Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients

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Abstract

Central nervous system (CNS) infections in cancer patients present a diagnostic and therapeutic challenge for clinicians. While CNS infections are not frequent complications of cancer, its therapies, or hematopoietic stem cell transplantation, the importance of CNS infections lies in their propensity to result in profound morbidity and substantial mortality in this vulnerable patient population. With an expanding population of patients with malignant disease undergoing more potent and aggressive therapies and with the advent of newer immunomodulatory agents, the incidence of CNS infectious complications is likely to rise. This chapter will summarize the clinical and diagnostic evaluation of potential infections of the CNS in these patients and will discuss particular pathogens of interest with regard to this at-risk patient population.

Keywords

Hematopoietic stem cell transplantation · Immunomodulatory agents · Immunodeficiencies · Antimicrobial resistance · Neurologic abnormalities · Neutropenia · Meningitis · Norcardiosis

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Contents

1 Introduction

Central nervous system (CNS) infections in cancer patients present a significant diagnostic and therapeutic challenge for clinicians. While CNS infections are not frequent complications of cancer, its therapies, or hematopoietic stem cell transplantation (HSCT), their importance lies in their propensity to result in profound morbidity and substantial mortality in this vulnerable patient population. Heightened clinical suspicion, early diagnosis, and prompt institution of therapy are essential for optimal outcomes of these infections.

The recognition and diagnosis of CNS infections are limited by a number of factors. First, cancer patients are susceptible to a wide range of both community-acquired and opportunistic pathogens as a consequence of the immunodeficiencies associated with malignancy and its therapies. The spectrum of infection is constantly evolving with the continual introduction of immunomodulatory therapeutic agents, outbreaks of novel pathogens, and emergence of antimicrobial resistance. Furthermore, cancer patients frequently have concomitant infections outside the CNS that complicate or confuse the diagnostic picture [1]. Under-recognition of infection may occur as a result of atypical clinical presentations due to the underlying disease state and the type of therapy received. Finally, non-infectious neurologic abnormalities are common in cancer patients and HSCT recipients, and thus, it is challenging to recognize the early symptoms and signs of CNS infections in these patients. This chapter will discuss the basic clinical presentation of CNS infections, pathogens of particular interest, and the approach to diagnosis and treatment in these patients.

2 Special Patient Populations and Epidemiology

Cancer patients are at higher risk of CNS infection than the general population. Investigators from Memorial Sloan–Kettering Cancer Center (MSKCC) reported an increasing incidence of CNS infection admissions from 0.03 to 0.2 % of hospital admissions from 1955 to 1973 [2]. In series from tertiary care and specialized cancer centers, CNS infections occurred in association with these underlying conditions: hematologic malignancies in 25–50 %, CNS malignancy and associated surgical procedures in 16–30 %, head and neck cancers in 38 %, and other solid malignancies in 18–27 % [1, 2]. In a retrospective study of meningitis at MSKCC, nearly 4 of 5 cases occurred following a neurosurgical procedure [3].

Bone marrow and HSCT, especially allogeneic transplantation, represent a special risk of CNS infection. Neurologic complications, both infectious and noninfectious, occur in 11–46 % of HSCT recipients [4]. The reported overall incidence of CNS infection following transplantation varies by patient population, type of transplant, and transplant center, ranging from approximately 2 to 4.2 % [5–7].

Regardless of the underlying disease or etiology, CNS infections in the cancer and transplant population result in significant mortality. In patients with meningitis at MSKCC, the overall 30-day mortality was 13 %. Patients with underlying leukemia had the highest mortality rate at 24 % in contrast to those with primary intracranial and head or neck tumors at 3 % [3]. Many studies report higher mortality rates in transplant patients with neurologic complications, including one study of bone marrow transplant recipients with 26 % of deaths found to be attributable to CNS lesions. As many as 40 % of these neurologic complications were caused by infections [4].

3 Types of Immunodeficiencies Encountered

Keeping the patient population subsets in mind, it is important to understand the type and duration of immune deficits that predispose to certain pathogens. Table 1 describes the broad categories of immunodeficiencies encountered in cancer patients and associated typical CNS pathogens. It is important to remember that patients may have more than one significant type of immunodeficiency concomitantly [8].

Immune deficits relate not only to the underlying disease process, but also to the types of treatment being undertaken. Barrier disruption is evident in those with primary CNS tumors who have had surgical therapy, intraventricular device placement, intrathecal chemotherapy, or radiation therapy. Additionally, chemotherapy-related mucositis and central venous catheters represent further infection risk. B-cell deficiency or hypogammaglobulinemia is often seen in association with multiple myeloma, chronic lymphocytic leukemia, or functional or surgical asplenia, and after lymphocyte depleting therapies such as rituximab.

Table 1 Central nervous system pathogens associated with immunodeficiencies of cancer patients

Immunodeficiency	Associated conditions or therapies	Typical spectrum of pathogens			
		Bacteria	Fungi	Viruses	Parasites
Barrier disruption	Neurosurgery	*S. aureus*	*Candida* spp.	–	–
	Intraventricular devices	CoNS			
	Mucositis	Enteric bacilli	*Aspergillus* spp.		
	CVC	Streptococci			
Neutrophil dysfunction and neutropenia	Infiltrative diseases of bone marrow	*S. aureus*	*Candida* spp.	HSV	–
			Aspergillus spp.		
	Chemotherapy		*Mucorales*		
	Radiation therapy	CoNS	-	HHV-6	
		Enteric bacilli			
		P. aeruginosa			
		L. monocytogenes			
Humoral immunity	Multiple myeloma	*S. pneumoniae*	–	Enteroviruses	–
	CLL	*H. influenzae*		JC virus	
	Asplenia	*K. pneumoniae*			
	Chronic GVHD	*P. aeruginosa*			
	Rituximab				

(continued)

Table 1 (continued)

Immunodeficiency	Associated conditions or therapies	Typical spectrum of pathogens			
		Bacteria	Fungi	Viruses	Parasites
Cell-mediated immunity	Lymphoma	*L. monocytogenes*	*C. neoformans*	CMV	*T. gondii*
	HSCT			VZV	*S. stercoralis*
	Corticosteroids			HSV	
	Fludarabine	*Nocardia* spp.	*Aspergillus* spp.	EBV	
		M. tuberculosis		HHV-6	
	Mycophenolate mofetil		*Mucorales*	Adenovirus	
	Alemtuzumab			JC virus	

CVC central venous catheter, *CoNS* coagulase-negative staphylococci, *HSV* herpes simplex virus, *HHV*-6 human herpesvirus-6, *CLL* chronic lymphocytic leukemia, *GVHD* graft-versus-host disease, *HSCT* hematopoietic stem cell transplantation, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *EBV* Epstein–Barr virus

T-cell deficiency occurs in those with HIV and lymphoreticular malignancy or after receipt of chronic corticosteroids and other immunosuppressive therapy, such as that used to prevent and treat graft-versus-host disease (GVHD). Neutropenia is a frequent complication of most chemotherapeutic regimens used for both solid tumors and hematologic malignancies. Neutropenia can also be a complication of radiation therapy or infiltrative processes that affect bone marrow [8, 9].

4 Clinical Syndromes

The basic clinical syndromes of CNS infections can be divided into meningitis, encephalitis, or a primary parenchymal process. The symptoms of meningitis are typically those of headache and meningismus, with or without fever, vision changes, photophobia, nausea or vomiting. With encephalitis, the presentation is one of altered mental status (AMS) ranging from confusion to bizarre behaviors to coma, along with seizures and fever. There is a continuum in the spectrum of meningitis (meningeal inflammation) and encephalitis (brain inflammation and edema), hence, the term, meningoencephalitis. Parenchymal processes can be further delineated based on anatomical patterns and will present with focal neurologic deficits. These infections may be further described as focal mass lesions or abscesses, vascular lesions, leukoencephalopathy, or brain stem lesions [8]. Regardless of the underlying etiology, patients with brain abscess classically present with fever and symptoms of a space-occupying lesion such as seizure, focal deficits, and altered sensorium.

Whereas meningitis or encephalitis tends to be the most common clinical presentation of CNS infection in the immunocompetent host, immunocompromised patients more commonly present with vascular lesions or mass lesions. The presentation tends to be more indolent or subacute in onset, and symptoms are frequently more severe and prolonged in course [9]. In a retrospective review of cancer patients with positive cerebrospinal fluid (CSF) bacterial or fungal cultures, only 8 % of patients presented with the classic triad of fever, meningismus, and headache. Very often, AMS may be the only presenting symptom [3].

