Neurologic Emergencies in Patients Who Have Cancer: Diagnosis and Management

Kelly Jo Baldwin, MD, Saša A. Živković, MD, PhD, Frank S. Lieberman, MD

The central and peripheral nervous systems can be significantly affected by cancer. Neurologic signs and symptoms are present in about 30% to 50% of oncologic patients presenting to the emergency department or in neurologic consultation at teaching hospitals. Neurologic emergencies in patients who have cancer frequently require (neuro)surgical intervention, and prompt diagnosis and effective collaborative effort with neurosurgeons are essential to improve the outcomes. There are many neurologic emergencies that can occur from direct or indirect involvement of cancer in the brain and spinal cord, and in the peripheral nervous system. The direct effects of cancer on the central nervous system (CNS) include brain metastases, cerebral edema, seizure, spinal cord compression, hydrocephalus, and leptomeningeal carcinomatosis. Indirect complications include stroke, cerebral venous sinus thrombosis, infectious disease, and paraneoplastic encephalitis. Different modalities of cancer treatment are also associated with various neurologic complications and emergencies (Box 1). Such a wide spectrum of neurologic emergencies causes significant morbidity.

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and mortality for patients who have cancer and requires prompt diagnostic and treatment measures. This article reviews the most common neurologic emergencies affecting patients who have cancer and discusses their epidemiology, clinical presentation, diagnosis, and treatment modalities.

**BRAIN METASTASES**

Brain metastases seem to be increasingly diagnosed in patients who have cancer as a result of advances in diagnostics and probably also because of improving outcomes and longer survivals. If left untreated, brain metastases typically lead to progressive neurologic deterioration. Many patients with cerebral metastases and primary brain tumors develop other neurologic complications such as cerebral edema and seizures.

**Epidemiology**

Epidemiologic studies documented symptomatic brain metastases in 8% to 10% of patients who have cancer. Metastatic brain disease is overall tenfold more common than primary brain tumors. Autopsy studies suggest that another third of patients with metastasis may have asymptomatic lesions. The most common malignancies to metastasize to the brain include lung (16%–19%), breast (5%), renal cell (6%–10%), melanoma (7%), and colorectal carcinoma (2%). Depending on molecular and histopathology profile, different neoplasm subtypes metastasize to the brain with varying frequencies. In breast cancer, HER-2 overexpression is associated with a significantly higher risk of brain metastases. Lung adenocarcinoma subgroup of non–small cell lung cancer is also more likely to metastasize than other types of lung cancer.

### Box 1

<table>
<thead>
<tr>
<th>Iatrogenic neurologic emergencies caused by treatment of cancer</th>
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<tr>
<td>Seizures caused by chemotherapeutic agents (ifosfamide, busulfan)</td>
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<td>Cerebrovascular complications</td>
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<td>Intracranial hemorrhage (thrombocytopenia caused by chemotherapy)</td>
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<td>Visual loss (vincristine, cisplatin)</td>
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<td>Peripheral neuropathy (vincristine, cisplatin, bortezomib, thalidomide, paclitaxel, oxaliplatin)</td>
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<td>Opportunistic CNS infections (related to immunosuppression and neurosurgical procedures)</td>
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<td>Viral encephalitis, bacterial and fungal meningitis</td>
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<td>Progressive multifocal leukoencephalopathy (PML)</td>
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<td>Radiation necrosis</td>
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<td>Brain and spinal cord edema (acute)</td>
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<tr>
<td>Radiation myelopathy and motor neuron injury (delayed)</td>
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<td>Radiation vasculopathy (delayed)</td>
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Clinical Presentation and Diagnosis

Brain metastases may present with symptoms of increased intracranial pressure, focal neurologic deficits, or they may be asymptomatic. Typically, patients present with signs and symptoms of increased intracranial pressure such as altered mental status, headache, or vomiting. They may also exhibit focal neurologic signs such as hemiparesis, aphasia, or seizures. When a patient with cancer presents with an acute neurologic decline, the initial imaging modality is usually noncontrast head computed tomography (CT), which allows for rapid diagnosis of intracranial hemorrhage, hydrocephalus, herniation syndromes, and large-vessel ischemia.\(^9\) In a nonemergent setting, magnetic resonance imaging (MRI) of brain with and without contrast is the study of choice for evaluating possible primary brain neoplasm or metastases (Fig. 1).\(^{10,11}\)

The results of brain MRI largely predict the next step in diagnosis and management. Although the presence of a solitary contrast-enhancing lesion may not always indicate a brain metastasis, a single contrast-enhancing lesion was reported to be a metastasis in more than 90% of patients.\(^{11}\) Differential diagnosis also includes

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Fig. 1. Multiple brain metastases in a 73-year-old patient with adenocarcinoma of the lung (MRI of brain; top left and bottom right, contrast-enhanced axial and coronal T1-weighted images; top right, diffusion-weighted imaging; bottom left, coronal fluid-attenuated inversion recovery [FLAIR]).
abscess, granuloma, and primary brain neoplasm. In a patient with an existing primary cancer, brain biopsy may not be necessary. It has been recommended to monitor small (<1 cm) asymptomatic lesions instead of pursuing more aggressive therapy or invasive diagnostic methods. In a patient with widespread metastatic disease and multiple brain lesions on MRI (see Fig. 1), further invasive testing is often deferred. If diagnosis remains uncertain, or when there is no primary malignancy identified, histopathologic analysis and biopsy remain the gold standard for diagnosis of intracranial lesions.

**Management**

Treatment of brain metastases depends on location and characteristics of the metastases and the individual patient’s features. Untreated brain metastases may lead to increased intracranial pressure and death within 1 to 2 months. Treatment options include surgical resection, whole-brain radiation, stereotactic radiosurgery, and chemotherapy. Treatment of brain metastases also includes symptomatic treatment of seizures and brain edema. Neurosurgical evaluation and decisions on treatment steps for metastatic brain lesions are based on number of lesions, location, and performance status. In patients with solitary lesions in noneloquent brain regions with good performance status and known primary tumor, surgical resection possibly followed by radiation therapy is generally preferred (class I evidence). If a lesion is located in an eloquent area, radiation therapy is preferred, especially for patients with poor performance status. Whole-brain radiation therapy (WBRT) is usually the treatment of choice for multifocal symptomatic brain metastases. Although treatment is often effective and relieves symptoms, the prognosis still remains poor and almost half of affected patients die from further CNS progression. In combination with WBRT, surgical resection may improve outcomes for selected patients with good functional status. Chemotherapy is usually considered as adjunctive therapy in treatment of brain metastases and its routine use is not recommended. Germ cell tumors and non-Hodgkin lymphoma with CNS involvement are treated with chemotherapy. In contrast, brain metastases from melanoma and renal cell carcinoma typically do not respond to chemotherapy. Despite aggressive therapy for brain metastases, many patients suffer from malignant cerebral edema and seizure. Adequate diagnosis and treatment of these overlying problems is important to reduce the morbidity and improve quality of life for patients.

