present patient, however, there was no clear evidence showing an additive or synergistic effect of thalidomide with melphalan. Because melphalan had not been used prior to MDT therapy, we could not exclude the possibility that our patient showed a good response to MP without thalidomide. An Italian multicenter randomized trial that compared MPT and MP therapy for newly diagnosed MM reported that patients treated with MPT had significantly higher response rates and longer event-free survival times than those who were treated with MP alone [5]. Thus, the addition of low-dose thalidomide to standard oral MP therapy significantly increased its antimyeloma activity in previously untreated patients. Although the efficacy of MDT therapy in refractory disease has not been reported, the results in our case are comparable with the results of these studies and demonstrate the efficacy of MDT therapy for refractory MM.

Our case has shown that treatment approaches using low-dose thalidomide in combination with dexamethasone and cytotoxic agents may induce significant tumor regression. As in the setting of high-dose chemotherapy and autologous HSCT [2], the significant tumor reduction induced by MDT therapy may lead to prolonged disease remission and longer overall survival. We used dexamethasone instead of prednisolone because the patient had been treated with a combination of thalidomide and dexamethasone, and we did not change the steroid to prednisolone from dexamethasone in order to precisely evaluate the effect of melphalan. Therefore, our regimen should be called MDT, although the combination of reagents is basically quite similar to MPT. MDT therapy may be suitable for refractory myeloma, because its low toxicity allows it to be well tolerated, even in situations of heavy treatment. In patients with hypocellular bone marrow, for instance, MDT could be applied safely as a salvage therapy for refractory myeloma. This combination therapy is also convenient because the regimen is given only as oral tablets. Although future studies with additional refractory cases are needed to prove the efficacy of MDT, we believe that this regimen should be considered for the treatment of refractory myeloma.

Acknowledgments

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ORIGINAL ARTICLE

High incidence of secondary failure of platelet recovery after autologous and syngeneic peripheral blood stem cell transplantation in acute promyelocytic leukemia

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Secondary failure of platelet recovery (SFPR), which is a delayed decline in platelet count after primary recovery following myeloablative hematopoietic SCT, is a significant problem in allogeneic SCT. However, its clinical characteristics have not been well described in autologous SCT for acute myeloid leukemia. We reviewed 11 consecutive patients who had received autologous or syngeneic SCT for acute promyelocytic leukemia. Seven of 11 patients (64%) had SFPR, which is defined as a decline in the platelet count to less than 30 000/μl for more than 7 days. The median onset of SFPR was day 36 (range, 25–51 days) and the median duration of thrombocytopenia was 13 days (range, 4–25 days). Of nine patients who received busulfan-containing preparative regimens, seven (78%) had SFPR and one had delayed primary platelet count recovery. Neither patient who received cyclophosphamide and total body irradiation as preparative regimens had SFPR. The clinical courses of SFPR were transient and self-limited. SFPR was not associated with relapse of underlying diseases, graft failure or other fatal morbidities. The unexpectedly high prevalence and the characteristics of SFPR may provide additional information on management following autologous SCT for acute myeloid leukemia.

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Introduction

Thrombocytopenia is a critical problem after myeloablative hematopoietic SCT.[1–5] Recovery of platelets is affected by several factors, including the stem cell source, the infused cell dose, disease status, graft-versus-host disease, infections, and, especially, CMV. Veno-occlusive disease of the liver (VOD), thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and allo-immunization to random donor platelets also contribute to thrombocytopenia.[1–3,6]

A delayed, persistent decline in platelets count after primary platelet recovery is termed secondary failure of platelet recovery (SFPR). Isolated thrombocytopenia may occur without the decline of any other cell lineage. In a large study by Bruno *et al.*,[6] SFPR was observed in 20% of patients undergoing allogeneic transplantation and in 8% of patients undergoing autologous transplantation. Although it is not related to disease recurrence or graft rejection, SFPR is associated with poor outcomes after transplant. Various factors that either affected platelet production in the marrow or caused decreased platelet survival in the peripheral circulation have been implicated in the pathophysiology of SFPR.[1,3,6]

Autologous HSCT offers favorable outcomes for patients with acute promyelocytic leukemia in the second or later remission with minimal residual disease.[7,8] We conducted a series of autologous or syngeneic HSCTs for patients with acute promyelocytic leukemia using mobilized PBSCs with granulocyte CSF. An unexpectedly high incidence of SFPR was observed. In this paper, we describe clinical and pathological features that will lead to a new method of SFPR management after HSCT.

Patients and methods

Study patients

We reviewed medical records of 11 consecutive patients who had received autologous or syngeneic HSCT for AML

at Nagoya University Hospital, Aichi, Japan, or JA Aichi Showa Hospital, Konan, Japan from 1 April 2000, to 31 December 2004. All patients were evaluated from the day of transplant, defined as day 0, until death or the last routine follow-up.

Transplant procedures

Schedules and doses of preparative regimens are shown in Table 1. Granulocyte CSF (filgrastim (patients 1–3 and 9–11) or nartograstim (patients 4 and 7–8) was administered intravenously from day 1 until neutrophil engraftment. Sodium valproate 400 mg/day (patients 1–3) or phenytoin 300 mg/day (patients 4–6 and 9–11) were administered for prophylaxis against BU-induced seizure. Prophylaxis against herpes virus infection was administered with acyclovir 1000 mg/day in patients 4–8. Fluoroquinolone and fluconazole or itraconazole were also administered for prophylaxis against bacterial and fungal infections, respectively. Patients 1 and 2 received trimethoprim/sulfamethoxazole for prophylaxis against *Pneumocystis jiroveci* from day −7 to −1.

Definitions

Primary platelet recovery after myeloablative conditioning regimens was defined as an increase in platelet count to $\geqslant 50 \times 10^3/\mu l$ without transfusion support. SFPR was defined as a decline in the platelet count to less than $30 \times 10^3/\mu l$ for more than 7 days or on two consecutive laboratory examinations, or as the requirement of platelet transfusions after primary platelet recovery. The first day of thrombocytopenia with a platelet count less than $30 \times 10^3/\mu l$ was designated as the onset of SFPR. Neutrophil engraftment was defined as an absolute neutrophil count $>0.5 \times 10^9/l$ for three consecutive days for neutrophil recovery.

Laboratory examinations

Complete blood cell count and blood chemistry were analyzed 2–3 times a week during hospitalization. Bone marrow aspiration was performed from the sternum to confirm engraftment in all eight patients, and additional examinations were carried out at the onset of SFPR in some patients. CMV pp65 antigenemia[9,10] was analyzed as a method of rapid CMV antigen detection in all patients. The results are reported as the number of antigen-positive cells per slide containing 150 000 polymorphonuclear leukocytes. Platelet-associated immunoglobulin G (PA-IgG) was assayed in two patients (patients 4 and 5) around the time of SFPR onset. CMV pp65 antigenemia was monitored weekly after engraftment. CMV antigenemia was managed according to the method reported by Kanda *et al.*[11] with some modifications. If CMV pp65-positive cells were detected, patients preemptively received ganciclovir (5 mg/kg) two times daily. Ganciclovir could also be started with less than 10 positive cells in the patients who had received more than 0.5 mg/kg of prednisolone.

Statistical analysis

Differences in the incidence of SFPR between patients conditioned with BU-containing regimens and the other

Table 1 Patient characteristics

Patient no.	*Age*	*Sex*	*Donor*	*Preparative regimens*	*Status at transplantation*	*CD34+cell dose ($\times 10^6$/kg)*	*Previous treatment*
1	**59**	**F**	**Autologous**	**BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)**	**Second CR**	**3.0**	**High-dose cytarabine**
2	**34**	**M**	**Syngeneic**	**BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)**	**Second CR**	**2.5**	**Arsenic trioxide**
3	**30**	**M**	**Autologous**	**BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)**	**Third CR**	**5.0**	**High-dose cytarabine, arsenic trioxide**
4	**63**	**F**	**Autologous**	**BU 8 mg/kg/day (day −8 to −5), CY 60 mg/kg/day (day −3 and −2)**	**Second CR**	**9.2**	
5	**55**	**M**	**Autologous**	**BU 8 mg/kg/day (day −8 to −5), CY 60 mg/kg/day (day −3 and −2)**	**Second CR**	**8.9**	
6	65	M	Autologous	BU 8 mg/kg/day (day −8 to −5), CY 60 mg/kg/day (day −3 and −2)	Third CR	3.7	Arsenic trioxide
7	36	M	Autologous	CY 60 mg/kg/day (day −4 and −3), TBI 6 Gy/day (day −6 and −5)	Second CR	4.0	
8	51	F	Autologous	CY 60 mg/kg/day (day −4 and −3), TBI 5 Gy/day (day −7 and −6)	Second CR	1.9	
9	41	M	Autologous	BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)	Second CR	2.8	High-dose cytarabine, arsenic trioxide
10	**46**	**F**	**Autologous**	**BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)**	**Second CR**	**3.4**	**High-dose cytarabine, arsenic trioxide**
11	**54**	**F**	**Autologous**	**BU 8 mg/kg/day (day −6 to −3), MEL 70/m^2/day (day −2 and −1)**	**Third CR**	**3.1**	**High-dose cytarabine, arsenic trioxide**

Abbreviation: MEL = melphalan.
Bold type indicates patients who expressed SFPR.

patients (conditioned with CY and TBI) were analyzed with Fisher's exact probability test for independent groups. The Mann–Whitney *U*-test was used to analyze the difference in the dose of $CD34^+$ cells between patients with SFPR and others. Statistical analyses were performed with the STATA version 8.2 Software (STATA Corp., College Station, TX, USA).