5 Approach to the Diagnosis of CNS Infection

Table 2 summarizes the initial diagnostic evaluation of a cancer patient with suspected CNS infection. A clinician may formulate the differential diagnosis by integrating knowledge of the epidemiology of CNS infections in cancer patients, the type of underlying malignancy, receipt of chemotherapeutic and immunomodulatory agents, and the sum resulting immune deficits. The initial evaluation includes a thorough history and physical examination, understanding that the presentation may be atypical or attenuated. History should include a thorough

Table 2 Initial diagnostic evaluation of suspected CNS infection in cancer patients

History and physical examination
Brain imaging
Chest radiograph
Blood studies
• CBC with differential
• Blood culture
• Fungal culture
• Serum cryptococcal antigen
• Cytomegalovirus viral load (especially in transplant recipients)
Respiratory tract cultures (if pulmonary infiltrate present)
EEG (if altered mental status or suspected seizures present)
CSF analysis
• Opening pressure measurement
• Cell count with differential
• Glucose
• Protein
• Bacterial gram stain and culture
• Fungal stain and culture
• AFB smear and culture
• Cryptococcal antigen
• Herpesviruses PCR studies
• VDRL
• Cytology

review of systems, focusing on other symptoms of infection outside of the CNS, as the etiology of neurologic infection may be related to infection elsewhere or to a disseminated process [10]. Initial evaluation should also include a thorough social history including sick contacts, recent and prior travel, and environmental exposures.

Imaging plays an important role in diagnosing CNS infections in cancer patients as it not only evaluates for focal lesions or abscess, but also can rule out non-infectious entities, including metastatic disease, hemorrhage, cerebrovascular accident, thromboembolic disease, and hydrocephalus from mass effect. Additionally, to identify those at risk of brain herniation, it is recommended that those with suspected meningitis who have an immunocompromised state, history of CNS disease, new-onset seizure, papilledema, abnormal level of consciousness, or

focal neurologic deficit undergo computed tomography (CT) scanning prior to lumbar puncture [11, 12].

Magnetic resonance (MR) is the preferred brain imaging method in those with suspected CNS infection, with CT scan reserved for patients with contraindications to MR or cases of limited access to MR. Advantages of MR versus CT scanning include better distinction of gray versus white matter involvement, as well as superior visualization of the posterior fossa and cerebellum, the leptomeninges, and the venous sinuses [1]. In those with suspected encephalitis, MR is the most sensitive imaging technique and certain patterns of findings may assist in determination of the etiologic agent [13]. Several studies have examined whether specialized MR sequencing, such as calculation of apparent diffusion coefficient (ADC) maps or MR spectroscopy, can differentiate infection from malignant processes with conflicting results [14–17]. MR angiography may be helpful in evaluating for arteritis associated with infections such as varicella zoster virus (VZV) [8].

There are inherent limitations of imaging in immunocompromised patients. The imaging modality of choice may not be practical due to renal dysfunction or concomitant use of nephrotoxic agents, thus limiting the administration of contrast dye or gadolinium. Concomitant steroid use may also reduce contrast enhancement, limiting the sensitivity of contrast-enhanced studies. Finally, findings such as leptomeningeal enhancement and mass lesions are often quite difficult to distinguish between recurrence and spread of malignancy versus infection [1].

In the early stages of encephalitis, an electroencephalogram (EEG) may indicate cerebral dysfunction; however, EEG is generally nonspecific with the exception of HSV encephalitis. More than 80 % of patients with HSV encephalitis will have lateralizing epileptiform discharges in sharp and slow wave complexes every 2–3 s from a focus in the temporal lobe. This finding is typically seen on days 2–14 after the onset of symptoms. Other than HSV, EEG is rarely able to help identify the infectious agent involved in patients with encephalitis; however, it is recommended to evaluate for epileptic activity in those with altered sensorium [13].

The recommendations for initial analysis of CSF remain identical to that of the immunocompetent patient. Opening pressure should be recorded, and initial studies should include white blood cell (WBC) count with differential, red blood cell count, glucose, protein, and gram stain. In all cases, CSF should be sent for bacterial and fungal culture. Further CSF analysis should be based upon the individual clinical scenario [10]. The diagnostic test(s) of choice for individual infections will be described throughout the chapter.

6 Mimics of CNS Infection in Cancer Patients

There are many non-infectious diseases or syndromes that mimic the signs and symptoms and, thus, complicate the recognition of CNS infection in cancer patients. This list includes drug-induced and chemical meningitis, allergic or

hypersensitivity reactions, and leptomeningeal spread of disease, among others [18]. It is important to remember that treatment regimens themselves, including chemotherapeutic agents and medications used to treat symptoms of pain, nausea, and emesis, can also cause signs or symptoms that can be confused with CNS infections. Calcineurin inhibitors used for GVHD prophylaxis can also be implicated in some cases of encephalopathic symptoms. Bleeding as a result of thrombocytopenia can also mimic CNS infection, as can primary or metastatic lesions in the CNS. Table 3 provides a list of some common imitators of CNS infection [9].

6.1 Drug-Induced Meningitis

A multitude of medications are implicated in cases of drug-induced meningitis, but one of the most common observed associations is with non-steroidal anti-inflammatory drugs (NSAIDs). The list of potential medications causing this syndrome also includes antibiotics, most commonly trimethoprim or sulfonamides, but also beta-lactams, fluoroquinolones, and isoniazid [18]. Immunomodulatory agents such intravenous immunoglobulins (IVIG), antithymocyte globulin, and OKT3 can also cause aseptic meningitis [19]. Symptomatically, drug-induced meningitis is indistinguishable from infection as patients present with HA, meningismus, fever, and altered sensorium. Rash, myalgias, arthralgias, facial edema, and abnormal liver chemistries may occur, although these too can be present with infectious meningitis, especially with viral etiologies [19]. Symptoms typically begin within several days to a week after drug exposure but can occur sooner if the patient has been previously sensitized to the offending agent. There are some reported cases that occur as long as 2 years from initial drug exposure [18]. CSF analysis typically reveals a neutrophilic pleocytosis, with CSF WBC ranging from several hundred to several thousand cells per cubic millimeter, elevated protein levels, and normal to slightly low glucose levels. Eosinophils occasionally are found in the CSF. Imaging is nearly always normal [19]. Because it is a diagnosis of exclusion, a negative CSF microbiologic evaluation is necessary. Prompt resolution of symptoms after discontinuation of the offending agent also supports the diagnosis [18].

6.2 Chemical Meningitis

Chemical meningitis (arachnoiditis) can occur with intrathecal administration of chemotherapeutic agents such as methotrexate and cytarabine, especially when used concomitantly with high-dose systemic administration of these drugs [18, 20, 21]. Symptoms of neurotoxicity typically begin acutely, 4–24 h after exposure to the offending agent, although cases have been reported to occur as long as 2 weeks after intrathecal infusion. Symptoms include fever, chills, headache, nausea, vomiting,

Table 3 Conditions that mimic central nervous system infection in cancer patients

Primary or metastatic CNS tumor
• Glioblastoma
• Primary central nervous system lymphoma
• Melanoma
• Breast cancer
• Bronchogenic carcinoma
• Renal cell carcinoma
• Germ cell tumor
Post-transplant lymphoproliferative disorders
Toxic metabolic encephalopathy
Drug-induced alterations in sensorium
• Narcotic and opioid analgesics
• Antiemetics
• Antihistamines
Drug-induced aseptic meningitis
• Nonsteroidal anti-inflammatory agents
• Antimicrobial agents
Trimethoprim–sulfamethoxazole
Beta-lactams
Fluoroquinolones
Isoniazid
• Immunomodulatory agents
Intravenous immunoglobulin
Anti-thymocyte globulin
OKT3
Chemical meningitis (arachnoiditis)
• Intrathecal methotrexate
• Intrathecal cytarabine
Leukoencephalopathy
• Calcineurin inhibitors
Cyclosporine A
Tacrolimus
• Chemotherapeutic agents

(continued)

Table 3 (continued)

Cisplatin
Cytarabine
Gemcitabine
Bevacizumab
Neoplastic meningitis
• ALL
• AML
• Lymphoma
• Solid tumor
Hematologic dysfunction and coagulopathy
• Leukostasis
• Subarachnoid or intracerebral hemorrhage
• Graft-versus-host disease
Marantic endocarditis with embolic and thrombotic complications
Cerebrovascular accident

and meningismus. In some cases, confusion and aphasia may predominate, with seizures also being possible [18]. CSF findings include a pleocytosis ranging from a mild increase to several thousand neutrophils per cubic millimeter along with low glucose and elevated protein levels. In acute cases, the opening pressure may be elevated. MRI may reveal diffuse leptomeningeal enhancement in acute cases. As in the case of drug-induced meningitis, clinical symptoms and CSF findings in cases of chemical meningitis significantly overlap findings in acute bacterial meningitis, and thus, this is a diagnosis of exclusion [18].

6.3 Posterior Reversible Leukoencephalopathy and Calcineurin Inhibitor Neurotoxicity

Calcineurin inhibitors, used for the prevention and treatment of GVHD in the HSCT population, have neurologic side effects that can be confused with CNS infection. Patients receiving cyclosporine have a 10–40 % incidence of neurotoxicity, with a similar incidence reported with tacrolimus [22, 23]. The spectrum of neurologic side effects is wide and ranges from mild symptoms, most commonly tremor, to more severe symptoms, including altered sensorium, psychosis, hallucinations, blindness, seizures, ataxia, and leukoencephalopathy.

