clinical aspects of HSCT-related CNS complications and provides clinical examples to illustrate the importance of accurate image interpretation.

Normal Hematopoietic Stem Cell Condition

Hematopoietic stem cells (HSCs) give rise to all blood cell types, including trilineage myeloid cells (eosinophils, basophils, monocytes and macrophages, neutrophils, erythrocytes, and platelets) and lymphoid lineages (T cells, B cells, and natural killer cells). HSCs are found in the bone marrow and are mostly contained in the femur, hip, ribs, sternum, and other bones. HSCs also are found in umbilical cord blood and the placenta. In HSCT, stem cells are obtained directly by bone marrow aspiration or from the peripheral blood after administration of granulocyte colony–stimulating factor, which induces mobilization of stem cells from the bone marrow compartment.

Types of HSCT

A diverse terminology has emerged to describe the type of HSCT based on the pretransplantation regimen (broadly categorized by the intensity of myeloablation, donor type, and source of stem cells) (Fig. 1). CNS complications have been found more frequently in allogeneic stem cell transplantation than in autologous or syngeneic stem cell transplantation. Reduced-intensity conditioning, in place of the combination of high-dose chemotherapy and total body irradiation, is used strategically for older patients and other patients at high risk. Owing to more rapid immune recovery, use of the reduced-intensity conditioning protocol has led to a reduction in therapy-related mortality after outpatient-based transplantation. However, a high incidence of relapse and delayed GVHD continues to be common. An infusion of harvested donor lymphocytes for induction of a graft-versus-malignancy effect is used in addition to HSCT and is associated with a higher survival rate.

Recovery of Immune Function After HSCT

The duration and degree of myeloaplasia in HSCT recipients depend on the conditioning regimen in the pretransplantation period. Engraftment of infused donor cells generally occurs on the 15th–30th posttransplantation day. This engraftment period and the duration of graft survival are influenced mainly by the source of the graft, successful immunosuppression, and the HLA-matching rate. Immune reconstitution after successful engraftment takes at least 4 months, and complete recovery is achieved after 1 year (Fig. 2).

Graft-Versus-Host Reaction

The acute and chronic forms of GVHD are partially overlapping but distinct major complications after allogeneic HSCT. Although the mechanism of acute GVHD, that is, alloreaction of donor T cells to host organs, is currently well understood, that of chronic GVHD is less well known. In chronic GVHD, two potential mechanisms—autologous reactivity of activated B cells and antibody-associated tissue injury—are suggested by the partial efficacy of rituximab and symptoms similar to those of autoimmune disease. Complications related to GVHD are more commonly seen in adult recipients than in pediatric patients. In long-term management of HSCT recipients, development of a therapeutic protocol that minimizes graft-versus-host reaction while inducing the least toxicity may offer the most benefit, creating the ideal balance of reduced morbidity, protection against opportunistic infection, and decreased risk of relapse [7].

Complications

Infection

In the initial posttransplantation period (0–30 days after HSCT), when patients are neutropenic, the primary risk is fungal and bacterial infection. HSCT recipients are most likely to have fungemia or bacteremia due to the long-term presence of an indwelling catheter, mucosal damage caused by high-dose chemoradiation therapy, inappropriate use of prophylactic antibiotics, and endemic or hygienic factors [8]. When GVHD occurs in the acute or subacute period after HSCT, additional immunosuppressive therapy for acute GVHD can cause profound, catastrophic depression of the immune system. The causative agents of early infection are mainly fungi (*Aspergillus* and *Candida* organisms),

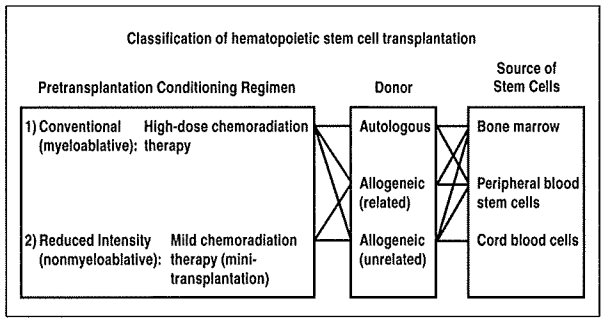


Fig. 1—Chart shows classification of hematopoietic stem cell transplantation.

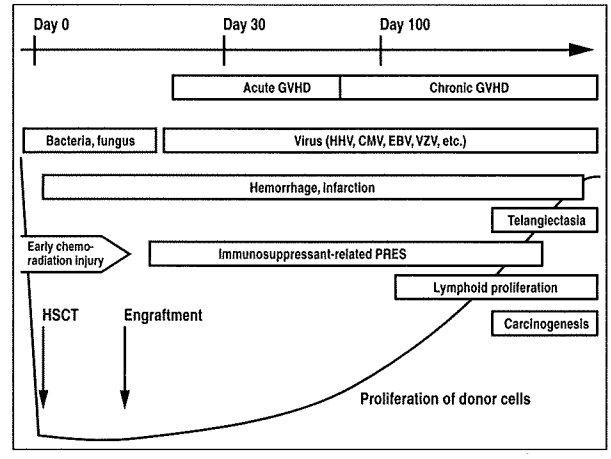


Fig. 2—Chart shows overview of specific CNS complications linked to timeline of transplantation. GVHD = graft-versus-host disease, HSCT = hematopoietic stem cell transplantation, HHV = human herpesvirus, CMV = cytomegalovirus, EBV = Epstein-Barr virus, VZV = varicella-zoster virus, PRES = posterior reversible encephalopathy syndrome.

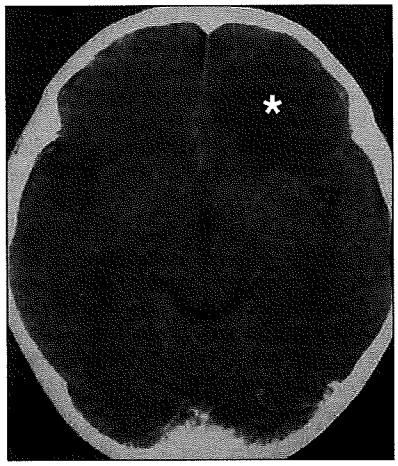


Fig. 3—9-year-old boy with brain abscess on 31st day after bone marrow transplantation. Patient underwent hematopoietic stem cell transplantation (HSCT) for acute myelocytic leukemia. Acute graft-versus-host disease occurred on 16th day after HSCT, and cyclosporine was administered. Serum WBC count was 11,800/μL with 2% lymphocytes (normal, 30–50%). Contrast-enhanced CT scan shows uniform low-attenuation area (*asterisk*) with subtle mass effect. No surrounding contrast enhancement is present. Deformation in left sylvian fissure is subtle for size of mass.

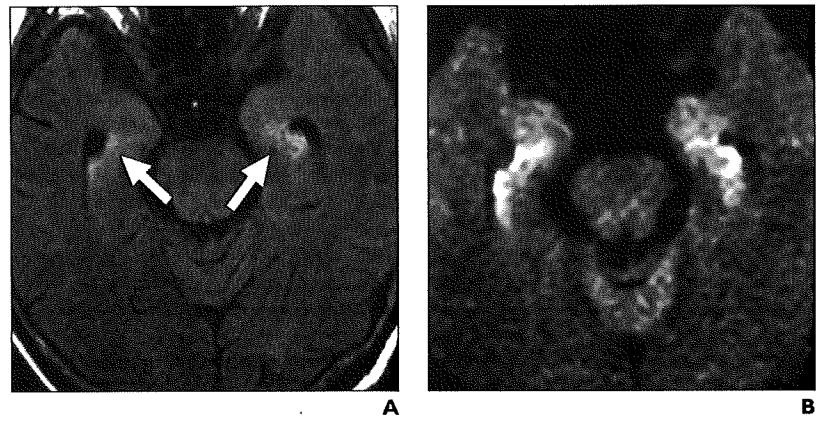


Fig. 4—57-year-old man with nonherpetic limbic encephalitis had short-term memory loss on 25th day after hematopoietic stem cell transplantation (HSCT). Abnormal signals on FLAIR MR images persisted through follow-up period.
A, FLAIR MR image obtained at presentation shows well-demarcated bilateral hyperintensity (*arrows*) in medial temporal lobes.
B, Diffusion-weighted image obtained at presentation shows robust hyperintensity corresponding to abnormal signal intensity on FLAIR image. No restricted water diffusion was visualized on apparent diffusion coefficient map (not shown).

gram-positive bacteria, and *Toxoplasma* organisms. The incidence of gram-negative bacterial and protozoan infections has decreased, but viral infections, cytomegalovirus in particular, have been reported to occur early in the course of HSCT [9]. The prevalence of these infections depends on the patient's immune status, although it can vary among populations and residential areas [10]. Cerebritis, ventriculitis, and meningitis due to hematogenous spread of pathogens to the brain are occasionally reported, and abscess formation sometimes occurs [11–13].

The imaging characteristics of cerebral infections are related to the immune status of recipients [4, 5]. As with brain abscesses in immunocompromised patients, encapsulation around the abscess cavity, which indicates the occurrence of sequential events involving neovascularization, inflammatory cell migration, and immune response, is not usually complete, and a mass effect or edema around the lesion caused by an inflammatory infiltrate of polymorphonuclear cells is relatively rare [14]. Therefore, brain abscess should be considered in the differential diagnosis when a low-density lesion is seen in the cerebral parenchyma, even if the lesion has minimal mass effect and negligible ring enhancement on contrast-enhanced CT or MR images (Fig. 3). It has been reported [15] that progressive vasogenic edema with mild ring enhancement, which develops after the increase in neutrophil count, may lead to cerebral herniation despite improved host defenses.

The risk of bacterial infection decreases after neutrophil recovery; however, recipients of HSCT remain at risk of infection with viruses and other opportunistic pathogens for several months because the full reconstitution of the immune system occurs more slowly. Cellular immunity (T-cell system) plays an especially important role in the regulation and mediation of the immune response in the subacute (30–100 days) to chronic (after 100 days) period [16]. Most posttransplantation infections in this period result from reactivation of latent herpes viruses, Epstein-Barr virus, and varicella-zoster virus [17]. Viral or virus-associated encephalitis is not an uncommon complication in the subacute period, and paraneoplastic limbic encephalitis is an occasional manifestation. Human herpes virus type 6 or 7 has been documented as one of the causative pathogens of limbic encephalitis in the hippocampal gyrus, amygdala, or both. Acute-onset mental alteration, drowsiness, and short-term memory loss are common clinical features.