**Cerebral Edema**

Metastatic brain disease precipitates cerebral edema through several mechanisms. Metastases cause direct disruption of the blood-brain barrier. In addition, tumor cells secrete various cytokines and growth factors including vascular endothelial growth factor (VEGF), which promotes angiogenesis. VEGF stimulates the creation of endothelial gaps, fragmentations, and fenestrations in the endothelium, which leads to degeneration of the basement membrane. These changes lead to leakage of fluid from the intravascular compartment to the parenchyma, and increased interstitial fluid pressure with vasogenic edema. Peritumoral edema eventually leads to signs and symptoms related to mass effect and increased intracranial pressure. Corticosteroids remain the backbone of treatment protocols for managing malignant cerebral edema, and dexamethasone is the recommended choice. Overall, in most patients, low-dose dexamethasone (4 or 8 mg/d) is as effective as a higher dose (16 mg/d), which is associated with more side effects, without additional clinical benefit. However, for patients with more severe symptoms, higher doses should be considered. Subsequently, corticosteroids are gradually tapered off over 2 weeks or longer.
Chronic steroid treatment is associated with multiple complications, including immunosuppression, increased risk of opportunistic infections, and hyperglycemia. Hyperventilation may decrease increased intracranial pressure promptly, but its effectiveness is limited by short duration of action. Hypertonic saline and mannitol may be helpful to reverse impeding cerebral herniation and decrease intracranial pressure. In an emergent setting, biologic therapies are not used (yet), but their effects improve understanding of the underlying pathophysiology. Antiangiogenic therapy with VEGF tyrosine kinase inhibitor cediranib showed encouraging results, with improved vasogenic edema, reduction of steroid dosage, and better short-term outcome (lack of progression at 6 months). A similar effect was also observed with bevacizumab (monoclonal antibody targeting VEGF-A) in glioblastoma multiforme. At this time, antiangiogenic therapies are not a standard of care for brain edema, especially in an emergent setting.

SEIZURES

Seizures related to brain metastases and primary brain tumors are a frequent neurologic complication and may manifest as simple or complex partial seizures, generalized seizures, or even status epilepticus. Prompt diagnosis and treatment are essential to avoid morbidity associated with prolonged convulsive seizures and status epilepticus. Seizures are more common with primary brain tumors, and up to 40% of patients with brain metastases develop seizures as well. Local milieux in tumors and peritumoral tissue may also increase susceptibility to seizures. Concurrent parenchymal metastases and neoplastic meningitis further increase the risk of seizures. In addition, paraneoplastic encephalitis may precipitate seizures or status epilepticus, and patients with systemic cancer without evidence of direct CNS involvement may also develop seizures.

Epidemiology

The frequency of seizure depends on the type of primary neoplasm and the location of the tumor. Seizures can present as focal, generalized, or nonconvulsive. Glioneural tumors may also exhibit intrinsic epileptogenicity. Seizure is more common with low-grade primary brain tumors and low-grade gliomas, and oligodendroglioma are associated with seizures about 60% to 80% of the time. The higher prevalence of seizures in low-grade gliomas is probably partly related to a longer survival. Low-grade gliomas also decrease seizure threshold by disrupting normal networks in cortical regions and white matter. High-grade gliomas have a lower incidence of seizures (about 30% to 50%). Typically, high-grade gliomas induce seizures by abrupt tissue damage caused by necrosis, hemorrhage, or edema. Tumor location in an epileptogenic area, such as the mesial temporal lobe and insular cortex, is more likely to be associated with intractable epilepsy. Cortical tumors are more likely to result in epilepsy than subcortical tumors. Glioneural tumors occur more commonly in the temporal lobe, which may in part explain their epileptogenic potential. Seizures may also occur in patients with systemic cancer and without evidence of brain metastases or neoplastic meningitis. Other causes of seizures in patients with cancer include neurotoxicity of chemotherapy and other medications (eg, busulfan, ifosfamide), ischemic and hemorrhagic strokes, opportunistic CNS infections, brain radiation injury, transient metabolic disturbances (eg, hypoglycemia), paraneoplastic disorders, and worsening of preexisting epilepsy (Box 2).
Diagnosis and Management

Diagnosis of seizure disorder is supported by clinical history and electroencephalogram. Electroencephalography (EEG) shows focal epileptiform changes localizing to the area of brain metastases. However, EEG may disclose electrographic seizures in the absence of a clinical equivalent or nonconvulsive status epilepticus, which can present with nonspecific impairment of alertness and may easily be missed if not clinically suspected. Treatment of tumor-associated epilepsy uses a combined approach with treatment of seizure origin (eg, resection of tumor) and symptomatic treatment with antiepileptic medications. Total tumor resection may provide relief with seizure freedom at 6 months after resection in up to 89% of patients with primary brain tumors, compared with resolution of seizures in 57% with subtotal tumor resection. However, other studies report lack of correlation with completeness of tumor resection. Emergent treatment of status epilepticus in patients who have cancer does not differ from standard treatment protocols, but the subsequent choice of maintenance antiepileptic treatment is more complex because older-generation antiepileptics such as phenytoin, carbamazepine, and phenobarbital are enzyme inducers.