Results

Patient's characteristics

Patient's characteristics are shown in Table 1. The median age of the patients was 49 (range, 30–65) years, with five male and six female patients. All patients had acute promyelocytic leukemia. Eight patients were in second CR, and the other three patients were in third CR. The median dose of infused $CD34^+$ cells was 3.4 (range, 1.9–9.2) $\times 10^6$/kg. Six patients received BU and melphalan, three patients received BU and CY, and two patients received CY and TBI as preparative regimens. The stem cell source in 11 patients was PBSCs.

Primary platelet recovery after transplantation

All 11 patients achieved primary neutrophil engraftment. In all patients, except patient 6, the platelet count was greater than $50 \times 10^3/\mu l$ within 20 days after transplant (range, 10–18 days; median, 14 days). In patient 6, platelet recovery to greater than $50 \times 10^3/\mu l$ did not occur until day 85.

Clinical course of SFPR

Seven of 11 patients (64%) had SFPR (patients 1–5, 10 and 11). The median onset of SFPR was day 36 (range, 25–51 days), and the median duration of thrombocytopenia was 13 days (range, 4–25). Platelet counts recovered in all patients developing SFPR (Table 2). None of the seven patients with SFPR showed the decline in WBC count or RBC count during SFPR. Patients 1 and 2 received platelet transfusions. In patient 1, the platelet count declined to $14 \times 10^3/\mu l$ on day 63 and recovered to $47 \times 10^3/\mu l$ on day 70. In patient 6, the primary platelet count recovery did not occur until after day 50, but SFPR was not observed after platelet recovery. Patients 4 and 5 had preceding febrile episode. In patient 10, platelet count declined to $29 \times 10^3/\mu l$ on day 51, and then to $22 \times 10^3/\mu l$ on day 53. Platelet count recovered to $30 \times 10^3/\mu l$ on day 55, and then to $52 \times 10^3/\mu l$ at day 85. In patient 11, platelet count declined to $42 \times 10^3/\mu l$ on day 33, and then to $20 \times 10^3/\mu l$ on day 36. Platelet count recovered to $33 \times 10^3/\mu l$ on day 44, and then to $74 \times 10^3/\mu l$ on day 58. Four of the seven patients with SFPR developed hepatic dysfunction during SFPR (Table 2). No patients developed renal dysfunctions (Table 2). No other remarkable clinical manifestations developed in the seven patients during SFPR.

Correlation between SFPR and conditioning regimens or infused cell doses

Of the nine patients who received BU-containing conditioning regimens, that is non-TBI regimens, seven (78%) had SFPR and one (patient 6) had delayed primary recovery of platelet count. Neither patient who received conditioning regimens without BU, that is, CY and TBI, had SFPR ($P = 0.067$: patient 6 was excluded from analysis because of prolonged thrombocytopenia following transplantation). The median number of infused $CD34^+$ cells was 3.4 (range, 2.5–9.2) $\times 10^6$/kg for patients with SFPR and 3.3 (1.9–4.0) $\times 10^6$/kg for patients without SFPR ($P = 0.35$).

Bone marrow findings

Bone marrow aspiration at the onset of SFPR was performed on day 51 for patient 1, on day 23 for patient 2, on day 20 for patient 3, on day 31 for patient 4 and on day 38 for patient 5. As shown in Figure 1, all specimens showed normal cellularity, without relapse of leukemia or decrease in the number of megakaryocytes.

CMV antigenemia

In Patient 1, CMV antigenemia (9 positive cells out of 150 000) was detected on day 14, almost at the same time that the stomatitis and fever appeared, and was successfully treated with ganciclovir. In patient 2, the antigenemia was negative on day 23, before onset of SFPR. At day 37, the antigenemia (2 positive cells out of 150 000) was detected at day 37 and it became negative after the administration of ganciclovir. In patients 3–5, the antigenemia was negative at the time of the onset of SFPR. None of the patients had documented CMV diseases.

Outcome of SFPR

Table 2 shows the outcomes of seven patients with SFPR. Of the seven patients, six are alive without recurrence of leukemia. One patient (patient 5) died of leukemia relapse on day 278.

Discussion

Here, we have demonstrated a high incidence of SFPR following autologous PBSC transplantation (PBSCT) for AML. Bruno *et al.*[6] have reported a low incidence (3.8%) of SFPR after autologous SCT.[12] Unlike their study, in which the 1-year mortality of patients with SFPR was high (44%), in our study SFPR was self-limiting and did not affect the relapse of underlying diseases. The different feature from their report was that SFPR in our patients were self limiting and did not affect the relapse of underlying disease; in contrast the 1-year mortality of patients developing SFPR was relatively high (44 %) in their study. This contrast might be due to differences in patient profiles.

A high prevalence (64%) of SFPR was consistently observed in our patients with AML who received autologous PBSCT. One report has shown that 5 (56%) of 9 patients with AML had SFPR, whereas 16 (11%) of 146 patients with diseases other than AML who received autologous PBSCT had secondary thrombocytopenia.[1] Underlying disease of AML was a statistically significant predictor of poor platelet engraftment after both autologous BMT and PBSCT, compared with transplants for

Table 2 Clinical and laboratory findings of the patients with SFPR

Patient no.	*Onset of SFPR*	*Lowest count of platelet during SFPR ($\times 10^3/\mu l$)*	*PA-IgG at SFPR onset*[a]	*Duration of SFPR (days)*	*Treatment*	*Outcome*	*Onset (peak level) of CMV antigenemia*	*Use of ganciclovir*	*Laboratory findings during SFPR*				*Concomitant medication at onset of SFPR*	*Status at last follow up*
									Maximum creatinine level (mg/dl)	*Maximum total-bilirubin level (mg/dl)*	*Maximum aspartate aminotransferase level (IU)*	*Maximum alanine aminotransferase level (IU)*		
1	Day 44	20	NA	18	Prednisolone	Resolved	Day 14 (9)	Days 15–34	0.5	0.7	25[b]	26[d]	Trimethoprim/ sulfamethoxazole, rebamipide, amphotericin B	Alive 60 months after transplant
2	Day 25	16	NA	25	Fresh-frozen plasma	Resolved	Day 37 (2)	Days 39–53	0.8	0.8	171[b]	207[d]	Rebamipide, glycyrrhizic acid	Alive 42 months after transplant
3	Day 35	17	NA	22	None	Resolved	NA	NA	0.7	0.9	47[b]	68[d]	None	Alive 12 months after transplant
4	Day 34	17	118	13	None	Resolved	NA	NA	0.5	0.4	76[c]	55[c]	Teprenone, glibenclamide, lactomin	Alive 61 months after transplant
5	Day 43	25	43.6	10	None	Resolved	NA	NA	0.7	0.7	31[c]	95[c]	Teprenone	Dead at day 278 due to relapse
10	Day 51	22	NA	5	None	Resolved	Day 12	Not used	0.4	0.6	28[b]	38[d]	Trimethoprim/ sulfamethoxazole, teprenone	Alive 41 months after transplant
11	Day 36	20	NA	8	None	Resolved	NA	NA	0.5	NA	32[b]	19[d]	Trimethoprim/ sulfamethoxazole, pantethine, magnesium oxide, teprenone	Alive 32 months after transplant

Abbreviations: NA = not applicable; PA-IgG indicates = platelet associated IgG.
[a]Calculated in ng/10^7 cells (normal: 9.0–25.0).
[b]Upper normal limit is 41 IU.
[c]Upper normal limit is 31 IU.
[d]Upper normal limit is 45 IU.
[e]Upper normal limit is 37 IU.