The syndrome of posterior leukoencephalopathy associated with calcineurin inhibitors can mimic meningoencephalitis or progressive multifocal

leukoencephalopathy, as the clinical symptoms are similar, including headache, AMS, and possibly seizure and cortical blindness. Distinguishing this from infectious etiologies, many of the patients with this syndrome are hypertensive and more than half have supra-therapeutic drug levels [23]. The occipital white matter is uniquely susceptible to the potential neurotoxic effects of cyclosporine. While tacrolimus-associated neurotoxicity tends to produce similar pathologic changes as cyclosporine, tacrolimus may cause additional neurotoxic changes, particularly vascular toxicity [22]. Brain imaging typically reveals abnormal multifocal, bilateral white matter findings in the parieto-occipital lobes although lesions may occur in the cerebellum, pons, thalamus, and temporal lobes. With a cerebellar syndrome, dysarthria and ataxia occur along with confusion and seizures. In most patients, the CSF analysis is normal, although elevated protein levels can be present [23].

Similar to the calcineurin inhibitors, some chemotherapeutic agents such as cisplatin, gemcitabine, cytarabine, and bevacizumab are reported to cause a reversible posterior leukoencephalopathy syndrome [24].

6.4 Neoplastic Meningitis

Neoplastic meningitis results from the metastatic spread of disease to the leptomeninges and is estimated to occur in 4–7 % of all patients with cancer [25]. It is clinically diagnosed in 4–15 % of patients with solid tumors, 5–15 % of patients with leukemia and lymphoma, and 1–2 % of patients with primary brain tumors [26].

The clinical presentation of neoplastic meningitis varies and the majority of patients present with multifocal symptoms based upon the CNS territories that are involved. The most common symptoms are headache, mental status changes, ataxia, neck or back pain, focal weakness, and seizures [27]. Cranial nerves can also be affected by leptomeningeal disease, and thus, cranial nerve palsy may be one of the presenting clinical signs or symptoms. Symptoms related to spinal cord involvement occur in more than 60 % of patients and include pain with or without radiculopathy, myelopathy, and cauda equina syndrome [28].

The diagnosis is established by neuroimaging and CSF analysis. Suggestive MR findings include parenchymal volume loss, ependymal or subependymal enhancement, and other abnormalities such as sulcal-cisternal enhancement, subarachnoid enhancing nodules, and communicating hydrocephalus [26]. The CSF analysis is almost always abnormal with elevated opening pressure in up to 50 %, pleocytosis, elevated protein levels, and low glucose levels. Abnormal CSF cytology confirms the diagnosis with a specificity of more than 95 %, albeit lower sensitivity [18]. CSF flow cytometry offers enhanced diagnostic sensitivity over traditional cytology [29]. Rarely, meningeal biopsy is necessary to confirm the diagnosis [28].

7 Spectrum of Infections with Emphasis on CNS Pathogens of Special Significance for the Cancer Patient

Cancer patients and stem cell recipients are susceptible to a broad range of CNS infections caused by bacterial, fungal, viral, and parasitic pathogens (Table 1). This section will review the predominant infectious etiologies, with a focus on organisms that pose a special problem for these vulnerable patient populations.

7.1 Bacteria

The spectrum of bacterial CNS infections is broader than the general population. An analysis of CSF and autopsy cultures obtained from patients at MSKCC from 1955 to 1973 demonstrated that the most prevalent bacterial meningitis pathogens, from more to less frequent, included *Listeria monocytogenes, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae*. Other bacteria found to cause meningitis in this series included the Enterobacteriaceae, other streptococci, and other staphylococci. This was in contrast to the most common causes of meningitis in the general community, *S. pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*. The spectrum of pathogens causing focal brain abscesses was also found to be different than that in the general population. Gram-negative bacilli including *E. coli, P. aeruginosa*, and *Proteus* spp. were the most common organisms identified, while staphylococci and streptococci were less common [2].

The epidemiology of bacterial infections has evolved over time. Staphylococci have gained importance as a CNS pathogen, presumably related to an increase in the use of intraventricular devices [30]. In a review of CNS infections at MSKCC between 1993 and 2004, there was a marked shift from gram-negative to gram-positive pathogen predominance in recent years: 70 % gram-positive cocci, 10 % gram-positive bacilli, and 14 % gram-negative bacilli. *Listeria* was a much less identified pathogen with only two cases found during this time period [3]. Finally, tuberculosis should also be kept in mind in those with known exposure or those at high risk of prior exposure and can present as basilar meningitis or tuberculoma [31].

7.1.1 *Listeria monocytogenes*

The gram-positive bacterium, *L. monocytogenes*, is a well-known opportunistic pathogen that causes sepsis and meningoencephalitis in cancer patients. The bacterium is acquired primarily via ingestion of contaminated foods, and up to 5 % of healthy adults have evidence of intestinal carriage of this organism [32–35]. Those with depressed cell-mediated immunity, due to underlying disease and therapies, are especially susceptible to disseminated infection with this organism [32, 33]. *Listeria* is a leading cause of community-acquired meningitis, accounting for 4–8 % of all cases in large epidemiologic studies [36, 37].

Established risk factors for non-perinatally acquired listeriosis include age older than 60 years, malignancy, and corticosteroid and other immunosuppressive therapies [32, 35, 38–45]. In cancer centers, listeriosis is a relatively infrequent but serious infection, accounting for 0.04–0.1 % of hospital admissions [46, 47], with a declining overall incidence in US cancer centers in recent years [3, 48]. This infection disproportionately affects patients with lymphoreticular malignancies, although patients with solid tumor malignancies, especially those receiving corticosteroid or other immunosuppressive therapies and those with advanced liver disease are at risk [3, 40, 44–47]. Hematopoietic stem cell transplant recipients are also susceptible to listeriosis, although the reported incidence is low, 0.38–0.58 % [46, 49–51]. In case reports and small series, listeriosis can complicate both autologous and allogeneic stem cell transplantation but is most often described in recipients of unrelated or HLA-mismatched donor transplants, cases complicated by GVHD, and those receiving corticosteroids [47, 49, 51–58].

Twenty-eight to 43 % of patients with non-perinatally acquired listeriosis have CNS involvement that most typically manifests as meningitis or meningoencephalitis [39, 40, 44]. Meningoencephalitis most often presents as an acute illness that is not easily distinguished from other causes of meningitis based on symptomatology alone. Common features include fever (86–100 %), headache (29–88 %), alterations in mental status and/or consciousness (42–100 %), nuchal rigidity (26–73 %), nausea and/or emesis (29–83 %), and focal neurologic deficits (35–37 %) such as cranial neuropathies, disordered speech, paresis, nystagmus, and ataxia [37, 40, 43, 46]. Seizures may occur in 11–29 % [37, 40, 46]. With meningoencephalitis, the CSF analysis demonstrates neutrophilic pleocytosis, elevated protein level, and varying degrees of hypoglycorrhachia [32, 37, 46]. Lymphocytic pleocytosis is occasionally observed. The gram stain will demonstrate gram-positive bacillary forms in only approximately 1/3 of cases [34, 37]. The diagnosis is confirmed by isolation of *Listeria* in culture; the culture yield is >80 % and 46–78 % in CSF and blood, respectively [32, 34, 37, 43, 48]. Serum hyponatremia, attributed to the syndrome of inappropriate antidiuretic hormone secretion, is reported [37].

A less common form of CNS listeriosis is cerebritis characterized by focal brain lesions or abscess often involving the basal ganglia or thalamus; 25 % of such cases have concomitant meningitis [32, 34, 35, 43, 46, 59], see Fig. 1. The CSF analysis in these cases is consistent with a parameningeal focus of infection unless meningitis is also present. *Listeria*-associated rhombencephalitis and spinal cord abscesses are exceptionally rare in the immunocompromised host [32, 34, 35].

Treatment guidelines for CNS listeriosis are based on cumulative clinical experience, in vitro antimicrobial susceptibility testing, and expert opinion [12, 32, 35, 46, 60]. The addition of ampicillin or penicillin for empiric treatment of bacterial meningitis is warranted whenever *Listeria* is a diagnostic consideration. For confirmed cases, parenteral ampicillin or penicillin is recommended for a duration of 3 weeks [12]. In the setting of cerebritis or brain abscess, the antibiotic duration is extended to 4–6 weeks [32, 33]. The addition of an aminoglycoside, for the initial portion or duration of treatment, is considered beneficial due to in vitro synergism.