<table>
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<tr>
<th>Causes of seizures in patients who have cancer</th>
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<tr>
<td>1. Tumor-related causes</td>
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<tr>
<td>Brain parenchymal metastases and primary brain tumors</td>
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<tr>
<td>Neoplasic meningitis</td>
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<td>Paraneoplastic limbic encephalitis</td>
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<td>2. CNS infections</td>
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<td>Meningoencephalitis</td>
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<td>Abscess</td>
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<td>3. Treatment-related causes</td>
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<tr>
<td>Toxicity of medications</td>
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<td>Chemotherapy (busulfan, ifosfamide, cisplatin)</td>
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<td>Other medications (cephalosporins, imipenem)</td>
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<td>Radiation necrosis</td>
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<td>4. Cerebrovascular complications</td>
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<td>Cerebral venous sinus thrombosis</td>
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<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Intracranial hemorrhage (coagulopathy, thrombocytopenia)</td>
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<td>5. Metabolic disturbances</td>
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<tr>
<td>Hypoglycemia/hyperglycemia</td>
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<td>Hyponatremia</td>
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<td>Hypocalcemia</td>
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<td>6. Other causes</td>
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<tr>
<td>Posterior reversible encephalopathy syndrome</td>
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<td>Worsening of preexisting epilepsy</td>
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and interact with chemotherapy regimens. Enzyme-inducing antiepileptic medications may accelerate metabolism of corticosteroids and commonly used chemotherapeutics metabolized through the cytochrome P450 system, complicating the dosing and potentially decreasing the effectiveness of chemotherapy protocols. A recent study showed improved outcomes of patients with glioblastoma treated with chemotherapy and enzyme-inducing antiepileptic medications. Newer classes of antiepileptics have less metabolic and pharmacokinetic interactions, and thus are frequently preferred in patients who have cancer. Levetiracetam does not inhibit the P450 enzyme system, it has no active metabolites, and it exhibits almost no protein binding. Other options include gabapentin, pregabalin, lamotrigine, and lacosamide. Topiramate is frequently avoided in patients who have cancer at risk of cachexia because of its appetite-suppressing properties. Side effects of levetiracetam are mild in most patients, and most commonly include somnolence, fatigue, and dizziness. However, levetiracetam may also precipitate potentially severe behavioral abnormalities requiring discontinuation in up to 7% of treated patients. Up to 37% of patients report negative behavioral changes including aggression, loss of self-control, and sleep problems. Up to 60% of patients with cerebral metastases remain seizure-free with antiepileptic medications, and most other patients have a decrease in seizure frequency. However, routine prophylactic use of anticonvulsant medications for patients with brain tumors without a history of clinical seizure is not well established. In adults with brain metastases without prior history of clinical seizures, routine prophylactic use of anticonvulsants is not recommended (class III evidence). Antiepileptic treatment may be further complicated by expression of multidrug-resistance proteins in tumor cells decreasing the local concentration and effectiveness of antiseizure medications.

Nonconvulsive status epilepticus (NCSE) is easily overlooked, especially in encephalopathic or comatose patients with other possible causes of altered mental status, and may be difficult to diagnose even with EEG. NCSE has been described in oncologic patients with neoplastic meningitis, with primary brain tumors and brain metastases but also occurs in patients with systemic cancer in the absence of evidence of CNS metastases. Seizure treatment becomes important in end-of-life care for patients with high-grade glioma because more than 50% of patients suffer from seizures during end-of-life care, with a third of patients experiencing seizures 1 week before death.

ACUTE OBSTRUCTIVE HYDROCEPHALUS

Hydrocephalus and increased content of cerebrospinal fluid (CSF) occurs as a result of discrepancy between cerebrospinal production and absorption, leading to enlargement of the ventricles. Prompt evaluation and timely intervention by a neurosurgeon are essential in reducing the morbidity associated with hydrocephalus.

Epidemiology

Hydrocephalus is a frequent concern and major neurologic emergency in patients with cancer, and carries a significant morbidity. Generally, hydrocephalus is classified as either obstructive or nonobstructive. Obstructive or noncommunicating hydrocephalus results when CSF cannot freely traverse the ventricular system, commonly because of an intraventricular mass. Nonobstructive or communicating hydrocephalus is caused by impairment of CSF reabsorption. Obstructive hydrocephalus can be a result of an intraventricular tumor, such as a colloid cyst, ependymoma, intraventricular meningioma, choroid plexus papilloma, or posterior fossa tumor. In adult
oncologic patients, obstructive hydrocephalus is frequently caused by bulky leptomeningeal carcinomatosis or metastases with intraventricular extension. In pediatric patients with posterior fossa tumors, hydrocephalus is common. Nonobstructive hydrocephalus in patients who have cancer is typically caused by impaired venous drainage from cerebral sinus venous thrombosis, infectious meningitis, metastatic seeding, or subarachnoid hemorrhage.

**Clinical Presentation**

Acute obstructive hydrocephalus develops rapidly over several hours, and reaches 80% of maximal ventricular dilatation by 6 hours. Tumors that interfere with CSF flow of the third and fourth ventricle may produce a ball-valve effect; this results in periodic increases in intracranial pressure (plateau waves of Lundberg). Symptoms largely depend on the length of time that the hydrocephalus has developed. Symptoms of rapidly occurring acute hydrocephalus include headache, double vision, transient visual obscurations, decreased mental status, ataxia, and vomiting. About 50% of patients with brain tumors complain of headache throughout their disease. Headaches related to increased intracranial pressure are classically occipital in location, worsened by Valsalva maneuver, and are often associated with nausea or vomiting.

**Diagnosis and Management**

Diagnosis of acute hydrocephalus should be considered in any patient who presents with altered mental status, headache, and vomiting. Fundoscopy shows papilledema, and focal neurologic signs may develop as well. Imaging by noncontrast head CT can give a rapid and accurate assessment of ventricular size. Obstructive hydrocephalus classically displays ventriculomegaly proximal to the site of obstruction with periventricular edema.

Acute hydrocephalus is a life-threatening emergency and, if quickly recognized, can be effectively treated. An emergency ventriculostomy can be performed by a neurosurgeon within minutes. Other neurosurgical options include ventricular shunting, endoscopic ventriculostomy, aqueductoplasty (for aqueductal stenosis), and septostomy (for isolated lateral hydrocephalus). In some patients, tumor debulking may be necessary to improve CSF flow, and prompt neurosurgical evaluation is necessary. A recent retrospective study showed the third ventriculostomy as a safe and effective procedure in controlling hydrocephalus related to posterior fossa tumors, which can relieve symptoms quickly in the perioperative period. In cases of hydrocephalus caused by leptomeningeal carcinomatosis or metastatic seeding of the CSF, most patients are managed with radiation therapy and chemotherapy. Another option is ventriculoperitoneal shunting.

**SPINAL METASTASES AND COMPRESSIVE MYELOPATHY**

In patients who have cancer, a new onset of back pain raises the concern of possible spinal metastases and should be promptly evaluated to avoid severe morbidity associated with untreated vertebral metastases. Timely evaluation and treatment are essential to reduce morbidity and maintain neurologic function.

**Epidemiology**

Spinal metastases are common and their incidence has been estimated at 5% in all patients who have cancer. The vertebral column is the most common site for osseous metastasis, and, in general, the spine is the third most common location for metastasis after the liver and lungs. Direct metastasis to spinal cord is rare. It
is estimated that 70% of patients who die with cancer have spinal metastasis at autopsy; however, only 14% of these have clinically apparent disease. Up to 20% of patients presenting with spinal metastases do not have prior diagnosis of cancer. The most common types of tumor to have spinal involvement include prostate, breast, and lung, followed by lymphoma, renal cell carcinoma, and multiple myeloma. Most commonly, spinal metastases involve the thoracic spine (70%), then lumbar (20%), followed by cervical spine (10%). In addition, lung and breast carcinoma more commonly metastasize to thoracic spine, whereas colon and pelvic neoplasm usually involve lumbosacral spine. Spinal involvement of systemic cancer typically arises by 2 mechanisms: hematogenous spread or direct extension. The seeding of tumor cells via hematogenous spread occurs via the Baston venous plexus to the vertebral column. Malignant invasion of the vertebral bodies is destructive and invariably leads to vertebral collapse. Less commonly, paravertebral malignancy can directly invade the spinal canal by destroying the vertebral body or by entrance through the vertebral foramen. Parenchymal metastases to spinal cord are rare. Regardless of the route of spinal entry, epidural spinal compression becomes the ultimate neurologic emergency. Epidural spinal cord compression affects 5% of all patients who have cancer. It is imperative to recognize the signs and symptoms of spinal cord compression, because early treatment can significantly improve morbidity and mortality. If spinal cord compression is not promptly treated, the patient will suffer cord edema followed by white matter ischemia and irreversible cord infarction.