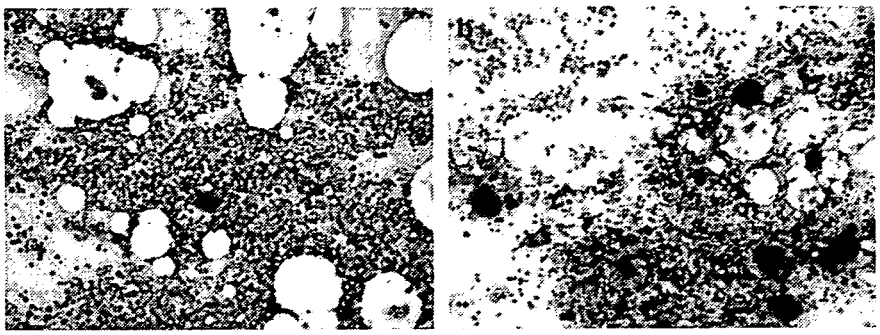

Figure 1 Bone marrow findings at SFPR onset (May-Giemsa stain, × 10) (**a**) patient 4 (**b**) patient 5.

other diseases.[6] Previous intensive chemotherapy for AML before PBSC harvest might deplete the primitive precursor cells that maintain long-term hematopoiesis.

Interestingly, seven of nine patients receiving BU-containing conditioning regimens had SFPR, whereas neither patient receiving TBI-based regimens had SFPR, although the difference was not statistically significant. The BU-containing regimen has particularly been used in transplants in patients with myeloid malignancies, and has been suggested to be associated with the development of VOD. Although VOD was not clinically evident in our patients, BU may have injured endothelial cells to induce platelet activation and sequestration resulting in subclinical VOD or TTP/HUS.

The elevation of PA-IgG in patients 4 and 5, and the preceding febrile episodes of possibly infectious origins in patients 1 and 3 suggest immunomediated thrombocytopenia. Bone marrow megakaryocytes did not decrease in any patients during SFPR. Auto-immune thrombocytopenia after high-dose chemotherapy and autologous BMT/PBSCT has been reported, but occurs infrequently in patients with AML, lymphoblastic lymphoma or breast cancer.[13–18] Although the exact mechanism for the development of autoimmune thrombocytopenia is unknown, several possible mechanism have been proposed including transient immune system perturbation, such as impaired suppressor T-cell function, immune deregulation related to thymic damage caused by irradiation and chemotherapy, and altered expression of self antigens as a result of stem cell damage during harvest and storage and viral infections after transplant.[13,18] Serum cytokine profiles observed in immunological imbalances might contribute to the activation of monocytes and macrophages, which are critical components in the elimination pathway of platelets.[1] Thus, immunological perturbations following transplants possibly caused decreased platelet survival by activating the elimination system in the peripheral circulation.

CMV infection after primary platelet recovery was most significantly associated with the incidence of SFPR in a previous report.[6] In the present study, CMV disease was not documented in any patient. Moreover, preemptive ganciclovir use was not related to the onset of SFPR or to clinical outcome. Thus, although CMV infection is a potential cause of SFRR, it was not involved in our series.

In summary, SFPR was observed frequently after autologous and syngeneic transplantation in patients with acute promyelocytic leukemia. The high prevalence of SFPR may be related to the use of PBSC as a stem cell source and the use of BU-containing preparative regimens. While multiple mechanisms are involved in the development of SFPR, the identification of etiology in each patient with precise descriptions of clinical characteristics should improve patient care.

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LETTERS AND CORRESPONDENCE

Philadephia Chromosome?

To the Editor: I am puzzled by the comment of Gürkan and Genç [1], in their description of a case of Bardet-Biedel syndrome, that a Philadelphia chromosome was detected. The Philadelphia chromosome is a derivative chromosome 22, resulting from a t(9;22)(q34;q11) translocation. This abnormality would not be expected in a patient with this syndrome and the fact that *BCR-ABL* fusion was not detected by PCR indicates that a Philadelphia chromosome was not present. Some further explanation appears to be needed.

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Reference

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Response to "Philadelphia Chromosome?"

To the Editor: We think that the presence of Philadelphia chromosome is rather unlikely an explanation for pancytopenia and lacks clinical significance in this case. The patient had completely recovered with appropriate treatment as mentioned before. The fusion gene produced by the BCR-ABL protein is leukemogenic, however, there are also reports demonstrating that BCR-fusion transcripts can be seen at very low frequency in the blood of healthy persons [1,2]. Absence of the fusion transcript might be due to small quantity of the clone, since Philadelphia chromosome was reported as positive only in few metaphases in our case. These observations suggest that the presence of the Philadelphia chromosome alone does not mean instant cancer or may not be sufficient to cause leukemia.

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Hyperammonemia and Encephalopathy in Patients With Multiple Myeloma

To the Editor: In recent years, a few case reports of hyperammonemic encephalopathy due to multiple myeloma (MM) have been published, but its prevalence and clinical significance remain unknown. We screened the database of the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences, and we

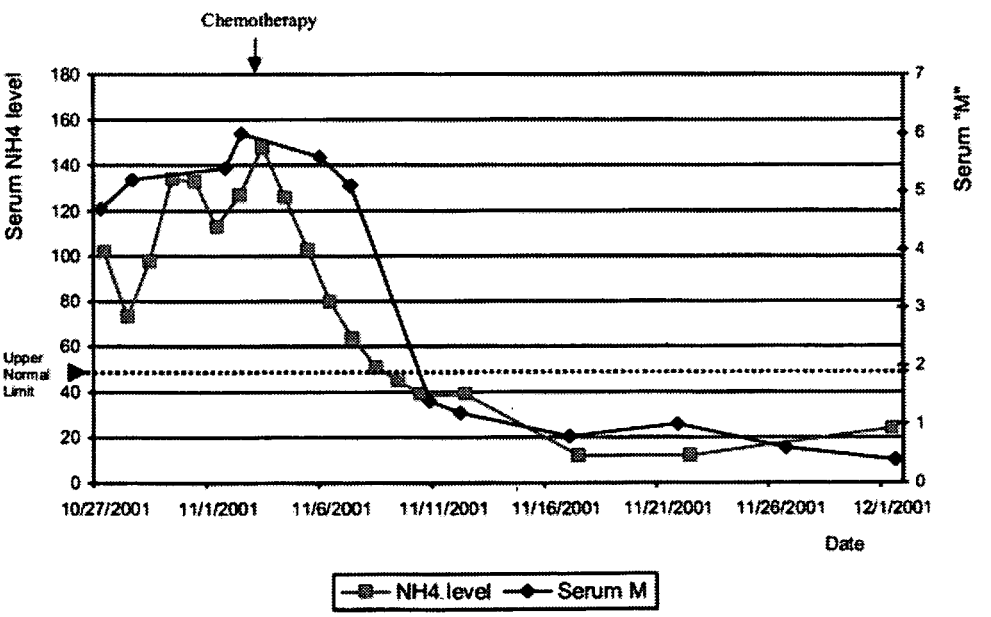

Fig. 1. Serum ammonia and serum paraprotein (M spike) levels in a patient with multiple myeloma treated with chemotherapy.

found 279 MM patients with altered mental status and available serum levels of ammonia (NH_4). Treating physicians requested the latter test as part of laboratory work-up used in the differential diagnosis of altered mental status.

Seventy patients were found to have hyperammonemia related to liver dysfunction. Among 209 MM patients with altered mental status and no evidence of liver dysfunction, the median serum NH_4 level was 21 μmol/l (range, 1–148). Only 8 patients (3.8%) were found to have encephalopathy associated with a serum NH_4 level >47 μmol/l (upper limit of institutional normal range). Although hyperammonemia could have contributed to the encephalopathy in all 8 patients, it was the single responsible factor only in two cases, because the remaining 6 patients had concomitant factors, such as hypercalcemia (1 patient), plasma hyperviscosity (1 patient), and CNS disease (4 patient), either alone or in combination, which could account for their altered mental status.

In one of those 2 patients with hyperammonemic encephalopathy and no other causes of altered mental status, tumor cytoreduction with chemotherapy was accompanied by a rapid normalization of both NH_4 levels (see Fig. 1) and mental status. No lactulose nor antibiotics were used.

Our report, which includes the largest number of patients with MM and an available serum NH_4 level, found that hyperammonemia is a rare finding in MM, because it was present in only 3.8% of 209 MM patients. This finding is consistent with the report of Matsuzaki et al. [1], who evaluated the NH_4 level in 85 MM patients, and found six cases (7%) of hyperammonemia. Nonetheless, hyperammonemic encephalopathy should be included in the differential diagnosis of altered mental status in MM patients, along with more common causes, such as sepsis, hypercalcemia, drug effect, and hyperviscosity syndrome.

The pathophysiology of hyperammonemia in MM is largely unknown. In vitro studies have demonstrated that myeloma cells in culture can produce excess NH_4, as a result of an altered amino acid metabolism [2,3]. Of note, 4 of our 8 patients with hyperammonemia and encephalopathy had also tumor involvement of the CNS, an event that has an overall incidence of ~1% in the course of MM [4]. We do not know the significance of this association.

Traditionally, the treatment of symptomatic hyperammonemia has involved restriction of dietary protein, antibiotic therapy (to inhibit the intestinal growth of urea-splitting bacteria), the use of nonabsorbable disaccharides, such as lactulose (to reduce the nitrogen load from the intestinal lumen), and, in severe cases, hemodialysis [5]. Here we have shown that in the presence of MM-related hyperammonemia, effective tumor cytoreduction results in a rapid normalization of both altered mental status and NH_4 levels.