MRI shows bilateral hyperintensity on T2-weighted and FLAIR images that is frequently detected in the limbic system (Fig. 4). It has been reported [18] that abnormal hyperintensity appears earlier on diffusion-weighted images than on T2-weighted and FLAIR images but that hyperintensity on T2-weighted and FLAIR images can persist. Temporomesial atrophy develops progressively in most cases. The pathologic–biophysical correlates of reduced water diffusivity include ischemic cytotoxic edema (with a failure of energy-dependent ion homeostasis), seizure-related excitotoxicity or hyperperfusion (glucose utilization exceeding oxygen delivery, leading to cellular lactate accumulation and osmotic shifting of extracellular and intracellular water), and acute myelin vacuolization [19]. Administration of acyclovir, which is widely used for prophylaxis of herpes simplex virus infection, is ineffective in cases of human herpes virus 6 or 7 and cytomegalovirus (herpes virus type 5) infection. For these pathogens, foscarnet or ganciclovir should be administered immediately.

Patients with chronic GVHD (more than 100 days after transplantation) are susceptible to late-onset infection due to not only immunoregulatory drugs but also long-term steroid therapy. Chronic GVHD seriously affects long-term survival, but it is less immediately life-threatening than acute GVHD [20]. Viral infections and reactivations of latent infections by varicella-zoster virus, Epstein-Barr virus, and other ubiquitous neurotropic viruses are still troublesome in this relatively late period.

Vascular Disorders

Although recipients gradually recover from marked pancytopenia after successful engraftment, thrombocytopenia and fluctuation of the

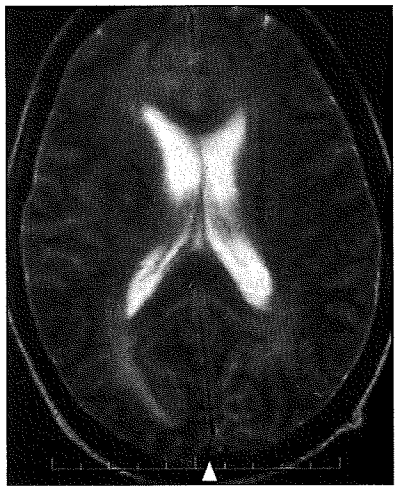


Fig. 5—55-year-old woman with venous sinus occlusion on 72nd day after hematopoietic stem cell transplantation (HSCT). T2-weighted MR image shows loss of flow void in superior sagittal sinus (*arrowhead*). Bilateral ill-defined diffuse hyperintensity is present in periventricular white matter, possibly indicating vasogenic edema due to venous congestion.

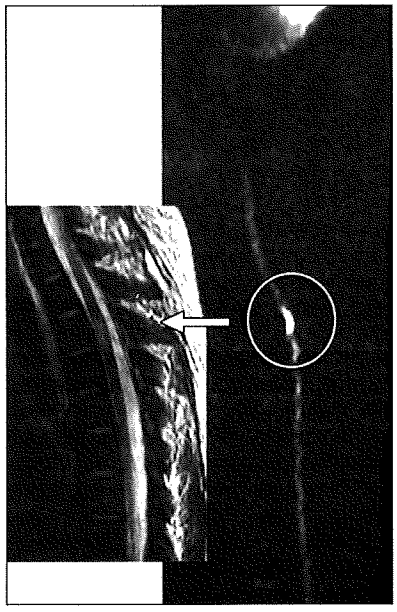


Fig. 6—31-year-old woman with spinal infarction presented with sudden-onset paralysis of right upper and lower extremities on 440th day after HSCT. MRI was performed 7 hours after onset. Sagittal diffusion-weighted image (b = 800) shows robust hyperintensity corresponding to abnormal signal intensity on T2-weighted image (*inset*). T2-weighted image shows ill-defined area of high signal intensity (*arrow*) in anterior part of spinal cord at T3 spinal level.

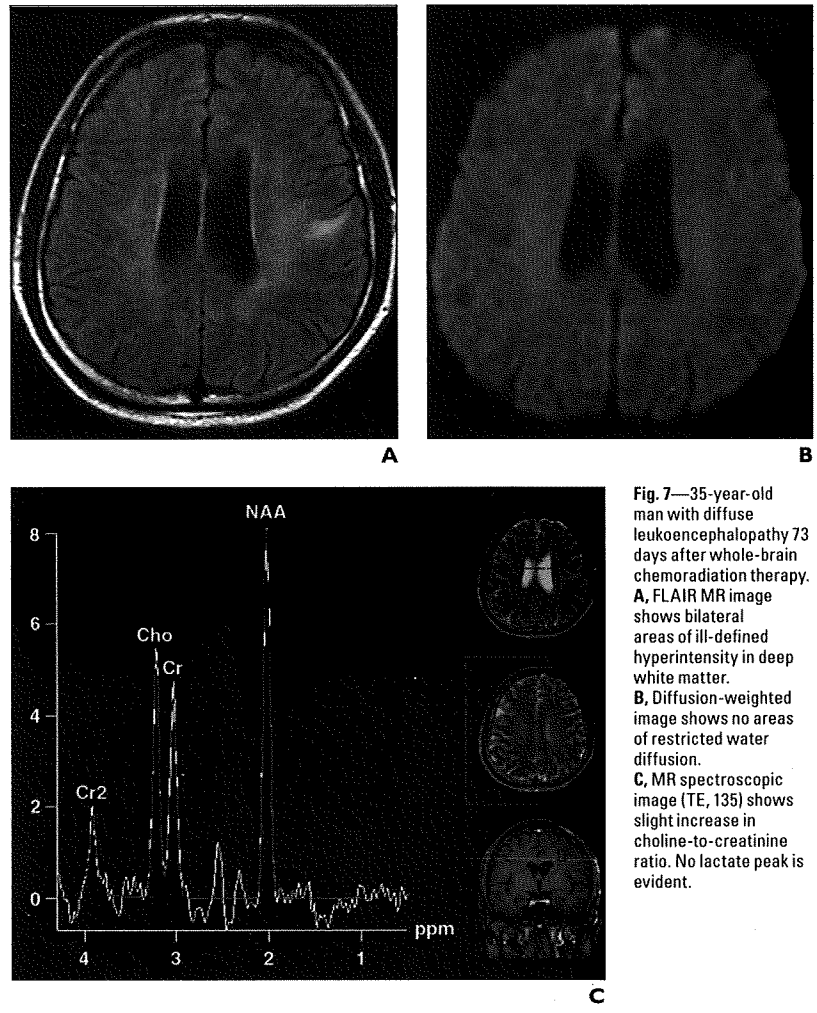


Fig. 7—35-year-old man with diffuse leukoencephalopathy 73 days after whole-brain chemoradiation therapy.
A, FLAIR MR image shows bilateral areas of ill-defined hyperintensity in deep white matter.
B, Diffusion-weighted image shows no areas of restricted water diffusion.
C, MR spectroscopic image (TE, 135) shows slight increase in choline-to-creatinine ratio. No lactate peak is evident.

coagulation system often occur in the relatively early posttransplantation recovery process. Intracranial hemorrhage is likely to occur in a variety of locations, including the subarachnoid space, subdural space, and brain parenchyma. The size of the lesions ranges from petechiae through focal subarachnoid bleeds to large hematoma, and one fifth of patients have more than one type of hemorrhage [21]. Coagulopathy resulting from disseminated intravascular coagulation and tumor-related tissue factors often causes thrombotic and embolic events in the cerebrovascular system [22]. These conditions are frequently associated with infection or underlying malignant disease. Arterial thrombosis and embolism most commonly are the result of nonbacterial and infective endocarditis [23]. Venous sinus thrombosis also can be caused by coagulopathy or direct infiltration of tumor and is a potential pitfall in image interpretation (Fig. 5). Spinal cord infarction is caused by the same mechanism, even though it is a rare disorder in the general population. Diffusion-weighted imaging is a novel technique for early diagnosis of spinal cord infarction (Fig. 6).

Most vascular complications in the late posttransplantation period are related to either chronic GVHD or tumor relapse. Transplantation-related microangiopathy generally occurs within 6 months after transplantation and is more frequently found, at the high incidence of 25–38%, in older patients who receive transplants from an unrelated donor [24]. The clinical findings include an increased schistocyte count due to endothelial injury; elevation of lactate dehydrogenase level, indicating microangiopathic hemolysis;

and anemia due to a decrease in hemoglobin level [25]. In HSCT recipients, the syndrome can range from asymptomatic to fulminant, and clinical and imaging manifestations occasionally are similar to those of hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura. The pathologic features of transplantation-related microangiopathy are intimal swelling and fibrinoid necrosis of the vessel walls of medium-sized to small arteries. This disorder is thought to be caused by immune-mediated systemic and focal endothelial damage related to chemoradiation therapy, immunosuppressive drugs, various pathogens, hemophagocytosis, and GVHD in combination with hypercytokinemia (cytokine storm) [24–26]. Transplantation-related microangiopathy can occur in conjunction with other neurotoxic processes. Reported imaging manifestations include a small, localized area of hyperintensity and diffuse extensive hyperintensity on T2-weighted and FLAIR MR images [26].

Therapy-Induced Complications

Therapy-induced cytotoxicity in HSCT recipients is caused by large-dose chemotherapy, radiation therapy, immunosuppressive therapy, and metabolic disturbances and generally occurs in the peritransplantation period. Therapy-induced cytotoxicity due to chemoradiation manifests itself as leukoencephalopathy in 6% of the pediatric age group. The finding on T2-weighted and FLAIR MR images is bilateral variable hyperintensity in the deep white matter of the cerebrum and brainstem (Fig. 7). Water molecule diffusion restriction on an apparent diffusion coefficient map varies depending on the nature and extent of damage relevant to the regimen. Most lesions disappear or become smaller as clinical symptoms subside. Progressive lesions, however, occasionally result in a chronic form of disseminated necrotizing leukoencephalopathy. It has been reported [27] that multifocal patterns on T2-weighted images may be an important early finding differentiating disseminated necrotizing leukoencephalopathy from mild leukoencephalopathy.