**Clinical Presentation**

Pain is the most common presenting symptom in patients with spinal metastasis and may be further characterized as progressive and unrelenting, worsened when laying flat, thoracic predominance, with direct tenderness to palpation. The most important management principle is the necessity to carefully evaluate any new complaint of back pain in a patient with cancer. Mechanical back pain may represent spinal instability and impending collapse, as well as acute-on-chronic pain from compression fractures. Radicular symptoms may also be present, and this symptom in a patient with known cancer demands expeditious evaluation to determine the cause. Although pain generally precedes neurologic symptoms, many patients go undiagnosed until weakness ensues. About 70% of patients have bilateral lower extremity weakness by the time of diagnosis. Sensory symptoms and bowel or bladder dysfunction are also common, but frequently occur late in the course.

**Diagnosis**

Diagnosis begins with an accurate history and physical examination. New onset of back pain or focal neurologic symptoms in a patient with diagnosed malignancy should be further evaluated with imaging. MRI of the entire spine remains the most sensitive and specific imaging modality for diagnosis of spinal metastasis (with reported 93% sensitivity and 97% specificity) (Fig. 2). This imaging modality is also useful for planning of radiotherapy and surgical resection. A radiologic study of 57 patients with cancer compared use of T1-weighted MRI alone versus combined T1-weighted and T2-weighted imaging for presence of vertebral metastasis, epidural metastasis, and spinal cord compression. The study found that, if used alone, T1-weighted sagittal MRI of the spine failed to detect 13% of the vertebral metastases that were detectable with comprehensive imaging protocol. In most patients with a known primary malignancy, diagnosis of spinal metastasis is based on imaging and does not require biopsy. If MRI is not obtainable (eg, pacemaker), CT myelography may provide diagnostically useful information. In patients without a previous
diagnosis of cancer, further work-up, including whole-body imaging, is required to
identify potential primary tumor, and the optimal site to biopsy for diagnosis.47

Management

Treatment of spinal metastases is mostly palliative and is based on preservation of
neurologic function.48 Treatment options consist of corticosteroids, radiation therapy,
chemotherapy, surgical decompression, and emerging minimally invasive interven-
tions.47 Epidural spinal metastatic disease with compressive myelopathy is a neuro-
logic emergency in which early recognition and intervention determines whether
neurologic catastrophe would follow. The most important predictor of outcome in
epidural cord compression from metastatic disease is the severity of deficit when
the treatment is instituted. It is incumbent on the physician to recognize the warning
sign, expeditiously obtain definitive imaging, and institute treatment. Indications to

Fig. 2. Vertebral metastases and epidural compressive myelopathy. Top left, epidural metas-
tasis from renal cell carcinoma with cervical spinal cord compression in 64-year-old man on
MRI, T1-weighted image; top right, epidural thoracic spine metastasis from breast adenocar-
cinoma with thoracic spinal cord compression in 61-year-old woman on MRI, T1-weighted
image; bottom, vertebral metastasis associated with thyroid carcinoma in 52-year-old
woman on MRI, T2-weighted images. (Courtesy of Dr P Gerszten. University of Pittsburgh
and Pittsburgh Cancer Institute, Pittsburgh, PA.)
proceed with surgical decompression include acute cord compression, spinal instability, and unrelenting pain from pathologic fractures. Following onset of compressive myelopathy, rapid progression is common, and 30% of patients with weakness progress to paraplegia within 1 week. Functional recovery is unlikely if paraplegia is present for more than 24 hours.

Corticosteroids are the initial symptomatic treatment of epidural spinal cord compression. Mechanism of action is thought to involve reduction of vasogenic edema, stabilization of membranes, and decreased local inflammation. In specific tumor types such as multiple myeloma, prostate cancer, and lymphoma, there is also a direct tumorlytic effect. Multiple randomized controlled trails of high-dose intravenous steroids before radiotherapy show improvement in patient ambulation at 6 months. Dosing for dexamethasone typically starts with a 100-mg intravenous loading dose followed by 96 mg orally daily for 3 days, then rapid taper is instituted. Surgery is the optimal therapy for appropriately selected patients (class I evidence). The first decision step is neurosurgical evaluation. Patients with radiosensitive tumors, minimal signs or symptoms, or limited functional status or limited survival are exceptions to this general rule.

A landmark study by Patchell and colleagues in 2005 analyzed treatment outcomes in 101 patients with epidural spinal cord compression restricted to a single area and at least 1 neurologic symptom or sign. Half of the study participants (50/101) were treated with decompressive surgery followed by radiotherapy, and the remaining 51 participants were treated with radiotherapy alone. The surgical group showed improved survival, longer time with neurologic improvement, continence, and ambulatory status. However, this study excluded the patients with radiosensitive tumors. Minimally invasive procedures, including vertebroplasty and kyphoplasty for malignant compression fractures, may provide significant pain relief in more than 80% of treated patients. A prospective trial with 139 male veteran participants with initial spinal epidural metastases showed that treatment with glucocorticoid therapy and radiotherapy was as likely to maintain ability to walk as combined surgical decompression of the spinal cord with radiotherapy and glucocorticoid therapy. This population was largely limited to prostate cancer (55%) or lung cancer (37%).

As with surgery, the primary goal of radiation therapy is to protect neurologic function and decrease pain. Lymphoma and primary germ cell tumors are most radiosensitive. Breast, prostate, and lung cancer are considered intermediately sensitive. Melanoma, osteosarcoma, and renal cell carcinoma are generally radioresistant. The seminal study that showed efficacy of radiation therapy showed pain relief in 71% of patients and 76% preserved or regained ambulatory status. About 36% to 40% of paraparetic patients and 13% to 15% of paralyzed patients become ambulatory after radiation. Radiation treatment typically targets 1 to 2 vertebral bodies above and below the site, and the standard therapy consists of 30 Gy divided in 10 fractions.

Chemotherapy has a limited role in selected responsive tumors without malignant compression, but, even with careful selection, response to chemotherapy remains unpredictable and slow. These tumors include Hodgkin and non-Hodgkin lymphoma, germ cell tumors, breast or prostate, or neuroblastoma.