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Chronic Myeloid Leukemia Following Radiotherapy for Carcinoma of the Cervix: Report of a Case and Brief Review of the Literature

To the Editor: The risk of second malignancies after radiotherapy (RT) is well described. Nevertheless, cases of secondary chronic myeloid leukemia (CML) after therapeutic RT have been rarely reported, although epidemiological studies have demonstrated a relationship between radiation exposure and CML after a latency period of 2–25 years in atomic bomb survivors as well as in patients receiving RT for different diseases [1].

Here, we describe the case of a patient with Philadelphia (Ph)-positive CML, 4 years after successful radiation treatment for uterine cervix carcinoma and briefly review the literature.

A 51-year-old woman presented with a hyperleukocytosis in December 2003. The hemogram was as follows: leukocytes 59.7 × 10^9/l (56% neutrophils, 19% stab, 11% metamyelocytes, 3% myelocytes, 1% promyelocytes, 1% blasts, 6% lymphocytes, and 3% erythroblasts), 680 × 10^9/l platelets, and 9.4 g/dl Hb. A bone marrow aspiration showed 1.3% myeloblasts, immature megakaryocytes, and increased cellularity with myeloid hyperplasia. The lactic dehydrogenase level was 1.086 U/l (normal: 200–900 U/l); other routine chemistry tests were unremarkable. Cytogenetic analysis demonstrated the presence of the Philadelphia chromosome t (9;22) (q34;q11) on 10 metaphases. Molecular analysis by polymerase chain reaction of the DNA from the bone marrow confirmed the classical bcr–abl rearrangement. She is currently in hematological and molecular remission with Gleevec 400 mg/day.

Past medical history included a hysterectomy plus RT for uterine cervix carcinoma in 2001 (Stage T2, TNM classification). A total dose of 5,000 cGy had been delivered on the pelvis (upper limit L5-S1). After this time, a right nephrostomy was required for treatment related urethral narrowing. No chemotherapy (CT) had ever been used in this patient.

Cancer treatment modalities, including RT and CT, could themselves increase the risk of developing secondary malignancies [2]. There is no defined definite radiation dose threshold for the induction of secondary malignancy after external beam RT in the literature. And there is little difference in the relative risk over the dose ranges from 2 to 80 Gy [2], although higher doses of radiation might increase the risk of bone and soft tissue sarcoma [3]. An increased risk of developing leukemia in women who have been treated with radiation for cervical cancer has been noted previously, but the dose–response relationship is complex. The risk increases with doses up to about 4 Gy and decreases at higher doses [4,5]. Any quantitative estimate of the cancer risk must involve some sort of model or assumption to allow an extrapolation to low doses, and any risk estimate is subject to debate and doubt [3].

This case of Philadelphia (Ph)-positive CML, 4 years following irradiation for uterine cervix carcinoma confirms that there is no defined definite radiation dose threshold for induction of secondary malignancies.

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Abdominal Pain and Syndrome of Inappropriate Antidiuretic Hormone Secretion as a Manifestation of Visceral Varicella Zoster Virus Infection in a Patient With Non-Hodgkin's Lymphoma

To the Editor: Lesions of varicella zoster virus (VZV) disease are usually limited to a few dermatomes. However, in immunocompromised patients, disseminated cutaneous and visceral involvement occurs. We report here a rare case of such a disseminated disease with manifestation of severe abdominal pain and syndrome of inappropriate anti-diuretic hormone (SIADH), which occurred 2 months after completion of conventional chemoradiotherapy for non-Hodgkin's lymphoma (NHL).

A 65-year-old woman was diagnosed as having diffuse large B-cell lymphoma of stomach origin. The clinical stage was III by the Lugano classification, and the International Prognostic Index score was low. HIV test was negative. She received chemotherapy consisting of three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), followed by radiation at a total of 40.5 Gray to the involved field, and a complete response was obtained. Two months later, she was re-admitted to our hospital because of severe abdominal pain lasting 2 days.

Her vital signs and physical examination were normal. Laboratory examination revealed prominent hyponatremia (Na 122 mmol/l, normal 138–146) and mild liver injury (GOT 74 U/L, normal 13–33; and GPT 63 U/L, normal 6–27). The serum osmolarity was 262 mOsm/kg, and urine osmolarity 532 mOsm/kg, which was consistent with SIADH. The pituitary size and intensity was normal but the occipital lobe of the cerebrum showed a high intensity on brain magnetic resonance imaging. In spite of fluid restriction, hyponatremia and her pain deteriorated. On the sixth hospital day, a subtle vesicular skin lesion on her abdominal wall was observed. We reasoned that her complaint might be attributed to the visceral involvement of VZV extending to the peritoneum, liver, brain, and skin. Upon starting treatment with acyclovir at 1,500 mg/day, her abdominal pain and hyponatremia improved, and she was discharged on the 14th hospital day. Polymerase chain reaction (PCR) for VZV of her peripheral blood and cerebrospinal fluid taken before acyclovir therapy was later found to be positive. The number of CD4-positive lymphocytes was 191/μL, and this low level has been maintained for as long as 1 year. The complete remission of NHL was also maintained throughout the episodes.

The occurrence of disseminated VZV including visceral involvement has been limited to immunocompromised patients; after stem cell transplantation (SCT), ~17–50% of cases develop VZV infection [1,2], and, among them, visceral infection is rare (3.6% [2]). Especially, there are only a few VZV infection cases after SCT consisting of SIADH [3]. And only one case has been reported which developed along with severe abdominal pain and SIADH after conventional chemotherapy [4].

Storek et al. reported that the CD4-positive lymphocyte count after allogeneic SCT was inversely correlated with the infection score [5]. We suppose that her low CD4 count might have contributed to the visceral VZV infection. The reason why she showed such a low CD4 cell count is currently unknown.

It should be noted that this rare manifestation could occur even after conventional chemotherapy in NHL patients. Importance of recognition of this manifestation should be stressed because it is critical for the prompt diagnosis of the disease and its successful treatment.

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Methylprednisolone Pulse Therapy for Severe Immune Thrombocytopenia Associated With Infectious Mononucleosis

To the Editor: Although mild thrombocytopenia is commonly observed in cases of acute Epstein-Barr virus (EBV) infections, severe thrombocytopenia is extremely rare. Here, we describe an infectious mononucleosis (IM) case that developed life-threatening thrombocytopenia.

A 16-year-old woman was admitted to our hospital. Fever and cervical lymphadenopathy developed 10 days prior to admission. Although the symptoms resolved spontaneously, petechiae and purpura developed in the trunk 2 days before presenting to us. On examination, liver, spleen, or superficial lymphnodes were not palpated. Her tonsil and pharynx were normal. Numerous petechiae and purpura were observed in the trunk and extremeties.

Her white blood cell count was 10,200/mm^3 with 42.5% atypical lymphocytes. The hemoglobin concentration was 13.1 g/dl. Her platelet count was 1,000/mm^3. Serum AST was 224 IU/l and ALT was 309 IU/l. Urinanalysis showed proteinuria and microscopic hematuria. Antiplatelet antibody was positive and platelet-associated IgG was 577 ng/10^7 platelets (reference range, 9.0–25.0 ng/10^7 platelets). Anti-EB-VCA-IgG was negative and EB-VCA-IgM was positive. An abdominal ultrasonography disclosed moderate splenomegaly.

Severe epistaxis developed soon after the admission and it had to be treated by an otorhinolarygologist. Ten units of concentrated platelet rich plasma were transfused to control the bleeding. However, no increase of the platelet count was observed on the next day. Fifteen units of the platelet plasma were also transfused subsequent consecutive 3 days with minimum benefit. Methylprednisolone pulse therapy (1 g/day for consecutive 3 days intravenously) started on a day after the admission, followed by oral prednisolone. The platelet count increased gradually and it had exceeded above 50,000/mm^3 from 7 days after the

admission. Her symptoms resolved and oral prednisolone was tapered uneventfully without recurrence of thrombocytopenia.

IM caused by EBV usually resolves without problems but may occasionally be complicated by a wide variety of complication. Though mild thrombocytopenia occurs in ~25–50% of patients during the second and third week of illness, severe thrombocytopenia is exceedingly rare. Both hypersplenism and antiplatelet antibodies may contribute to thrombocytopenia [1]. The development of the antiplatelet antibodies may be related to polyclonal B cell activation induced by the EBV. In the present case, antiplatelet antibodies were detected and splenomegaly was found.

