



Nervous system infections in patients with cancer

Amy A. Pruitt, MD

*Department of Neurology, Hospital of the University of Pennsylvania School
of Medicine, 3400 Spruce Street, Philadelphia, PA 19014, USA*

Central nervous system infections in patients with cancer: overview

During the past 30 years, the lives of patients with cancer with many types of malignancies have been prolonged by improvements in diagnostic techniques, surgery, radiation therapy, chemotherapy, and biologic response modifying therapies. A corollary of these successes is the presentation to the neurological consultant of complicated patients whose associated diseases and their treatment may predispose them to the development of infections of the nervous system. In these patients, the presentation and course of familiar infections may be different from that in patients without cancer. As cancer therapies have entailed greater degrees of immune suppression, new diseases specific to certain cancers and their treatment have emerged, as well.

Central nervous system infections remain a major cause of morbidity and mortality among patients with cancer. In a large series from Massachusetts General Hospital in the period from 1985 to 1990, one of every six patients with a CNS infection had an underlying malignancy [1]. In an earlier series from the same institution, 60% of immunocompromised patients with CNS infection died as a result of their infection, many at a time when the underlying disease was under good control [2,3]. To improve these statistics the consultant must be aware of changing patterns of bacterial, fungal, viral, and parasitic infections as well as novel treatment complications, and must maintain a high index of suspicion in clinical situations where myriad infections and noninfectious considerations are possible.

This article presents a practical approach to the problem of infection in patients with cancer. Pitfalls in diagnosis, including noninfectious causes specific to the underlying disease states, are discussed along with predictable

E-mail address: pruittm@mail.med.upenn.edu (A.A. Pruitt).

setting-specific complications and sequelae, as well as several newly-described infectious entities and treatment complications.

Approach to the cancer patient with potential central nervous system infection

Clinical challenges

Several characteristics of CNS infections in patients with cancer make their identification and treatment challenging:

- The list of potential pathogens includes many organisms of normally low pathogenicity in the intact host.
- Infection with more than one agent or sequential infection is not uncommon. In one series, 40% of patients with CNS infections had extra-neural infections with an organism other than that infecting the CNS [2].
- The manifestations of CNS infections, such as headache, meningismus, and fever, may be mild or absent because of the host's diminished inflammatory response.
- Coexisting conditions, such as metabolic encephalopathy, may complicate the picture, and a clinical syndrome caused by infection, such as aseptic meningitis, may mimic a drug or therapy-induced complication.
- Meaningful survival without neurological sequelae is dependent on rapid diagnosis and initiation of effective treatment. The appropriate duration of such treatment and the need for maintenance therapy is not yet resolved for many infections.
- Drug therapy of CNS infections is complicated by numerous factors, including the status of the blood–brain barrier and lipid solubility, molecular weight, protein binding, and removal of the drug from the cerebrospinal fluid. Neurotoxicity is a limiting factor for some anti-infectious agents.
- Emerging resistance of nosocomial pathogens to major antimicrobials is a growing problem.

Clinical clues

Despite the challenges listed above, the majority of CNS infections in patients with cancer follow predictable patterns. Epidemiologic clues help to heighten suspicion of CNS infection in specific situations and to narrow the range of potential pathogens:

- Series from specialized cancer hospitals and tertiary referral centers suggested that patients with leukemia and lymphoreticular malignancies represent more than 25% of all patients with cancer with CNS infection [1]. Another 16% of patients with CNS infections had primary CNS tumors.

- Bacterial meningitis is the most common clinical syndrome and three organisms account for two thirds of the meningitides: *S aureus*, *S pneumoniae*, and *L monocytogenes*. In only half of the patients with bacterial meningitis is there a fulminant picture of acute meningeal inflammation.
- Neutropenia is the primary risk factor for bacterial meningitis in patients with leukemia or lymphoma. Seeding of the meninges from systemic sepsis is the likely mechanism in another group of patients with gram-negative meningitis, many of whom have solid tumors. Skin-derived organisms such as *S aureus* or *S epidermidis* account for infections in patients with primary CNS tumors.
- Procedures are a major risk factor for CNS infection. Chemotherapy ports, cranial shunts, and ventricular reservoirs account for the majority of procedure-related infections. Long-term catheters have been associated with fungal infections such as *Candida* or *Aspergillus*, as well as with more indolent bacterial infections, such as *Acenatobacter*. Gastrointestinal tract surgery is a risk factor for *L monocytogenes* infection. Craniotomy infections are derived from skin organisms such as *S aureus*, *S epidermidis*, or *Propionobacterium acnes*.

Pathophysiology

The type of immunologic deficit present is a major consideration in the search for a potential infectious cause for neurologic dysfunction. Table 1 outlines a classification of immune deficits and common pathogens.

Barrier disruption

Central lines and other monitoring devices break down the normal skin barrier and chemotherapeutic agents can produce mucous membrane disruption. Neurosurgical procedures also breach the skin barrier, that, in turn, may be weakened by previous radiation therapy or surgery. In a recent pediatric series of patients with cancer with bacterial or fungal meningitis, nearly two thirds had recent neurosurgery, a central nervous system device, or cerebrospinal fluid leak. *S aureus* and *S pneumoniae* were the most common microbiologic isolates [4].

Neutrophil dysfunction

Deficits in neutrophil function or number are usually associated with bacterial infections by organisms derived from the skin, gastrointestinal, or respiratory tracts. Limiting the duration of neutropenia below 500/mm³ with granulocyte colony-stimulating factor reduces the risk of bacterial infection, as well as fungal infection, with such organisms as *Aspergillus* and *Candida*. Neutropenia is the usual risk factor in patients with leukemia, aplastic anemia, and pancytopenia because of marrow invasion or intensive chemotherapy or radiation therapy.

Table 1
Classification of immunologic deficits and common pathogens

Immunologic deficit	Granulocyte	B-lymphocyte/ immunoglobulin	T-lymphocyte/ macrophage	Barrier disruption
Associated diseases or risk factors	Infiltrating disorders of marrow (leukemia, lymphoma, solid tumors) Chemotherapy Radiotherapy Bone marrow transplantation	Chronic lymphocytic leukemia Multiple myeloma Splenectomy	Lymphoreticular neoplasms Organ transplantation Chronic corticosteroid or other immunosuppressive therapy AIDS	Indwelling ventricular reservoir Cranial surgery Hyperalimentation or other central IV lines Loss of cutaneous integrity ^d
CNS pathogens in rough relative order of importance	Bacteria <i>S aureus</i> <i>S epidermidis</i> <i>P aeruginosa</i> <i>Enterobacter</i> <i>L monocytogenes</i>	Bacteria <i>S pneumoniae</i> <i>H influenzae</i> <i>Enterobacter</i> <i>P aeruginosa</i>	Viruses HIV Cytomegalovirus Varicella-zoster Epstein-Barr virus ^c JC virus (PML) Measles Adenovirus Bacteria <i>L monocytogenes</i> <i>N asteroides</i> <i>M tuberculosis</i>	Bacteria <i>S aureus</i> <i>S epidermidis</i> <i>Enterobacter</i> <i>E coli</i> <i>Klebsiella</i> Streptococci Diphtheroids Fungi <i>A fumigatus</i> <i>C albicans</i>
	Fungi <i>A fumigatus</i> Mucoraceae <i>C albicans</i>	Viruses Measles Enteroviruses (echo, polio)		