**LEPTOMENINGEAL CARCINOMATOSIS/LYMPHOMATOSIS**

Leptomeningeal carcinomatosis/lymphomatosis (LMC) or lymphomatous/carcinomatous meningitis is defined as malignant seeding or infiltration of the leptomeninges. In patients with leukemias, the term leukemic meningitis is frequently used.
Epidemiology

Leptomeningeal progression is most common with hematologic malignancies (5%–15% of patients), followed by solid tumors (1%–5%) and primary brain tumors (1%–2%). Autopsy studies revealed that up to 19% of patients who have cancer with neurologic symptoms may also have leptomeningeal disease. Malignant cells gain access to the subarachnoid space by 2 mechanisms: direct extension and hematogenous dissemination. Direct extension mainly occurs in primary intracranial neoplasm and metastases from solid tumors. Primary intracranial tumors such as medulloblastoma, ependymoma, choroid plexus carcinoma, primary CNS lymphoma, and malignant cerebellar astrocytoma are particularly prone to LMC. Metastatic brain tumors and cancers of the head and neck can also directly invade the CSF by making direct contact with the meninges and disrupting the subarachnoid and ventricular spaces.

Clinical Presentation

Signs and symptoms affecting multiple areas of the neuraxis simultaneously are typical of leptomeningeal carcinomatosis. Symptoms occur because of the involvement of the brain hemispheres, brainstem and cranial nerves, and spinal cord and roots. The most common neurologic signs include a triad of symptoms that suggest brain hemisphere disturbance (eg, headache and encephalopathy), multiple cranial nerve deficits (eg, diplopia), and spinal root involvement (eg, weakness and pain following radicular distribution). Cranial nerve signs also include trigeminal neuropathy, facial weakness, and hearing loss, and some patients may also manifest meningeal signs including nuchal rigidity. Leptomeningeal carcinomatosis may precipitate obstructive hydrocephalus, particularly with bulky disease of the CNS. Radionuclide scans reveal limitation of CSF flow in about 70% of patients with LMC.

Diagnosis

Diagnosis of LMC is made by clinical examination, CSF analysis, and radiologic data. Repeated lumbar punctures may be needed, and opening pressure, protein and glucose content, cell count, and cytology should be routinely evaluated. Common findings include increased protein (75%), increased opening pressure (50%), leukocytosis (64%), and low glucose (40%). Flow cytometry improves the sensitivity of diagnosis for leukemic meningitis. The sensitivity of a single large-volume lumbar puncture is 38% to 66%, and performing 3 large-volume lumbar punctures increases the sensitivity to 90%. Gadolinium-enhanced MRI has replaced CT as the imaging modality of choice for diagnosing LMC. The sensitivity of nonenhanced MRI in identifying patients with LMC is about 70%. However, because these MRI findings are not specific for LMC, imaging alone should not be used to establish the diagnosis. Typical imaging features of LMC include contrast enhancement of the meninges, cortical convexities, basilar cistern, and cauda equina. Meningeal biopsy of contrast-enhancing lesions remains the gold standard for definite diagnosis of leptomeningeal carcinomatosis/lymphomatosis.

Management

The primary goal of early diagnosis and treatment is to stabilize, and possibly improve, neurologic symptoms. Without treatment, overall survival is typically 4 to 6 weeks secondary to neurologic decline. With aggressive treatment, survival generally improves by 1 to 3 months, but there are only a few reported cases of long-term survivors. Treatment of LMC includes focal radiotherapy for bulky disease, local
chemotherapy, and systemic chemotherapy. Combination treatment strategies with radiotherapy and chemotherapy may be necessary when managing bulky disease with compromised flow of CSF. Intrathecal chemotherapy showed clinical improvement or stabilization in 50% of patients, with median survival of 5.8 months after diagnosis, but the poor long-term prognosis remained unchanged.61

ISCHEMIC STROKE AND INTRACRANIAL HEMORRHAGE

Ischemic stroke and intracranial hemorrhages are major sources of morbidity and mortality in patients who have cancer. In addition to typical risk factors for stroke, direct and indirect effects of neoplasm and side effects of treatment must be considered.

Epidemiology

Neoplastic diseases increase the risk of ischemic and hemorrhagic stroke compared with the general population. Large autopsy studies indicate that up to 15% of patients who have cancer have evidence of prior ischemic infarcts, and only half of these patients had symptomatic lesions at some point during their illness.62 Conversely, in a large retrospective study of 1274 patients who presented with stroke, 12% of patients had a secondary diagnosis of cancer. In that study, 86% of strokes were ischemic and the remaining 14% were hemorrhagic.63 In another retrospective study of patients who had cancer with acute stroke, 30% had lung cancer, 9% primary brain tumors, 9% prostate, and 6% each of breast, hematologic, gynecologic, and gastrointestinal neoplasms.64 In addition to the usual stroke risk factors (eg, hypertension, hypercholesterolemia), there are multiple other direct and indirect mechanisms that lead to an increased risk of stroke in patients who have cancer. These mechanisms can be divided into direct tumor effect, coagulopathies, and consequences of therapy.65 Typical stroke risk factors such as hypertension, hyperlipidemia, and tobacco use do not seem to be significantly different in patients with stroke who have cancer versus patients with stroke who do not have cancer.66 The frequency of intratumoral cranial hemorrhages varies among different cancer types, and more frequent occurrences were reported with melanoma metastases and glial and germ cell primary brain tumors. Intracranial hemorrhage related to tumor must be distinguished from other causes, including hypertension, cerebral aneurysms, and arteriovenous vascular malformations.

Direct Tumor Effects

Tumors can also damage the cerebral vasculature directly. For example, primary brain neoplasms can directly compress or invade surrounding vessels. Cardiac and pulmonary tumors, such as atrial myxomas, can also directly cause stroke by embolizing to the large intracranial vessels. Hematologic malignancies can also directly cause stroke via hyperviscosity associated with polycythemia vera and hyperleukocytosis from acute leukemia, which may impair cerebral perfusion, resulting in ischemia. Hyperleukocytosis can also manifest as altered mental status, seizure, and sudden death. There is a fourfold increase in the incidence of stroke in hyperleukocytosis (>100,000) compared with patients with normal white blood cell counts. Fatal intracranial hemorrhage occurs in more than 5% of patients with acute leukemias, especially acute myelogenous leukemia (AML).67 Cerebrovascular complications are less common with lymphomas than with leukemias. Primary intravascular neoplasms such as intravascular lymphomatosis have a predilection for cerebral vessels and can cause cerebral infarction.
Coagulopathies

