Neurological Complications of Transplantation: Part I: Hematopoietic Cell Transplantation

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Abstract

Hematopoietic cell transplantation (HCT) is the preferred treatment for an expanding range of neoplastic and nonmalignant conditions. Increasing numbers of solid organ transplantations (SOTs) add an additional population of immunosuppressed patients with multiple potential neurological problems. While the spectrum of neurological complications varies with conditioning procedure and hematopoietic cell or solid organ source, major neurological complications occur with all transplantation procedures. This 2 part review emphasizes a practical consultative approach to central and peripheral nervous system problems related to HCT or SOT with clinical and neuroimaging examples from the authors' institutional experience with the following conditions: the diversity of manifestations of common infections such as varicella zoster virus, *Aspergillus*, and progressive multifocal leukoencephalopathy (PML), drug therapy-related complications, stroke mechanisms, the spectrum of graft versus host disease (GVHD), and neurologically important syndromes of immune reconstitution inflammatory syndrome (IRIS), posterior reversible encephalopathy syndrome (PRES), and posttransplantation lymphoproliferative disorder (PTLD). These complications preferentially occur at specific intervals after HCT and SOT, and neurological consultants must recognize an extensive spectrum of syndromes in order to effect timely diagnosis and expedite appropriate treatment.

Keywords

Aspergillus, graft versus host disease, hematopoietic cell transplantation, immune reconstitution inflammatory syndrome, organ transplantation, posterior reversible encephalopathy syndrome, posttransplantation lymphoproliferative disorder, progressive multifocal leukoencephalopathy, varicella zoster virus

Introduction

Hematopoietic cell transplantation (HCT) has become the preferred treatment for increasing numbers of neoplastic as well as nonmalignant systemic and neurological diseases. The median age of patients is 10 years older than it was two decades ago and indications for transplantation may be conditions associated with significant pretransplantation neurological deficits.¹⁻⁶ In the authors' institutions, these patients, who are frequently in hospital both for the acute procedures and for later complications, now represent nearly one quarter of all consultations to the inpatient neurology service. Part one of a 2-part review provides a practical guide for the evaluation of patients with potential neurological complications of HCT. It concentrates on situations likely to be seen in the hospital setting, which require urgent or emergent treatment, prolongation of hospitalization and investigations into specific etiologies of altered mental status or focal neurological deficits.

We begin with the premise that the added value of a neurological consultation is not only to recognize and address the common, often metabolically driven neurologic complications of transplantation but also to discern, differentiate, and sometimes anticipate more subtle infectious and vascular as well as treatment-specific toxicities that may not be the immediate question posed for the consultation, may have occurred since the last hospitalization, and may have salient implications for the health of the transplant recipient. The review analyzes the literature on infectious, vascular, neoplastic, and autoimmune

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problems occurring during 3 time periods of the transplantation process: (1) the first month including HCT conditioning, transplantation procedures for HCT, and the period before HCT engraftment; (2) the second through sixth months after transplantation; and (3) beyond 6 months after transplantation.

Transplantation Procedure Indications and Terminology

Hematopoietic cell transplantation involves the intravenous infusion of progenitor cells to restore bone marrow function eradicated by high doses of chemotherapy. Procedures and anticipated complications can be classified by (1) the pretransplantation conditioning regimen, either full intensity (myeloablative [MA]) or reduced intensity (nonmyeloablative [RIC]), (2) donor type, either from a relative or unrelated human leukocyte antigen (HLA)-compatible donor (allogeneic transplantation) or from the patient prior to marrow ablation (autologous transplantation), and (3) source of stem cells (bone marrow, peripheral, or umbilical cord blood). With recognition that graft versus tumor effects are important therapeutic adjuncts, RIC protocols have emerged for many hematologic disorders, and this less toxic procedure is commonly used in patients over age 50. Minimal intensity conditioning (MIC) using antibody-based cell depletion is an investigational strategy currently under study for primary immunodeficiency diseases.⁷

Hematopoietic Cell Transplantation: General Overview

Each type of transplantation procedure is associated with a variety of neurologically relevant complications that are determined by the “net state of immunosuppression” based on underlying disease, donor cell origin, and type of conditioning. The conditioning regimen determines the duration and degree of bone marrow suppression. Although engraftment of infused donor cells occurs between 2 and 4 weeks after transplantation, immune reconstitution continues for at least 4 months and complete recovery is achieved after about 1 year. Other contributors to risk of neurological complications are geographically specific exogenous factors such as preexisting infections in donor or recipient, nosocomial infections, viral coinfection or reactivation, and choice of antimicrobial prophylaxis.⁸

In most large series, the occurrence of a neurological complication related to any transplant procedure increases mortality.⁹⁻¹¹ The reported frequency and type of complications varies depending on case ascertainment definition and population examined.¹²⁻¹⁵ In most studies, participants receiving allogeneic HCT are reported to have a higher risk of neurological complications compared to autologous HCT participants. However, one large retrospective study found the incidence similar but the frequency and distribution of complications varied. For example, subdural hematoma was more common in patients with acute myelogenous leukemia (AML)

receiving autologous HCT, whereas infections were more frequent in allogeneic HCT.¹⁶

Autopsy studies have reported up to a 90% rate of nervous system pathology but do not clearly distinguish clinically significant from incidental findings.¹⁷ Similarly, definitions of those neurological complications that occur “early” versus “late” in the HCT process vary widely. Here “early” complications are defined as those occurring within 1 month of transplantation, “middle” period subsumes the second through sixth months, and “late” refers to any point thereafter. Acute graft versus host disease (GVHD) is defined as occurring within 100 days of the transplantation procedure, while chronic GVHD refers to the condition after this interval.