Although a number of cases with severe thrombocytopenia associated with IM have been published [1], life-threatening cases with platelet counts less than or equal to 3,000/mm^3 were limited [1,2–4]. Corticosteroids have been used for cases with severe thrombocytopenia after EBV infection although several weeks may pass before the platelet counts increases above 30,000/mm^3 [2]. Use of intravenous immunoglobulin (IVIG) refractory to corticosteroid was reported to be effective [3,5]. However, IVIG therapy is very expensive. In the present case, initial platelet count was 1,000/mm^3 and severe existaxis developed shortly after the admission. We started methylprednisolone pulse therapy because we considered this case to be life-threatening. Fortunately, the platelet count increased promptly and no fatal complication developed. Methylprednisolone pulse therapy might be considered as an initial therapy for immune thrombocytopenia with IM if the platelet count is extremely low.

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Complete Response to Alemtuzumab in a Patient With B Prolymphocytic Leukemia

To the Editor: A previously healthy 64-year-old male presented in April 2005 with worsening dyspnea on exertion, vague abdominal discomfort, and left shoulder pain of 2 months duration. He noted an enlarging abdominal mass. He denied fever, night sweats, nausea, or vomiting, but reported an unintentional 37 pound weight loss in the past year. Physical examination revealed massive splenomegaly, but no hepatomegaly or lymphadenopathy. A complete metabolic profile was normal. LDH was 816 units/l (normal 80–210). His white blood cell count was 68.2 $\times$ 10^9/l with 63% lymphocytes and 30% atypical lymphocytes. His hemoglobin and platelet count were 9.0 g/dl and 103 $\times$ 10^9/l respectively. The peripheral smear showed abundant prolymphocytes. A bone marrow aspirate and biopsy revealed a hypercellular marrow that was mostly replaced by a diffuse neoplastic proliferation of predominantly small lymphoid cells, many of which had prominent nucleoli. The malignant cells had bright surface kappa immunoglobulin light chain expression and co-expressed CD20, CD19, and CD23, and lacked the expression of CD10 and CD5 by flow cytometry. The neoplastic cells were negative for cyclin D1 by immunohistochemistry. The patient was diagnosed with B-cell prolymphocytic leukemia (B-PLL). Prior to starting chemotherapy with fludarabine and cyclophosphamide, he developed chest pain associated with dyspnea at rest. Evaluation revealed coronary artery disease with critical left main stenosis. He underwent an uneventful urgent four vessel coronary artery bypass grafting procedure. Cytotoxic chemotherapy was delayed to allow for wound healing. Due to worsening anemia, thrombocytopenia, and lymphocytosis, the patient was started on intravenous therapy with alemtuzumab. During the 12 weeks of therapy, the spleen size and peripheral blood counts normalized. At the end of therapy, a bone marrow aspirate and trephine biopsy confirmed complete remission. An autologous bone marrow transplant was recommended. After 10 months of appeals with the patient's insurer, he underwent an uneventful autologous peripheral hematopoietic stem cell transplant. He was in complete remission at the time of transplantation.

B-PLL represents 1% of lymphocytic leukemias [1]. Conventionally, alkylating agents, purine analogues or a combination of the two were used to treat this entity [2]. Recently there have been emerging reports of responses to the monoclonal antibody rituximab [3,4]. Little data is available about the role of alemtuzumab in the treatment of this disease, although significant activity in chronic lymphocytic leukemia and T-prolymphocytic leukemia has been reported. McCune et al. reported on 23 patients with relapsed/refractory chronic lymphocytic leukemia or prolymphocytic leukemia treated with alemtuzumab for up to 12 weeks. Among these patients five had prolymphocytic leukemia (B or T cell origin not specified). Among the four patients evaluable for response, 50 and 25% achieved a complete and partial response respectively [5].

We hereby report a treatment-naïve case of B-PLL that achieved a complete and prompt response with 12 weeks of alemtuzumab therapy. We believe that this agent deserves further evaluation in this disease.

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Rituximab as Preventive Therapy of a Clinical Relapse in TTP With ADAMTS13 Inhibitor

To the Editor: Acquired thrombotic thrombocytopenic purpura (TTP) is associated with circulating inhibitors to ADAMTS13 [1]. In these patients,

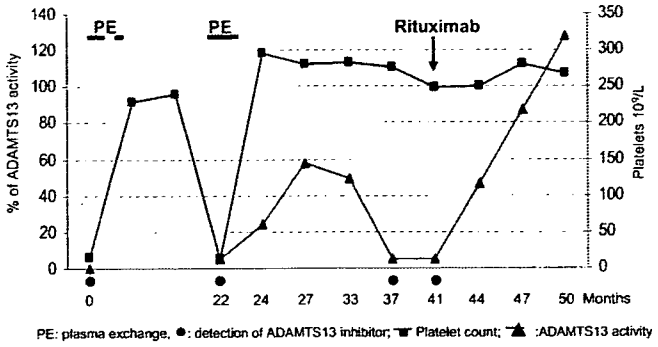

Fig. 1. Evolution of ADAMTS13 activity and platelet count during follow-up.

ADAMTS13 serum activity is usually above 5%. Plasma exchange (PE) is recognized as the standard therapy but is not effective in some refractory TTP and at least 30% of patients will experience one or several relapses. Predicting which patients will relapses remains a challenge as low levels of ADAMTS13 are not always associated to clinical relapse. Therefore adjuvant therapies have been proposed and most recently, rituximab has been shown to give promising results as an adjuvant curative treatment in acquired refractory or frequently relapsing ADAMTS13-deficient TTP associated with an inhibitor [2–4].

We report the case of a 27-year-old woman who presented in 2001 with TTP during pregnancy (hemoglobin 5 g/dL, platelets 16 $\times$ 10^9/L, undetectable haptoglobin levels, 2% of schizocytes on the blood smear, normal creatinine levels, and transient neurological symptoms). ADAMTS13 serum activity was undetectable, associated with an inhibitor. She recovered after a course of 10 PE and had a safe delivery (hemoglobin 12 g/dL, platelets 240 $\times$ 10^9/L). Her child was healthy without hematological abnormality. A relapse shortly after delivery was treated by a course of 7 PE. TTP relapsed in October 2003 (hemoglobin 5.2 g/dL, platelets 12 $\times$ 10^9/L, 1.4% of schizocytes on the blood smear without neurological symptoms) and was treated by a course of 31PE associated to a 1 mg vincristine infusion and a short course of corticosteroids. ADAMTS13 serum activity increased to 58% during the following at five months and anti-ADAMTS13 antibody disappeared. Follow-up showed a decrease of ADAMTS13 activity (5%) with recurrence of the inhibitor in January 2005. Despite the absence of any clinical or biological symptoms of relapse (hemoglobin 13.5 g/dL, platelets 248 $\times$ 10^9/L, normal haptoglobin, and LDH levels, absence of of schizocytes on the blood smear), we proposed to treat the patient by rituximab infusion, 375 mg/m^2 weekly for four weeks after informed consent, to prevent a new relapse. Treatment was well tolerated without any side effects. Low levels of activity were restored to normal and the inhibitor was negated (Fig. 1). At nine months the ADAMTS13 activity is at 128%. B cell count show the persistence of the B cell depletion (CD19 cells at 7/mm^3) with normal immunoglobulin blood levels.

Acquired TTP is a rare life-threatening disease whose prognosis has been improved by plasma exchange. However acute TTP and PE are associated with non negligible morbidity and mortality. Other treatments with immunosuppressive agents, splenectomy or high dose intravenous immunoglobulins have been proposed in regards of small series results. Recently, rituximab has been shown to be effective in refractory TTP. In a few patients this has been shown to prevent a relapse in the remission phase as single therapy [2,4].

Our case suggests the efficiency of rituximab as single therapy to prevent a relapse of TTP with ADAMTS13 inhibitor. The effect on long term remission, the time of administration, and careful selection of patients with high risk of relapses has to be ascertained by careful follow up and forthcoming studies as well as long term complications of rituximab.

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Original Articles

Primary Ocular Adnexal MALT Lymphoma: A Long-term Follow-up Study of 114 Patients

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Background: Although primary ocular adnexal MALT (mucosa-associated lymphoid tissue) lymphoma (POAML) is a recently recognized unique entity, its natural history, prognostic factors, behavior of progression and death, and standard initial management have not been fully elucidated.
Methods: The data of 114 patients with histologically verified POAML who were treated at our institution between 1970 and 2003 were retrospectively analyzed.
Results: With a median follow-up duration of 5.7 years (0.6–34.0), estimated overall survival (OS) rate and progression-free survival (PFS) rate at 10 years was 89% and 57%, respectively. Thirteen (11%) patients died, but only three (3%) of them due to progressive lymphoma. Thirty-one (27%) patients progressed: eight who progressed at contra lateral sites were limited to those who had initially involved in the orbit ($P = 0.036$) and their OS and PFS were significantly longer ($P = 0.035$ and 0.039, respectively). Patients who initially received radiation-containing therapy were superior in PFS but not in OS to those initially treated with other modalities ($P = 0.016$ and 0.091, respectively). When we compared the outcomes of the observation cohort and the immediate therapy cohort, there were no significant differences in OS and PFS ($P = 0.499$ and 0.073, respectively).
Conclusions: The majority of patients with POAML showed the behaviors of localized and indolent diseases. Our preliminary observation that no initial therapy is an acceptable approach for selected patients was confirmed. Considering the possible heterogeneity of POAML among initial sites, further investigations are warranted.