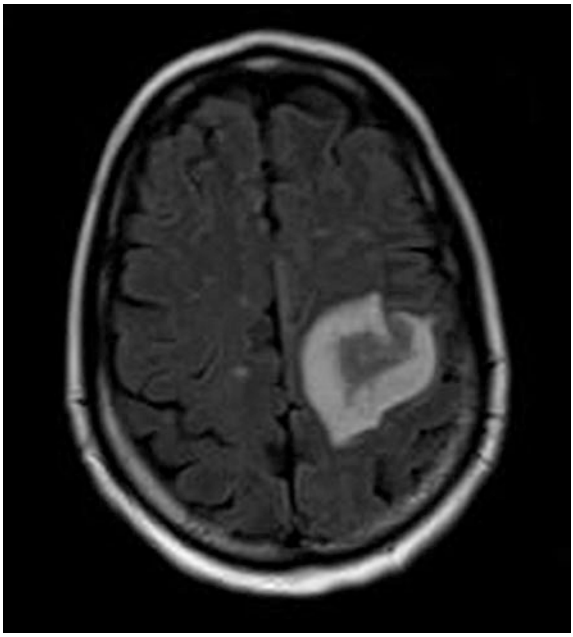

Fig. 1 A 60-year-old male with Waldenstrom's macroglobulinemia with large cell transformation presented day + 97 status post matched sibling donor non-myeloablative stem cell transplantation with new-onset seizures, right upper extremity weakness, and word-finding difficulties. Brain MR demonstrated a heterogenous mass lesion within the left frontoparietal region associated with a 4.5-cm area of vasogenic edema. Due to suspicion for lymphoma, a brain biopsy was undertaken. *Listeria monocytogenes* was isolated from blood and brain tissue cultures

In the penicillin-allergic patient, the preferred alternative agents are trimethoprim–sulfamethoxazole (TMP-SMX) or meropenem. Although *Listeria* exhibits in vitro susceptibility to vancomycin, cases of listeriosis have developed in patients during vancomycin therapy [61, 62]. Cephalosporin and chloramphenicol treatment failures are reported [49]. There is no clear role for corticosteroids if the diagnosis of *Listeria* meningitis is established. Surgical intervention and intrathecal antimicrobial therapy may be required for refractory cases [35, 43, 63].

The reported mortality for *Listeria* meningitis is 3.1–50 % [37, 39, 40, 46, 48, 64], and the overall mortality of listeriosis is higher in those with malignancy as opposed to other medical conditions [44]. Risk factors for mortality with non-perinatally acquired listeriosis include non-hematologic malignancy, steroid use, and chemotherapy [64–66]. Even with successful treatment for the initial infection, relapsing and recurring infection can occur and permanent neurologic sequelae can result from listeriosis [34, 40, 43, 49]. The prevention of listeriosis focuses largely on avoidance of undercooked meats, raw eggs, and unpasteurized dairy products; thorough washing of raw vegetables prior to ingestion; and cleaning of food preparation utensils and boards after contamination [32, 33, 67]. Additionally, immunocompromised patients should avoid uncooked processed meats such as cold cuts, hot dogs and soft cheeses. While TMP-SMX prophylaxis is effective in reducing *Listeria* infections in AIDS patients and solid organ transplant recipients, breakthrough infections have occurred in stem cell transplant recipients receiving this drug in prophylactic doses [46, 52].

7.1.2 *Nocardia* Species

Nocardia spp. are aerobic actinomycetes that are widely distributed in nature as a component of soil and decaying matter. At least 16 species are capable of causing human disease, usually as a consequence of inhalation. The more common pathogenic species include *Nocardia asteroides* sensu stricto, *Nocardia brasiliensis*, *Nocardia farcinica*, and *N. nova* [68–70]. Although overall population estimates are difficult to ascertain, previous surveys report that the annual incidence of nocardiosis is 500–1,000 and 150–250 cases in the USA and France, respectively [71, 72]. *Nocardia* spp. are opportunistic pathogens, primarily afflicting patients with underlying conditions, especially those with deficiencies in cell-mediated immunity but also those with neutrophil dysfunction and deficiencies in humoral immunity [68, 73]. Malignancy, corticosteroid therapy, and cytotoxic chemotherapy are well-recognized risk factors for nocardiosis [68, 74–85]. At MD Anderson Cancer Center, nocardiosis accounted for 0.06 % of hospital admissions during 1988 to 2001 [79]. Cases are more frequently described in association with hematologic malignancy, but solid tumor patients are also susceptible [79]. Nocardiosis is also seen as a late complication of bone marrow and HSCT, [78, 79, 86–101] with reported incidences of 0.2 and 1.7 % in recipients of autologous and allogeneic transplants, respectively [89, 94]. Many cases have occurred following the development and steroid treatment of GVHD [79, 89–97, 100–102].

While pulmonary disease is the most common clinical manifestation of nocardiosis, hematogenous dissemination can result in CNS disease [68, 69]. In fact, 7.7–33 % of nocardiosis cases involve the CNS [71, 72, 76, 78, 80, 85, 103]. CNS disease most commonly presents as brain abscess, with a course that is more indolent than with other bacterial causes. The clinical presentation is one of space-occupying brain lesion and elevated intracranial pressure, and because of this, *Nocardia* can be confused for primary or metastatic brain tumors [68, 104]. Common symptoms include headache, nausea, vomiting, confusion, altered consciousness, and seizures [68, 70, 82]. Parkinsonism is also described [68]. Alternatively, but uncommonly, meningoencephalitis occurs, and spinal cord involvement has been reported [68, 82]. Imaging studies will show one or more multiloculated abscesses. Because CNS infection can be silent, it is imperative to perform brain imaging whenever pulmonary nocardiosis is diagnosed.

When the diagnosis of nocardiosis is entertained, respiratory specimens and brain abscess aspirate or tissue are required for routine microbiological studies. *Nocardia* spp. are weakly staining, beaded and branching, gram-positive bacilli. They are also weakly acid fast, a property that is useful in the identification scheme. *Nocardia* can be isolated from routine bacterial cultures within 2–7 days of plating, and recovery can be enhanced by selective and enriched media such as buffered charcoal–yeast extract, colistin–nalidixic acid, modified Thayer-Martin agars and fungal media [68, 69]. If concomitant pulmonary disease is present, it may not be necessary to perform brain biopsy or aspiration. Since there are important species differences in antimicrobial susceptibility patterns, speciation is clinically important, and molecular diagnostic assays, such as 16S rDNA

sequencing, are playing an increasingly important role in the management of nocardial disease. Due to the varying susceptibility patterns of *Nocardia* species, antimicrobial susceptibility testing is generally recommended to guide therapeutic choices [70].

For decades, the primary agents for treatment of nocardiosis have been sulfonamides such as TMP-SMX. With CNS involvement, dual or triple combination therapy with TMP-SMX, imipenem or a third-generation cephalosporin, and amikacin are administered empirically until antimicrobial susceptibility testing results can guide therapy [69, 70]. Other active agents include minocycline and linezolid [70, 105]. Parenteral therapy is continued for a minimum of 3–6 weeks, depending on the severity of infection and response to therapy, and then, oral therapy is continued for at least 12 months to minimize risk of relapse. For refractory cases, surgical intervention may be required [68, 90]. Reduction in immunosuppressive therapies is warranted [68].

While nocardiosis is an infrequent infection, its importance lies in its propensity to cause serious morbidity and mortality. Regardless of whether there is CNS involvement, *Nocardia* is associated with a high mortality rate in cancer patients, ranging from 25 to 100 % [76, 78–80, 84]. Experts advocate for TMP-SMX prophylaxis to reduce the risk of infection in susceptible patients, such as HSCT recipients [94, 97, 106], although breakthrough infections do occur [79, 107].

7.2 Fungi

Fungal pathogens are much more frequently isolated from cancer patients with CNS infections compared to the general population and are associated with high mortality. In a series from MSKCC from 1955 to 1973, the etiologic agent of meningitis was fungal in origin in almost one-third of cases [2]. Most cases are caused by *Cryptococcus neoformans*, but other etiologies include *Aspergillus* spp. and *Candida albicans* [2, 3].

The experience at specialized cancer centers varies, but the majority of brain abscesses, particularly post-transplantation, are caused by fungi [108]. The most common fungal etiology of focal brain abscess is *Aspergillus*, followed by Mucorales and *Candida* [2, 6]. Other more rare causes of fungal brain abscess in patients with hematologic malignancy include *Scedosporium* species, *Pseudallescheria boydii*, phaeohyphomycetes such as *Cladophialophora bantiana*, and *Fusarium* species [109].

7.2.1 *Aspergillus* Species

The CNS is the most common target organ of disseminated aspergillosis due to hematogenous spread from the lungs. Alternatively, invasive CNS aspergillosis may also occur as a result of direct extension from invasive sinus disease. With an overall reported incidence of only 0.8 % following HSCT, its importance lies in the high rate of mortality [6]. Less than 5 % of cases of CNS aspergillosis are

isolated to the CNS, and the vast majority are associated with invasive disease in other locations, most commonly the lung or sinuses [108, 109].

One of the most important risk factors implicated in the development of invasive aspergillosis includes neutropenia, with a strong relation to both the degree and duration of this deficit. Other host defense deficits that contribute to infection risk include defects in phagocyte function, cell-mediated immunity, and mucosal immunity. These deficits may result from treatment course, underlying malignancy, and/or corticosteroid use [110]. In a retrospective review of 14 cases of CNS aspergillosis in HSCT recipients, 79 % were neutropenic at the time of diagnosis, 93 % had acute GVHD, and 93 % received high-dose methylprednisolone [111].