Viruses	
Cytomegalovirus ^a	
Herpes simplex	
Adenovirus ^b	
Human herpes virus ^c	
	Fungi
	<i>C neoformans</i>
	<i>A fumigatus</i>
	<i>C albicans</i>
	Mucoraceae
	<i>P boydii</i>
	Parasites
	<i>T gondii</i>
	<i>S stercoralis</i>

^a After bone marrow transplantation.

^b After blood transfusion.

^c Post transplant lymphoproliferative disorder.

^d Including prior varicella-zoster infection.

Adapted from Pruitt AA. Central nervous system infections in organ transplant recipients and cancer patients. In: Ross KL, editor. Central nervous system infectious disease and therapy. New York: Marcel Dekker; 1997; with permission.

B-lymphocyte/immunoglobulin impairment

Encapsulated bacterial organisms, such as *H influenzae* and *S pneumoniae* are the major pathogens in this setting; they are usually encountered in patients with chronic lymphocytic leukemia, multiple myeloma, or other blood dyscrasias.

Impaired T-cell-mediated immunity

Patients with T-cell deficits have a wider variety of potential CNS pathogens than do those with deficient B-cell function. This type of host compromise occurs in patients with AIDS and lymphoreticular malignancies, and in those who receive chronic corticosteroid or cytotoxic therapy. The typical pathogen spectrum varies somewhat depending on the underlying disease. For example, AIDS patients are more prone to infection with *M tuberculosis* and *T gondii* than are those on chronic corticosteroid therapy. All conditions that involve impaired T-cell immunity, however, are associated with increased rate of infection by viruses, fungi such as *C neoformans*, and intracellular pathogens such as *L monocytogenes*.

Diagnosis

The response of the nervous system to infection, unfortunately, is limited to a relatively small, nonspecific repertoire of clinical signs and symptoms. Five sets of data help the clinician narrow the range of micro-organisms.

Clinical setting

Identification of the major immune deficiency is the first step in diagnosing a potential CNS infection. The symptoms in patients with different diseases but similar immune deficits may resemble one another more than the symptoms in patients with the same disease but different infection risk factors. Thus, patients who have received more than 6 weeks of corticosteroids for disparate neoplasm treatment resemble patients with lymphoma more than they do patients with the same malignancy at the stage in treatment when neutropenia is the major risk factor.

Special clinical settings and “new” diseases

Bone marrow transplantation. As stem-cell, myeloablative, and nonmyeloablative bone marrow transplantation have become the preferred treatments for many leukemias, lymphomas, and solid tumors, a new series of neurologic infectious complications has been described, many of which are predictable based on the time elapsed since transplantation and the clinical syndrome that is produced [5,6]. These diseases are discussed in a subsequent section.

Primary brain tumor therapy. In the last 5 years, implantation of chemotherapy-containing polymers (Gliadel) wafers has become a common therapy of recurrent, high-grade, astrocytic neoplasms (N.P. Fishman, personal communication 2000). The vigorous cerebritis and vasogenic edema that sometimes associated with these wafers requires large doses of corticosteroids and can mask the presence of infection. Extremely high infection rates were reported from several institutions and infection should be suspected when the patient develops a persistent, ring-enhancing, edematous lesion at the implantation site (Fig. 1). Organisms that are responsible for the wafer-associated infections include skin-derived pathogens similar to those that develop in patients who have had multiple craniotomies and radiation therapy.

Pace of illness

The time course of symptoms may be altered because of ongoing therapy that blunts the inflammatory response; often the duration of symptoms helps pinpoint specific pathogens. In general, symptoms of less than 2 days' duration bespeak bacterial processes, often meningitis. A subacute presentation of fever and headache more often results from infection with herpesviruses, *C neoformans*, *M tuberculosis*, or *L monocytogenes*. A more indolent course over several weeks should lead to work-up for progressive multifocal leukoencephalopathy (JC virus).

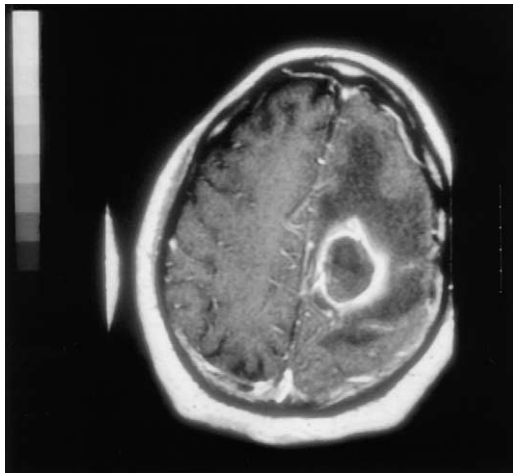


Fig. 1. T1 gadolinium-enhanced MRI of patient who received Gliadel wafer implants for recurrent high-grade astrocytoma 3 weeks earlier. Marked vasogenic edema and ring-enhancing lesion raised question of abscess versus wafer-induced cerebritis. Re-exploration and removal of wafers showed bacteria (*Propionibacter acnes*) adherent to the wafers.

Extraneural infection sites

Identification of infection outside the nervous system helps focus the pathogen identification process. More than 20% of immunocompromised patients with cryptococcal meningitis have skin lesions that may have been present for months before examination of the CSF [2]. Pulmonary infection with *A fumigatus*, *C neoformans*, or *N asteroides* is often present before CNS dissemination. Therefore, a patient with the picture of a mass lesion and pulmonary abnormalities should be suspected of having *Aspergillus* or *Nocardia* infection, whereas a patient with pulmonary lesions and a meningitis clinical syndrome is more likely to have cryptococcal meningitis. Varicella zoster (VZV) infection can occur without skin lesions, but their presence along with a diffuse encephalitic picture simplifies diagnosis.

Neuroanatomic distribution of deficit

Often the patient with cancer's inflammatory response is so blunted as to mask infection entirely or to indicate it only by mild headache and mental status changes. Corticosteroids may suppress fever. In many situations, the presence of localizing findings with specific neuroanatomic syndromes provides a helpful diagnostic clue. Table 2 summarizes typical anatomic syndromes and their associated pathogens. The three most common presentations of CNS infection include an acute meningitis syndrome, progressive focal or multifocal deficits, and an "aseptic meningitis" syndrome.