The histopathologic characteristics of disseminated necrotizing leukoencephalopathy are diffuse demyelination, gliosis, and coagulative necrosis caused by vascular damage. In contrast, mild leukoencephalopathy involves vasogenic edema and axonal degeneration as a result of the direct toxic effect of therapy. Therapy-induced leukoencephalopathy should be differentiated from other pathologically more critical diseases,

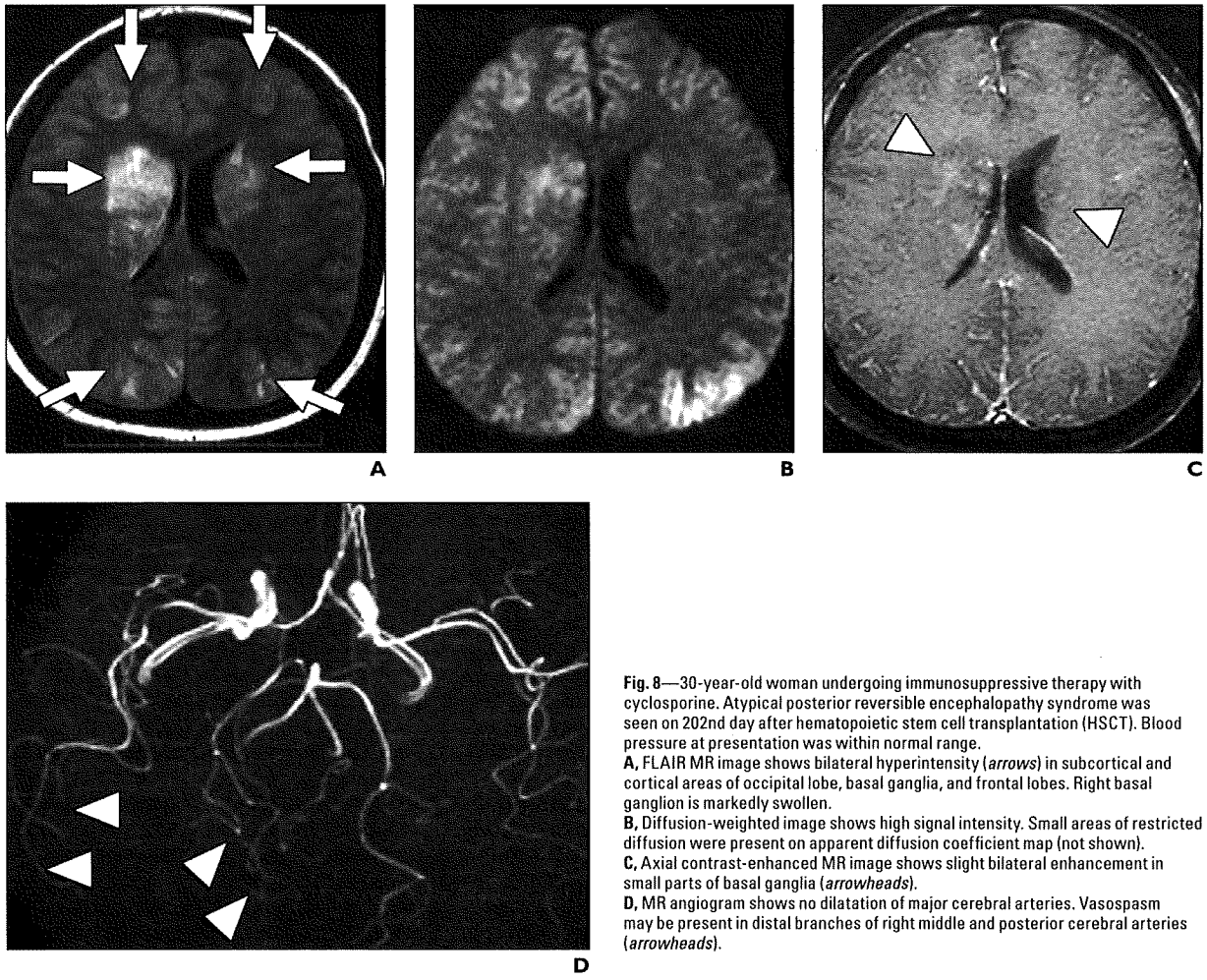


Fig. 8—30-year-old woman undergoing immunosuppressive therapy with cyclosporine. Atypical posterior reversible encephalopathy syndrome was seen on 202nd day after hematopoietic stem cell transplantation (HSCT). Blood pressure at presentation was within normal range.
A, FLAIR MR image shows bilateral hyperintensity (*arrows*) in subcortical and cortical areas of occipital lobe, basal ganglia, and frontal lobes. Right basal ganglion is markedly swollen.
B, Diffusion-weighted image shows high signal intensity. Small areas of restricted diffusion were present on apparent diffusion coefficient map (not shown).
C, Axial contrast-enhanced MR image shows slight bilateral enhancement in small parts of basal ganglia (*arrowheads*).
D, MR angiogram shows no dilatation of major cerebral arteries. Vasospasm may be present in distal branches of right middle and posterior cerebral arteries (*arrowheads*).

such as progressive multifocal leukoencephalopathy. Both lesions exhibit a variable lactate peak, high choline-to-creatinine ratio, and decreased *N*-acetyl aspartate–to–creatinine ratio on ^{1}H MR spectroscopy [28, 29]. In therapy-induced encephalopathy, patients generally experience symptomatic remission within several weeks, facilitating differentiation from progressive multifocal leukoencephalopathy, which is fatal.

Cytotoxicity related to cyclosporine or FK-506, which predominantly appears in the cortical and subcortical areas in the posterior circulation territory, has been synonymous with posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome [30]. After transplantation, several PRES-related risk factors, such as postinfective sepsis, shock associated with multiple organ dysfunction, chemotherapy, and GVHD, coexist with cyclosporine or FK-506 toxicity. The pathophysiologic mechanism of PRES remains unsolved. A sudden increase in blood pressure (50 mm Hg from baseline), subsequent hyperperfusion, and autoregulation breakdown in the posterior circulation territory with less sympathetic innervation and vasogenic brain edema have been considered the chief mechanisms of PRES. Hypertension reaching the upper limits of autoregulation is not present in all patients, even though moderate-to-severe blood pressure elevation is found in most patients [31, 32]. Today, cyclosporine and FK-506 cytotoxicity is considered an aspect of widespread vasculopathy. Cyclosporine or FK-506, which is widely used for preventing graft rejection and GVHD after successful engraftment, carries a risk of endothelial damage with an incidence ranging from 1.6% to 10% [31, 33].

Direct endothelial cell damage may be responsible for the injury to the capillary bed that alters the blood–brain barrier. Capillary endothelial injury may alter microvasculature permeability, leading to vasogenic edema, first in the subcortical white matter and then in the gray matter, deep gray matter, and deep white matter. Increased microvascular permeability in turn results in release of vasoactive peptides such as endothelin and thromboxane, which cause vasospasm [34]. In such situations, sudden hypertension seems to act as a modulator of disease progression. According to Bartynski et al. [35], who analyzed the cases of 114 patients with PRES, the lesion was found in the superior frontal gyrus in 68% of cases, inferior temporal lobe in 40%, cerebellum in 30%, basal ganglia in 14%, and brainstem in 13%. It has been suggested that if autoregulatory local vasospasm is present in the arterioles or precapillaries, reduced blood flow should occur, particularly at the watershed zone. This mechanism may explain the minor ischemic changes in these cerebrovascular territories [36]. Lesion distribution does not always correspond to the bilateral posteroanterior gradient in HSCT recipients, and partial and asymmetric imaging patterns, including completely unilateral involvement, have been recognized [35, 37]. With predominantly or completely unilateral distribution, the differential diagnosis should include neoplasm, encephalitis, and leukoencephalopathy.

Clinically, cyclosporine and FK-506 cytotoxicity can affect HSCT recipients at any time after HSCT, most commonly in the first month after HSCT in association with immunosuppression therapy. Sudden mental alteration, headache, unconsciousness, and convulsions are the most common initial clinical manifestations. Blood levels of immunosuppressants do not appear to correlate with the severity of neurotoxicity, although neurologic improvement can be seen after discontinuation of the drug [29, 30]. The prognosis is mostly favorable without sequelae if the lesion is reversible. On T2-weighted and FLAIR MR images, hyperintensity in the subcortical and cortical regions of the bilateral parietooccipital lobes is typical. Subtle gray-matter enhancement on contrast-enhanced T1-weighted images can occur when the damage is severely prolonged (Fig. 8). Irreversible changes are observable in some parts of the lesion, reflecting intramyelinic or intracellular cytotoxic edema of varying degrees on apparent diffusion coefficient maps [38].

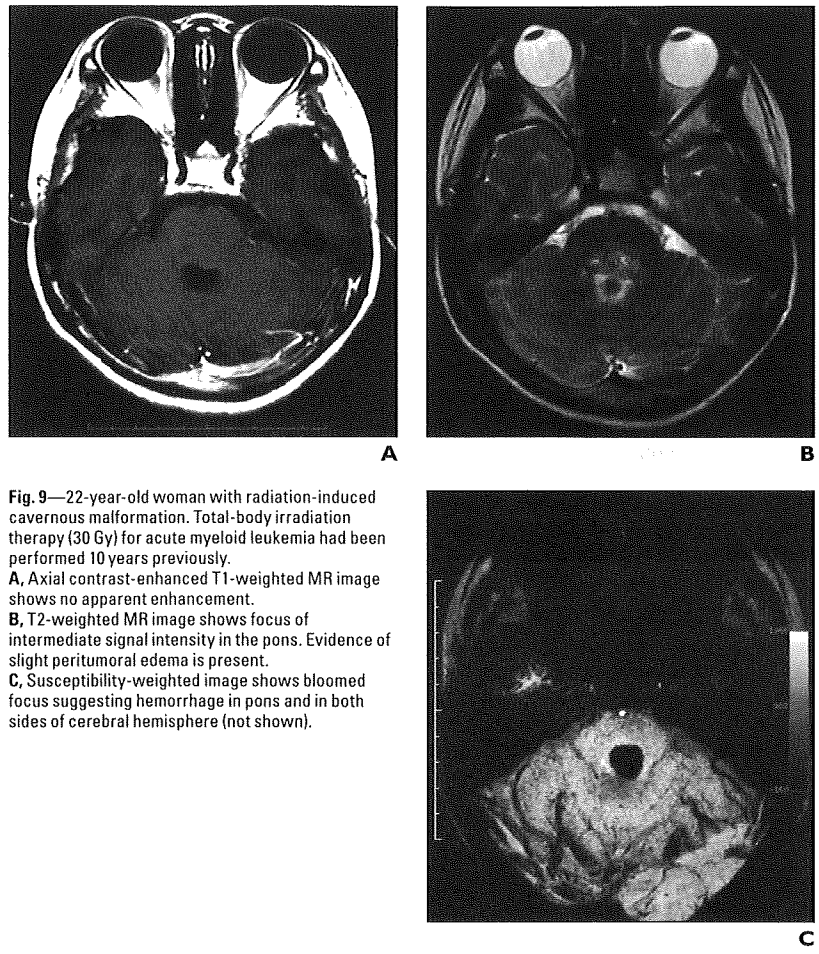


Fig. 9—22-year-old woman with radiation-induced cavernous malformation. Total-body irradiation therapy (30 Gy) for acute myeloid leukemia had been performed 10 years previously.
A, Axial contrast-enhanced T1-weighted MR image shows no apparent enhancement.
B, T2-weighted MR image shows focus of intermediate signal intensity in the pons. Evidence of slight peritumoral edema is present.
C, Susceptibility-weighted image shows bloomed focus suggesting hemorrhage in pons and in both sides of cerebral hemisphere (not shown).