Keywords: MALT lymphoma – heterogeneity – observation – retrospective study

INTRODUCTION

Since the first description by Isaacson and Wright in 1983, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) has been recognized as a distinct entity of low-grade B-cell lymphoma; it is described in the revised European–American lymphoma (REAL) classification and also in the more recent classification by the World Health Organization (WHO) (1–3). The majority of patients with MALT lymphoma show an indolent natural history it manifests as localized diseases in two-thirds of patients (4,5).

Malignant lymphoma arising in the ocular adnexa is a rare disorder, and previous reports indicated that they account for about 8% of all extranodal lymphomas (6). Several reports indicate that the majority of lymphomas in the ocular adnexa are of MALT type (7–11). It was reported that histology according to the REAL or WHO classification can be used to accurately predict the prognosis of patients with lymphomas in the ocular adnexa, and those with MALT type have a more favorable prognosis than those with lymphomas of

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differing histology (8–11). Although there have been a few analyses carried out on small numbers of patients with primary ocular adnexal MALT lymphoma (POAML), its natural history and prognostic factors have not been fully elucidated (12,13).

For localized MALT lymphoma, radiotherapy is recognized as the most frequently applied management and most patients show good responses (14,15). For the initial management of POAML, especially for localized diseases, radiotherapy is a safe and effective treatment (16–21). However, several reports recently suggested that radiotherapy alone may not provide superior outcomes in patients with MALT lymphoma (22). Based on the long-term follow-up results at our institution, we previously reported that in selected patients with POAML no initial therapy might be an acceptable approach (23). The investigators in Italy reported the detection of *Chlamydia psitacci* DNA in 80% of POAML and the regression by *C. psitacci*-eradicating antibiotic therapy in some patients (24,25). However, a recent report from South Florida indicated no association of *C. psitacci* in 57 patients with primary ocular adnexal lymphoma (26). Thus, the optimal initial management of POAML has not been fully elucidated.

Although the prognosis of the majority of patients with POAML is thought to be favorable, disease progression and/or death occurs in a fraction of patients. To our knowledge, there have been few analyses on its behavior of progression and death focusing on patients with POAML (12,13). Therefore, we analyzed the long-term follow-up results of 114 patients with POAML at our institution. The objective of this study was to analyze its natural history, behavior of progression and death, initial managements and prognostic factors.

PATIENTS AND METHODS

Selection of Patients

We utilized the database of the National Cancer Center Hospital, Japan. Criteria for selection included patients who developed lymphoma in the ocular adnexa as the primary lesion, and were initially diagnosed or reviewed as POAML and managed at our institution. Their diagnosis of MALT lymphoma was established by biopsy or surgical resection sample in the primary lesion. For all patients, the histopathologic diagnosis of MALT lymphoma was reviewed according to the REAL or the WHO classification by two hematopathologists (Y.M., A.M-M.).

Preliminary clinical data of 36 patients with POAML who had been followed up with no initial therapy were published separately (23), and they were included in the present study for the all cohorts regardless of initial management.

Clinical Features

In patients with the confirmed diagnosis of POAML, the following clinical data were analyzed based on the medical

Table 1. Patients characteristics

	No. of patients (n = 114)
Sex	
Male/Female	71 (62%)/43 (38%)
Age (years)	
Median/Range	57.5/15–90
Involved sites	
Conjunctiva	42 (36%)
Orbit	67 (59%)
Lachrymal gland	3 (3%)
Eyelid	2 (2%)
Laterality	
Right	40 (35%)
left	57 (50%)
Bilateral	17 (15%)
Stage	
I	107 (94%)
II–IV	7 (6%)
LDH	
>Normal	15 (13%)
IPI	
Low	100 (88%)
Low intermediate	11 (9%)
High intermediate	3 (3%)
Initial management	
Radiation	58 (51%)
Chemotherapy	15 (13%)
Chemotherapy with radiation	5 (4%)
Observation	36 (32%)

LDH, lactate dehydrogenase; IPI, International prognostic index.

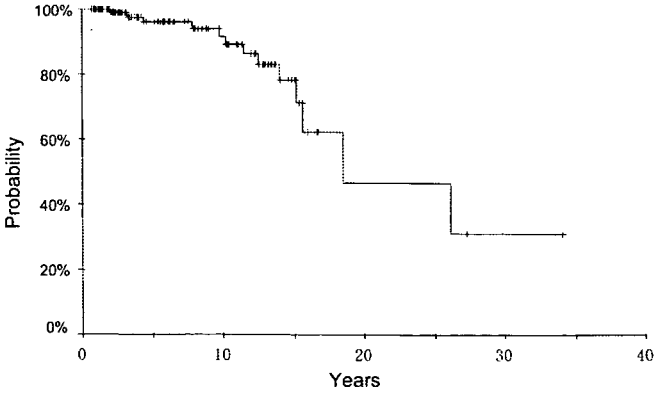

Figure 1. Estimated overall survival in all patients with primary ocular adnexal MALT lymphoma (n = 114).

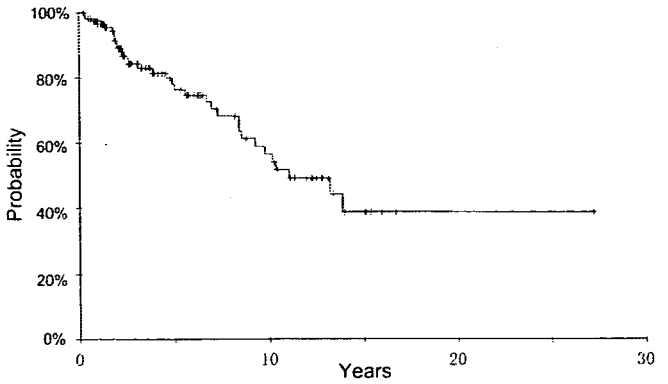

Figure 2. Estimated progression-free survival in all patients with POAML ($n = 114$).

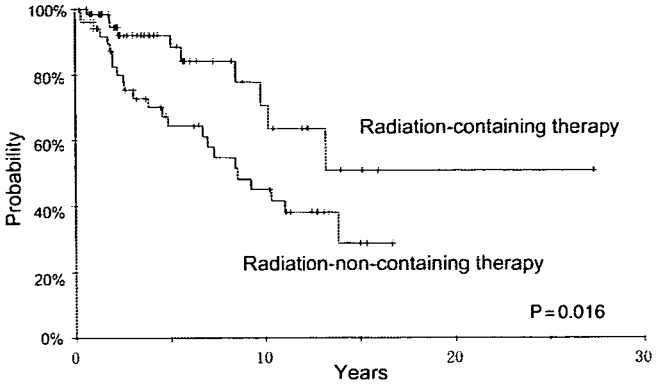

Figure 3. Progression-free survival according to their initial treatment: radiation-containing therapy cohort ($n = 63$) versus radiation-non-containing therapy cohort ($n = 51$).

charts; sex, age, clinical stage, involved site and laterality, performance status (PS) according to the Eastern Cooperative Oncology Group scale and the serum lactate dehydrogenase (LDH) value at initial presentation. The involved sites were anatomically classified according to Knowles et al. (27). Physical examination, chest X-ray, computed tomography of the head/eye, neck, chest, abdomen and pelvis, gallium scintigraphy, bone marrow and peripheral blood examination were performed. The clinical stages were determined according to the Ann Arbor staging classifications. International prognostic index (IPI) (28) was calculated based on these data.

Prognostic Factors and Initial Management Analyses

All patients were followed up exclusively at the National Cancer Center Hospital. If patients were lost to follow-up for more than one year, we contacted via telephone for information regarding survival, progression and treatment. Overall survival (OS) was defined as time period from the date of diagnosis until the date of death due to any cause or until the date of the last follow-up for patients who were alive. Progression-free survival (PFS) was defined as time period from the date of the diagnosis until the date of first progression, or the date of last follow-up, or the date of death due to any cause, whichever occurred earlier. In the

Table 2. Univariate analysis of initial managements affecting overall survival and progression-free survival

Therapy	Probability (%)			
	10-year OS	*P*-value	10-year PFS	*P*-value
Initial management		0.284		0.053
Radiation	92.3		72.2	
Chemotherapy	77.1		41.6	
Chemotherapy with radiation	100.0		50.0	
Observation	93.5		46.1	
Radiation-containing	93.3	0.091	70.7	0.016
Radiation-non-containing	89.6		45.1	
Immediate initial therapy	88.8	0.499	64.9	0.073
Observation	93.5		46.1	

OS, overall survival; PFS, progression-free survival.