The presence of a focal cerebral deficit with ring enhancement leads to the consideration of brain abscess with conventional bacterial pathogens or *Aspergillus*, *Toxoplasma*, tuberculosis, or *Nocardia*. Single or multifocal progressive deficits without enhancement are consistent with progressive, multifocal leukoencephalopathy.

A "step-wise" or stroke-like syndrome could be caused by infections such as endocarditis, *Listeria*, or vasculitis associated with varicella zoster infection. Several noninfectious etiologies, such as nonbacterial thrombotic endocarditis, superior sagittal sinus thrombosis, metastatic tumor, or, in the appropriate setting, radiation therapy toxicity or intravascular lymphoma (neoplastic angioendotheliosis) must be considered as well (Fig. 2).

Investigation of mild headache, meningismus, and mental status change may lead to the diagnosis of a mild lymphocytic pleocytosis with normal glucose and mild to moderate elevation of CSF protein, the aseptic meningitis syndrome. Table 3 summarizes the numerous infectious and noninfectious etiologies that are associated with this syndrome.

A narrower differential diagnosis applies to persistent neutrophilic meningitis. Entities to be considered in this situation include Nocardiosis, Candidiasis, Aspergillosis, Zygomycosis, Herpes simplex viruses types 1 and 2 as well as, less commonly, Brucellosis, Histoplasmosis, Pseudoallescheriosis, Coccidioidomycosis, and chemical or drug-associated meningeal inflammations [8].

Table 2
Neuroanatomical correlation of infection site and possible nervous system infection

Typical pathogen	Focal cerebral deficit (localized mass)	Acute meningitis/meningoencephalitis	Chronic meningitis	Myelopathy	Neuropathy or plexopathy	Myositis	Cranial nerve deficit
Bacteria	<i>S aureus</i> <i>Anaerobes</i> <i>L monocytogenes</i> <i>N asteroides</i>	<i>L monocytogenes</i> Gram-negatives <i>H influenzae</i> <i>S pneumoniae</i>	<i>L monocytogenes</i>	Mycobacteria Epidural abscess from organism causing sepsis	<i>L interrogans</i> <i>T pallidum</i>	<i>S aureus</i> <i>S pneumoniae</i> <i>E coli</i>	<i>M tuberculosis</i>
Fungi	<i>A fumigatus</i> <i>C neoformans</i> <i>Mucoraceae</i>	<i>C neoformans</i>	<i>C neoformans</i> <i>C immitis</i> ^a <i>H capsulatum</i> ^a <i>Candida</i> species				<i>Mucoraceae</i> <i>A fumigatus</i> <i>C neoformans</i>
Viruses	JC virus (PML) Varicella-zoster	Herpes simplex types 1 and 2 Human herpes virus ^b Cytomegalovirus Varicella-zoster		Cytomegalovirus Herpes simplex Varicella-zoster	Cytomegalovirus ^b Epstein Barr virus ^b		Cytomegalovirus
Parasites	<i>T gondii</i>	<i>T gondii</i> <i>S stercoralis</i>					

^a Regional.

^b Associated with Guillian-Barre Syndrome.
PML, Progressive multifocal leukoencephalopathy.

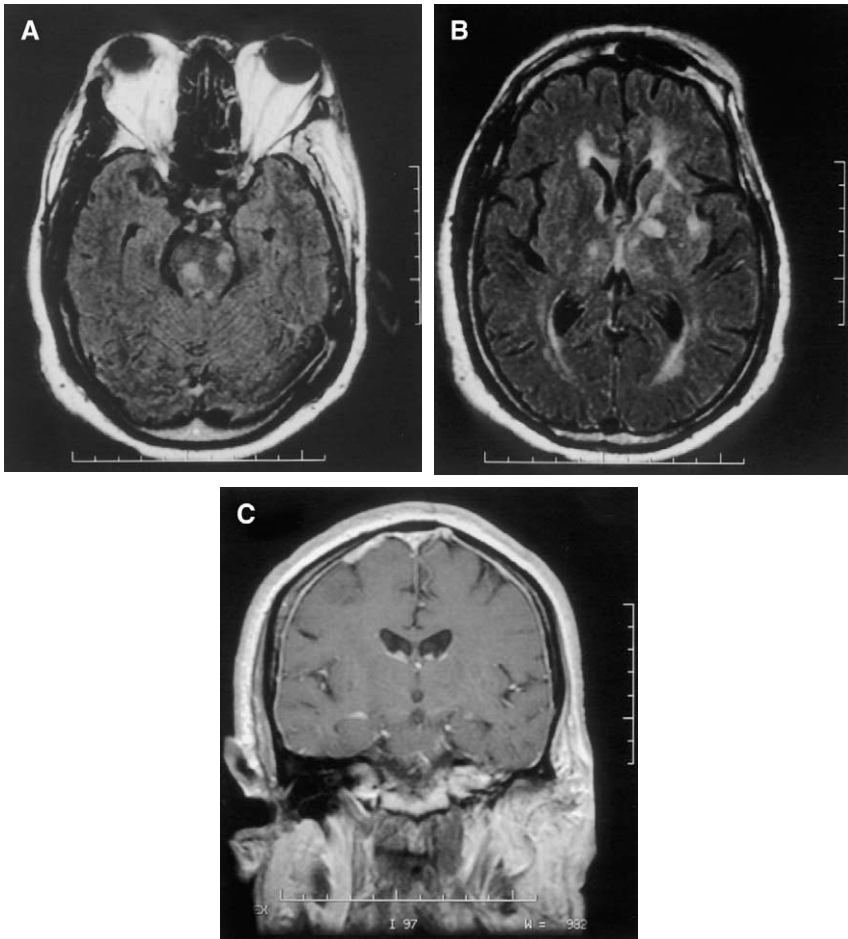


Fig. 2. (A,B) FLAIR MRI images of patient with fever and multiple stroke-like episodes after intensive chemotherapy for nonHodgkin's lymphoma. Brainstem (A) and supratentorial structures (B) are involved. (C) Coronal T1 gadolinium-enhanced MRI shows leptomeningeal enhancement. The patient's CSF had elevated protein and hypoglycorrhachia with 124 white blood cells with lymphocyte predominance. He was initially suspected of having *Listeria* meningitis, but cultures were negative, antibiotics failed to improve clinical situation, and postmortem evaluation showed large cell intravascular B-cell lymphoma.

Laboratory data

Readily available neuroradiological and laboratory procedures make rapid diagnosis of CNS infections realistic. All imaging studies and blood and CSF abnormalities must be viewed as adjuncts to the clinical diagnosis suggested by the previous information gleaned from clinical setting, pace of illness, and neurologic examination.