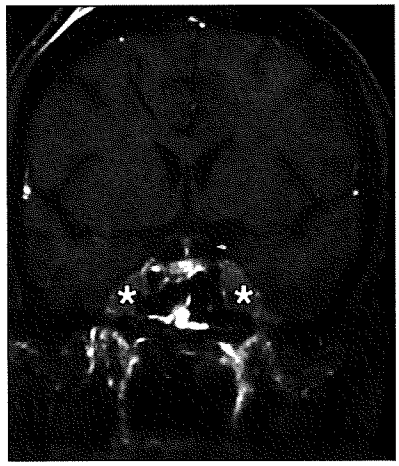


Fig. 10—24-year-old woman with CNS infiltration of malignant lymphoma. Coronal contrast-enhanced T1-weighted MR image shows bilateral masses in Meckel's cave (*asterisks*) and left foramen ovale.

As a late-onset complication, radiation-induced vascular injury such as telangiectasia (cavernoma formation) has been well recognized. Compared with conventional MRI, susceptibility-weighted imaging overwhelmingly depicts hemorrhagic foci and can contribute to the diagnosis (Fig. 9).

Tumor and Tumor-Mimicking Lesions

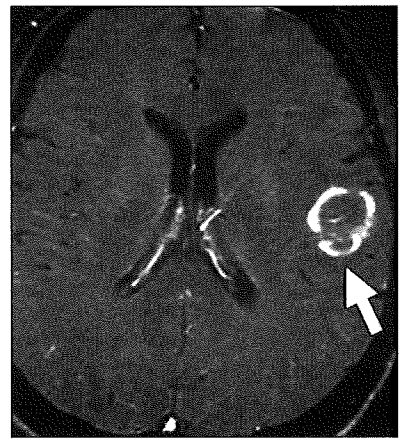
CNS relapse of underlying disease, especially in patients with leukemia or lymphoma, can occur depending on the initial treatment or depletion of the graft-versus-malignancy effect on the underlying disease (Fig. 10). An increased incidence of newly emerged cancer, mainly lymphoma and hematopoietic disorders, in the early follow-up period has been found among HSCT recipients. Patients treated for hematopoietic malignant disease, especially those who received high doses of total-body irradiation at a young age, are at high risk of development of a new solid malignant tumor 10 or more years later in life, the cumulative incidence being 2.2–6.7% [39]. In the CNS, tumors such as glioblastoma, astrocytoma, lymphoma, and meningioma can occur [22]. The clinical findings of relapse of leukemia or lymphoma can mimic the late neurologic sequelae of HSCT and should be carefully evaluated [40].

A tumefactive demyelinating lesion is an example of a tumor-mimicking lesion. This lesion is indistinguishable from a brain tumor in a single imaging analysis, especially when it occurs incidentally in the chronic phase after HSCT, during which an increased incidence of secondary malignant diseases is of great concern (Fig. 11). The tumefactive demyelinating lesion is thought to be a solitary lesion larger than 2 cm in diameter with imaging characteristics mimicking a neoplasm. Tumefactive demyelinating lesion affects young women with atypical clinical symptoms compared with those of conventional multiple sclerosis [41]. A good response to steroid therapy can be a clue to differentiation from neoplastic lymphoid infiltration, although this finding is not always definitive. Penetrating vessels, which are well depicted on susceptibility-weighted images, and the chemical composition of the demyelinating lesion, which is well depicted with proton MR spectroscopy, have been postulated to aid the differential diagnosis [42, 43]. Immune-mediated acute disseminated encephalomyelitis, Guillain-Barré syndrome, and chronic idiopathic demyelinating polyneuropathy have been reported [44–46] to occur in temporal relation to posttransplantation immunologic cross-reactions to a central or peripheral nerve protein, which can be triggered by various viral infections, reactivation of immunized pathogens, and chronic GVHD.

Progressive multifocal leukoencephalopathy can occur in immunocompromised patients. Although it is mostly found in HIV-positive populations and has been reported to be rare among HSCT recipients, this disorder should be considered in the differential diagnosis when an HSCT recipient has worsening of neurologic symptoms [47].

Lymphoproliferative Disorders

Latent viral infection or reactivation contributes to various abnormal immune reactions, including posttransplantation lymphoproliferative diseases. These diseases are a spectrum of unregulated proliferation of B cells ranging from polyclonal lymphoid hyperplasia to monoclonal malignant lymphoma. Epstein-



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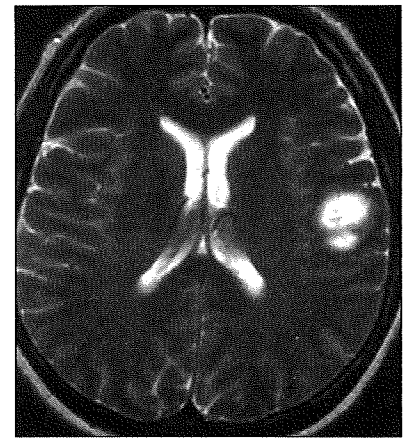

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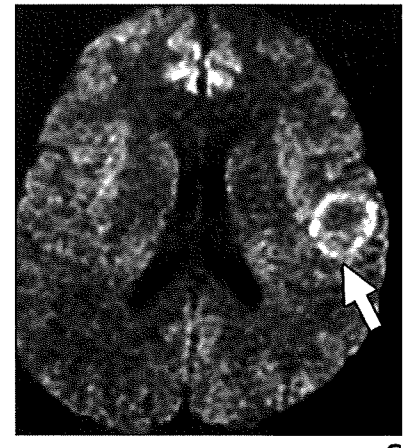
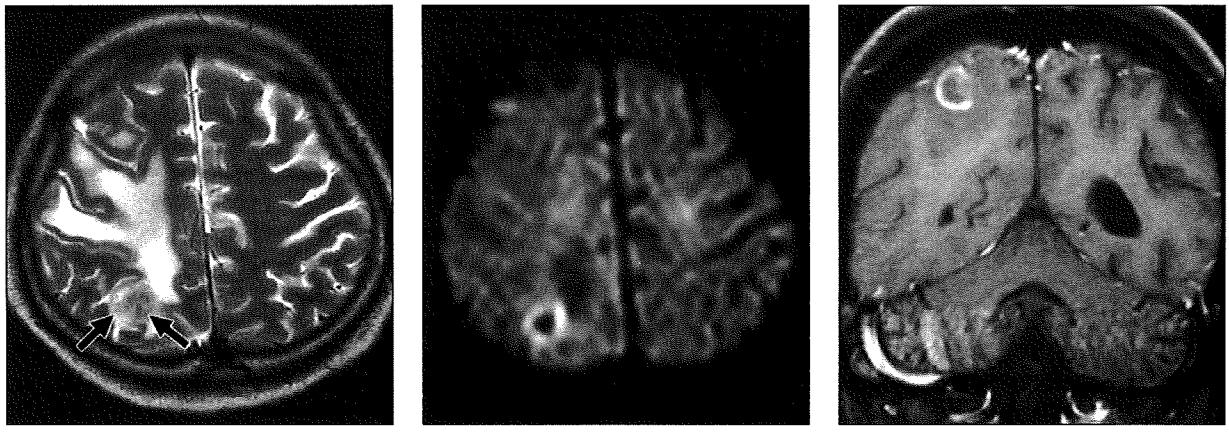


C

Fig. 11—31-year-old woman with tumefactive demyelinating lesion and clinically relapsed acute myeloid leukemia.
A, Axial contrast-enhanced T1-weighted MR image shows lesion has interrupted ring enhancement (*arrow*).
B, Axial T2-weighted MR image shows minimal mass effect and no perilesion edema.
C, Diffusion-weighted image (b = 1,000) depicts hyperintense rim suggesting increased extracellular space due to myelin vacuolization (*arrow*).



A B C

Fig. 12—32-year-old man with posttransplantation lymphoproliferative disorder on 180th day after hematopoietic stem cell transplantation (HSCT). (Courtesy of Ichihashi S, Kurashiki Chuo Hospital, Okayama, Japan)
A, Axial T2-weighted MR image shows mass (*arrows*) of low to intermediate signal intensity with prominent peritumoral edema.
B, Diffusion-weighted image shows restricted water diffusion suggestive of hypercellularity in mass.
C, Contrast-enhanced T1-weighted coronal image shows lesion with ringlike enhancement.

Barr virus–induced B-cell proliferation (85%) in combination with suppression of the T-cell system by immunosuppressive therapy is strongly related to the pathophysiologic mechanism [48]. The frequency is less than 2.0–7.4% of HSCT patients, and CNS involvement is rare (1–6%) with a reported incidence of 64% in the abdomen, 50% in the thorax, and 25% in the head and neck. Lymphoproliferative disorders generally occur 0.5–4 years after HSCT, in the first year in 60% of affected patients. The clinical symptoms of posttransplantation lymphoproliferative diseases are nonspecific, such as fever, malaise, and lymphadenopathy. It is difficult to differentiate the lesion from infection and tumor relapse in a single imaging assessment.

In general, CNS posttransplantation lymphoproliferative disease preferentially occurs in the cerebral subcortical white matter and periventricular white matter rather than in the cerebellum or brainstem. The lesion can be solitary or multifocal depending mostly on the immunologic status of the patient. The solitary mass is reported to be more common in nonimmunocompromised patients [49]. The imaging manifestations are ringlike enhancement after IV injection of contrast material, closely resembling that of CNS lymphoma in persons with AIDS-related conditions and in elderly persons. On T1-weighted, T2-weighted, and FLAIR MR images, the lesion has a slightly heterogeneous internal intensity, reflecting hypercellularity, hemorrhage, and necrosis [48, 50] (Fig. 12). Diffusion-weighted imaging cannot always be used to differentiate posttransplantation lymphoproliferative disease from CNS lymphoma, because necrosis is found in posttransplantation lymphoproliferative disease in 30–90% of cases [49]. The clinical history, immune status of the recipients, and response to therapy are important in diagnosis. Long survival is associated with accelerated reduction of immunosuppressive therapy and immune restoration by eradication of the Epstein-Barr virus.