More common than cancer directly causing a stroke are the indirect effects of malignancy on the coagulation pathways. In general, solid tumors are more associated with venous thrombosis and hematologic malignancies with bleeding diathesis. Two distinct mechanisms have been proposed: disseminated intravascular coagulation (DIC) and nonbacterial thrombotic endocarditis. In DIC, there is a disruption in balance of thrombus formation and thrombolysis, resulting in microthrombi formation in small vessels, and thrombocytopenia causing hemorrhage in other areas. DIC is more common in hematologic malignancies than in primary solid tumors. DIC is diagnosed in approximately 15% of patients with acute leukemia, and bleeding manifestations prevail rather than thrombosis. Nonbacterial thrombotic endocarditis (NBTE) can occur in association with DIC, which may predispose cardiac valves to edema and degeneration. Subsequently, platelets and thrombin are deposited on the valves. Embolic strokes from NBTE are one of the most common mechanisms for stroke in patients who have cancer. Autopsy studies find that up to 27% of strokes in patients who have cancer may be related to NBTE. This condition seems to be more common in patients with mucin-producing adenocarcinoma of the lung and gastrointestinal tract, pancreatic adenocarcinoma, and lymphoma. However, other studies reported conflicting results, suggesting that only 1% to 3% of patients with stroke who have cancer are a result of NBTE. Such discrepancies with autopsy studies may be attributable to diagnostic difficulties when clinicians try to establish diagnosis of NBTE with certainty.

There have been several other proposed mechanisms to explain a relative prothrombotic state in patients who have cancer that predispose them to cerebral infarction. It is well established that many patients have increased D-dimer levels, protein S and C deficiency, activated protein C resistance, antiphospholipid antibodies, hyperfibrinogenemia, thrombocytosis, and a general state of inflammation. The exact mechanism for a hypercoagulable state in most patients who have cancer is poorly understood. Transcranial Doppler has been used to monitor the risk of embolic strokes in patients who have cancer, and embolic signal was observed in patients with ischemic stroke who have cancer, particularly in those without conventional stroke risk factors. This study also found that increased D-dimer levels were independently correlated with embolic signal, which greatly decreased with anticoagulation.

Treatment Effects

Cancer treatment protocols using techniques such as cranial/neck radiation and chemotherapy can also predispose patients to stroke. Postradiation vasculopathy can damage the intracranial and extracranial vessels and lead to stroke. Typically, this affects the large vessels of the head and neck, leading to stenosis at about 3 to 5 years after radiation therapy. Studies indicate that 12% to 60% of patients with a history of neck radiation develop internal carotid artery stenosis. A recent study of risk factors in carotid stenosis showed that a history of radiation alone was comparable with having a history of hypertension, hyperlipidemia, diabetes, or coronary artery disease. Radiation-associated carotid stenosis was associated with lesions that were much longer, at atypical sites, and had more aggressive plaques. Because of the unusual and long segments of artery involved, this study suggested the use of carotid stenting rather than carotid endarterectomy in the prevention of ischemic infarction. This recommendation was supported in another study comparing patients with stenosis from radiation versus no radiation for durability of carotid...
angioplasty and stenting. This study found that freedom from restenosis did not differ significantly between the 2 groups.\textsuperscript{72} Prior history of brain irradiation increases the risk of ipsilateral stroke and is reported in up to 25\% of patients with stroke who have cancer.\textsuperscript{73} Increased risk of stroke was also reported with chemotherapy protocols with cisplatin.\textsuperscript{74} Other chemotherapeutic agents that have been reported to cause cerebrovascular events include intrathecal methotrexate, L-asparaginase, and intra-arterial chemotherapy regimens.

**Diagnosis and Recommendations**

Diagnosis of stroke is made by clinical examination and imaging of the brain parenchyma and the intracranial and extracranial arteries. In the acute setting with a convincing clinical history and examination, CT head and CT angiogram may be more accessible to establish the diagnosis in a timely manner. MRI of the brain with diffusion-weighted imaging sequences is another option for diagnosing acute stroke, and is helpful in evaluation of suspected brain metastases or leptomeningeal carcinomatosis. In the acute setting, without known brain metastases, a patient who has cancer may be a candidate for intravenous thrombolysis. However, clinical trials of stroke treatment in patients who have cancer are lacking. Recent small case series reported successful treatment of stroke in 3 patients who had cancer with intravenous tissue plasminogen activator.\textsuperscript{75} However, thrombolytic therapy may also precipitate intratumoral bleeding.\textsuperscript{76} Standard anticoagulation may not prevent recurrent strokes in some patients with possible hypercoagulable states.\textsuperscript{77} Standard evaluation of patients with stroke should include echocardiogram (at least transthoracic) to investigate possible intracardiac thrombus, tumor, or vegetation. Although there are several proposed mechanisms of hypercoagulability, there are still no established guidelines for when to perform comprehensive laboratory analysis of hypercoagulable state. Although not established by class I evidence, clinical experience suggests that secondary stroke prevention in a patient with NBTE should use low-molecular-weight heparinoids rather than warfarin or antiplatelet agents.

**Cerebral Venous Sinus Thrombosis**

Cerebral venous sinus thrombosis (CVST) in patients who have cancer can be caused by direct compression from primary brain malignancies or from secondary hypercoagulability. Other risk factors include dehydration and infections. The most common malignancy associated with CVST is acute lymphoblastic leukemia. CVST can progress to both ischemic and hemorrhagic venous infarctions with an atypical anatomic distribution, different than with arterial strokes. Clinical features of headache, altered consciousness, focal neurologic deficit, and seizure are frequent with CVST. Conventional brain imaging alone is of little diagnostic value in CVST, because it usually shows nonspecific lesions, such as hemorrhage, infarct, or edema, and is normal in up to 25\% of cases. Prompt diagnosis should be made by pursuing detailed imaging of the venous vascular system. The 2 most common imaging modalities to evaluate CVST remain CT venogram and magnetic resonance (MR) venogram, whereas conventional angiograms are now infrequently used. The main limitation of these imaging techniques is their inability to differentiate thrombosis and hypoplasia, a frequent diagnostic dilemma for the lateral venous sinuses. MRI sequence with T2 susceptibility-weighted imaging may be of additional diagnostic value in evaluation of CVST, particularly during the acute phase of CVST when the sensitivity of the other sequences is incomplete, and may reveal isolated cortical venous thrombosis.\textsuperscript{78}

Treatment of CVST includes supportive or symptomatic measures such as hydration, appropriate antimicrobials, control of seizures with anticonvulsants, and
control of intracranial pressure with neurosurgical procedures. Antithrombotic treatments include unfractionated and low-molecular-weight heparin, oral anticoagulants, thrombolysis, and endovascular approaches. A randomized double-blind placebo-controlled trial showed safety and effectiveness with the use of heparin in the treatment of CVST, and showed that limited intracerebral hemorrhage is not a definitive contraindication for anticoagulation. A randomized, placebo-controlled trial of subcutaneous low-weight-molecular heparin in adults showed a trend for better outcome in the treated group. Therefore, subcutaneous (low-molecular-weight) and intravenous (unfractionated) heparin are commonly considered as a first-line treatment of CVST, even in the presence of hemorrhagic infarction. If the patient deteriorates despite supportive care and heparin treatment, selective catheter-guided local thrombolysis may be an option, if available. Randomized trials investigating interventional techniques for CVST in patients with or without cancer are needed, and there is still no consensus on available treatment options, although anticoagulation is generally considered as a safe treatment with potential reduction of mortality and morbidity. Despite treatment, mortality from CVST remains at 8%, and patients with underlying malignancy may have worse outcomes.