Table 3
Major causes of aseptic meningitis syndrome in patients with cancer

Infectious causes		Noninfectious causes
Viruses	Diagnostic test (on CSF, unless indicated)	
Enteroviruses	PCR	Leptomeningeal carcinomatosis
Herpes simplex Types 1 & 2	PCR	Adverse drug reaction: NSAIDS
Varicella-zoster	PCR	OKT-3
Epstein-Barr	Virus-specific antibody	Azathioprine
HIV	PCR	Isoniazid
	Blood	Intravenous immunoglobulin
		Intrathecal chemotherapy
		Methotrexate
		Cytosine arabinoside
Bacteria		
Partially-treated Bacterial meningitis	Culture, CSF low glucose	Posttransplantation lympho-proliferative disorder
Endocarditis	TEE ^a , blood cultures	CNS vasculitis
Parameningeal infection	MRI CT	Arachnoiditis
<i>M pneumoniae</i>	Chest radiograph, blood	Postinfectious syndromes
<i>M tuberculosis</i>	CSF PCR	
<i>B burgdorferi</i>	Blood: ELISA, Western blot	
	CSF: antibody	
<i>T pallidum</i>	VDRL/RPR, blood and CSF	
Fungi		
<i>C neoformans</i>	India ink, cryptococcal antigen	
<i>H capsulatum</i> ^b	CSF: antibody	
<i>C immitis</i> ^b	CSF: *antibody	
Parasites		
<i>Toxoplasma gondii</i>	Antibody	

* = acute and convalescent sera for virus-specific IgG to enteroviruses, HSV, arboviruses, adenoviruses, Epstein-Barr virus, Brucella, and *B burgdorferi* may be obtained in appropriate setting.

^a Transesophageal echocardiogram.

^b If patient lives in appropriate geographic region.

Modified from Pruitt [7].

Neuroimaging studies

Computed tomography without contrast excludes intraparenchymal hemorrhage and reveals ventricular size and mass effect. Cancer patients with impaired renal function cannot receive iodinated contrast material and those with intracranial mass lesions may be at some risk for seizure activity following contrast administration. Magnetic resonance imaging has specific advantages over CT in the differentiation of CNS lesions; it provides better distinction between gray versus white matter involvement in progressive multifocal leukoencephalopathy, superior views of the posterior fossa and

spine, higher resolution of leptomeningeal disease, and better delineation of venous sinus thrombosis.

CT and MRI have special limitations in the cancer population. Neither neuroimaging method can distinguish tumor reliably from abscess or radiation treatment effect [9,10]. Corticosteroids can reduce contrast enhancement and lowered hemoglobin in anemic patients with cancer can produce confusion about the presence or age of intracranial blood. Diffuse meningeal enhancement can be seen with breakdown of blood–brain barrier caused by neoplastic, chemical, or infectious meningitis and is also seen on MRI after lumbar puncture. Diffuse enhancement in the area of a tumor can mimic recurrent tumor in patients who have had prolonged seizures; follow-up MRI studies are required to make the distinction [11]. Magnetic resonance spectroscopy (MRS) and positron emission tomography scanning are used increasingly to help differentiate tumor, infection, and radiation treatment effect. The major indication for MRS and PET is the question of recurrent tumor versus gliosis in patients with cerebral neoplasm [12]. Single photon emission computed tomography (SPECT) scanning has been used to differentiate toxoplasmosis from primary central nervous system lymphoma in patients with AIDS [13]. More recent studies suggested that the technique is not reliable, however, and that after an empiric trial of toxoplasmosis therapy brain biopsy is indicated to establish the diagnosis [14].

Lumbar puncture

In a patient with known cancer, most clinicians would advise a screening CT or MRI if there is suspicion of metastatic disease or other mass lesion before performing a lumbar puncture. A platelet count of less than 50,000 should prompt platelet transfusions before lumbar puncture.

For patients whose immune status is severely compromised by tumor or its treatment, only general guidelines about CSF formulas can be given. Predominantly polymorphonuclear leukocytes and CSF cell count of greater than 200 is suggestive of bacterial meningitis; the finding of a CSF glucose that is 50% or less than the concurrent blood glucose supports a bacterial or fungal infectious pathogen.

CSF pleocytosis with a lymphocytic predominance could be consistent with many bacterial, fungal, viral, or parasitic pathogenesis. The work-up of the aseptic meningitis CSF formula must be tailored to the specific circumstances of the patient's underlying disease and therapy. Drug-induced aseptic meningitis is associated with several drugs that are routinely used for antimicrobial prophylaxis or treatment or immune suppression in patients with cancer, particularly bone marrow transplant recipients. DeMaracaida and Reik [15] and Marinac [16], provide an excellent discussion of disorders that mimic central nervous system infections and an extensive list of drug-induced meningitides. Drug-induced meningitis most often is seen after the use of nonsteroidal anti-inflammatory medicines but can occur after cephalosporins, ciprofloxacin, isoniazid, penicillin, and sulfonamides, as well as

trimethoprim [17,18]. Meningitis is a common complication of immunosuppressive agents, such as OKT-3 and azathioprine and is also well-described after the use of intravenous immunoglobulin (IVIG) [19]. Clinical clues to the presence of a drug-induced meningitis include a short interval between drug ingestion and the start of symptoms (usually within hours) which include fever and stiff neck as well as some signs of allergy, pruritus, conjunctivitis, myalgia, and arthralgia. Drug-induced meningitis can be confused with acute bacterial meningitis when hypoglycorrhachia is present. Rapid resolution of symptoms after discontinuation of the drug is definitive confirmation of the problem, although empiric antibiotic therapy may be necessary until the association of drug and meningeal reaction is secure. Chemical meningitis was reported after the intrathecal injection of antibiotics, cytosine arabinoside, baclofen, radioactive isotopes, methotrexate, spinal anesthetics, and lipid- and water-soluble contrast agents [18].

Specialized tests on the CSF are crucial to the early diagnosis of many potentially treatable pathogens in patients with cancer. CSF tests may identify an organism directly by culture, its nucleic acid by polymerase chain reaction, or surface components by antigen detection. Antibody to an organism may be identified by enzyme-linked immunosorbent assay, Western blot, or complement fixation. Polymerase chain reaction is useful for the detection of several organisms that are common in patients with cancer. These include cytomegalovirus, enteroviruses (Coxsackie, ECHO virus), human herpesvirus 6 (limbic encephalitis in bone marrow transplant recipients which is discussed later), herpes simplex virus types 1 and 2, JC virus, varicella-zoster virus, mycobacterium tuberculosis, and Epstein-Barr virus (primary CNS lymphoma in AIDS patients) [1,20–22].