Conclusion

CT and MRI can show various CNS lesions in HSCT recipients. Dedicated imaging sequences and a comprehensive approach focusing on the patient's immune status, interval after treatment, and the pathophysiologic mechanisms of a spectrum of CNS complications will aid in achieving the correct diagnosis and prompt treatment. Radiologists can play a pivotal role in supporting proper treatment decisions and achieving better clinical prognoses in the era of advanced HSCT.

Acknowledgments

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ORIGINAL ARTICLE

Heart rate variability during and after peripheral blood stem cell leukapheresis in autologous transplant patients and allogeneic transplant donors

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Abstract Side effects of varying severity are frequent in peripheral blood stem cell harvest (PBSCH). Life-threatening complications associated with PBSCH have also been reported. Heart rate variability (HRV), which reflects sympathovagal balance and autonomic cardiovascular control, has been a subject of intense interest in various diseases precipitating sudden death. Here, we prospectively assessed the impact of leukapheresis on HRV among autologous hematopoietic cell transplant patients and healthy donors. We found that HRV indicators, the standard deviation of normal-to-normal intervals (SDNN) value, the square root of the mean of the sum of squared differences between the adjacent normal-to-normal interval (r-MSSD) value, total frequency (TF), high frequency (HF) and low frequency (LF) powers decreased significantly to morbid levels during leukapheresis (all $P < 0.01$). Morbid changes in SDNN value, TF and LF powers were significantly sustained for 6–9 h after leukapheresis (all $P < 0.05$). Furthermore, TF and LF powers prior to leukapheresis were significantly lower in subjects with symptomatic hypotension than in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) ms^2, $P = 0.03$; 93 (42–144) vs. 237 (142–360) ms^2, $P = 0.03$, respectively]. Our results suggest that HRV analysis might be of use in evaluating and predicting the adverse effects of cardiovascular complications in PBSCH.

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1 Introduction

Peripheral blood stem cell harvesting (PBSCH) has been widely used for rescue following high-dose chemotherapy, or as an alternative to bone marrow as a stem cell source for allogeneic hematopoietic cell transplantation. The most common side effects are associated with recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration, securing peripheral venous access, or anticoagulation with acid-citrate-dextrose (ACD) solution. These adverse effects are usually transient, not severe and easily controlled with adequate treatment. Severe adverse events in PBSC donors, the majority of which are acute and transient, occur at an incidence of 0.6% [1]. However, although extremely rare, life-threatening complications relating to PBSC donation, including sudden death or transient cardiac arrest, have been reported [2–5]. In several sudden death cases following PBSCH, the underlying mechanisms that led to the occurrence of sudden death have not been clearly described or clarified.

In normal sinus rhythm, the heart rate varies from beat to beat. The impulse generated by the sinus node is affected by the automatic nervous system and various humoral factors. The cardiovascular signal variability of the R–R period (heart rate variability, HRV) is an established tool that can be used to assess autonomic control. HRV assessment enables the evaluation of dynamic changes in the automatic nervous system and humoral factors without an invasive procedure. Recent evidence shows that a decrease in HRV is strongly associated with sudden death

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and/or a cardiac event after a myocardial infarction. The usefulness of HRV as a clinical tool has been explored in numerous conditions, such as ischemic sudden death, sustained ventricular tachycardia, myocardial infarction, congestive heart failure, vasovagal syncope, hypertrophic cardiomyopathy, obstructive sleep apnea, diabetic neuropathy and various neurological alterations [6–14]. Two types of analysis, time domain and frequency domain, are included in HRV analysis. In time domain analysis, acknowledged simple markers are the standard deviation of normal-to-normal intervals (SDNN) and the square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals (r-MSSD). In frequency domain analysis, markers include TF, total frequency (0.0001–0.5 Hz); LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.4 Hz); and LF/HF ratio. These HRV power spectrum analyses are used to investigate sympathovagal balance, autonomic cardiovascular control and/or target function impairment. The LF component, which is called perfusion rhythmicity, reflects the rennin–angiotensin system or angiokinetic activity. The HF component, called respiratory rhythmicity, reflects breathing variability. Thus, the LF/HF ratio and HF have been used as markers of sympathetic and parasympathetic activity, respectively [15]. The aim of this study was to assess HRV during or after leukapheresis in autologous transplant patients and healthy PBSC donors.

2 Subjects and methods

2.1 Baseline characteristics

In this study, we enrolled 29 subjects (22 allogeneic transplant donors and 7 autologous transplant patients; 10 males, 19 females; median age: 38 years; interquartile range (IQR): 27–53). Median age of the autologous transplant patients and healthy allogeneic donors was 56 (IQR: 33–62) and 35 (IQR: 27–50) years, respectively. Diagnoses of the 7 autologous transplant patients were non-Hodgkin's lymphoma (6 patients) and plasmacytoma (1 patient). All the autologous transplant patients had a history of previous chemotherapy including anthracycline. The median cumulative dose of anthracycline in the 7 autologous transplant patients was 245 mg/m^2 (IQR: 160–297).

The study was conducted in accordance with a protocol approved by the IRB at our institution. Written informed consent was obtained from each patient or healthy donor.

2.2 Peripheral blood collection procedure

Autologous PBSCH was performed during the recovery phase after chemotherapy and was supported by subcutaneous administration of 10 μg/kg/day of rhG-CSF. In allogeneic PBSCH from healthy donors, on the other hand, leukapheresis was initiated following the administration of 10 μg/kg/day of rhG-CSF for 4 days. Of the 29 leukapheresis, 18 were performed using a CS3000 Plus (Baxter, Tokyo, Japan), 4 using an Amicus^{TM} Separator (Baxter, Tokyo, Japan) and 7 using a COBE Spectra (BCT Japan, Tokyo, Japan). In all 7 autologous harvest patients and 7 allogeneic harvest donors, central venous access via the femoral vein was secured.

2.3 HRV analysis

In all patients and donors, ambulatory ECG recording was performed for 24 h during the first leukapheresis day but also for 24 h prior to leukapheresis to obtain control data. As control data, we employed the values of HRV indicators obtained during the same time period as leukapheresis on another day before leukapheresis. The data obtained from the 24-h ambulatory ECG recording were stored in a computer. Beat-by-beat cardiac cycle data were obtained by off-line computer analysis methods. The maximum entropy spectral analysis method was used to calculate HRV (MemCalc/CHIRAM version 1, Suwatrust, Tokyo, Japan). This program can perform time domain and frequency domain analyses simultaneously, and is superior to the fast Fourier transform and autoregressive methods in terms of the reproducibility of the original time series. The analysis was automatically performed in short segments and then averaged. In the program, all extrasystolic beats and artifacts were eliminated. We used markers, including heart rate (HR), normal-to-normal intervals (NN), SDNN and r-MSSD in time domain analysis, and TF, LF, HF and LF/HF ratio in frequency domain analysis. The program represents the average values of all markers every 5 min. In the program, TF was defined as the frequency range from 0.0001 to 0.5 Hz and included HF, LF, very low frequency and ultra low frequency. Therefore, at least 3 h of data are needed for TF power measurement; however, since leukapheresis took less than 3 h in 3 of the 29 subjects, TF power during leukapheresis was used in only 26 subjects. We applied the average values of all markers during the leukapheresis periods to assess HRV during leukapheresis, and applied the average values of all markers every 3 h following leukapheresis to assess HRV after leukapheresis.

We compared HRV control data measured for 24 h before leukapheresis between autologous transplant patients and allogeneic transplant donors in all 29 subjects. Control data were available in 26 of the patients, obtained on the day before leukapheresis during the same time period as leukapheresis. We therefore compared HRV data obtained during leukapheresis with control data acquired during the same time period prior to leukapheresis in 26

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evaluable subjects. Furthermore, to evaluate HRV changes after leukapheresis, we compared HRV data obtained during the nine-hour period after leukapheresis with control data obtained during the same time period prior to leukapheresis. This last comparison was possible in 24 subjects.

2.4 Statistical analysis

To evaluate the association between Hb levels just before leukapheresis and HRV indicators, we used Pearson's correlation coefficient. The Mann–Whitney U test was employed to analyze differences in HRV value between autologous transplant patients and healthy donors. The Wilcoxon's rank test was used to compare differences between HRV values during leukapheresis, or transitional changes in HRV values following leukapheresis, with control data measured during the same time period as the measurements taken during or following leukapheresis. Repeated measurements of analysis of variance were used to evaluate the effect of factors [age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant patients] on rate of change in HR and HRV values from before to during leukapheresis. All P values less than 0.05 were considered significant.

3 Results

At HRV measurement, the median processed whole blood volume was 173 ml/kg (IQR: 140–196 ml/kg), the median leukapheresis time was 215 min (IQR: 188–248 min) and the median leukapheresis rate was 43 ml/min (IQR: 37–52 ml/min).

In all subjects, the r-MSSD value, TF, LF and HF powers at baseline showed a significant correlation with Hb levels before leukapheresis [Correlation coefficients: 0.61, 0.45, 0.58 and 0.45 (all $P < 0.05$), respectively]. In the autologous transplant patients, Hb levels before leukapheresis were significantly lower than in the healthy donors [(Median (IQR): 10.2 (9.4–11.5) vs. 13.5 (12.2–14.1) g/dl, respectively, $P = 0.0007$]. The r-MSSD value and LF power were significantly lower in the autologous transplant patients than in the healthy donors in the data for the 24 h prior to leukapheresis [Median (IQR); 21.8 (15.3–28.0) vs. 30.3 (26.1–39.4) ms, $P = 0.01$, 393 (205–416) vs. 603 (436–761) ms^2, $P = 0.03$, respectively] (Fig. 1).

In all the 26 evaluable subjects, SDNN, r-MSSD, TF, LF and HF values significantly and markedly decreased to morbid levels during leukapheresis (all $P < 0.001$) (Fig. 2). The HR and NN values and LF/HF ratio during leukapheresis did not change significantly compared with the control data. Similarly, among the allogeneic transplant donors, SDNN, r-MSSD, TF, LF and HF values decreased significantly (all $P < 0.05$) and the HR and NN values and LF/HF ratio did not change significantly during leukapheresis. When limited to the autologous transplant patients, HR became significantly elevated during leukapheresis [Median (IQR): 84.3 (77.4–88.4) vs. 93.4 (82.6–97.6) beats/min, respectively, $P = 0.03$]. NN, SDNN, r-MSSD, LF and HF values decreased significantly (all $P < 0.05$) and TF tended to decrease ($P = 0.07$) during leukapheresis. The LF/HF ratio did not change significantly during leukapheresis.