Diagnostic Guidelines for Clinicians

When a neurological problem occurs in an HCT patient, it is useful to assume for initial purposes that the problem is related to the procedure. Of course, such patients, especially the older patients increasingly represented in the population receiving RIC, may have preexisting vascular risk factors or other neurologically relevant diseases that are not directly attributable to and are simply aggravated by the transplantation. In all published series and in daily clinical experience, metabolic and drug-related toxicities represent a large percentage of neurological complications. Highly problematic drugs are fludarabine, busulfan, and the calcineurin inhibitors whose toxicities are summarized in Table 1. Having reviewed medications, the hospitalist then should consider:

1. Patient demographics. Figure 1 displays the complex temporal evolution of neurological and concurrent medical problems arising post HCT. In one large retrospective study of patients with allogeneic HCT, 69% of clinically significant neurologic complications and 86% of all episodes of posterior reversible encephalopathy syndrome (PRES) occurred within the first 100 days after the procedure.¹¹ Factors that have been shown to increase the risk of central nervous system (CNS) complications include a diagnosis of leukemia, the prior use of imatinib or intrathecal methotrexate, fludarabine use prior to conditioning, high-dose total body irradiation (1200 cGy in 6 fractions), and use of cyclosporine plus methotrexate as GVHD prophylaxis.^{11,18}
2. The neurological syndrome. From the physical examination, two groups of syndromes emerge with differing implications for the consultant. The first group of patients has transient nonfocal phenomena such as impaired consciousness and/or generalized seizures from a metabolic encephalopathy, while the second group has focal signs suggesting a mass lesion, hemorrhage, stroke, or spinal cord syndrome. For example, a brain stem syndrome raises the possibility of Wernicke encephalopathy, osmotic demyelination, *Listeria* infection or progressive multifocal leukoencephalopathy (PML), while infectious causes of myelitis in the transplant population have

Table 1. Neurologic Complications of Commonly Used Transplantation Drugs^a

Drug	Neurologic Toxicity	Uses/Indications
Preparative Regimens		
Alemtuzumab	PML, Listeria, myelitis, CMV, IRIS, GBS	RIST
Busulfan	Seizures common (10%) several days posttreatment: AED prophylaxis suggested	Autologous or allogeneic for acute or chronic leukemia, particularly CML
Carboplatin	PRES, peripheral neuropathy, ototoxicity	Autologous transplants
Carmustine	Delayed onset encephalopathy (up to 1.5 months posttreatment), optic disc and retinal microvasculopathy	Autologous transplants
Cyclophosphamide	Transient confusion after high dose	Autologous or allogeneic transplants
Cytarabine	Pancerebellar syndrome, seizures, lymphocytic meningitis (IT)	
Etoposide (VP-16)	Sudden delayed (1-2 wks) encephalopathy, PRES, acute dystonia, neuropathy	Conditioning regimen
Fludarabine	Severe encephalopathy with white matter MRI changes PML risk increased	RIST
Ifosfamide	Severe acute encephalopathy, increased risk in children, with prior cisplatin treatment, hypoalbuminemia, and when aprepitant used for nausea(see text), seizures	Salvage therapy with autologous transplants
Melphalan	Seizures/encephalopathy	Multiple myeloma-peripheral blood stem cell transplants
Methotrexate	Necrotizing microangiopathy, additive toxicity with cranial irradiation, transient stroke-like episodes with DWI MRI abnormalities transverse myelitis	Posttransplant GVHD prophylaxis, PTLT, combination therapy in primary CNS lymphoma
Thiotepa	Lymphocytic meningitis	
Antibiotics (prophylaxis or treatment of infection)		
Acyclovir	Seizures, encephalopathy	HSV
Amphotericin B	Parkinsonism, confusion	Fungal infections
Cefepime	Seizures (may be nonconvulsive); encephalopathy, myoclonus	Bacteremia, meningitis
Imipenem	Seizures	Bacteremia
Linezolid	Ischemic optic neuropathy, PRES, serotonin syndrome, neuropathy	
Metronidazole	Cerebellar dentate nuclei: reversible dysarthria, ataxia	Long-term wound infection
Posaconazole	Enhances vincristine neuropathy	Antifungal prophylaxis
Voriconazole	Visual hallucinations	Antifungal prophylaxis
Posttransplant GVHD prophylaxis		
Cyclosporine	Tremor, PRES, seizures ^b CIDP, mutism, pseudotumor cerebri ^c	Posttransplant GVHD treatment and prophylaxis
Mycophenolate	PML risk	GVHD prophylaxis
Tacrolimus	Tremor, PRES, demyelination, CIDP, brachial plexopathy, optic neuropathy, hearing loss, seizures ^b	Same indications as for cyclosporine
Sirolimus	PRES	Same indications as for cyclosporine