Arteriography

The use of arteriography has declined as MRI and magnetic resonance angiography have become readily available. In several specific situations, however, this procedure may be valuable for the diagnosis and management of CNS infections. In a patient with known or suspected endocarditis, arteriography remains the definitive test to exclude infectious aneurysm. Arteriography may also be useful in suspected cases of *A fumigatus* of the CNS, as this organism invades blood vessel adventitia and produces aneurysms. Arteriography remains the preferred procedure for the diagnosis of vasculitis associated with lymphoproliferative disorders and with several infections, including varicella-zoster, mycobacteria, and mucormycosis. Arteriography may help define an abnormal area which can then be approached with brain or meningeal biopsy [23,24].

Brainmeningeal biopsy

Despite the aforementioned array of laboratory procedures, brain biopsy remains a useful adjunct to the diagnosis of some CSN infections. Biopsy should be undertaken to seek treatable infections and to offer prognostic

information for those infections without definitive therapy. Indications for brain biopsy include:

- Presence of a nonspecific, ring-enhancing lesion or lesions whose bacterial, fungal, or neoplastic nature remains unclear after MRI, MRS, and CSF studies
- Failure of a suspected toxoplasmosis lesion to respond to 2 to 3 weeks of appropriate therapy.
- Progressive MRI or CT abnormality of unclear nature.
- Transcranial Doppler, arteriographic, or magnetic resonance angiographic data that are consistent with vasculitis with inconclusive CSF studies.

CNS infections in high-risk, groups of patients with cancer

Most CNS infections occur in a relatively small subset of patients with cancer. The two highest risk groups are patients with leukemia/lymphoma and those with primary brain tumors. Patients with systemic solid tumors treated with aggressive chemotherapy regimens, including bone marrow transplantation, are the third group. The problems of differential diagnosis and therapy-related infections in patients with primary brain tumors were discussed earlier. This section covers problems that are specific to patients with bone marrow transplantation and related therapeutic procedures.

Bone marrow transplantation

As the consultant approaches a transplant recipient with potential CNS infection, the diagnostic considerations should be grouped into four main types: (1) complications related to the underlying disease; (2) problems arising from the transplant procedure itself; (3) posttransplant disorders including infections that occur predictably at specific intervals after transplantation; and (4) side effects of immunosuppression.

The three main types of bone marrow transplantations (BMTs) are autologous, syngeneic, and allogeneic. Autologous marrow transplantation involves infusion of the patient's own marrow, which has been harvested and preserved, while the patient receives high-dose chemotherapy. A variant of this procedure involves "mini" or "nonmyeloablative BMT" in which the patient receives sublethal doses of chemotherapy. Syngeneic transplant involves transplantation between identical twins. Allogeneic BMT involves infusion of marrow from a matched, but unrelated donor. These recipients are often severely immunosuppressed; 60% to 70% experience neurological complications that causes death in up to 10% [25]. Patients who receive BMT share features with patients who receive organ donation of other types, but they may be more severely immunosuppressed for months because of their underlying diseases. Therefore, infections usually occur earlier in patients who underwent BMT than in other organ recipients. In addition,

patients who underwent BMT are profoundly granulocytopenic for about 1 month until the new marrow begins to function. During this period, bacterial, viral, and fungal infections may become established. Even after granulocyte recovery, altered cell-mediated and humoral immunity persists for up to 1 year. CMV infections and *T gondii* infections become common [26].

Patterns of infection in patients who underwent BMT may be divided roughly into three major periods posttransplantation [1,4]:

1. Less than 1 month after transplant. Infections that occur during this period are often caused by common bacterial pathogens that are found in the general population and are most often associated with neutropenia. Occasional clusters of opportunistic infections, such as *Aspergillus*, that are found in hospital ventilation systems or present before the surgery (*M. tuberculosis*, *S. stercoralis*) have been described.
2. One to 6 months after transplant. This is the period of most intense immunosuppression. Some of the most common pathogens are viruses, such as EBV and CMV, that further depress the immune system, along with *Listeria*, *Aspergillus*, and *Nocardia*.
3. More than 6 months after transplant. As the degree of immunosuppression is reduced, pathogens that are common in earlier transplant periods become less likely. Patients who continue to require high-dose immunosuppressive maintenance or who have received additional antirejection therapy (usually with OKT-3 or antilymphocyte globulin) continue to be at risk for *Listeria* and *Nocardia*. Most cases of cryptococcal meningitis occur during this period, as do chronic disorders like progressive multifocal leukoencephalopathy (PML).

Infections specific to patients who have undergone bone marrow transplantation

Several viral infections that seem to be unique to patients who underwent BMT and related procedure recipients were described. These include a fatal adenovirus, meningoencephalitis, that was possibly acquired from the infused marrow [27]. A recently described syndrome with specific MRI features was attributed to human herpesvirus 6 variant B in patients who underwent stem cell transplants (SCT). Wainwright and others [28–31] described selective involvement of the hippocampus in patients with a characteristic syndrome that consisted of short-term memory dysfunction, confusion, and in some cases, insomnia. The differential diagnosis included paraneoplastic limbic encephalitis, herpes simplex encephalitis, status epilepticus, and immunosuppressive-treatment related toxicity. Hyperintense signal of the hippocampi on T2-weighted or FLAIR MRI (Fig. 3), hypermetabolism in the hippocampal regions on fluorodeoxyglucose (FDG-PET), and temporal lobe seizure activity on EEG were seen. HHV6 DNA was detected in CSF by PCR assay. The clinical onset of symptoms correlated with the start of white blood cell engraftment posttransplant (defined as

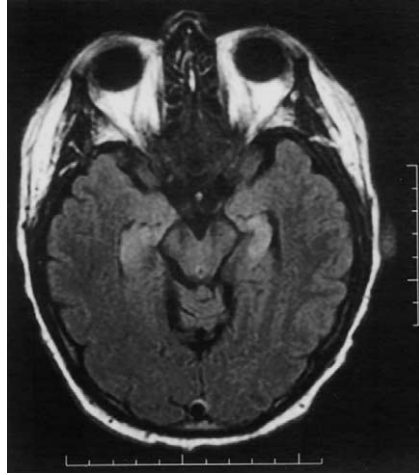


Fig. 3. FLAIR axial MRI shows hyperintense signal symmetrically in both hippocampi of patient who became acutely confused with marked short-term memory loss 4 weeks after allogeneic bone marrow transplantation for acute lymphoblastic leukemia. He had human herpes virus 6 infection.

an absolute neutrophil count of 500). Patients were treated with foscarnet and several improved. This condition is important to consider in patients who underwent SCT with short-term memory loss, partial complex seizures, and other alterations of mental status. Aggressive treatment of seizures and antiviral therapy may help minimize the long-term effects of this syndrome.

Complications of bone marrow transplantation

Patients who underwent BMT may develop graft versus host disease (GVHD) that produces several neurological syndromes including polymyositis, peripheral neuropathy, and myasthenia gravis. GVHD only occasionally affects the brain; autopsy series of some of these patients revealed lymphocytic infiltration that was consistent with possible CNS viral infections [32–34].