The clinical presentation can be nonspecific and misdiagnosed as cerebral infarction or hemorrhage. Fever is present in 40–76 % of patients and is more commonly present when concomitant pulmonary aspergillosis is present. AMS is also common and found in 30–65 % of patients. Other signs or symptoms that have been found in one-fourth to one-third of patients include seizure, hemiplegia, and cranial nerve palsies [109]. Neurologic symptoms tend to progress rapidly, and in one study, the time from the initial neurologic symptoms to the diagnosis of cerebral aspergillosis or to death was a median of 7 days with a range of 0–27 days [111]. In HSCT recipients, the median time to diagnosis generally occurs >100 days post-transplant; however, cases have been diagnosed in a range from 49 to 347 days [6, 111].

Diagnostic imaging, typically MRI, will demonstrate findings that are typical for that of fungal brain abscess, including hyperintensity on T2-weighted imaging, hyperintensity on diffusion-weighted imaging (DWI), and hypointensity on ADC mapping. In organized abscesses, contrast enhancement occurs and the lesion will show ring enhancement (Fig. 2a); however, this may not be the case in acute or subacute cases. Because aspergillosis is a vasoinvasive pathogen, evidence of hemorrhagic brain infarction may also be seen on neuroimaging studies [112]. One group of investigators have suggested that "target-like" lesions on DWI may aid in distinguishing *Aspergillus* from other fungal causes of brain abscess and malignancy [113].

Ideally, the diagnosis of CNS aspergillosis requires histopathologic, cytopathologic, or direct microscopic evidence of the pathogen and associated cell damage from brain tissue, with a culture positive for *Aspergillus* spp. (Fig. 2b). In the absence of a positive tissue culture, a positive blood culture would also suffice to make the diagnosis, though this is rarely found with infections due to *Aspergillus* spp. Indirect tests such as detection of galactomannan antigen or 1,3-beta-d-glucan can support the diagnosis [114]. As brain biopsy may not always be feasible, evidence of invasive pulmonary or sinus disease combined with typical CNS imaging findings may lend weight to the diagnosis of cerebral aspergillosis [108].

Generally, CSF examination is of low yield, though it may aid in ruling out other infectious etiologies. CSF findings are typically nonspecific with negative fungal smear and culture. The use of CSF-PCR for diagnosis of cerebral

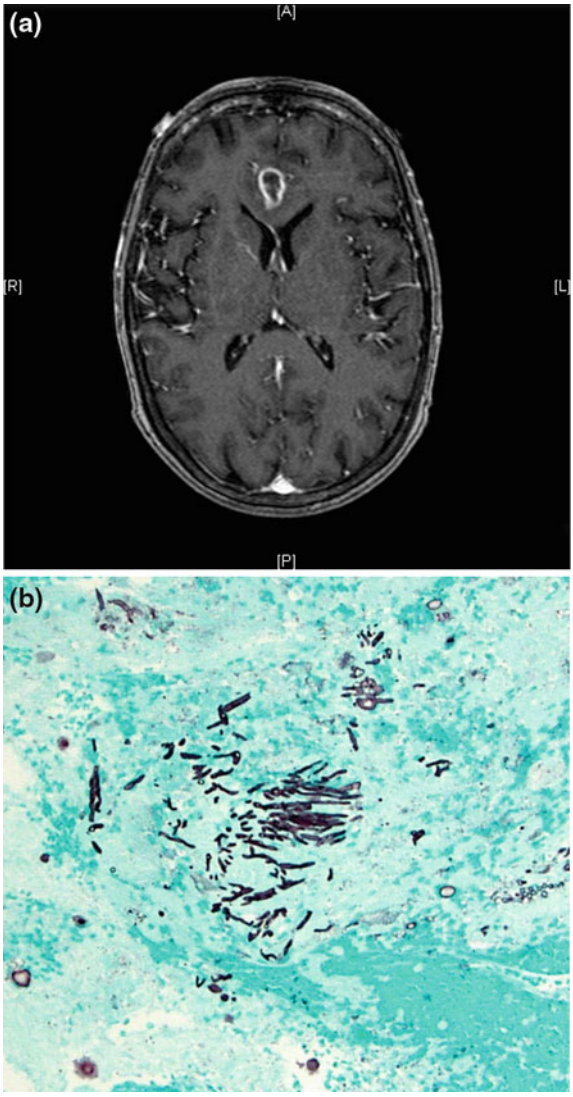

Fig. 2 A 62-year-old female with diffuse large B-cell lymphoma and invasive pulmonary aspergillosis presented with *right* foot drop; **a** brain MR imaging demonstrated a ring-enhancing lesion within the medial *right* frontal cortex and subcortical white matter; and **b** stereotactic brain biopsy specimen with Gomori's methenamine silver staining revealed fungal hyphae with acute angle branching, consistent with *Aspergillus* spp.

aspergillosis has been reported, but this test is not widely available [115, 116]. Measurements of CSF galactomannan antigen may have some utility [115, 117].

First-line therapy for invasive aspergillosis, including CNS disease, is voriconazole. Voriconazole has wide tissue distribution and achieves levels in the CSF that are approximately 50 % of plasma levels [118]. An open-label, non-comparative multicenter study evaluated the efficacy and safety of voriconazole and demonstrated a therapeutic response in 48 % of cases, including 16 % with cerebral invasive aspergillosis. An additional 26 % of patients with cerebral invasive aspergillosis were found to have had a stable response with voriconazole

therapy [119]. In a randomized trial comparing voriconazole versus amphotericin B (AmB) for primary therapy of invasive aspergillosis, in the subset of patients with extrapulmonary disease, favorable therapeutic responses were achieved in 42.9 % of those receiving voriconazole versus only 12.5 % in those receiving AmB. Additionally, an overall survival benefit was achieved in the voriconazole treatment group [120]. With voriconazole, there is evidence that therapeutic drug monitoring may be of some utility in guiding therapy, as several studies have shown a lack of response to therapy at lower levels as well as an increase in toxicity at higher levels [121].

Agents that can be used for salvage therapy include lipid formulations of AmB, posaconazole, and itraconazole. While there is no definitive evidence that combination therapy is of added benefit, it may be considered [118]. In several studies, adjunctive surgical therapy of CNS disease was associated with improved outcomes [122].

The prognosis of invasive aspergillosis, particularly with cerebral disease, is quite poor. Historically, the mortality rate approaches 100 % in most studies [6]. In all types of invasive aspergillosis, crude mortality rates at 1 year are reported to be anywhere from 70 to 93 % [123].

7.2.2 Mucorales

Mucormycosis is the third most common invasive fungal infection after *Aspergillus* and *Candida* spp. infections [124]. These fungi are ubiquitous in nature and are commonly found in soil as well as decomposing plant and animal material. Infection is caused by inhalation or ingestion of airborne sporangiospores [125]. The classic distribution of this opportunistic pathogen is pulmonary or rhinocerebral with destruction and necrosis of the palate allowing extension to nearby structures, including the eyes and brain. Disseminated disease is seen in up to 40 % of patients with hematologic malignancy [124]. The most common cause of invasive mucormycosis is *Rhizopus oryzae*, but other *Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp., *Absidia* spp., and *Cunninghamella* spp. are other agents of mucormycosis [110]. The two most significant risk factors found in a large case series included diabetes and hematologic malignancy in more than 50 % of cases. Some case series also report the use of voriconazole to be a risk factor for the development of mucormycosis [126]. As with aspergillosis, other known risk factors include prolonged neutropenia, receipt of stem cell transplant, and those receiving immunosuppressives that deplete cell-mediated immunity [124].

Patients with rhinocerebral mucormycosis typically present with fever, nasal congestion, sinus tenderness, headache, and periorbital edema with or without proptosis. Mental status changes occur with cerebral involvement [110]. Because direct extension of the infection to the brain from the sinuses occurs via the dura, patients may also present with cranial nerve palsies, thrombosis of the internal carotid artery, hemiplegia, lethargy, and seizures [127].

Imaging studies of the sinuses and brain should be performed if clinical suspicion dictates. CT of the brain with contrast may reveal ring-enhancing lesions in

the frontal or temporal lobes [127]. MRI is typically more sensitive than CT and may reveal minimal enhancement on DWI, with hyperintense lesions in the case of cerebral abscess. In those who present with symptoms of fungal sinusitis, sinus endoscopy may show necrotic or ulcerated tissue due to hyphal invasion into blood vessels, leading to tissue infarction and hemorrhage [110]. Isolated cerebral mucormycosis is more common than that seen with aspergillosis and may occur in up to 20 % of cases. Distinction between cerebral mucormycosis and aspergillosis is difficult to make based on clinical or radiologic findings alone, and histopathology is usually required [109]. Biopsy is thus essential to diagnosis, and in the case of sinus disease, it is usually well tolerated. Cultures are positive in only 40–70 %, but pathology can usually differentiate mucormycosis from other causes of infection [110]. Findings on histopathology that may lead to the diagnosis of mucormycosis include broad, non-septate, hyaline pale, acidophilic hyphae in hematoxylin and eosin stain. Periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) stains can better define the morphology and will reveal irregular branching and angioinvasion. Other pathologic findings that may be demonstrated include vasculitis, thrombosis, and infarction with neutrophilic infiltration and sometimes a granulomatous response [128]. CSF analysis is usually not helpful in the case of fungal abscess, and blood cultures are rarely positive, even in disseminated disease [127]. In addition, no serologic tests are available to aid in diagnosis [109].