Abbreviations: AED, anti-epileptic drug; CIDP, chronic inflammatory demyelinating polyneuropathy; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; DWI, diffusion-weighted imaging; GBS, Guillain-Barré syndrome; GVHD, graft vs host disease; HHV, human herpesvirus; IRIS, immune reconstitution inflammatory syndrome; IT, intrathecal; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; PTLT, post-transplant lymphoproliferative disorder; RIST, reduced intensity stem cell transplantation.

^a Modified from Quant, Rosenfeld, Weathers, Balu.^{1,18,22,33}

^b Metabolized by P450 enzymes; nonenzyme-inducing AED such as valproate, levetiracetam, or gabapentin recommended for seizure control.

^c Idiopathic raised intracranial pressure.

different but restricted considerations including herpesviruses (cytomegalovirus [CMV], varicella zoster virus [VZV], human herpesvirus 6 [HHV6], Herpes simplex, Epstein Barr virus [EBV]), JC virus, and Human T-lymphotropic virus 1 (HTLV1).¹⁹

3. Appropriate and cost-effective laboratory procedures. Neuroimaging with contrast-enhanced computerized

tomography (CT) or magnetic resonance imaging (MRI) is often very helpful for patients with focal syndromes.²⁰ Analysis of cerebrospinal fluid (CSF) can be definitive, but studies should be tailored to appropriate demographic considerations. Brain biopsy is reserved for focal lesions unexplained by less-invasive procedures and can be useful for the diagnosis of PML, vasculitis, posttransplant lymphoproliferative disorder (PTLD) including primary CNS lymphoma

Figure 1. This time line reflects occurrence of neurological complications after allogeneic HCT. The specific conditioning regimen and donor source as well as travel, zoonotic exposures, and antibiotic/vaccination prophylaxis will impact timing and type of neurological problems. Bars indicate the most likely time of occurrence and arrowheads denote continuing risk. HCT indicates hematopoietic cell transplantation.

(PCNSL), recurrent or secondary neoplasm and fungal infections. Electroencephalography (EEG), in the authors' opinion, is underutilized in the management of HCT neurological complications as seizures or periodic epileptiform discharges can occur in nearly half of monitored patients, many without clinically apparent signs.²¹ In critically ill patients with depressed level of consciousness, seizures should be excluded by early use of bedside long-term monitoring, particularly in the presence of drugs such as cefepime that can mimic multifocal myoclonus and are known to lower seizure threshold.²²

Complications by Interval From Transplantation Procedure

The First Month

Complications due to stem cell harvesting. Harvesting of stem cells is very safe, with only rare complications of un-intended entry into the subarachnoid space leading to a syndrome of intracranial hypotension (positional headache, sometimes horizontal diplopia with abduction deficits and dural

enhancement on MRI). During the administration of hematopoietic growth factors (hGCSF) prior to cell harvesting patients, with preexisting autoimmune diseases such as multiple sclerosis may experience flares of their underlying condition. Use of cyclophosphamide in the cell mobilization regimen reduces this disease exacerbation risk.^{23,24}

Complications during conditioning. Drugs used during conditioning and for GVHD prophylaxis are the largest cause of neurologic complications during the transplantation process (Table 1). Myocardial infarction and stroke associated with infusion of stem cells have been linked to dimethyl sulfoxide (DMSO) cryopreservative.²⁵ A case of transient global amnesia lasting 4 hours also has been reported with MRI signal abnormality in the hippocampus.²⁶ Of the drugs used in conditioning regimens, several have predictable and frequent neurological toxicities. Ifosfamide, particularly in patients with low albumin, with prior cisplatin treatment, and those receiving aprepitant for nausea, can cause visual and auditory hallucinations, encephalopathy, and seizures often beginning

Figure 2. Posterior reversible encephalopathy syndrome (PRES) variants. A, Classic PRES with bilateral posterior signal abnormality on FLAIR MRI. B, Bilateral predominantly but not exclusively posterior signal abnormality on FLAIR MRI reflects vasogenic edema. C, Multiple areas of FLAIR abnormality in periventricular region on FLAIR MRI in patients with thrombocytopenia on tacrolimus after HCT for AML. D, Same patient as in B with gradient echo MRI (C) showing evidence of small hemorrhages in affected areas. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia.

during the infusion and treated with methylene blue.²⁷⁻²⁹ Busulfan causes seizures with sufficient frequency to justify phenytoin or other antiepileptic drug (AED) prophylaxis.