CNS INFECTIONS

Infections involving the CNS cause significant morbidity and mortality in patients with cancer, and their manifestations may mimic cancer recurrence, treatment-related toxicities, and paraneoplastic encephalitis. In addition, cancer treatment and neurosurgical procedures increase the risk of CNS infections, and careful and timely evaluation and treatment are needed to reduce associated morbidity and mortality.

Epidemiology

It has been estimated that 16% of CNS infections may occur in patients with an underlying CNS malignancy. The risk of opportunistic CNS infection is determined by the extent of immunosuppression and intensity of exposure to infectious agents. There are several participating mechanisms proposed to explain the pathophysiology of infection in patients with cancer, including neutrophil disruption and bone marrow suppression, which are common in patients with lymphoma and leukemia. Iatrogenic factors contributing to blood-brain barrier disruption include central lines and CNS ports or reservoirs, and neurosurgical procedures can also predispose patients who have cancer to CNS infection. Immunosuppression may also occur with lymphocyte and immunoglobulin dysfunction in chronic lymphocytic leukemia, multiple myeloma, or patients with splenectomy. Impaired T cell function is significantly affected by chemotherapy and corticosteroids and increases the risk of infection. Each of these mechanisms impairs patients’ ability to protect themselves from common infections, and puts them at risk for developing opportunistic infections. Overall risk of CNS infections is mostly determined by the extent of immunologic compromise and intensity of (environmental) exposure to specific pathogens. Meningitis, encephalitis, brain abscesses, and catheter-related or shunt-related infections are the most common neurologic infections in patients who have cancer. Neurosurgical procedures are associated with an increased risk of CNS infections, and prior neurosurgical procedures were reported in 78% of patients who have cancer with bacterial or fungal meningitis. Meningitis associated with external ventricular shunts typically present within a month from surgery.

Baldwin et al
CNS infections in patients who have cancer are caused by a wide array of bacterial, viral, and fungal pathogens, and infections with multiple pathogens (simultaneous or sequential) are common.\textsuperscript{85–87}

**Diagnosis**

There are several diagnostic challenges in diagnosing patients who have cancer with CNS infections. Many patients do not display the characteristic signs and symptoms for meningitis, such as fever, nuchal rigidity, or headache because of their diminished immune response. Coexisting conditions such as encephalopathy, metabolic derangements, CNS involvement of cancer, seizures, aseptic meningitis, and treatment side effects may also precipitate new symptoms mimicking a CNS infection. Diagnostic procedures such as lumbar puncture may be dangerous to complete because of thrombocytopenia or coagulopathies. Both typical and atypical infectious agents may not have typical presentations in an immunocompromised patient. Diagnosis of CNS infection is made by clinical history, laboratory studies (including CSF analysis), and imaging. Subacute presentation may be more suggestive of a fungal process, whereas an acute meningoencephalitis would suggest a more probable bacterial or viral cause. A focal neurologic deficit typically involves a bacterial or fungal abscess, whereas diffuse encephalitis is more likely to be viral.\textsuperscript{87}

CSF analysis obtained via lumbar puncture is helpful in identifying the causative organism. The classic CSF abnormalities in bacterial meningitis include increased opening pressure, polymorphonuclear leukocytosis of more than 100 cells/mm\textsuperscript{3}, glucose less than 40 mg/dL or less than 30\% of serum glucose, and protein greater than 45 mg/dL. CSF Gram stain and culture should also be obtained. CSF findings may be deceiving with catheter-associated ventriculitis because up to 22\% of patients may have normal cell counts with positive cultures.\textsuperscript{89} In viral meningitis, opening pressure is normal, and there is lymphocytic pleocytosis, with normal glucose, and normal or slightly increased protein content. There is also a growing number of new diagnostic tests using immunology and molecular diagnostics to rapidly identify specific pathogens that may be difficult to culture. Molecular diagnostic testing using polymerase chain reaction analysis is more widely available for herpes viruses 1, 2, and 6, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, John Cunningham (JC) virus, and enteroviruses. Additional testing for emerging infectious agents is available through research and commercial laboratories. Neuroimaging studies, including CT or MRI brain, may be helpful in identifying ring-enhancing or discrete focal lesions concerning for abscess or metastases, but are usually not sufficient to distinguish CNS infections from their mimics. Definitive diagnosis for solitary brain lesions is provided by histopathologic analysis of specimens obtained by image-guided or open biopsy. Clinicians must maintain a high index of suspicion for CNS infection in any patient with an underlying malignancy who presents with new onset of focal or nonlocalizing neurologic signs or symptoms.

**Management**

Early in the course, before cause has been established, broad-spectrum empiric treatment is started. Empiric therapy for community-acquired bacterial meningitis includes dexamethasone, a third-generation or fourth-generation cephalosporin, and vancomycin.\textsuperscript{90} Ampicillin is added to the empiric regimen for coverage of *Listeria monocytogenes* in an individual with impaired cell-mediated immunity, and metronidazole is added in individuals with the predisposing conditions of otitis, mastoiditis, and sinusitis, and also in neurosurgical patients, especially those with
ventriculostomies. Adjunctive dexamethasone improves the prognosis of pneumococcal meningitis (class III evidence). Amphotericin B and fluycytosine are used in the treatment of infections caused by Cryptococcus neoformans and Aspergillus, and other antifungal treatment options include voriconazole, itraconazole, and ketoconazole. Treatment options for viral infections are largely limited to acyclovir (for herpes simplex virus [HSV] and varicella zoster virus infections) and ganciclovir (cytomegalovirus and human herpesvirus 6). Less commonly, foscarnet and cidofovir are used. It is imperative to use a targeted therapy as soon as the causative organism is identified.