Posttransplantation lymphoproliferative disorders (PTLD) involve polyclonal B-cell infiltration of multiple organ systems. In 15% to 25% of these patients the CNS is involved and is the sole site of abnormality in 85% of patients with CNS PTLD [35,36]. Several lines of evidence implicate Epstein-Barr virus infection in the oncogenesis of PTLD. EBV selectively infects B lymphocytes which causes proliferation; immunosuppressive agents, such as cyclosporine and corticosteroids, allow continued proliferation of these cell lines. The clinical presentation of PTLD that involves the CNS is quite nonspecific with altered mental status and systemic symptoms that are suggestive of a viral syndrome. MRI may reveal periventricular white matter variably enhancing nodules; 25% of patients have leptomeningeal spread. CSF examination for EBV PCR may be helpful, but biopsy may be necessary for definitive diagnosis. PTLD can be confused with

tumor recurrence, primary malignant (monoclonal) B-cell lymphoma (into which some lesions may develop), and infection. It is treated by reduction of immunosuppression, or, at times, by radiation therapy or chemotherapy; the prognosis is guarded with 2-year survival rates of only 30% [36].

Neurotoxicity of immunosuppressive drugs

The major immunosuppressive drugs in current use are cyclosporine, azathioprine, corticosteroids, OKT-3, polyclonal antilymphocyte and antithymocyte globulins, and tacrolimus. Direct neurotoxicity was reported with all of these agents in many instances which results in a picture that could be confused with CNS infection.

Cyclosporine is the most commonly used antirejection agent for acute suppression of rejection and for chronic maintenance therapy. Although it is not myelosuppressive, it inhibits lymphokine production and preferentially suppresses CD4+ T-cell function. Elimination is by way of the cytochrome P450 enzyme system. There is considerable interindividual variability in pharmacokinetic properties. Adverse effects, therefore, correlate only approximately with blood levels in patient populations. The most important neurologic complications, that occur in 15% to 40% of patients on cyclosporine, are confusion, inattention, visuospatial disorientation, and seizures; all are variable components of the syndrome that is called “reversible posterior leukoencephalopathy” which is also associated with malignant hypertension and tacrolimus therapy [37]. The white matter disease of immunosuppressive therapy must be distinguished from other toxic or infectious encephalopathies, including progressive multifocal leukoencephalopathy [38].

Clinical manifestations and management of specific central nervous system infections

This section emphasizes specific, common clinical manifestations and unusual variants of important CNS infections in patients with cancer. Two types of bacterial pathogens, four groups of fungi, and four viruses comprise the 10 important infections with which the clinician should be familiar.

Bacterial diseases

Table 4 lists the appropriate antimicrobial regimens for important pathogens. Appropriate coverage for presumed bacterial meningitis must take into account local resistance patterns [39].

Listeria monocytogenes

Listeria represented nearly 7% of meningitis cases in the large series of Durand et al [40]. Host factors such as immune status, age, and underlying conditions influenced the risk and outcome of infection. In the series of Skogberg et al [41], nearly all of the patients with a solid or hematologic

Table 4
Treatment of common infections in patients with cancer^a

Organism	Treatment ^b	Prophylaxis/maintenance
Bacteria		
<i>S aureus</i>	Oxacillin 2 g q4h and Cefotaxime 2 g q6h or Vancomycin 500 mg q6h	No longterm maintenance for bacterial infections
<i>H influenzae</i>	Ceftriazone 2 g q12h or Ampicillin 3 g q6h	
<i>S pneumoniae</i>	Penicillin 2 mU q2h or Ceftriaxone 2 g q12h	
<i>L monocytogenes</i>	Ampicillin 2–3 g q4h and Gentamicin 1–1.5 mg/kg q8h	
<i>N asteroides</i>	Sulfadiazine 8–12 g/d	
Gram-negatives (<i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i>)	Ceftriaxone 2 g q12h and Gentamicin 1.5 mg/kg q8h	
<i>Pseudomonas</i>	Ceftazidime 2 g q8h and Gentamicin 1 mg/kg q8h	
Fungal		
<i>C neoformans</i>	Amphotericin B and Flucytosine for 2 weeks (see text)	Fluconazole 200 mg/d (duration dependent on underlying disease)
<i>Aspergillus</i>	Amphotericin B, Flucytosine or ambisome or liposomal preparations (see text)	
Viral		
Cytomegalovirus	Ganciclovir 5 mg/kg q12h	Ganciclovir
Herpes simplex	Acyclovir 12 mg/kg q8h × 10–14 days	IV Acyclovir in BMT recipients
Varicella-zoster	Acyclovir as for HSV ^c	None
JC virus	Not established—see text	

^a Initial treatment recommendations only; final antimicrobial choice dependent on resistance patterns in each hospital setting, particularly with respect to *S aureus* resistance issues.

^b Doses IV unless otherwise indicated.

^c IV treatment for disseminated VZV, oral acyclovir or famciclovir for dermatomal lesions.

malignancy had received immunosuppressive therapy within the month before the development of listeriosis. The most common presentation is a febrile syndrome. Despite the fact that ingestion is the usual route of infection, symptoms of gastroenteritis occur in as few as 16% of cases with CNS involvement [42]. Mylonakis et al [42] reported that one third of patients failed to develop meningeal signs during hospitalization for listeriosis. This is a significant difference from other community-acquired meningitis cases. Focal neurologic signs are less common, but brainstem rhombencephalitis with pontine and medullary signs may occur in about 9% of all patients with

listeriosis [43]. In contrast to patients with meningitis and meningoencephalitis, most patients with rhombencephalitis do not have underlying serious medical illness. Cerebritis and abscess with focal dysfunction, sometimes mimicking transient ischemic attacks, were also described. In contrast with abscesses that are caused by other bacterial pathogens, antibiotics successfully treat *Listeria* abscess without surgical intervention.

Listeria is not sensitive to third generation cephalosporins, and, therefore, a penicillin must be part of initial broad-spectrum coverage when this organism is suspected. In patients who are allergic to penicillin, trimethaprim sulfamethoxazole is an appropriate choice. Recurrence of listeriosis following successful treatment for bacteremia or meningitis was described.

Nocardia asteroides

Chronic corticosteroid treatment is the most common predisposing factor for *Nocardia* infection. There is often a pulmonary source and CNS seeding results in a single or small number of brain abscesses. If pulmonary infection cannot be documented, then a brain biopsy may be necessary. Conservative medical therapy with trimethaprim-sulfamethoxazole, without surgical intervention, usually is associated with successful responses [44].