Calcineurin Inhibitors are associated with numerous neurological adverse effects. Cyclosporine's most common adverse effect is tremor, somewhat related to drug level. Pseudotumor cerebri has been reported in 2 obese children and the authors have seen this in 1 adult with appropriate cyclosporine levels at the time of the events.³⁰ Additional toxicities, reported somewhat more frequently with tacrolimus than with cyclosporine, are mild symptoms such as frequent tremor, insomnia,

nightmares, headache dysesthesias, and mood disturbances and more serious problems such as akinetic mutism, optic neuropathy, hearing loss, and chronic inflammatory demyelinating polyneuropathy (CIDP), and reversible brachial plexitis.³¹⁻³⁴ Large enhancing lesions with mass effect resembling radiographically and pathologically tumefactive multiple sclerosis have been described.³⁵

Among the most important and reversible conditions for the neurologic consultant to recognize is the PRES. Also known as reversible posterior leukoencephalopathy syndrome (RPLS), PRES is most common during this early posttransplant period but risk continues throughout the patient's course.

Figure 3. *Listeria rhombencephalitis*. FLAIR (A) and gadolinium-enhanced T1 MRI (B) show pontine lesion of *Listeria monocytogenes* rhombencephalitis, presenting as several days of facial numbness and weakness and ataxia progressing rapidly to a locked-in syndrome. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Calcineurin inhibitors such as cyclosporine and tacrolimus are the major offenders, but PRES has been described with sirolimus and everolimus as well as with dexamethasone.³⁶⁻³⁸ Acute mental status changes, cortical blindness, hypertension, and seizures are the most common clinical manifestations; radiographically, petechial, lobar, or subarachnoid hemorrhage may be discerned (Figure 2A-C).³⁹ The syndrome likely results from dysregulation of cerebral vasculature, leading to vasogenic edema preferentially but not exclusively, affecting the parieto-occipital regions. Brain stem, basal ganglia, and spinal cord involvement all have been reported as has status epilepticus.⁴⁰⁻⁴⁴ The development of PRES with the use of 1 immunosuppressive drug does not preclude safe use of another related agent.

A frequent question to the consultant evaluating a patient with PRES is appropriate choice and duration of AED therapy. It is the practice in the authors' institutions to treat with a nonenzyme-inducing AED during and for 1 month following the acute episode of PRES if accompanied by clinical seizures. EEG findings during PRES episodes include generalized and focal slowing with periodic lateralized epileptiform discharges (PLEDs) but chronic non-PRES-related epilepsy is rare.⁴⁵ Along the spectrum of disorders due to endothelial damage is thrombotic microangiopathy with thrombocytopenia, schistocytes, elevated lactate dehydrogenase (LDH), renal, and neurological dysfunction as variable features in the setting of GVHD and various immunosuppressive agents. This coagulopathy is treated with the removal of the offending drug, control of hypertension, and, investigatively, substitution of daclizumab or defibrotide for calcineurin inhibitors to control GVHD.⁴⁶

Complications during pancytopenia. The major neurological complications that occur in the period between the infusion of stem cells and marrow reconstitution include systemic organ failure with metabolic abnormalities, coagulation deficits, nosocomial or donor-derived infections, and drug toxicity. Multiple organ dysfunction associated with hepatic veno-occlusive disease (VOD), also called sinusoidal obstruction syndrome, may present with encephalopathy, fluid retention, and rising bilirubin.⁴⁷

During the neutropenic period, infections may be due to bacteria, viruses, or fungi, and classic clinical clues may be absent due to the host's impaired inflammatory response. Thus, a CNS infection should always be suspected if the patient has new neurological signs, fever, or a systemic, particularly pulmonary, infection. Nosocomial infectious patterns specific to each institution reflect distribution of methicillin-resistant *Staphylococcus aureus* (MRSA), pan-resistant enterococci, and gram-negative organisms, while intravenous lines remain a potential source of infection with *Candida*. Other pathogens include *Listeria monocytogenes*, though increasing use of trimethoprim-sulfamethoxazole has reduced the risk of this infection and also of a previously more frequent cause of brain abscess, *Nocardia asteroides*. Appropriate prophylaxis has delayed the onset of herpesvirus and CMV infections until later after the transplant. Reactivation of CMV has been associated with an increased risk of *Listeria* meningitis that can present as diffuse cerebritis or rhombencephalitis (Figure 3).^{48,49} Reactivation of preexisting neurocysticercosis has been described and, given the increasing seroprevalence of this infection in the United States, needs