Successful treatment for CNS mucormycosis relies on early diagnosis and a multifactorial approach including surgical debridement, antifungal therapy, and resolution of modifiable risk factors. Risk factors that can be modified include correction of hyperglycemia, discontinuation of corticosteroid or immunosuppressive therapy, and aiding in recovery from neutropenia [127].

First-line antifungal therapy for mucormycosis remains the polyene class. Traditionally, AmB, 1–1.5 mg/kg/day, was used and is still the only antifungal agent licensed for the treatment of mucormycosis, but major disadvantages include nephrotoxicity and poor CNS penetration [129]. Lipid formulations of AmB, especially liposomal AmB (L-AmB), have become the preferred therapy for mucormycosis based on several studies. One study of salvage therapy with AmB lipid complex (ABLC) found a 71 % success rate [130]. In another review of zygomycosis in patients with hematologic malignancy, patients who received L-AmB had improved survival versus those who received traditional AmB [131]. With regard to specific lipid formulations, one review of rhino-orbital-cerebral mucormycosis found inferior success rates and higher clinical failure rates with the use of ABLC versus both L-AmB and conventional AmB. It is suggested that poorer outcomes in cases of mucormycosis with CNS extension is worse with ABLC due to decreased CNS penetration compared to L-AmB or AmB, as seen in rabbit models [132].

Fluconazole and voriconazole do not have reliable activity against the pathogens of mucormycosis. Itraconazole has activity limited to *Absidia* species. Posaconazole has in vitro activity against Mucorales; however, variability in levels achieved, especially in patients at risk for malabsorption, such as those with severe

mucositis and GVHD of the gastrointestinal tract, has limited its use. Several murine models of mucormycosis found posaconazole to be inferior in efficacy to AmB and no better than placebo in other studies with *R. oryzae*. Thus, posaconazole is not recommended for primary therapy but can be considered for salvage therapy in those who are refractory to or intolerant of polyenes [129].

Other strategies for the treatment of mucormycosis include combination antifungal therapy. One retrospective study of rhino-orbital-cerebral mucormycosis found a significantly improved outcome in those receiving polyene–caspofungin combination therapy, with the most pronounced improvement in those with cerebral involvement. In this small group of patients, success rate was 100 % versus only 25 % with polyene monotherapy [132]. Animal studies have not shown a benefit to posaconazole–polyene combination therapy, and no clinical studies have yet been performed [129].

Iron chelation therapy has recently been investigated as an adjunctive treatment method for mucormycosis. The basis of this therapy arose from the knowledge that deferoxamine enhances delivery of iron to *Mucorales* and thus predisposes to mucormycosis. Other iron chelators, such as deferasirox, however, cannot be used by *Mucorales* to acquire iron. Deferasirox was also found to be fungicidal for clinical isolates of *Mucorale*s in vitro. Animal studies are promising in showing synergistic efficacy with the use of L-AmB and deferasirox in the treatment for disseminated mucormycosis. A phase II double-blinded, randomized, placebo-controlled trial for the safety and efficacy of adjunctive deferasirox-L-AmB therapy for mucormycosis is currently ongoing [129].

In cases of cerebral mucormycosis, the overall mortality rate is near 80 %. The prognosis is slightly better for those with localized cerebral and rhinocerebral infection, with mortality rates of approximately 60 %. In cases of disseminated disease with CNS involvement, however, mortality approaches 100 % [126].

7.2.3 *Cryptococcus* Species

Cryptococcus is a ubiquitous basidiomycetous yeast that has approximately 20 known species, of which *C. neoformans* is the main human pathogen. Infection is acquired by inhalation, resulting in focal lung disease and frequent dissemination to the CNS [133]. While 80–90 % of cases now occur in the context of advanced HIV infection, >30 % of non-AIDS-related cryptococcosis cases occur in cancer patients [134]. In fact, there was early recognition of a relationship between hematologic malignancy and cryptococcosis [135].

Trends from major cancer centers suggest a declining frequency of cryptococcosis, perhaps due to improvements in the management of underlying diseases of these patients [3, 30, 136–138]. Most recently, 7 % cases of meningitis cases at MSKCC were attributed to *Cryptococcus* [3].

In cancer patients, identified risk factors for cryptococcosis include hematologic malignancy, corticosteroid therapy, lymphopenia, fludarabine therapy, advanced neoplasia, extensive prior chemotherapy, and leukopenia [136–139]. Cryptococcosis most commonly occurs in those with lymphoma [137–141], chronic

leukemias [142, 143], and other hematologic malignancies such as acute leukemia [144–146] and multiple myeloma [147]. A minority of cases occur in patients with solid tumors, especially those receiving corticosteroids [138, 148]. Cryptococcosis is rarely reported following HSCT [138, 139, 147–154].

Clinically, cancer patients have subacute or chronic onset of meningitis, and compared with AIDS-related cryptococcosis, they have symptoms for longer durations before presentation [140, 155]. The predominating features are altered sensorium and fever [136, 138]. Other presenting signs and symptoms include headache, meningismus, seizures, nausea and vomiting, visual disturbances, and cranial nerve deficits.

The diagnosis of cryptococcal meningitis largely relies on clinical suspicion and obtaining the appropriate clinical specimens for laboratory testing. Brain imaging should be performed to evaluate for mass lesions and elevated intracranial pressure. Lumbar puncture may demonstrate elevated opening pressure, and CSF analysis will reveal widely varying degrees of inflammation with mononuclear pleocytosis, elevated protein, and low glucose [136, 155]. A presumptive diagnosis is based on rapid antigen detection in CSF and serum. This test has supplanted India ink stain for rapid diagnosis of cryptococcal meningitis. The sensitivity and specificity of commercially available latex agglutination assays are 90–100 % and 97–100 %, respectively [156–158]. False-negative results have occurred with early infection (low organism burden) [159], chronic indolent meningitis (high organism burden and prozone effect), and capsule-deficient *C. neoformans* infection [160]. Low-titer false-positive results can occur as a result of cross-reactivity with rheumatoid factor, syneresis fluid (surface condensation from agar) [161, 162], *Trichosporon beigelii* meningitis [163], or *Capnocytophaga canimorsis* (bacterium DF-2) septicemia [164]. False-positive results have also occurred in cancer patients. In a series of twelve such cases, 50 % had a malignant process involving the CNS, and the majority had a positive CSF cryptococcal antigen of 1:8 dilution or lower (range 1:2 to 1:256) but no culture evidence of cryptococcosis [165]. The definitive diagnosis of cryptococcal infection is established by isolation of the pathogen in culture of CSF, blood, lung, and other tissues.

Untreated meningitis in the immunocompromised host is uniformly fatal, and thus, successful management requires early disease recognition, aggressive antifungal therapy, and management of elevated intracranial pressure. The standard induction regimen for cryptococcal meningitis is AmB, 0.7 mg/kg/d plus flucytosine, 100 mg/d. Combination therapy is superior to AmB monotherapy, as demonstrated by better mycological response rates and reduction in early mortality [136, 155, 166–170]. Beyond the induction phase of treatment, a longer course of consolidation therapy is recommended due to high disease relapse rates [171, 172]. An early study demonstrated lower relapse rates by continuing AmB and flucytosine for 6 rather than 4 weeks [173]. Based largely on clinical trials data in the AIDS population, consolidation therapy, alternatively, can be accomplished with oral fluconazole 400 mg/d for a minimum of 10 weeks [167, 169, 171]. The total duration of therapy is determined by clinical resolution of disease. Although limited comparative clinical data exist regarding the use of lipid-based

amphotericin formulations for the treatment of meningitis, these agents offer a more favorable toxicity profile than conventional AmB and are acceptable alternative therapies [172, 174, 175].

In order to prevent adverse neurologic outcomes, patients with elevated ICP are managed with serial lumbar punctures and drainage of CSF [172, 176, 177]. Refractory cases can be managed by lumbar drain placement or with ventriculoperitoneal shunts [178–181]. In general, corticosteroids are not recommended in this setting [172, 176]. Intrathecal or intraventricular instillation of amphotericin can be used when systemic administration of antifungal therapy has failed [182], but this technique is associated with a high rate of toxicity. Lowering doses of immunosuppressive agents, when feasible, are desirable to control infection.

Patients with hematologic malignancies have the highest mortality with cryptococcosis in comparison with other groups [155, 170, 171, 183], perhaps because the underlying immune deficits are not easily reversible. Indicators that predict treatment failure and mortality include corticosteroid therapy, advanced age, organ failure, disseminated infection (with >1 extraneural culture-positive site), abnormal neurologic exam or brain imaging, elevated ICP, high initial serum or CSF cryptococcal antigen titer, persistently low CSF glucose level, and lack of CSF inflammation (CSF WBC <20 cells per cubic millimeter) [140, 155, 171, 183].

