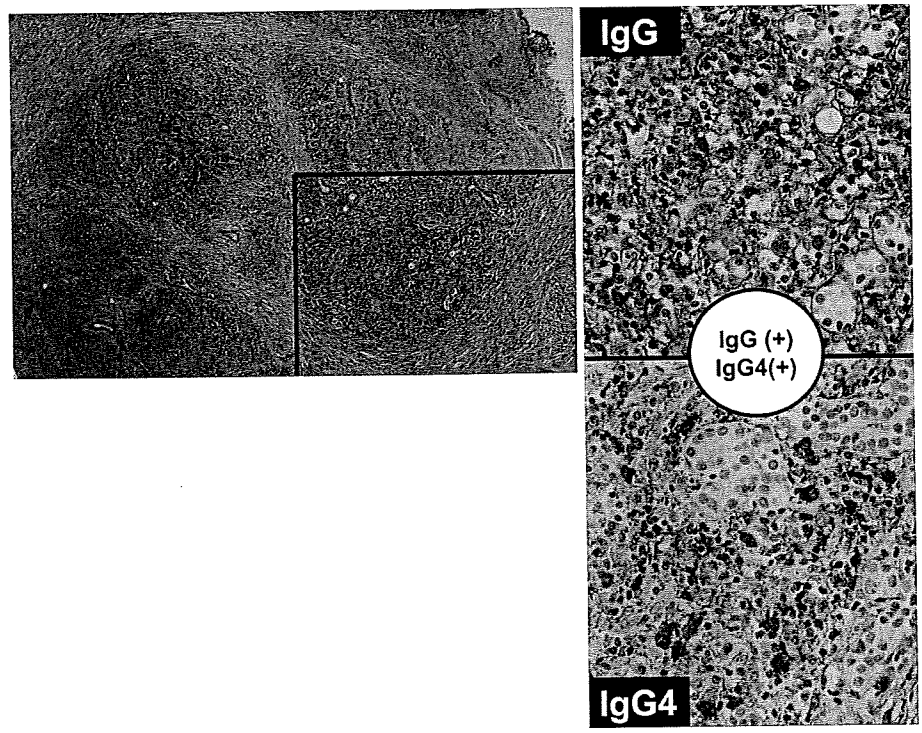


Fig. 3 Photomicrographs of biopsy specimens of the salivary gland. A biopsy specimen of the masses shows the pathological features of chronic sclerosing sialadenitis with marked involvement of IgG4-positive plasma cells

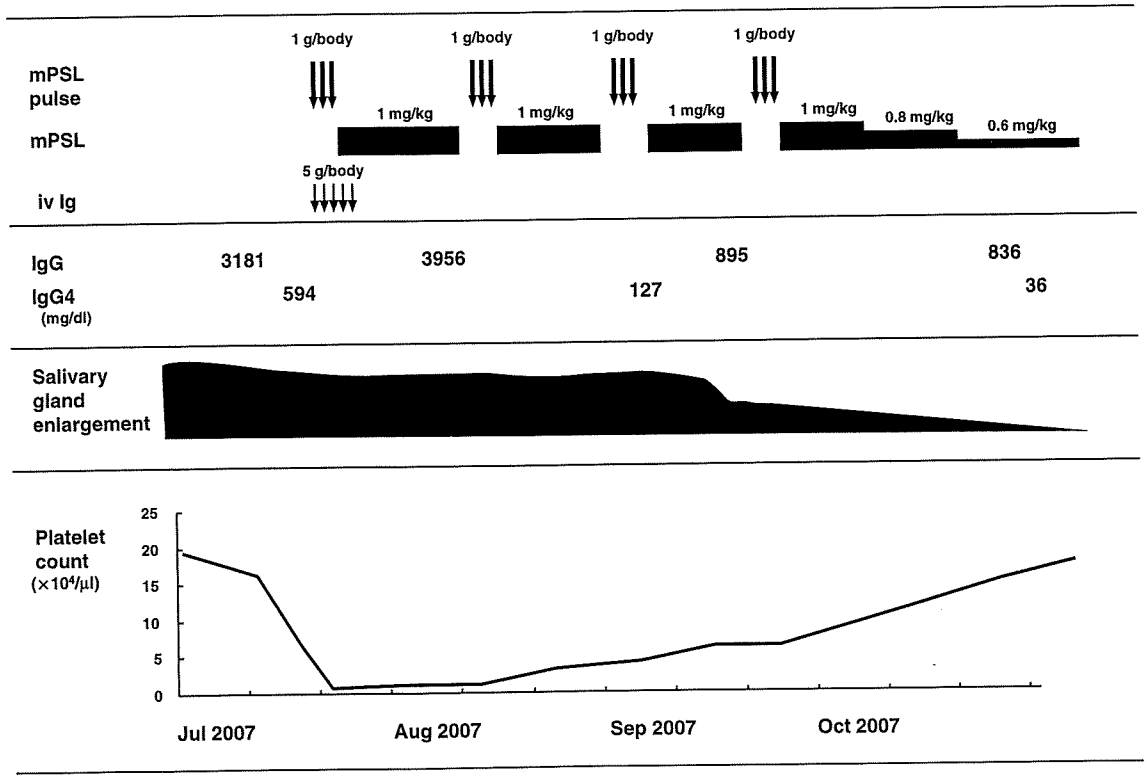


Fig. 4 Clinical course of the patient. *mPSL* methylprednisolone, *ivIG* intravenous administration of a bulk doses of immunoglobulin

Autoimmune disorders can be observed in up to 5% of autologous transplant recipients, and most cases are hematological disorders, such as hemolytic anemia, immune-mediated thrombocytopenia, or factor VIII inhibitors. Non-hematological autoimmune disorders, such as MD, are extremely rare [2].