Figure 4. Differential diagnosis of limbic encephalitis. A, Human herpesvirus 6 infection in a patient 28 days post HCT with fever, seizures, and short-term memory loss. FLAIR MRI shows bilateral hippocampal signal abnormality, which, as shown in B, is not etiologically specific. B, MRI of patient with drug reaction with eosinophilia and systemic symptoms on phenytoin developed reactivation of herpesvirus with increased subarachnoid FLAIR signal consistent with increased CSF protein and hyperintensity in the left temporal lobe; CSF PCR positive for HSV1. C, Patient with MRI picture consistent with HSV 1 encephalitis but was shown to have VZV encephalitis on biopsy. FLAIR MRI shows extensive abnormality in temporal lobe, insula, and frontal lobe with bright cortical ribbon signal consistent with laminar necrosis. Cortical signal looked bright on T1 images before gadolinium (not shown), suggesting petechial hemorrhage. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; HCT, hematopoietic cell transplantation; CSF, cerebrospinal fluid; VZV, varicella zoster virus.

to be considered.⁵⁰ Additional donor-derived infections range from hepatitis B and C and CMV to neurologically specific viral contaminations such as adenovirus or Coxsackievirus B4 that produce encephalitis^{51,52} and that have been the cause of several transplant-associated deaths.⁵³ Infections contracted by solid organ transplantation (SOT) recipients also include West Nile Virus,⁵⁴ lymphocytic choriomeningitis virus (LCMV),⁵⁵ and rabies virus,⁵⁶ but these conditions have not been described in HCT patients.

Engraftment of hematopoietic cells can be accompanied by rash, fever, and headache occurring 2 to 4 weeks post transplantation as the absolute neutrophil count (ANC) exceeds 500. This syndrome must be differentiated from posttransplant acute limbic encephalitis (PALE) characterized by anterograde amnesia, the syndrome of inappropriate antidiuretic hormone secretion, mild CSF pleocytosis, and EEG abnormalities with or without clinical seizures.⁵⁷ While various paraneoplastic syndromes, herpes simplex virus 1, and status epilepticus can produce similar clinical and radiographic pictures, the most common cause of the syndrome is HHV6 (Figure 4A, C). Most HHV6 disease represents a reactivation of host infection, though allograft transmission has been reported as well as 2 cases during the second month after transplantation. The disease appears to be more common in the presence of severe GVHD from unrelated donors or when the conditioning regimen includes antithymocyte globulin, sirolimus, or interleukin 12 antibodies. A high frequency (11%) of HHV6 encephalitis was reported in a transplant series in which patients

received alemtuzumab as part of the anti-GVHD-conditioning protocol. Treatment includes vigorous antiseizure therapy and ganciclovir or foscarnet.

In the appropriate circumstances, the consultant should also consider a syndrome that closely resembles PALE: drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) is a severe drug reaction with skin eruption, fever, lymphadenopathy, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion with hyponatremia and multiorgan involvement that can be triggered most frequently by sulfonamides or AEDs and is associated with reactivation of herpesvirus including CMV, EBV, and HHV-1,6,7 (Figure 4B).⁵⁸ The syndrome resembles that of herpesvirus reactivation occurring as a harbinger of GVHD and skin biopsy may be necessary to help distinguish the 2 conditions.⁵⁹

Subdural hematoma is the most common hemorrhagic HCT complication. This complication is associated with underlying myeloblastic leukemia and prolonged thrombocytopenia and can occur after both allogeneic and autologous HCT. Lumbar puncture has been associated with subdural hematoma development. Intraparenchymal brain hemorrhages are more frequent in allogeneic HCT particularly when accompanied by severe GVHD (Figure 5).

Immune reconstitution inflammatory syndrome. Immune reconstitution inflammatory (IRIS) was first described in the HIV population and denotes an exuberant host inflammatory response to recent systemic and CNS infections after a rapid

Figure 5. Subdural hematoma and subarachnoid blood. A, Pancytopenic patient after HCT for AML has blood along falx on gradient echo MRI. B, The FLAIR image shows increased signal in CSF consistent with blood (or elevated protein) and subdural hematoma. Such increased CSF signal can also be seen in patients ventilated with high oxygen concentrations. HCT indicates hematopoietic cell transplantation; AML, acute myeloid leukemia; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

rise in CD4 count with highly active antiretroviral treatment (HAART). There is often dramatic elevation in CSF pressure and pleocytosis with enhancement of affected areas on MRI. The syndrome may occur during engraftment but has also been reported later in the course of the HCT and even several months after discontinuation of immunosuppression.⁶⁰ The phenomenon of IRIS is relevant to transplanted patients as recovery from T cell depletion in these patients resembles HAART-associated immune rebound inducing the Th1 immune response against infectious antigens and, in some instances the unknown antigens that evoke the granulomatous inflammation of sarcoidosis.⁶¹ Alemtuzumab, an anti-CD52 monoclonal antibody, has been reported to put patients at risk of IRIS with both systemic (Graves disease) and neurological involvement after initial cryptococcal meningitis treatment.⁶² The IRIS affecting the eye has been documented in association with CMV retinitis (immune recovery uveitis) in HIV patients and recently in HCT recipients.⁶³ Recognition of IRIS with recovery from iatrogenic immune suppression is important to avoid unnecessary investigation or antimicrobial therapy and to consider institution of anti-inflammatory corticosteroids. IRIS should be considered when a patient has had an infection and there are (1) new or worsening clinical or radiologic manifestations consistent with an inflammatory process; (2) symptoms during receipt of appropriate antibiotic therapy that cannot be explained by newly acquired infection; and (3) negative results of cultures or stable or reduced biomarkers for the initial pathogen during the diagnostic workup for the inflammatory process.⁶⁴