7.3 Viruses

Herpesviruses are important pathogens in meningoencephalitis in patients with impaired cell-mediated immunity, especially in the post-transplant setting. Herpes simplex encephalitis is the most common cause of viral encephalitis in the general population and also affects the immunocompromised; thus, acyclovir is administered to all patients with encephalitis until a specific etiology is determined. VZV causes meningoencephalitis, either in the setting of disseminated zoster or with primary infection. The characteristic vesicular rash may be absent. Human herpesvirus-6 (HHV-6) may cause meningoencephalitis in the early post-transplant period and is associated with poor outcomes. Primary or reactivation EBV may result in systemic infection, including meningoencephalitis, and EBV-associated post-transplant lymphoproliferative disorder may affect the CNS [184]. Finally, cytomegalovirus (CMV) is an infrequent cause of encephalitis post-transplant, but is occasionally encountered in the setting of disseminated CMV infection [185]. Combination ganciclovir–foscarnet therapy is recommended for the treatment of CMV encephalitis [13]. It is important to note that widespread use of antiviral prophylaxis has successfully reduced the risk of infection due to herpesviruses, including CMV [31]. Additionally, the declining incidence of CMV-associated CNS disease has been attributed to improvements in diagnostics, surveillance strategies, therapeutic advances, and the selective use of CMV-negative blood products [6].

The herpesviruses are important examples of infections that result from endogenous reactivation or donor-derived disease. It is also important to consider the differential diagnosis of viral meningoencephalitis within the context of seasonal and geographic exposures. For example, West Nile virus meningoencephalitis is described in HSCT recipients and is associated with severe disease presentations, long-term neurologic deficits, and fatal outcomes. This flavivirus may be transmitted through marrow transplantation and blood product administration, but it is also naturally acquired via mosquitoes in endemic regions [186–191].

Finally, JC virus and its associated CNS infection, progressive multifocal leukoencephalopathy, can affect cancer patients and has received renewed attention due to increased reports of cases with the introduction of new immunomodulatory agents into clinical practice.

7.3.1 Human Herpesvirus-6

HHV-6 is seroprevalent in the adult population with primary infection occurring in early childhood and lifelong viral persistence thereafter [192–194]. There are two distinct viral variants, HHV-6A and HHV-6B. Viral reactivation, most often due to HHV-6 type B, may be triggered by immunosuppression and occurs in 28–81 % of HSCT recipients, with median onset of viremia at 23–40 days post-transplant [192, 195–199]. Identified risk factors for HHV-6 reactivation after HSCT include younger age, leukemia or lymphoma diagnosis, hematologic malignancy with more than one remission, HLA-mismatch donor or unrelated donor transplant, gender mismatch transplant, IVIG use, and steroid use [196, 200–202]. In a subset of HSCT recipients, viral reactivation can lead to clinical disease, including encephalitis. In fact, several studies have shown a correlation between higher levels of HHV-6 viremia and the development of CNS dysfunction [196, 198, 200, 202]. In single-center series and one multicenter survey, the reported incidence of HHV-6 encephalitis following HSCT ranges from 0.41 to 0.96 % [197, 203, 204].

In the setting of malignancy, HHV-6 encephalitis is limited to the allogeneic HSCT population [197, 198, 202–230], with only a few cases reported following autologous HSCT or chemotherapy for hematologic malignancy [231–233]. This clinical entity is most often described in the setting of unrelated or HLA-mismatch donor transplantation [197, 203, 204, 206, 208, 211–214, 221, 222, 224, 225, 227, 228] and cord blood transplantation [203, 204, 215, 220, 223, 229]. A higher incidence (11 %) of encephalitis was recently reported in allogeneic HSCT recipients after alemtuzumab conditioning [226].

Clinically, patients present early in the post-transplant course, with median onset of symptoms occurring 22–60 days post-HSCT [193, 197, 204, 225, 226]. Encephalitic symptoms may be preceded by a viral exanthem and fever; however, neither are consistently reported findings [197, 204]. Virtually all present with alterations in mental status ranging from confusion, disorientation, and agitation to somnolence and coma [197, 203, 204, 212, 218, 226]. Anterograde memory loss,

which can be profound, is reported in 45–100 % of patients [193, 194, 197, 204, 218, 225, 226]. Seizures (10–80 %), insomnia, and emotional and behavioral disturbances are frequent findings [197, 203, 204, 212, 218, 225, 226]. Hyponatremia as a result of the syndrome of inappropriate antidiuretic hormone secretion may be present [194, 225]. Although the CSF analysis may be entirely normal, two-thirds of patients will have an elevated CSF protein level and a mild lymphocytic pleocytosis occurs in approximately 50 % [193, 203, 204, 212, 225, 226, 234]. In 50–100 % of cases, MR imaging abnormalities are reported and classically include hyperintense signal abnormalities in the temporal lobes and limbic system on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [193, 194, 197, 204, 218, 226, 234, 235]. Nonspecific or diffuse EEG abnormalities are common, but occasionally temporal or fronto-temporal seizure foci are found [193, 194, 226, 234].

In the appropriate clinical setting, the diagnosis is confirmed by the detection of HHV-6 DNA in CSF by PCR; the reported sensitivity of this assay is >95 % [13, 234]. In stem cell recipients with encephalitis, the reported median quantitative PCR results are 3,300–10,000 copies/mL [197, 204, 226]. Most will have concomitant HHV-6 viremia. Because HHV-6 may be detected in the CSF of asymptomatic individuals, it is important to exclude other etiologies of CNS infection.

Antiviral agents with in vitro efficacy against HHV-6 include ganciclovir, foscarnet, and cidofovir. While no controlled trials have proven effective antiviral therapy for HHV-6 infections, there are multiple reports of successful treatment for HHV-6 encephalitis with ganciclovir or foscarnet as evidenced by improvement in clinical parameters and measured reductions in HHV-6 serum and CSF viral loads [192, 203, 208, 210, 212]. As such, both agents (or combinations of the two) are recommended for the treatment of HHV-6 encephalitis [13, 234, 236]. Ganciclovir resistance in HHV-6 has occurred via mutations in the protein kinase, U69, and polymerase, U38, genes [230, 237, 238]; however, it is unknown whether this will become a clinically significant problem. Because of its side effect profile, cidofovir alone or in combination with other antivirals is considered a second-line therapeutic agent [234, 239]. Therapy with donor lymphocyte infusions has also been attempted [204, 221].

The overall prognosis for stem cell recipients with HHV-6 encephalitis is poor, and in published series, the attributed mortality is 9–30 % and overall mortality is greater than 50 %. In recipients who survive the acute infection, the incidence of neurologic sequelae is significant, ranging from 18 to 56 %. Consequently, experts emphasize the importance of early recognition and treatment of this entity. While there are small non-randomized studies that report the effective prevention of HHV-6 reactivation with ganciclovir prophylaxis and its pre-emptive use for HHV-6 viremia to prevent encephalitis, there are no current guidelines that routinely recommend such practices to prevent HHV-6-associated disease after stem cell transplantation [240–242].

7.3.2 JC Virus

The polyomavirus, JC virus, is the causative agent of PML, a rapidly progressive demyelinating disorder in immunocompromised patients [243–245]. JC virus infection is common, with adult seroprevalence exceeding 50 % [246]. The virus persists in tissues of the urinary tract and bone marrow (including lymphocytes), and impairment of cell-mediated immunity may result in viral reactivation and hematogenous spread to the CNS [245, 247]. In the CNS, JC virus produces a lytic infection of oligodendrocytes leading to demyelination; astrocytes and cerebellar granular cells may also be infected [245, 247].

While PML most often occurs in the setting of HIV infection (50 > 80 % of cases attributed to HIV), the majority of non-HIV-related cases occur in patients with lymphoproliferative disorders, particularly lymphoma and fludarabine-treated CLL [243, 245, 248]. Previous investigations established a 0.07 % incidence of PML in those with hematologic malignancies [249], although the disease frequency may be increasing as a result of the introduction of potent immunomodulatory therapies into clinical practice [245, 250]. There are multiple descriptions of PML complicating the course of leukemia [243, 251–257], lymphoma [243, 254, 258–261], myelodysplastic syndrome [262], mycosis fungoides [263], multiple myeloma [264], polycythemia vera [265], and Waldenstrom's macroglobulinemia [266]; following fludarabine therapy [253, 254]; and affecting those undergoing HSCT [267–277]. There are increasing reports of PML in patients receiving immunomodulatory therapies, especially rituximab [259–261, 275, 278–283], mycophenolate mofetil [284], and alemtuzumab [285].

The clinical presentation of JC virus is dependent upon the areas of brain affected in individual patients. Patients may present with focal neurologic deficits such dysarthria, hemiparesis, visual loss, or ataxia; alterations in cognition; and seizures. The presumptive diagnosis of PML is made by the clinical picture, combined with MR finding of demyelinating brain lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted and FLAIR images, see Fig. 3. Subcortical white matter, cerebellar white matter, and brain stem involvement are most common [245]. Inflammatory variants of PML can be seen with corresponding enhancing MRI lesions [286]. Definitive diagnosis is established by detection of JC virus in CSF by PCR; this assay has reported sensitivity and specificity of 60–80 % and 92–100 %, respectively [287]. In PCR-negative cases, brain biopsy is necessary to confirm the diagnosis; typical histopathologic findings include white matter vacuolization, oligodendrocytes with basophilic nuclei, enlarged bizarre astrocytes, and foamy macrophages. JC virus can be detected in tissue by immunohistochemical staining in situ DNA hybridization [245, 247].