Advanced age (≤60) significantly affected HR elevation during leukapheresis in comparison to baseline (Mean ± SD: 76.4 ± 12.9 and 87.7 ± 9.4 beats/min, $P = 0.02$). However, the factors including age (>60 or ≤60), sex, weight (>50 or ≤50 kg) and autologous transplant did not significantly affect the degree of decrease in HRV values during leukapheresis from the baseline.

Furthermore, r-MSSD power improved almost to control levels 6–9 h following leukapheresis (Table 1). On the other hand, SDNN, TF and LF values did not normalize to control levels even 6–9 h following leukapheresis (all $P < 0.05$). Furthermore, HF also did not completely normalize to control levels even 6–9 h following leukapheresis; however, this was not statistically significant ($P = 0.22$).

Of the 29 harvest cases, symptomatic hypotension occurred during leukapheresis in 2 subjects and about 3 h after leukapheresis in 1 subject. All 3 subjects were female, their systolic blood pressure decreasing significantly from 108, 96 and 114 mmHg to 82, 72 and 76 mmHg, respectively. In a 47-year-old female, anginal chest pain and dyspnea occurred; in a 52-year-old female, nausea, blurry vision and chest oppression were evident; and another 52-year-old female experienced nausea and dizziness with hypotension. However, symptomatic hypotension immediately improved with saline infusion, tilting the patient head-down, or discontinuance of leukapheresis. Notably among the HRV indicators, in the three subjects with symptomatic hypotension, TF and LF powers were significantly lower prior to leukapheresis than those in the other subjects [3282 (3121–4427) vs. 6018 (4983–9816) ms^2, $P = 0.03$; 93 (42–144) vs. 237 (142–360) ms^2, $P = 0.03$, respectively].

4 Discussion

In the present study we detected that the time domain indicators including SDNN and r-MSSD, and the frequency domain indicators including TF, HF and LF markedly decreased during leukapheresis and that this decrease was sustained over several hours after leukapheresis.

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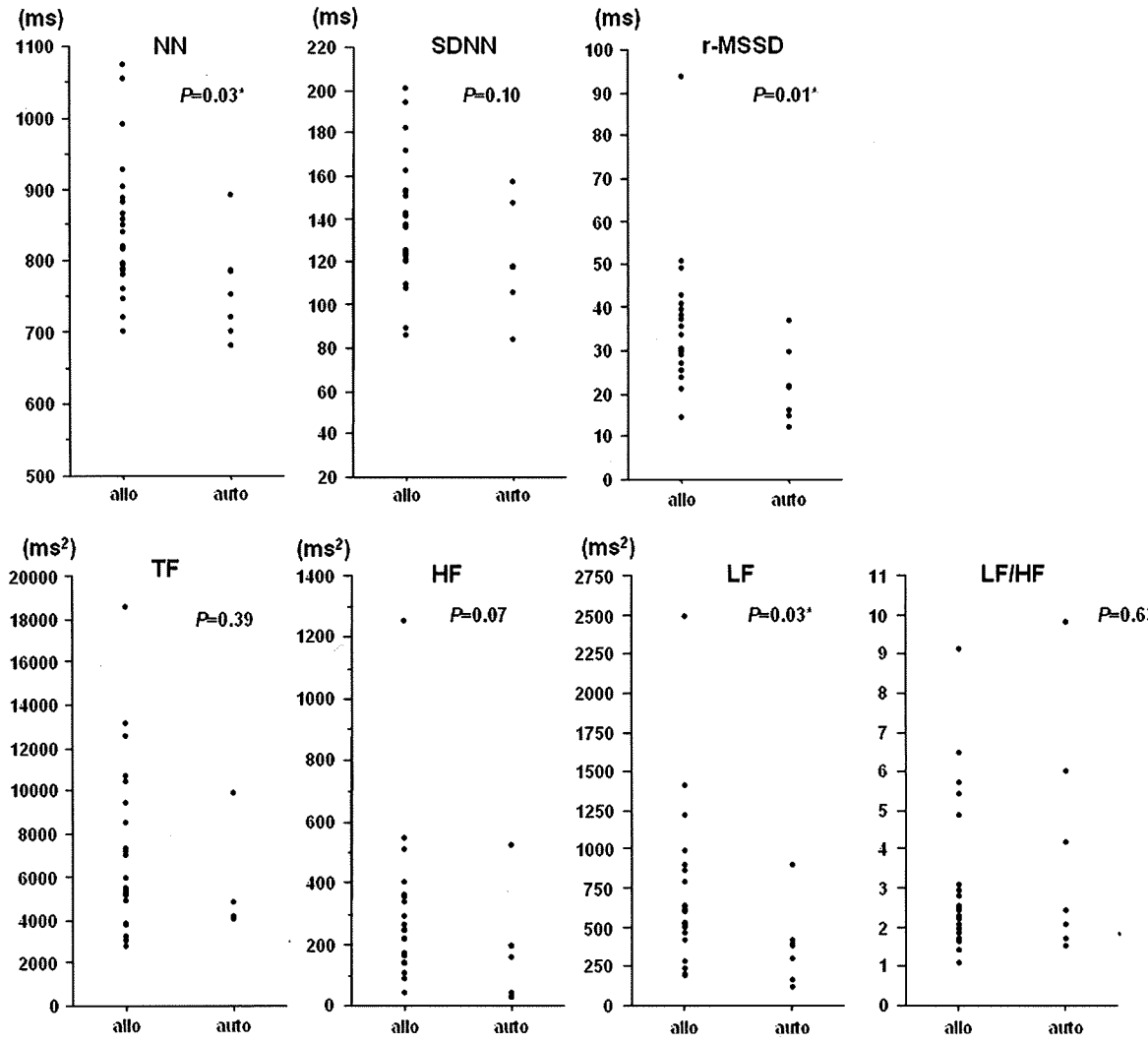

Fig. 1 Comparison of heart rate variability (HRV) indicator values between autologous transplant patients and healthy donors. NN, r-MSSD and LF were significantly lower in the autologous hematopoietic cell transplant patients than in the healthy donors. *auto* autologous hematopoietic cell transplant patients, *allo* allogeneic hematopoietic cell transplant healthy donors, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

Interestingly, in subjects who had symptomatic hypotension, TF and LF powers at baseline were significantly lower than for subjects without adverse cardiovascular effects.

It is reported that in patients with chronic heart failure, those with an SDNN value of less than 44 ms are at risk of cardiac events and all-cause mortality [16]. Surprisingly, in the 6 (86%) out of the 7 autologous transplant patients and in 7 (32%) out of the 22 allogeneic transplant donors, the SDNN value decreased to less than 44 ms during leukapheresis. Additionally, in 2 out of the 3 subjects with symptomatic hypotension, SDNN values decreased to less than 44 ms during leukapheresis.

Although we cannot clearly explain the underlying mechanism of HRV alteration during leukapheresis, we speculate that such a major change in HRV indicators was induced by heightened sympathetic activity and parasympathetic withdrawal, mediated by a hemodynamical or neural effect of the leukapheresis procedure and/or other pathogenesis, including altered concentrations of electrolytes in serum and metabolic alkalosis [17]. Both r-MSSD and HF are known to reflect parasympathetic activity; thus the significant reduction in the r-MSSD value and HF power suggested parasympathetic activity was reduced during leukapheresis. It has been reported that

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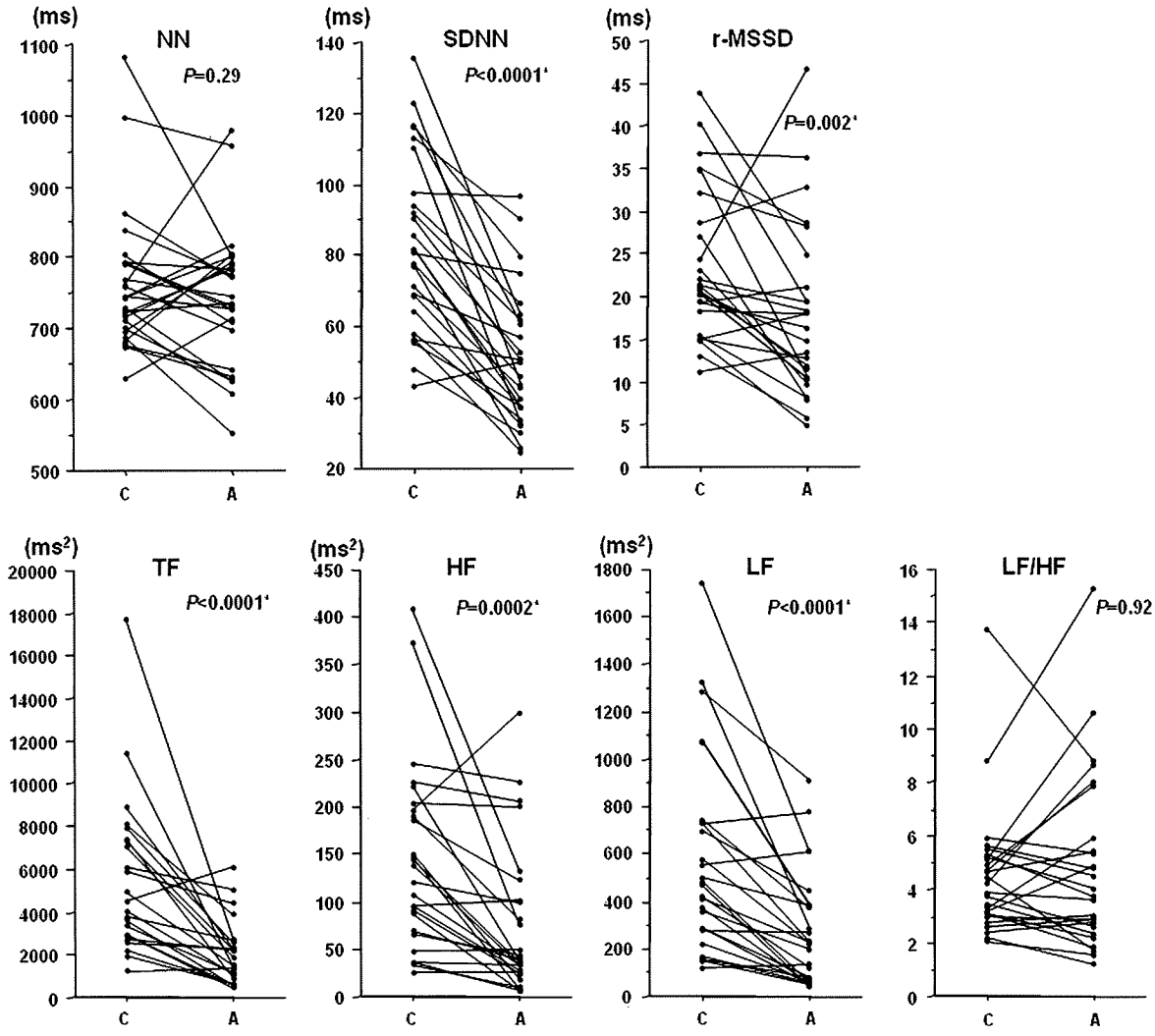

Fig. 2 Comparison of control data and heart rate variability (HRV) indicator values during leukapheresis. Many HRV indicators decreased significantly during leukapheresis. *C* control HRV values, *A* HRV values during leukapheresis, *NN* normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

parasympathetic withdrawal is seen in patients with congestive heart failure and parasympathetic withdrawal causes a decrease in HRV [18]. Therefore, we speculated that the suppression of parasympathetic activity might be causally related to critical cardiovascular complications in PBSCH.