The Second Through Sixth Months Post Transplantation

As patients receiving allogeneic HCT enter the second month post HCT, many have been neutropenic for prolonged periods. Prolonged neutropenia with more than 10 consecutive days of an ANC <500/ μ l is the most important risk factor for invasive aspergillosis; this risk reaches 10% in the allogeneic HCT group.⁶⁵ Additional risk factors include nonmyeloablative therapy with purine analogue conditioning (fludarabine) and alemtuzumab.⁶⁶⁻⁶⁸ Magnetic resonance imaging shows multiple, usually nonenhancing lesions, frequently with hemorrhage, involving the corpus callosum, basal ganglia, and cerebral hemispheres.⁶⁹ The usual route of infection is inhalation with pulmonary and paranasal sinus disease. Hematogenous spread to blood vessels leads to mycotic aneurysm, vasculitis, and subarachnoid hemorrhage. Corpus callosal and brain stem lesions are particularly suggestive of Aspergillosis. There may be little or no pleocytosis in the CSF and daily serum galactomannan testing has been used to determine when to offer preemptive therapy.⁷⁰ Definitive diagnosis of invasive Aspergillosis is usually made by lung biopsy after appropriate brain MRI (Figure 6A, B). The CNS aspergillosis infection is treated with amphotericin B lipid formulation, voriconazole or caspofungin, but the mortality rates remain high. Clinicians should be attuned to the sentinel combination of headache, sinusitis, or chest lesions, and cranial neuropathies, particularly visual problems mimicking optic neuropathy to avert the catastrophic advent of brain stem infarction or subarachnoid or parenchymal hemorrhage.⁷¹

Figure 6. Spectrum of Neuroimaging manifestations of CNS *Aspergillus* and other invasive fungi. A, DWI shows brain stem, thalamic, and basal ganglia infarctions as well as corpus callosum infarction, a characteristic finding for *Aspergillus*. B, Angiogram shows evolving basilar vertebral and basilar aneurysms in patient with AML and *Aspergillus* of the CNS. CNS indicates central nervous system; DWI, diffusion-weighted imaging; AML, acute myeloid leukemia.

Rarely, brain biopsy may be necessary when fungal infection is strongly suspected but lung, sinus, and serologic tests fail to suggest the pathogen.

The protozoan parasite *Toxoplasma gondii* causes disease in both humans and animals and assumes a quiescent lifelong persistent form that can reactivate and cause severe disease in HCT patients. Reactivated toxoplasmosis manifests as encephalitis often with multiple deep ring enhancing MRI brain lesions, pulmonary disease, or eye infections and is more common in Europe than in the United States. *Toxoplasma gondii* allograft transmission is most strongly associated with cardiac transplantation but among HCT recipients the rates vary from 0.3% to 13% and are higher in countries where toxoplasmosis is more prevalent.^{72,73} Virtually all cases occur within the first 100 days after HCT, and the occurrence is reduced by the use of trimethoprim-sulfamethoxazole prophylaxis.

Once the transplant engrafts and neutrophil counts rise, the risk of bacterial infection decreases but hosts remain susceptible to a variety of opportunistic infections. Varicella zoster virus with its many neurologic manifestations (Box 1) previously was a significant risk in the period immediately after engraftment. However, with appropriate antiviral prophylaxis peritransplantation, the risk of VZV now emerges later and continues well into the period after the first 6 months. Dermatological or disseminated skin lesions are the most common manifestation and are associated with significant risk of post-herpetic neuralgia for which extended valacyclovir treatment may be helpful.⁷⁴ Other recognized VZV-associated syndromes are vascular events with a combination of large- and small-vessel strokes as well as segmental pontine myelitis, acute retinal necrosis, and spinal cord infarction.⁷⁵⁻⁷⁷

Pleocytosis in the CSF is absent in one-third of cases and rash is not required for diagnosis. Confirmation of VZV vasculopathy requires detection of viral DNA by polymerase chain reaction (PCR) or more commonly measurement of anti-VZV immunoglobulin in the CSF.