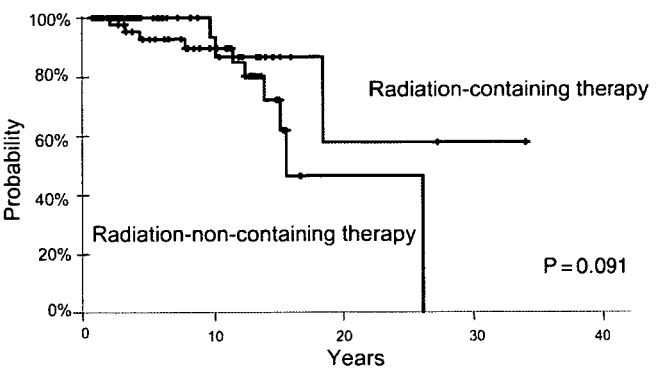

Figure 4. Overall survival according to their initial treatment: radiation-containing therapy cohort ($n = 63$) versus radiation-non-containing therapy cohort ($n = 51$).

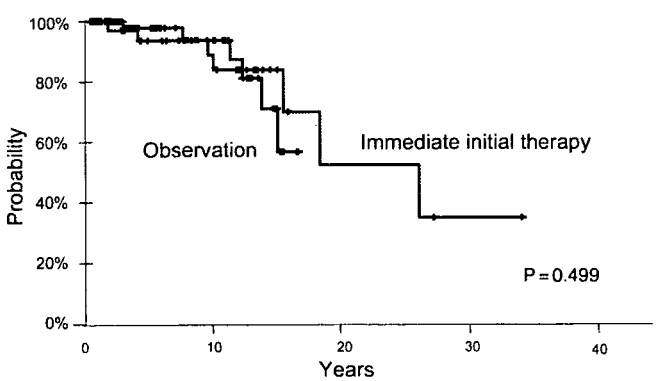

Figure 5. Overall survival according to their initial treatment: immediate therapy cohort ($n = 78$) versus observation cohort ($n = 36$).

Table 3. Clinical features of 31 patients who showed progression

Age	Sex	Initial site	Site at PD	Initial laterality	Laterality in PD	Initial management	PFS (year)	OS (year)	Cause of death
				A. Distant disease in progression					
41	M	Orbit	Waldeyer's ring	L		CHT + RT	1.8	2.8	
59	M	Orbit	Extramedullaly mass	R		CHT	0.4	7.8	Lung Ca
54	M	Orbit	Cervical LN, stomach	Bi		Obs	3.0	14.8	
51	F	Conj	Liver, spleen, systemic LN	L		RT	0.6	1.9	
76	M	Conj	Inguinal LN	L		CHT	0.2	3.1	Esophageal Ca
68	F	Conj	Cervical LN	R		Obs	11.0	12.4	PD
65	M	Conj	Eye ball	R		CHT	1.7	8.9	
				B. Contra lateral site in progression					
61	M	Orbit	Orbit	L	R	RT	13.2	13.3	
36	M	Orbit	Orbit	L	R	CHT + RT	2.2	34.0	
54	F	Orbit	Orbit	L	R	RT	1.7	2.5	
51	M	Orbit	Orbit	R	L	RT	5.0	14.5	
56	M	Orbit	Orbit	R	L	RT	8.4	13.5	
68	F	Orbit	Orbit	R	Bi	Obs	10.3	12.9	
65	M	Orbit	Orbit	R	Bi	Obs	7.2	11.4	PD
56	M	Orbit	Orbit	R	Bi	Obs	8.5	9.7	
				C. Same lateral site in progression					
59	M	Orbit	Orbit	L	L	Obs	2.5	13.6	
63	M	Orbit	Orbit	L	L	Obs	6.9	16.6	
57	F	Orbit	Orbit	L	L	Obs	0.9	10.2	
73	F	Orbit	Orbit	L	L	Obs	8.4	15.1	Pancreatic Ca
61	M	Orbit	Orbit	L	L	Obs	2.5	5.0	
79	M	Orbit	Orbit	L	L	Obs	1.2	4.3	Pancreatic Ca
71	F	Orbit	Orbit	R	R	Obs	1.9	15.5	
46	F	Conj	Conj	R	R	Obs	2.1	8.4	
61	M	Conj	Conj	R	R	Obs	4.9	7.5	
41	M	Conj	Conj	R	R	RT	5.5	6.0	
69	F	Conj	Conj	L	L	Obs	3.8	7.9	
60	M	Conj	Conj	L	L	CHT	4.5	5.5	
30	F	Conj	Conj	L	L	CHT	6.7	8.0	
28	F	Conj	Conj	Bi	R	Obs	9.2	10.9	
31	F	Conj	Conj	Bi	L	Obs	1.8	3.0	
27	M	LG	LG	Bi	Bi	CHT	0.2	15.5	PD

PD, progressive disease; M, male; F, female; conj, conjunctiva; LG, lacrimal grand; LN, lymph node; L, left; R, right; Bi, bilateral; CHT, chemotherapy; RT, radiation; Obs, observation; Ca, cancer.

univariate and multivariate analyses of prognostic factors influencing OS and PFS, we compared sex (male versus female), age (<60 versus ≥ 60), clinical stage (I versus II–IV), the value of serum LDH at initial presentation ($\leq$ normal value versus $>$ normal value), anatomical involved site (orbit versus the remaining sites) and laterality (unilateral versus bilateral).

After diagnosis, we informed therapeutic options to all patients. Patients received one of four kinds of initial management, including radiation alone, chemotherapy alone,

Table 4. Clinical features of 13 patients who died

Age	Sex	Initial site	Laterality	LDH	IPI	Stage	Progression	Initial management	OS (years)	Cause of death
76	M	Conj	U	N	LI	III	Yes	CHT	3.1	Esophageal Ca
68	F	Conj	U	N	L	I	Yes	Obs	12.4	PD
75	F	Eyelid	U	N	L	I	No	RT	9.7	Unclear
27	M	LG	Bi	>N	L	I	Yes	CHT	15.5	PD
47	F	Conj	U	N	L	I	No	CHT	26.1	Renal failure
73	F	Orbit	U	>N	LI	I	Yes	Obs	15.1	Pancreatic Ca
62	M	Orbit	U	N	L	I	No	RT	18.4	Cerebral infarction
65	M	Orbit	U	N	L	I	Yes	Obs	11.4	PD
69	M	Conj	U	N	L	I	No	RT	10.1	Pneumonia
84	M	Orbit	U	N	L	I	No	Obs	1.9	Lung Ca
59	M	Orbit	U	N	L	I	Yes	CHT	7.8	Lung Ca
65	M	Orbit	U	N	L	I	No	Obs	13.9	Heart disease
79	M	Orbit	U	N	L	I	Yes	Obs	4.3	Pancreatic Ca

M, male; F, female; conj, conjunctiva; LG, lacrimal grand; U, unilateral; Bi, bilateral; N, normal range; LI, low-intermediate; L, low; CHT, chemotherapy; Obs, observation; RT, radiation; Ca, cancer; PD, progressive disease.

radiation combined with chemotherapy and observation with no initial therapy. We compared OS and PFS among the initial management cohorts.

Behavior of Progression and Death

In all patients who progressed, the following clinical data were extracted; sex, age, involved site at initial and progression, laterality at initial and progression which were limited to the ocular adnexal progression, initial management, PFS, OS and cause of death. We divided patients who progressed into the following three categories according to the site of progression; category A, distant disease at progression; category B, contra lateral site at progression; category C, the same lateral site at progression. We compared the clinical factors among these three categories to elucidate the character in association with progression.

In all patients who died, clinical data at initial presentation were extracted to elucidate the character in association with death.

Statistical Analysis

OS and PFS were calculated by the Kaplan–Meier method. In the univariate and multivariate analyses of prognostic factors and initial managements influencing OS and PFS, we compared them using the log-rank test and multiple Cox regression models (backward stepwise selection of variables). Analyzing the correlations of the three categories at progression, we assessed each clinical factor by cross tabulation and Fisher's exact test. OS and PFS were compared by student's *t*-test among these three categories. All statistical analyses were performed using the software package SPSS for Windows, version 13.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients' Characteristics

One hundred and fourteen patients between 1970 and 2003 were included for this retrospective analysis. The characteristics of the patients are shown in Table 1. The median age was 57.5 years (range, 15–90 years), with 43 female and 71 male patients. Fifty-one patients (45%) were 60 years of age or older. The site most frequently involved was orbit (59%). In 97 patients (85%), the disease was located in a unilateral ocular adnexal region, whereas 17 patients (15%) had the disease in bilateral regions. One hundred and seven (94%) patients had stage I disease, whereas only seven (6%) had stage II–IV disease. In 15 (13%) patients, their LDH values were elevated. One hundred patients (88%) had low risk according to IPI. No patient exhibited the coexistence of MALT lymphoma and other types of lymphoma.