In this study, LF power also significantly decreased during leukapheresis. In recent reports, reduced LF spectral power was also identified as a risk of all-cause mortality [19] and sudden cardiac death [20] in chronic heart failure. LF power is more complicated because it is jointly mediated by the sympathetic and parasympathetic nervous systems [21]. Reduced R–R interval variability and parasympathetic activity withdrawal might also be associated with reduced LF power.

In addition, citrate-based anticoagulants, such as the ACD solution used for leukapheresis, decrease the concentration of electrolytes in serum by chelation and cause hypocalcemia, hypomagnesemia [22] and intermittent hypotension [23] in leukapheresis. A previous report showed that electrolyte abnormalities mediated by citrate, such as hypocalcemia, may change HRV [24].

Life-threatening complications associated with PBSC donation reportedly occur after, rather than during, leukapheresis [2, 3]. Notably, our data showed that abnormal HRV indicators persisted 6–9 h after leukapheresis

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Table 1 Changes in HRV indicators following leukapheresis

	0–3 h [Median (IQR)]			3–6 h [Median (IQR)]			6–9 h [Median (IQR)]		
	Control	Post-leukapheresis	*P*	Control	Post-leukapheresis	*P*	Control	Post-leukapheresis	*P*
SDNN (ms)	92 (74–110)	75 (65–82)	0.002*	96 (82–110)	69 (60–86)	0.002*	86 (74–103)	75 (60–91)	0.01*
r-MSSD (ms)	26 (15–37)	23 (13–31)	0.002*	30 (24–37)	19 (12–34)	0.001*	33 (22–42)	28 (15–42)	0.34
TF (ms^2)	5996 (3861–10229)	4291 (2925–5188)	0.02*	5723 (3408–8008)	3772 (2760–6092)	0.04*	4909 (3647–7392)	3097 (2556–5145)	0.01*
HF (ms^2)	157 (44–266)	107 (27–196)	0.02*	215 (83–300)	74 (28–235)	0.002*	277 (120–430)	180 (46–417)	0.22
LF (ms^2)	489 (382–751)	471 (136–685)	0.04*	523 (340–846)	287 (160–605)	0.0008*	688 (387–879)	337 (190–579)	0.0004*
LF/HF	3.6 (2.9–5.1)	4.0 (3.3–5.8)	0.27	2.9 (2.3–4.5)	3.1 (2.1–7.3)	0.10	2.6 (1.5–5.5)	2.3 (1.1–3.6)	0.15

IQR interquartile range, *SDNN* standard deviation of normal-to-normal intervals, *r-MSSD* square root of mean of sum of squared differences between adjacent normal-to-normal intervals, *TF* total frequency, *HF* high frequency, *LF* low frequency

* $P < 0.05$

(Table 1). The altered concentration of electrolytes in serum, mediated by ACD solution or hypovolemia, which remained long after leukapheresis, might cause symptomatic hypotension and reduce HRV. Such pathologic conditions might, in extremely rare instances, lead to severe cardiovascular complications in a patient with latent cardiovascular diseases.

In the 3 subjects with symptomatic hypotension, tachycardia was not observed at the onset of hypotension (Subject 1: 82/46 mmHg, 72 beats/min; Subject 2: 72/42 mmHg, 66 beats/min; Subject 3: 76/48 mmHg, 60 beats/min). Vasovagal hypotension, which occasionally occurs during leukapheresis, is a neurally mediated reaction due to blood pressure decreases without compensatory tachycardia. In patients with vasovagal hypotension, bradycardia is therefore often observed. We therefore speculate that vasovagal reflex played a critical role in the development of symptomatic hypotension in these subjects.

Finally, some HRV indicators in the autologous transplant patients were significantly lower than those in healthy donors. In the present study, ages were higher and Hb levels before leukapheresis were lower in autologous transplant patients than in the healthy donors. Furthermore, all patients scheduled to receive an autologous transplant had a history of chemotherapy. Chemotherapy including anthracycline has been reported to reduce the values of HRV indicators [25]. Therefore, decreased values of some HRV indicators might have been caused by advanced age, anemia and/or the cumulative toxicity of chemotherapy, especially that caused by anthracycline drugs.

The major obstacle which precludes translating HRV analysis into clinical practice is that we can analyze HRV during leukapheresis only retrospectively. However, our data suggest that HRV prior to leukapheresis might have potential as a useful non-invasive tool for predicting autonomic or cardiovascular complications. Therefore, in the future, we need to examine the prognostic value of HRV for autonomic or cardiovascular complications in more detail by using a larger cohort.

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Infectious complications in patients receiving autologous CD34-selected hematopoietic stem cell transplantation for severe autoimmune diseases

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Abstract: Long-term analysis of infectious complication after high-dose immunosuppressive therapy with CD34-selected autologous hematopoietic stem cell transplantation for patients with severe autoimmune diseases (AD) was performed. Theoretically, CD34 selection can reduce the risk of reinfusion of autoreactive lymphocytes. However, it is also associated with a significant reduction in T cells, natural killer cells, and monocytes, which in turn may compromise immune reconstitution, thereby increasing the risk of infection. Moreover, AD compromises host immunity and causes organ damage resulting in dysfunction of the cutaneous or mucosal barrier. In this study, the incidence rate of infections is reported in 14 patients who underwent high-dose (200 mg/kg) cyclophosphamide therapy followed by reinfusion of CD34-selected autologous peripheral blood stem cells. Bacterial complication occurred in 3 of 14 (21%) patients. Cytomegalovirus reactivation and adenovirus hemorrhagic cystitis were observed in 9 (64%) and 2 (14%) patients, respectively. As for late infectious complications, 7 patients (50%) developed dermatomal varicella zoster virus infection. No infection-related mortality was seen in this case series. Because the risk for infections approaches that seen in allogeneic transplant recipients, infection surveillance, diagnostic workup, and prophylactic strategies similar to those applicable to allogeneic recipients are warranted.

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Pilot studies comprising high-dose immunosuppressive therapy followed by transplantation of autologous hematopoietic stem cells (HSC) were conducted to obtain safety and preliminary efficacy data in patients with severe autoimmune diseases (AD) (1–5).

Both unselected and CD34-selected peripheral blood stem cells (PBSC) have been used as sources of HSC (1–5). Theoretically, CD34 + cell selection of PBSC can reduce the possibility of reinfusion of autoreactive lymphocytes. However, the superiority of CD34-selected PBSC over unmanipulated PBSC has not been established. The safety and efficacy of CD34-selected autologous PBSC transplantation (PBSCT) for refractory AD have been investigated at our institute (6).

PBSCT-related complications include regimen-related toxicities and various infections. For the treatment of AD, PBSCT is a more toxic treatment modality than the conventional immunosuppressive therapies. Organ damage due to AD puts the patients at risk of regimen-related toxicities. Thus, careful selection of refractory AD patients for PBSCT is essential to minimize transplant-related mortality.

Infections are major contributors to morbidity and mortality in PBSCT. In hematological malignancies, CD34-selected autologous PBSCT has been reported to increase incidences of opportunistic infections compared with non-CD34-selected autologous PBSCT (7–11). Most AD patients had undergone immunosuppressive therapy, including cyclosporine and corticosteroids, before transplantation. AD

itself compromises host immunity to various infections. Furthermore, AD causes organ damage such as skin ulcers, esophageal dysmotility, and interstitial pneumonia (IP) resulting in dysfunction of the cutaneous or mucosal barrier. Thus, the understanding of infectious complications is important in increasing the safety of CD34-selected autologous PBSCT for AD.

Here, we retrospectively analyze infectious complications during the course of CD34-selected autologous PBSCT for severe AD.

Materials and methods

Protocol

The protocol of this phase I/II clinical trial (6) was approved by the ethics committee of Kyushu University Hospital. Written informed consent was obtained from all patients.

Patients and eligibility

Patients between 16 and 65 years of age were eligible at the time of pre-transplant evaluation. Patient eligibility depended on the diagnosis of AD, as previously described (6).

PBSC mobilization and CD34 + cell selection

PBSC were mobilized during hematological recovery after administration of cyclophosphamide (CY) (2 g/m^2/day) for 2 days, followed by a recombinant human granulocyte-colony stimulating factor (G-CSF, filgrastim; Kirin Brewery, Tokyo, Japan) at a dosage of 2 μg/kg/day. After collecting PBSC to obtain 2×10^6 CD34 + cells/kg or more by apheresis, CD34 + cells were positively selected using immunomagnetic beads with an anti-CD34 monoclonal antibody (CliniMACS, Miltenyi Biotec, Cologne, Germany).

Autologous PBSCT and supportive care

Patients were kept in HEPA-filtered rooms until engraftment. For pre-transplant conditioning, high-dose CY (50 mg/kg/day) was administered for 4 days, from days −5 to −2. Frozen-thawed CD34-selected PBSC were infused on day 0. All immunosuppressive and disease-modifying agents were discontinued upon HSC procurement, except systemic corticosteroids, which were tapered to a relatively low dose (5–15 mg of prednisolone/day) over 2–6 months after PBSCT. Acyclovir (intravenous 250 mg/day, from days 1 to 18), ciprofloxacin (by mouth [PO] 600 mg/day, from days −7 to 14), fluconazole (PO 200 mg/day, from days −7 to 30), and trimethoprim-sulfamethoxazole (TMP-SMX) (each 1920 mg/day; from days −14 to −2, and twice a week from days 30 to 180, respectively) were prophylactically administered, as previously described (6). Neutropenic fever was treated with intravenous administration of broad-spectrum cephalosporins according to the guidelines for the use of antimicrobial agents in neutropenic patients (12). After engraftment, weekly monitoring of cytomegalovirus (CMV) pp65 antigenemia was conducted until day 100 after transplant (13). If CMV antigenemia was detected, preemptive therapy was initiated with ganciclovir.