Progressive multifocal leukoencephalopathy, a subacute demyelinating disorder due to JC virus, a polyoma DNA virus that targets myelin-producing oligodendrocytes, has become a significant pathogen due to HIV/AIDS and to the increasing use of intensive immunosuppressive therapy in patients with autoimmune as well as neoplastic disease.⁷⁸ In the transplantation population (both SOT and HCT), PML has been associated with fludarabine therapy and rituximab. Symptoms typically develop more than 1 month after HCT and have been reported as late as several years posttransplantation at a time of apparent minimal immunosuppression.⁷⁹⁻⁸¹

The diversity of radiographic manifestations of PML reflects variable severity of the underlying immune deficit and ranges from white matter lesions without enhancement or mass effect to tumor-like lesions with vivid gadolinium uptake (Figure 7). A JC virus (JCV)-related cerebellar neuronopathy with no early MRI findings has been described as well.⁸² Complicating both the diagnosis and the radiographic evaluation of PML is the phenomenon of immune reconstitution which can lead to dramatic changes in enhancement pattern and edema and clinical worsening and which has occasioned debate about the role of steroids to suppress inflammation.⁸³

Brain biopsy provides definitive diagnosis, though DNA PCR of the CSF is an excellent test with sensitivity and specificity of 72% to 92% and 92% to 100%, respectively.⁸⁴ However, in the AIDS population with IRIS, the sensitivity of PCR has decreased to 58% and negative JCV PCR in the CSF has

Box 1. Manifestations of Varicella Zoster Virus (VZV) in HCT and SOT Recipients^a**Epidemiology:**

Most common after engraftment but risk continues throughout course

Risk factors: calcineurin inhibitors, tumor necrosis factor- α inhibitors, chronic glucocorticoid use

Clinical presentation:

Dermatomal zoster—up to 3 dermatomes

No rash (sine herpete) in 37% cases with stroke or meningoencephalitis

Vasculopathy: TIA ischemic or hemorrhagic (due to aneurysm), stroke

Segmental motor weakness

Polyneuritis: cranial nerves (Ramsay Hunt involving third division trigeminal and facial nerves)

Lower cranial neuritis (glossopharyngeal, vagus)

Cerebellar ataxia

Transverse myelitis

Necrotizing (acute or progressive outer retinal) retinitis, Zoster keratitis

Postherpetic neuralgia

Diagnosis:

Anti-VZV IgM in serum or CSF, or

VZV DNA by PCR in blood or CSF, or

Anti-VZV IgG in CSF (more often positive in chronic vasculopathy than PCR)

Treatment:

Acyclovir IV

Postherpetic pain: topical lidocaine, gabapentin, amitriptyline, nortriptyline, desipramine, pregabalin, duloxetine

Retreatment with IV acyclovir then po valacyclovir

Retinal necrosis: ganciclovir and foscarnet

Abbreviations: HCT, hematopoietic cell transplant; PCR, polymerase chain reaction; SOT, solid organ transplant; TIA, transient ischemic attack; Ig, immunoglobulin; CSF, cerebrospinal fluid.

^a Based on references 74-77.

been reported in HCT patients as well, particularly after umbilical cord blood HCT.⁸⁵ Patients with subacute decline and unexplained white matter lesions of the brain should be investigated for PML using the most sensitive commercial PCR assay available or sending the CSF to a laboratory specializing in PML diagnosis.⁸⁶ Apart from attempts to reduce immunosuppression, treatment of PML remains in doubt with a question of responsiveness to IL-2 with recovery of CD4 counts and immune reconstitution as well as reports of improvement with mefloquine and cidofovir.^{87,88} The recognition that JC virus uses serotonin receptors to infect cells has led to consideration of mirtazapine therapy.⁸⁹

Special Considerations After RIC and cord blood transplantation.

In most series, peripheral nervous system (PNS) complications of HCT are much less common than are CNS complications and consist mostly of acute or chronic inflammatory demyelinating polyneuropathy. However, in one recent report almost 9% of patients who received RIC with alemtuzumab developed either Guillain-Barré syndrome or myelitis at a median of 151 days after transplantation; the latter was associated with reactivation/infection with VZV or HHV7.⁹⁰ It was postulated that delayed immunological reconstitution and increased viral infections associated with a loss of T-cell regulation by alemtuzumab led to these complications.

The population of patients receiving cord blood transplantation (CBT) includes those lacking suitable donors and those

over age 50 with organ dysfunction receiving either RIC or MA conditioning. Unique immune-mediated syndromes such as pre-engraftment immune reaction and hemophagocytic syndrome have been observed in this population. In one series 13% of these patients developed CNS complications. The major difference when compared with conventional HCT was that CBT patients had a higher incidence of early immune reactions called acute GVHD before engraftment or hyperacute GVHD.⁹¹

Clinicians should be aware of immune reconstitution-associated sarcoidosis that usually affects skin and lungs but occasionally can affect the nervous system and can be confused with tuberculous or fungal meningitis or lymphomatous or other neoplastic mass lesion. Case reports following alemtuzumab therapy are beginning to emerge.⁹² The onset of these symptoms may extend well into the period beyond 6 months from transplantation and is attributed to immune dysregulation due to aberrant reconstitution of T-cell populations after HCT.