Fungal infections

In the past 2 decades fungal infection has become as frequent a cause of death in patients with acute leukemia as bacterial infection. Some fungal infections thrive in patients with neutrophilic deficits (candidiasis, aspergillosis and mucormycosis), whereas others become established as a result of disordered T-lymphocyte-mediated immunity (cryptococcosis, histoplasmosis, and coccidioidomycosis).

Cryptococcus neoformans

Cryptococcus was the causative organism of one third of CNS infections in one series of patients with defects in cell-mediated immunity; the duration of immunosuppression is greater than 6 weeks in most patients [2]. There are two major risk factors for cryptococcal meningitis in the twenty-first century. The first is HIV infection associated with profound depletion of CD4+ helper cells; the highest risk occurs when counts fall below 100. Even after the advent of highly active antiretroviral therapy (HAART) therapy, the disease remains difficult to treat and can surface in patients who are intolerant of, or noncompliant with, medications. The use of corticosteroids is the second risk factor for cryptococcal meningitis. Prednisone doses of 10 to 20 mg/d or greater increase the risk for cryptococcal disease. Fewer than 20% of patients with cryptococcal disease have no underlying immune deficit [45]. There is a distinct association between immune status and *C neoformans* variety. In one Australian series, infections of *C neoformans* var. *gattii* occurred in healthy hosts and 90% of infections of *C neoformans* var. *neoformans* occurred in immunocompromised hosts [46]. Focal CNS lesions

usually occurred in healthy hosts whereas isolation of *Cryptococcus* from blood and urine was associated with immunosuppression and infections caused by *C neoformans* var. *neoformans* were associated with a higher mortality rate.

Other clinical differences are present in immunosuppressed hosts when compared with immunocompetent patients. The duration of symptoms is commonly 1 to 2 weeks in previously healthy patients although it can be much longer; occasionally, severely immunosuppressed patients present with a fulminant picture. The usual symptoms are headache and meningeal symptoms, but focal infarctions have been reported [47]. Patients with impaired immunity, particularly those with AIDS, usually have a low CSF white blood cell count. This lack of an inflammatory response indicates a poor prognosis despite therapy. Diagnosis is made easily and rapidly by the detection of cryptococcal antigen. High titers reflect a large burden of disease and correlate with prognosis.

Primary treatment of cryptococcal meningitis is with triple drug therapy. Induction therapy involves amphotericin B 0.7mg/kg/d with or without flucytosine 100 mg/kg/d for 2 weeks. The combination is preferred because of more rapid CSF sterilization. Substitution of AmBisome or amphotericin B lipid complex can be made for amphotericin B in patients with impaired renal function. After 2 weeks of induction therapy, patients are switched to fluconazole 400 to 800 mg/d, or as an alternative, itraconazole 400 mg/d for 8 to 10 weeks [45]. For patients with AIDS patients and heavily immunosuppressed patients with cancer, a third phase of treatment continues with fluconazole 200 mg/d for at least 6 months.

This three-phase therapy program resulted in improved survival rates, but the morbidity from cryptococcal meningitis remains high. Early complications include CSF obstruction that requires ventriculostomy or ventriculoperitoneal shunt. Hydrocephalus can develop later in the course of the disease [48]. Sudden, acute visual loss has been attributed to hydrocephalus, but also can be ascribed to direct cryptococcal invasion of optic nerves in patients with poor immune status [49].

Aspergillus species

Aspergillus species are ubiquitous and can be found in the ventilation systems of most hospitals. Neutrophil and macrophage deficits provide important risk factors for the susceptibility to spores and hyphae of *Aspergillus*. The major risk factors are high-dose corticosteroids or other chemotherapy and broad-spectrum antibiotics. Neutropenia and concurrent CMV infection are additional risk factors. CNS infection is almost always accompanied by invasive pulmonary disease. Affinity of the organism for blood vessels leads to the most characteristic neurologic syndrome, multiple small hemorrhagic infarctions with subarachnoid hemorrhage when the circle of Willis blood vessels are invaded. CSF leukocytosis may be neutrophil predominant. Failure to diagnose the organism antemortem remains common.

Appropriate therapy is with amphotericin B and flucytosine and debulking of large infectious masses, but prognosis is poor [45].

Candida species

Candida species are part of the normal, human, microbial flora. Invasive human disease is usually caused by *C albicans*. The yeast gains access to the bloodstream and then to the CNS through catheters, particularly parenteral alimentation catheters, or as a result of operations, most commonly on the gastrointestinal tract. Virtually all patients who have *Candida* infection have received several weeks of antibiotics. The most common, clinical manifestation of CNS candidiasis is meningitis that is sometimes associated with base of skull infiltration and cranial nerve palsies. Endocarditis with cerebral embolism has been reported, as well. Removal of all potential sources of infection such as drains, shunts, and intravenous lines is an important part of therapy. Neutropenia and steroid use must be minimized.

Mucoraceae

The Mucorales or Zygomycetes organisms affect neutropenic patients, particularly those with poorly-controlled diabetes, hematologic malignancies, or steroid therapy. They enter the CNS by way of adjacent structures, such as the paranasal sinuses of orbit where they can mimic posttransplantation lymphoproliferative disorder and can be mimicked by *Aspergillus* masses. Commonly, there is facial or orbital pain and nasal discharge. Carotid artery thrombosis may occur. The palate and nasopharynx may contain necrotic areas that can be biopsied. Neurosurgical intervention is critical to obtain biopsy material. Hypoglycemia should be treated; early treatment with amphotericin B followed by maintenance amphotericin was reported to control disease.

Viral infections

Human herpes viruses are the most common pathogens in patients with cancer with CNS infection. Human herpes virus 6 and its unique MRI presentation were discussed earlier (see section on bone marrow transplantation). Epstein-Barr virus and its associated diseases were discussed in the section on PTLD.

Varicella-zoster virus

As many as 15% of patients with lymphoma and leukemia develop symptomatic varicella-zoster infection (VZV). One quarter of these will have symptomatic dissemination. The risk of VZV dissemination is significantly correlated with the presence of active tumor at the time of infection and shows some correlation with dermatomal localization. Thus, patients with gastrointestinal or genitourinary malignancies usually have lower lumbar or sacral dermatomal involvement, whereas patients with breast cancer may

have thoracic dermatomal sites of viral activation. More than 60% of patients who received radiation therapy before VZV infection developed their lesions in the previously irradiated site [50].

VZV is associated with many neurological syndromes. The most common form is shingles or dermatomal VZV. The frequency of postherpetic neuralgia is two to three times that of patients without cancer. Other peripheral forms of VZV include focal segmental motor weakness and reactivation of VZV without a rash. The diagnosis can be confirmed by detection of VZV antibody, VZV DNA, or both in CSF [51].