Diagnosis and definition of infections

The day of onset of infection was defined as the day the diagnostic test was performed.

Bacterial infections were categorized as bacteremias and site-specific infections (14). Varicella zoster virus (VZV) infections were defined as typical cutaneous vesicular lesions. CMV infection and disease were defined as previously described (13, 15). In brief, CMV infection was defined as isolation of the CMV virus or detection of the viral proteins or nucleic acids in body fluid or tissue specimen. CMV disease is defined by the presence of organ-specific signs and/or symptoms with the detection of CMV in test specimens (e.g., bronchoalveolar lavage in the lungs or biopsy samples in other organs). CMV infection with unexplained fever for at least 2 days within a 4-day period and the presence of neutropenia or thrombocytopenia is considered CMV syndrome. Hemorrhagic cystitis (HC) due to adenoviruses (AdV) was diagnosed when AdV were detected by either viral culture or polymerase chain reaction in macroscopic hematuria with clinical signs of cystitis. To exclude regimen-related HC, patients with *de novo* hematuria at least 10 days after HSC transplantation (HSCT) and no tendency toward generalized bleeding or bacteriuria were considered to have AdV HC (16). Fungal infection was defined by proven or probable invasive fungal infection (17) and clinical or radiological manifestation along with positive microbiological tests.

Results

Patients

Fourteen patients (4 males, 10 females) with a median age of 54 years (range 21–63 years) were examined (Table 1). Patients No. 1–11 were diagnosed as diffuse systemic sclerosis (SSc). Patient No. 1 was suffering from systemic lupus er-

Clinical characteristics of the autoimmune patients receiving CD34-selected transplant

Patient number	Disease	Age (years)	Sex	Complication	Previous therapies	Follow up (months)[1]
1	SSc/SLE	54	F	IP, digital ulcer	DEX, IVCY	72
2	SSc	55	M	IP, digital ulcer	PSL, IVCY	65
3	SSc	58	M	IP	PSL, IVCY	61
4	SSc	54	F	IP	PSL, IVCY	58
5	SSc	53	F	IP	PSL	56
6	SSc	49	F	IP	m-PSL, CsA, IVCY	52
7	SSc	33	F	IP	–	21
8	SSc	63	F	IP	PSL	36
9	SSc	61	F	IP	PSL, CsA	31
10	SSc	44	F	IP	PSL, IVCY	27
11	SSc	52	M	IP, digital ulcer	PSL, CsA, IVCY	23
12	DM	54	F	IP	PSL pulse, CsA, IVCY	70
13	DM	44	F	IP, skin ulcer	PSL pulse, CsA	12
14	WG	21	M	Exophthalmos	PSL pulse, IVCY	55

[1]After transplantation.
SSc, systemic sclerosis; SLE, systemic lupus erythematosus; IP, interstitial pneumonia; DEX, dexamethasone; IVCY, intravenous cyclophosphamide; PSL, prednisolone; m-PSL, methyl prednisolone; CsA, cyclosporine; DM, dermatomyositis; WG, Wegener's granulomatosis.

Table 1

ythematosus (SLE) for 22 years and SSc for 2 years. Although SLE was inactive, she had progressive IP and severe digital ulcers due to SSc. Patients No. 2–11 (SSc) and 12 and 13 (dermatomyositis) developed IP, which did not respond to immunosuppressive agents. Patients No. 3–6, 8, 9, and 11 showed severe skin sclerosis. Patient No. 3 had been in complete remission from non-Hodgkin's lymphoma for 1 year and was considered eligible. Patient No. 14 (Wegener's granulomatosis) presented with severe exophthalmos due to granuloma formation (18 mm in diameter) in the upper lateral region of the left orbit affecting the superior rectus muscle. He needed monthly steroid pulse therapy to prevent further growth of the granuloma. The Eastern Cooperative Oncology Group performance status (18) was <3 in all patients. CY and cyclosporine were administered to 9 patients and 5 patients, respectively. All patients, except Patient No. 7, were treated with corticosteroids. The median follow-up duration was 53.5 months after transplant (range 8–72 months).

Results are reported as of March 2008.

Infections

Bacterial

Nine of 14 patients developed febrile neutropenia at a median of 6 (0–9) days after PBSCT (Table 2). Among these, Patients No. 6 and 11 revealed *Streptococcus mitis* bacteremia on days 8 and 9 after PBSCT, respectively. Both were empirically treated with broad-spectrum cephalosporins. Vancomycin was added when the blood culture was reported positive. Patient No. 12 developed high-grade fever without signs of local infection on day 119 post PBSCT, and a blood culture turned out to be positive for *Listeria monocytogenes*. Empirical therapy was initiated with broad-spectrum cephalosporin but switched to penicillin/β-lactamase inhibitor after detection of the microbe. All patients responded to the therapy, and no fatal complications occurred.

Patient No. 14 developed *Mycobacterium gordonae* pneumonia 1343 days after PBSCT. However, he was on anti-tumor necrosis factor (TNF) antibody therapy because of the relapse at that time; thus the case is omitted from this study.

Viral

CMV. Nine of 14 patients developed CMV antigenemia at a median of 28 days (range 10–60 days) after PBSCT. All patients who developed CMV infection were seropositive for CMV antibody before PBSCT, and this was considered as reactivation. Patients were preemptively treated with ganciclovir (5 mg/kg twice a day) and none developed CMV disease. High levels of antigenemia were detected in Patients No. 1 and 6. With their clinical symptoms, these patients were considered to have CMV syndrome. Foscarnet

was administered to Patient No. 12 because CMV antigenemia persisted despite ganciclovir therapy.

VZV. Seven of 14 patients developed VZV infection at a median of 409 days (range 351–1263 days) after PBSCT. All patients were treated with either oral valacyclovir or intravenous acyclovir promptly after diagnosis. All patients had dermatomal disease, and no dissemination was observed.

AdV. Patients No. 1 and 6 developed AdV HC on days 64 and 33, respectively. Cidofovir was administered in both patients.

Fungal

No fungal infection was observed in this case series.

Discussion

We present a long-term analysis of infectious complications in AD patients who had undergone CD34-selected autologous PBSCT.

Bacterial infections were observed in 3 patients. Despite the increased frequency of isolation of viridans streptococci from the blood of neutropenic patients (19, 20), bacteremia from *S. mitis* was observed in only 2 patients in the present study. The incidence of streptococcal bacteremia (2/14; 14%) was the same as that reported in other studies (16–31%) (21, 22). Although antibacterial prophylaxis was undertaken with ciprofloxacin (23), the susceptibility of the pathogen to penicillin was intermediate in both cases; hence, vancomycin was added to the treatment regimen. *L. monocytogenes* infection in HSCT is rare (24) because TMP-SMX, traditionally used for prophylaxis, is active against the microbe. However, the patient did not take TMP-SMX when she developed *L. monocytogenes* bacteremia. As TMP-SMX is effective not only in prophylaxis for *Pneumocystis jirovecii* pneumonia but also against Listeria, Nocardia, and Toxoplasma, its prophylactic administration is mandatory.

CMV reactivation has been reported to be uncommon in unselected autologous PBSCT (25–27). However, 64% of our patients (9/14) became positive for CMV antigenemia after PBSCT and were treated with ganciclovir. Although no patient developed CMV disease, the level of antigenemia in 2 patients was so high that they might have developed CMV disease without monitoring and preemptive therapy. Although it is still not clear whether CD34 selection of autograft itself is a risk for CMV infection (7, 28), this proportion of CMV reactivation is comparable to that of CD34-selected autologous HSCT for hematological malignancies, or allogeneic HSCT (13). Thus, we consider CMV monitoring necessary in AD patients undergoing CD34-selected autologous PBSCT.

Infectious complications in autoimmune patients receiving CD34-selected transplant

Patient number	FN (days)	Bacterial infection (days)	CMV Ab	CMV (days)	VZV (days)	Others (days)
1	5	–	+	38	1263	AdV cystitis (64)
2	–	–	+	–	–	–
3	–	–	+	10	351	–
4	–	–	+	24	418	–
5	–	–	+	–	409	–
6	7	*Streptococcus mitis* (8)	+	33	–	AdV cystitis (31)
7	0	–	–	–	–	–
8	1	–	+	–	–	–
9	5	–	+	22	374	–
10	–	–	+	60	427	–
11	8	*Streptococcus mitis* (9)	+	28	–	–
12	5	*Lysteria monocytogenes* (119)	+	22	358	–
13	9	–	+	–	–	–
14	9	–	+	–	–	–

FN, febrile neutropenia; days, days after hematopoietic stem cell transplantation; CMV, cytomegalovirus infection; Ab, antibody VZV, varicella zoster virus infection; AdV, adenovirus.

Table 2

AdV HC developed in 2 of 14 patients (14%). The incidence of AdV infection in the autologous HSCT is reported to be 1% (29), and HC is a rare development. T-cell depletion and lymphopenia are the risk factors (30, 31) for AdV disease in adults, and severe lymphopenia was seen in both the patients (139 and 318/μL, respectively). They were successfully treated with cidofovir (16).

Regarding late infectious complications, 50% of the patients (7/14) developed VZV infection at a median of 409 days (range 351–1263 days) after PBSCT. Delayed recovery of CD4 + T cell (32, 33) and increased incidences of the VZV infections (8) have been reported in CD34-selected transplantation. In addition to CD34 selection of auto-graft, low-dose steroids were continued after PBSCT in our study. Delayed CD4 + T-cell recovery along with high incidence of late infection were both observed. We used prophylactic acyclovir from days 1 to 35 and did not use long-term low-dose acyclovir prophylaxis (25, 34, 35).

Data are conflicting whether CD34-selected PBSCT for hematologic malignancies and breast cancer cause increased incidence of infections compared with non-CD34-selected PBSCT. In this study, underlying AD itself, prolonged immunosuppressive therapy before PBSCT, CD34 selection of the auto-graft, and low-dose systemic steroid administration after the PBSCT might contribute to the high incidence of infectious complications.

In conclusion, our findings confirm a very high incidence of infectious complications after CD34-selected autologous PBSCT for AD. Because the risk for infections approaches that seen in allogeneic transplant recipients, infection surveillance, diagnostic workup, and prevention strategies similar to those applicable to allogeneic recipients are recommended.

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