More Than 6 Months Post Transplantation

Graft versus host disease remains a major hazard after allogeneic HCT, occurring in 2 major forms acute (<100 days post transplant) and chronic (>100 days). It most frequently involves skin, liver, gastrointestinal tract, eyes, and peripheral nerves. Ocular GVHD can be acute (during the first 3 months) or chronic. The most common ocular manifestation is

Figure 7. The MRI spectrum of progressive multifocal leukoencephalopathy (PML). A, Typical appearance of nonenhancing, confluent white matter abnormality on FLAIR MRI. B, PML in the posterior fossa on FLAIR MRI; the patient progressed locked-in state. C, D, Flair (C) and gadolinium-enhanced MRI (D) in a patient with minimal immune suppression and vividly enhancing biopsy-proved PML. The amount of gadolinium enhancement in PML reflects the host's immune status and may be very extensive. E, F: FLAIR (E) and gadolinium-enhanced T1 (F) MRI of patient with multiple myeloma on multiple drugs with atypical plasma cells in CSF but also progressive enhancing lesions of PML in brain parenchyma. This occurred at a time of disease improvement and reduction of immune suppression, raising suspicion for an IRIS-like physiology in an increasingly immunocompetent host. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IRIS, immune reconstitution inflammatory syndrome.

keratoconjunctivitis sicca. Anterior uveitis has been described after both allogeneic MA and RIC HCT.⁹³ Manifestations of PNS involvement in GVHD include polymyositis, myasthenia gravis, and CIDP, often developing late in the course of transplantation at a time of reduction in immunosuppressive therapy.⁹⁴

The CNS can be a target of GVHD but, though the literature is replete with a variety of clinical descriptions, it is likely that CNS GVHD is quite rare, occurs almost most exclusively during chronic GVHD, and requires distinction from B-cell lymphoproliferative processes (PTLD, see below).^{95,96} This diagnosis should be considered only if there is no evidence of other diseases with overlapping clinical features or alternative explanations such as HHV6, drug toxicity, and PRES, among others. The presence of T-cell infiltrates by histologic and immunophenotypic criteria and response to immunosuppressive therapy are the strongest diagnostic

features. Systemic GVHD is not always present at the time of CNS manifestations. Neurologic presentation is highly variable and includes (1) a vasculitis with angiographic manifestations of dilated and narrowed arterial segments and aneurysm leading to focal parenchymal hemorrhage⁹⁷⁻⁹⁹; (2) focal lymphocytic encephalitis with or without a mass lesion, sometimes called inflammatory pseudotumor^{100,101}; (3) an acute demyelinating encephalomyelitis or relapsing-remitting disorder, sometimes involving the splenium of the corpus callosum and periventricular white matter or spinal cord and responsive to steroids¹⁰²⁻¹⁰⁵ as well as de novo relapsing remitting multiple sclerosis 8 months following autologous HCT for plasma cell leukemia in a patient over age 60¹⁰⁶; and (4) a polyclonal T-cell meningitis with elevated CSF protein and no specific changes on MRI.¹⁰⁷ Definitive brain biopsies have been reported in only 8 patients among the above case reports and have shown mature lymphohistiocytic

inflammatory infiltrates with perivascular cuffing and no viral cytopathic changes.

Organ-specific and systemic autoimmune disease are recognized during recovery from lymphopenia in HIV infection but are also increasingly diagnosed after lymphocyte-depleting monoclonal antibody therapy, ablative chemotherapy, and HCT. As chronic GVHD leads to what has been deemed as loss of self-tolerance patients may develop autoimmune conditions that affect the nervous system such as scleroderma and a Sjogren-like syndrome.¹⁰⁸ Posttransplantation lymphoproliferative disorder will be discussed in part II of this review.

Long-Term Follow-Up of HCT Patients

As HCT patients survive longer, a host of new complications impacting long-term quality of life is becoming apparent. Chronic corticosteroid use confers a lifelong risk of nonendocrine late complications such as cataracts and avascular necrosis.¹⁰⁹ Patients who received total body irradiation at a young age are at risk of developing metabolic syndrome and a new solid malignant tumor many years later. CNS tumors of the astrocytic and meningeal lineages occur as can CNS lymphoma. Thyroid cancer and breast cancer are both associated with prior irradiation and drugs such as etoposide, anthracyclines, and alkylating agents are risk factors for later AML or myelodysplastic syndromes. Revaccination is required for vaccine-preventable diseases including polio, tetanus, measles, *Hemophilus influenzae* type B, *Neisseria meningitidis* type C, and *Streptococcus pneumoniae*.¹¹⁰ Of particular concern is the risk of cognitive impairment due to total body irradiation, GVHD treatments, and cytotoxic agents. A recent prospective study examined cognitive changes in 284 patients 2 years after HCT. Allogeneic HCT recipients demonstrated worse scores in processing speed, executive function, and verbal fluency compared with autologous recipients. Only two-thirds of all patients were working part time or full time 1 year after diagnosis, although employment status clearly depended on the underlying diagnosis.¹¹¹ Thus, despite successes in reducing infectious and other complications, the long-term outlook for HCT survivors continues to hold hazards for neurologic problems whose early recognition, often by hospitalists, will improve the quality of life after transplantation.

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