Natural History

With a median follow-up duration of 5.7 years (range, 0.6–34.0 years), the estimated median OS was 18.4 years.

The proportion of patients alive at 5, 10 and 15 years was 96, 92 and 71%, respectively (Fig. 1). The estimated median PFS was 11.0 years. The proportion of patients who were alive and progression-free at 5, 10 and 15 years was 77, 57 and 39%, respectively (Fig. 2).

Initial Managements

After the various therapeutic options were carefully explained to patients, most patients agreed with their physicians' recommendations. One hundred and fourteen patients were initially managed with the following four kinds of therapy; 58 (51%) patients receiving radiation alone, 15 (13%) chemotherapy alone, 5 (4%) radiation combined with chemotherapy and 36 (32%) observation as watchful waiting. The total dose of radiation ranged from 30 to 40 Gy, and the rate of achieving complete response was 83%. The radiation management was generally well tolerated, however, the clinical manifestation of cataract development was documented in four of the 63 patients who received radiation. Several kinds of chemotherapy were performed; most patients were treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, procarbazine, vincristine and prednisolone (C-MOPP) regimen. The overall rate of complete response in the chemotherapy alone cohort was 67%. As we discussed in our previous report (23), reasons for no initial therapy varied; seven patients (19%) selected no initial therapy when informed of various therapeutic options, 28 (78%) accepted no initial therapy according to physicians' suggestions and one (3%) because of advanced age.

The results of the univariate analysis of initial managements affecting OS and PFS are shown in Table 2. There were no significant differences in OS among the initial management cohorts ($P = 0.284$). However, the radiation cohort showed a trend toward superior PFS to those initially treated with other modalities ($P = 0.053$). To analyze the efficacy of radiation as the initial management, we compared the radiation-containing cohort (radiation alone or radiation combined with chemotherapy) and the radiation-non-containing cohort (observation or chemotherapy alone). Figures 3 and 4 show that patients who received radiation-containing therapy were superior in PFS but not in OS to those who received other modalities ($P = 0.016$ and 0.091, respectively).

To confirm the acceptability of observation as an initial management, we compared the observation cohort and the immediate therapy cohort. As shown in Table 2 and Fig. 5, there were no significant differences in OS ($P = 0.499$), although the slightly superior tendency of the immediate therapy cohort in PFS ($P = 0.073$) was recognized.

Behavior of Progression and Death

Thirty-one (27%) patients progressed after the initial management. Among them, only two (2%) patients showed the histology of transformed high-grade lymphoma. One patient died of progressive lymphoma, while the other was salvaged by chemotherapy after initial radiotherapy. Table 3 lists the clinical features of the 31 patients who showed progression. The most frequent sites of progression were the same as the initial sites: seven (6%) patients progressed at distant diseases (category A), eight (7%) at contra lateral sites (category B), and 16 (14%) at the same sites (category C). All eight patients who belonged to the category B were limited to those who had involved initially in the orbit ($P = 0.036$) and their OS and PFS were significantly longer than those who belonged to the remaining categories ($P = 0.035$ and $P = 0.039$, respectively). When we analyzed the relationship between the sites of progression and the initial managements, patients who were initially managed with observation progressed more frequently at the same sites than those who were treated with other modalities ($P = 0.016$).

Table 4 lists the clinical features of 13 patients (11%) who died. Six (5%) patients showed progressive diseases and three of them died of lymphoma progression. The remaining 10 (9%) patients died of the following various causes: pancreatic cancer ($n = 2$), lung cancer ($n = 2$), esophageal cancer ($n = 1$), cerebral infarction ($n = 1$), heart failure ($n = 1$), renal failure ($n = 1$), pneumonia ($n = 1$) and unclear ($n = 1$).

Table 5. Univariate analysis of prognostic factors affecting overall survival and progression-free survival

Characteristics	Probability (%)			
	10-year OS	*P*-value	10-year PFS	*P*-value
Age (years)				
<60	96.3	0.002	57.3	0.343
≥60	86.2		55.7	
Sex				
Male	90.4	0.433	56.1	0.796
Female	94.1		58.1	
Involved sites				
Other than orbit	90.9	0.765	55. 9	0.873
Orbit	92.1		56.9	
Laterality				
Unilateral	90.7	0.825	57.9	0.773
Bilateral	100.0		45.2	
LDH				
Normal	90.3	0.982	57.4	0.938
>Normal	100.0		51.0	
State				
I	92.5	0.376	55.7	0.953
II–IV	75.0		71.1	
IPI				
Low	89.4	0.339	56.3	0.590
Low or high intermediate	85.7		58.0	

Prognostic Factors

The results of the univariate analysis of the prognostic factors affecting OS and PFS are shown in Table 5. No clinical factors affected OS except for age. No factors significantly affected PFS. Because we considered that the choice of no initial therapy might have been related to selection biases, we analyzed prognostic factor affecting PFS in the immediate therapy cohort only. However, no factor affected PFS (data not shown). In the multivariate analysis of the factors affecting OS or PFS, there were also no significant factors (data not shown).

DISCUSSION

POAML is recognized as a distinct entity of low-grade B-cell lymphoma and is thought to be localized and indolent diseases (7–13). However, in most of the previous analyses the nature of POAML may have been masked, because various histopathological entities of lymphoma occurring in the ocular adnexa were analyzed together. In the present study, to elucidate its clinical behaviors, we analyzed 114 patients with POAML who were treated at our institution for more than 30 years follow-up.

As shown in Table 1, the majority of patients with POAML in the present series show the behaviors of localized diseases and having low IPI. These results are similar to those by other investigators (7,9–13).

In the present analysis, we confirmed that POAML was an indolent disease because the proportions of patients alive at 5, 10 and 15 years were 96, 92 and 71%. However, the proportions of patients who were alive and progression-free at 5, 10 and 15 years were 77, 57 and 39%, respectively. It was suggested that nearly half of POAML patients might progress during the long-term follow-up period. Because there was a difference between OS and PFS rates, it was suggested that even if progression occurred, disease control of POAML is possible by the subsequent therapy and progression does not directly affect a patient's survival.

As shown in Table 2, this study suggests that radiation is superior to other modalities as initial management in especially PFS. However, this superiority is obscure in OS among all the cohorts. Because the majority of the previous studies analyzed the radiation cohort alone, there were few comparative studies regarding OS or PFS between the radiation-containing cohort and the radiation-non-containing cohort (16–21). We recently reported the results of our preliminary observation that no initial therapy might be acceptable in selected patients with POAML (23). When we compared the outcomes of the observation cohort and the immediate therapy cohort in the present study, there were no significant difference in OS and PFS ($P = 0.499$ and 0.073, respectively). We therefore consider that observation approach with no initial therapy for selected patients was further confirmed in this study for the all cohorts. Because various treatment modalities were principally based on physicians' choices, however, there might be some biases affecting prognoses. Thus, the efficacy of each treatment modality in POAML should be evaluated by prospective studies in future, for example, by a randomized control trial comparing local radiotherapy and watch-and-waiting for asymptomatic patients with localized diseases.

There has been no previous analysis, to our knowledge, focusing on progression behavior of POAML. Partly because very few patients developed histological transformation (2%), the OS rate was excellent with long-term follow-up. Although the radiation-containing cohort was superior in disease control of the initial sites, the majority (88%) of progression in the radiation-containing cohort occurred in the distant sites or contra lateral sites, in contrast with the frequent same initial sites in the observation cohort, as shown in Table 3.

According to the sites in progression, we divided patients with POAML into three categories. As shown in Table 3, we found that patients who belonged to the category B had a unique character compared to those who belonged to the remaining categories. We recently found that patients with POAML having trisomy 18 might have unique clinicopathological characteristics (29). Other investigators reported that some ocular adnexal lymphomas were related to *C. psittaci* infection and the involvement of this agent might partly explain the heterogeneity of POAML (24,25).

When we analyzed the prognostic factors affecting PFS, there was no clinical factor significantly affecting its prognosis. A few previous analyses indicated that there were several prognostic factors (8–11). However, most of these analyses included several different histopathological entities of malignant lymphomas occurring in the ocular adnexa. We recently showed that in POAML, patients with trisomy 18 had worse PFS than those without (29). Other investigators reported that patients with $t(11;18)$ had a significantly longer median time to relapse than those without (22). Further analyses of genetic and histopathological features are warranted to predict the prognosis of each patient with POAML more accurately.

In conclusion, the majority of patients with POAML showed the behavior of localized and indolent disease, although a fraction of them slowly progressed. Our previous observation was further confirmed in this study that no initial therapy is an acceptable approach for selected patients with POAML. Considering the possible heterogeneity of POAML suggested in the present study and the genetic heterogeneity revealed by our and other studies, further investigations on POAML are warranted.

Acknowledgment

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Conflict of interest statement

None declared.

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