Dissemination of VZV to the brain can take two forms, an acute, necrotizing encephalitis with marked inflammation and a multifocal, stroke-like or PML-like picture with little inflammation. These two syndromes probably represent a spectrum of host response. The distinction of VZV from progressive multifocal leukoencephalopathy (PML), by biopsy if necessary, is important, because VZV is a potentially treatable condition. Other forms of VZV infection include a progressive or remitting myelopathy. Detection of VZV DNA in the CSF months after any rash may be useful in diagnosis [52].

Acyclovir therapy for VZV is summarized (see Table 4). Patients with ophthalmic zoster should be referred urgently to an ophthalmologist for eye care [53].

Herpes simplex

Although herpes simplex can affect healthy hosts and patients with underlying malignancy, the differential diagnosis of what seems to be herpes simplex encephalitis in a patient with cancer is broader than that in the previously healthy patient [54]. The acute confusional state that best resembles limbic encephalitis could be caused by a paraneoplastic process (anti-Hu, or anti-Ma or Ta antibodies) that is most commonly seen in patients with small cell lung cancer, gynecologic malignancies, and occasionally, non Hodgkin's lymphomas. Additional infectious considerations include VZV, CMV, *Listeria* and toxoplasmosis. Status epilepticus can produce a sudden and prolonged confusional state and may be associated with a slight CSF pleocytosis. Diagnosis of herpes simplex infections is greatly aided by the advent of PCR technology. See Table 4 for a treatment summary.

Cytomegalovirus

Cytomegalovirus, a DNA virus, causes no symptoms in most immunocompetent hosts, although previously healthy individuals may develop occasional, neurological manifestations, such as Guillian-Barre syndrome. Retinitis, with or without associated encephalitis is the most common neurologic manifestation of CMV in the patient with cancer. Persons who have undergone BMT are the most likely group of patients with cancer to be affected by CMV. CMV may also cause radiculomyelitis, which usually involves the cauda equina, although cranial nerves or brachial plexus may

occasionally be involved [55]. CMV may be detected by PCR. There were reports of significant neurologic improvement following treatment with ganciclovir and foscarnet. Extraneural clues to the presence of recent CMV infection are acute monoarticular arthritis, hepatitis, an infectious, mononucleosis-like syndrome, myocarditis, and pneumonia.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy is a subacute, demyelinating disease that is caused by the JC virus of the papovavirus family and occurs most frequently in patients with cell-mediated immunity defects [56]. Clinical presentation is usually a progressive dementia or slowly progressive focal deficits that mimic a mass lesion. Visual cortex is often involved with resulting clinical variants of cortical blindness, anosognosia, and hemianopias. Isolated PML lesions in the brainstem were described [57]. CSF is usually normal; PCR was used to detect JC virus genome with excellent specificity but only 75% sensitivity [20].

Progressive multifocal leukoencephalopathy is usually fatal within months, although as the patient population with AIDS and cancer chemotherapy-related PML is treated by reduction of immunosuppression, many patients have some clinical and radiographic regression of disease. Before the advent of MRI and HIV it was difficult to mount clinical trials because of the rarity of the condition, but vidarabine and acyclovir were tried in several patients and found to be ineffective [58]. Cytarabine produced clinical improvement in some studies. The efficacy of systemic and intrathecal cytarabine in patients with MRI-guided stereotactic biopsy confirmation of the disease was studied in larger populations; there was no significant difference in survival among patients who were treated with antiretroviral therapy alone or with any combination of systemic and intrathecal routes of cytarabine administration. Controlled, clinical trials are currently evaluating drugs with specific activity against JC virus, including inhibitors of DNA topoisomerase I activity, such as camptothecin [59]. Isolated case reports of continuous infusion IL-2 in patients with PML who have undergone BMT reported sustained clinical and radiographic improvement [60]. The IL-2 resulted in an increasing CD4+ count, an effect that suggests that the first step in treating PML is to minimize immunosuppressive treatment. The situation is similar in AIDS patients with PML for whom the addition of zidovudine therapy has normalized CD4+ counts and improved survival [61].

Central nervous system toxicities of antimicrobial agents

After the diagnosis of a CNS infection and the institution of appropriate therapy, the clinician must be wary of subsequent neurologic complications that may be caused by the chosen antimicrobial drugs or drugs [62]. It is difficult to sort out the nonspecific effects of fever (eg, headache) from a potential antimicrobial adverse effect, but other, more specific, symptoms should

be attributed to the appropriate drug in the correct clinical setting. Aseptic meningeal reactions to drugs were discussed earlier in this article.

- Seizures have been reported with penicillins, usually in high doses and often in the presence of renal impairment. Other drugs that can cause seizures are amphotericin B, izonizaid, metronidazole, ciprofloxacin, acyclovir, foscarnet, and praziquantel.
- Delirium has been reported with virtually any antibiotic and is hard to sort out from the pre-existing infection that dictated the institution of antimicrobial therapy, but most clearly is associated with ciprofloxacin, ofloxacin, isoniazid, rifampin, flucytosine, acyclovir, foscarnet, and chloroquine.
- Hearing loss with or without vestibular toxicity is associated with aminoglycoside antibiotics, erythromycin, minocycline and azithromycin.
- Pseudotumor cerebri is reported with tetracycline.
- Peripheral neuropathy may result from the administration of metronidazole, isoniazid, or amphotericin B.
- Potentiation of neuromuscular blockade with aggravation or precipitation of myasthenic symptoms was reported with many different classes of antibiotics, but most prominently aminoglycosides.

Summary

- The diagnostic approach to the patient with cancer with suspected CNS infection depends on an analysis of the patient's immune defect, the time course of development of manifestations of infection, and the type of clinical syndrome with supportive evidence for a specific diagnosis coming from laboratory and neuroradiographic data.
- Most patients with CNS infections can be grouped into those with signs of meningitis or meningoencephalitis and those with focal mass lesions. A smaller group presents with stroke-like onset. Except for the group with strokes, those with focal deficits usually present in a more indolent fashion, whereas those with meningitis and encephalitis present more acutely [63].
- Patients with B-lymphocyte dysfunction are susceptible to encapsulated bacterial pathogens. Patients with T-lymphocyte impairment develop CNS infections that are caused by intracellular pathogens, particularly viruses (HSV, JC, CMV, HHV-6), *Nocardia*, *Aspergillus*, and *Toxoplasma*.
- Many noninfectious entities, such as drug treatment complications, radiation effects, recurrent tumor, and paraneoplastic syndromes, can mimic CNS infections.
- Although cryptococcosis, bacterial meningitis, and some viral infections are easily diagnosed from Gram's stain, culture, or PCR, patients with mass lesions may require tissue biopsy to confirm diagnosis.

- Patients with cancer differ from normal hosts in the distribution of pathogens, and there is a wider range of differential diagnostic issues, both infectious and noninfectious, for the relatively few clinical syndromes that present as potential CNS infections.

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