Other than withdrawal of immunosuppressive therapy and, thus, immune restoration [288], there are no established effective therapies for HIV-seronegative patients with PML [243]. Therapies with interleukin-2 [250, 262, 268, 271, 275], intravenous immunoglobulin [250], cidofovir [250, 275, 289, 290], topotecan [291], and nucleoside analogs such as cytarabine [248, 250, 275] have been

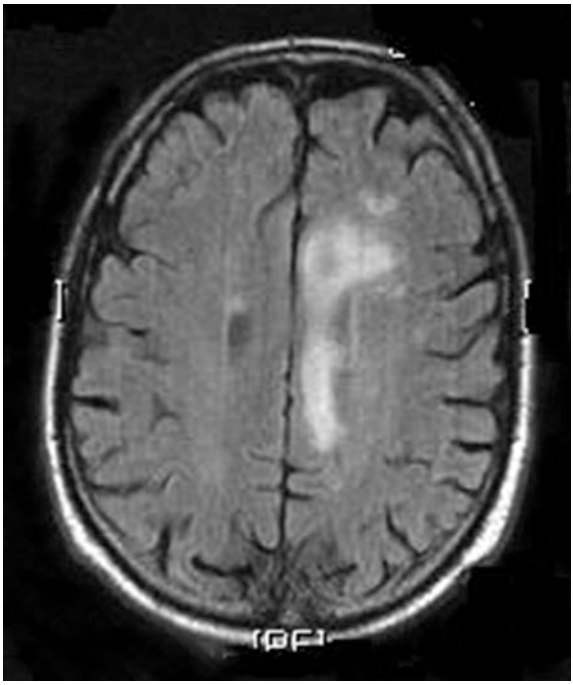

Fig. 3 A 73-year-old male with chronic lymphocytic leukemia receiving rituximab therapy presented with AMS, expressive aphasia, and ataxia. MR imaging demonstrated FLAIR signal hyperintensity involving the subcortical white matter of the *left* cerebral hemisphere. The diagnosis of progressive multifocal leukoencephalopathy was confirmed by detection of JC virus in CSF by PCR

attempted, but successful treatment is limited to anecdote, and no clear benefit is demonstrated in any clinical trials with these agents. In stem cell transplant recipients, withdrawal of GVHD prophylaxis and donor lymphocyte infusions has been tried as therapy for PML [243]. Recent studies have determined that JC viral entry into oligodendrocytes occurs via the serotonin receptor, $5HT_{2A}$ [292], and so represents a potential for pharmacologic intervention with the use of serotonin receptor antagonists such as mirtazapine [256, 265, 293]. Other proposed therapies in various stages of the development include intrathecal interferon-α and β [294, 295], *R*-roscovitine [296], siRNA [297], and mefloquine [298].

In the absence of immune restoration, PML rapidly progresses to death within months of the initial diagnosis [276]. Mortality rate of 90 % is reported, although the prognosis may be better in HSCT recipients [250].

7.4 Parasites

Parasites are often overlooked as important CNS pathogens, but in those with impaired cellular immunity, these pathogens can cause serious infection and warrant consideration for patients with endemic exposures and risks. The hyper-infection syndrome caused by *Strongyloides stercoralis* can result in enteric gram-negative meningitis [9]. Toxoplasmosis is the most common parasite infection following stem cell transplantation and is discussed in detail below.

7.4.1 Toxoplasmosis gondii

Infection with the protozoal organism, *Toxoplasma gondii*, is extremely common with seroprevalence rates of 16–40 % in the USA and UK, 50–80 % in Europe and Central and South America, and 10–15 % in Japan [299–302]. Despite this, it is an uncommon opportunistic infection following HSCT and lymphocyte depleting therapies. The reported prevalence of toxoplasmosis in transplant centers mirrors the geographic seroprevalence: in the USA 0.2–0.3 % [303, 304], Japan 0.2 % [301], Brazil 1.1 % [305], and Europe 1–5 % [6, 300, 302, 306]. In one European series, toxoplasmosis was the most common CNS infection following bone marrow transplantation [6]. In patients undergoing HSCT, clinical infection most often results from reactivation of latent infection in seropositive allogeneic stem cell recipients [300–302, 304–314]; however, cases of primary infection, presumably as a consequence of donor transmission and leukocyte transfusion or from community exposure or faulty serologic testing have been described [309–312, 315, 316]. Seropositive recipients with unrelated donors [305, 310], haploidentical donors [300], T-cell-depleted allogeneic HSCT [310], acute GVHD [303, 311], and cord blood transplants [302] appear to be at higher risk of reactivation disease. However, toxoplasmosis complicating autologous HSCT or chemotherapy for leukemia and lymphoma is rare and limited to anecdotal reports [300, 317, 318].

Toxoplasma encephalitis typically occurs during the first 6 months following HSCT with most cases occurring within the first 3 months post-HSCT with a reported median onset of 45–78.5 days post-HSCT [300, 303, 307, 310, 311]. Later onset cases have occurred, especially in those with courses complicated by GVHD [301, 319–321]. Patients present with fever and neurologic symptoms ranging from headache, seizures, AMS, and focal neurologic deficits [302, 305, 310, 311]. *Toxoplasma* has a predilection for the basal ganglia and the supra- and infratentorial subcortical areas of the brain [321]. MR demonstrates iso- or hypointense multifocal lesions on T1-weighted imaging and iso-, hypo-, or hyperintense lesions on T2-weighted imaging. Ring enhancement, hemorrhage, and edema can be seen with contrast imaging. Alternatively, *Toxoplasma* lesions in HSCT recipients may fail to enhance; a potential explanation for this lack of enhancement is a blunted inflammatory response in the setting of neutropenia or corticosteroid therapy [322–324]. Rarely, imaging will be compatible with meningoencephalitis [304, 305]. There is also an isolated reported of toxoplasmic myelitis following peripheral blood stem cell transplantation [314].

The presumptive diagnosis of toxoplasmosis often is based on the clinical presentation, characteristic radiographic findings, and response to anti-*Toxoplasma* therapy in susceptible (seropositive) patients. CSF findings are nonspecific and may demonstrate elevated protein and some degree of pleocytosis. No diagnostic method is consistently reliable for the definitive diagnosis of toxoplasmic encephalitis, and often a combination of modalities, including serologies, PCR-based detection of *T. gondii* in CSF and brain tissue, and histopathology, is employed [299, 306, 325, 326]. The tachyzoites and cysts of *T. gondii* are visualized in tissue by Giemsa, hematoxylin, and eosin, and immunohistochemical staining.

Toxoplasmic encephalitis is a rapidly fatal illness with a reported mortality of 60–80 % [305, 310, 311]. Too often, toxoplasmosis is a post-mortem diagnosis in HSCT recipients. Because of this, an emphasis should be placed on high clinical suspicion with early treatment; more favorable outcomes have been reported with such a strategy [300]. The standard treatment for toxoplasmic encephalitis is sulfadiazine plus pyrimethamine and leucovorin, although myelosuppression may be problematic following HSCT [299]. Other active agents include: clindamycin, atovaquone, azithromycin, and spiramycin [299, 300, 313].

Efforts to prevent toxoplasmosis after HSCT should focus on identification of recipients at risk of disease by serologic testing of transplant candidates and their donors and education regarding exposure reduction measures, such as avoidance of cat feces and litter boxes, both of which can have a high burden of *Toxoplasma* oocysts, and proper meat handling and preparation [67, 299]. Prophylaxis with TMP-SMX is recommended for susceptible (seropositive) recipients who have GVHD or a history of toxoplasmic chorioretinitis; however, optimal prophylaxis regimens are not well-defined and breakthrough infections do occur in HSCT recipients who receive TMP-SMX for *Pneumocystis* prophylaxis [67, 301–303, 305, 306, 327]. For TMP-SMX-intolerant patients, pyrimethamine and leucovorin plus clindamycin may be considered. Additionally, pyrimethamine–sulfadoxine (Fansidar) was effective in preventing *Toxoplasma* reactivation in allogeneic HSCT recipients, although this agent may result in myelosuppression [328]. Finally, prospective monitoring of the blood of seropositive recipients for *Toxoplasma* reactivation by PCR has been proposed [329], but more data are needed before this approach can be recommended.

8 Summary

CNS infections are devastating complications of cancer and its therapies. Due to the multitude of infectious etiologies, a thorough understanding of the epidemiology and clinical presentations of these infections is essential for recognizing and formulating a diagnostic evaluation for suspected CNS infection. Heightened clinical suspicion, expeditious (including empiric) treatment, and modification of immunosuppression may optimize the outcomes of CNS infections in cancer patients and stem cell recipients.

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