**PARANEOPLASTIC LIMBIC ENCEPHALITIS**

Once considered a rare syndrome, paraneoplastic limbic encephalitis is now recognized as a diverse, clinically and immunobiologically heterogeneous group of disorders with relevance to the differential diagnosis of acute neurologic, psychiatric, autonomic, and epileptic disorders (Table 1). Early description of cases of limbic encephalitis (LE) showed frequent association of increased titers of anti-Hu antibodies in serum and CSF and the presence of small cell lung carcinoma (SCLC). Subsequently, a different antibody was described in patients with testicular cancer. In a series of 13 patients with testicular cancer and LE, 10 of them had increased titers of antibodies targeting another onconeural antigen named Ma-2. Less commonly, LE has been described in patients with other types of cancer and with other paraneoplastic antibodies including Ta, Tr, CV-2/CRMP-5, and Ri antibodies. In addition to paraneoplastic syndromes associated with solid tumors, LE has also been described in patients with Hodgkin and non-Hodgkin lymphoma. More recently, additional variants of paraneoplastic LE have been described and characterized by the presence of increased autoantibody titers in serum and CSF of autoantibodies directed against synaptic proteins, including the N-methyl-D-aspartate receptor (NMDAR), 2-amino-3-(5-methyl-3-oxazol-4-yl) propanoic acid receptor (AMPAR), γ-aminobutyric acid-B receptor (GABAbR), leucine-rich glioma-inactivated (LGi-1) protein, contactin-associated protein 2 (CASPR-2), and voltage-gated potassium channel (VGKC); these define LE variants that are distinct from anti-Hu–associated LE.

A spectrum of autoantibody-associated variants of LE continues to evolve and, in many cases, eradication of the underlying neoplasm may produce strong recovery (for the paraneoplastic forms). There is also increasing evidence that immunotherapy may be effective in specific clinical settings.

**Epidemiology**

There are no reliable epidemiologic estimates of LE frequency, but it is probably underdiagnosed. In the PNS Euronetwork Database, LE has been reported in 10% of patients with paraneoplastic neurologic syndromes (PNS). If this is extrapolated to the estimate of prevalence of paraneoplastic disorders at 3%, it may be that 0.3% of patients who have cancer may develop paraneoplastic LE. However, reports in the literature are not as numerous. A recent review by Dalmau and colleagues suggests that recently described anti-NMDAR-LE (133 cases reported per year) may be more common than anti-Hu (15 cases/y) and anti–voltage-gated potassium channel antibody encephalitides (83 cases/y).

Most patients with NMDAR-LE are women (80%), usually younger than 40 years, and tumors are rare in patients younger than 7 years or older than 40 years. Only 5% of affected men older than 18 years have an underlying neoplasm. Typically, AMPAR-LE has been described in middle-aged women.
### Table 1
Paraneoplastic limbic encephalitides

<table>
<thead>
<tr>
<th>Antigen</th>
<th>% Women; Median Age (y)</th>
<th>Most Common Tumor Types</th>
<th>Typical Symptoms</th>
<th>Other Paraneoplastic and Autoimmune Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu/Anna-1</td>
<td>25; 63</td>
<td>SCLC (NSCLC, neuroendocrine tumor, ovarian dysgerminoma)</td>
<td>Memory loss, confusion, seizures</td>
<td>Sensory neuropathy, cerebellar ataxia</td>
</tr>
<tr>
<td>Ma-2</td>
<td>32; 64</td>
<td>Testicular Ca (NSCLC, lymphoma</td>
<td>Memory loss, confusion, seizures</td>
<td>Brainstem and diencephalic encephalopathy</td>
</tr>
<tr>
<td>Tr/PCA-Tr</td>
<td>Rare</td>
<td>Hodgkin lymphoma</td>
<td>—</td>
<td>Cerebellar degeneration</td>
</tr>
<tr>
<td>Ri</td>
<td>Rare</td>
<td>Breast Ca</td>
<td>—</td>
<td>Brainstem encephalitis, opsoclonus myoclonus,</td>
</tr>
<tr>
<td>CV-2/CRMP-5</td>
<td>24; mean 63</td>
<td>SCLC (thymoma, breast Ca)</td>
<td>Memory loss, confusion, seizures</td>
<td>Neuropathy, cerebellar ataxia, chorea, dysautonomia</td>
</tr>
<tr>
<td>NMDAR</td>
<td>80–90; 23</td>
<td>Ovarian teratoma (lymphoma, neuroblastoma, breast Ca)</td>
<td>Psychiatric symptoms, abnormal movements</td>
<td>—</td>
</tr>
<tr>
<td>AMPAR</td>
<td>90; 60</td>
<td>Thymoma (breast Ca, SCLC, NSCLC)</td>
<td>Psychiatric symptoms, memory loss, confusion, seizures</td>
<td>Stiff-person syndrome</td>
</tr>
<tr>
<td>GABAbR</td>
<td>47; 62</td>
<td>SCLC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Seizures, memory loss, confusion</td>
<td>—</td>
</tr>
<tr>
<td>CASPR-2</td>
<td>Rare</td>
<td>(Thymoma)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>Neuromyotonia, myasthenia</td>
</tr>
<tr>
<td>LGi-1</td>
<td>35; 60</td>
<td>Thyroid Ca, renal cell Ca, NSCLC, ovarian teratoma&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Memory loss, myoclonus, seizures</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ca, carcinoma; NSCLC, non–small cell lung carcinoma; SCLC, small cell lung carcinoma.

<sup>a</sup> Tumor reported in 40% of cases.

<sup>b</sup> Most reported cases of LE were nonparaneoplastic.

<sup>c</sup> Tumors present in 11% to 20% of cases.

*Data from Refs.* 93,97,100,104,109,110,116
Clinical Presentation

The first clinical and immunobiologic variant of LE associated with anti-Hu antibodies was described in the early 1990s. The clinical presentation of LE may be mistaken for HSV encephalitis, with symptoms of memory disturbance, agitation, and seizures. Variants of LE have been defined by the presence of specific autoantibodies, and some patients may simultaneously have increased titers of several paraneoplastic antibodies. LE associated with anti-Hu antibodies may present as an isolated neurologic syndrome or in the context of a more widespread neurologic syndrome with involvement of cerebellum, brainstem, and spinal cord (paraneoplastic encephalomyelitis). Paraneoplastic encephalomyelitis is less common in the absence of anti-Hu antibodies. Depression, anxiety, and hallucinations have been reported in patients with anti-Hu-associated LE, but these symptoms are not as prominent as with LE associated with anti-NMDAR antibodies.

Patients with the anti-NMDAR variant of LE commonly present with rapidly developing psychiatric symptoms including anxiety, insomnia, fear, grandiose delusions, hyperreligiosity, mania, and paranoia. Other symptoms may include alterations of consciousness (even coma), abnormal movements (especially dyskinesias), seizures, and autonomic instability. Central hypoventilation may occur when consciousness is still preserved. Generalized or complex partial seizures typically develop at an early stage.

The initial differential diagnosis in early stages mimics primary psychiatric disorders. In later stages, possible viral encephalitis, neuroleptic malignant syndrome, and the other forms of LE are the important differential diagnostic considerations.

Anti-AMPAR-LE also presents with acute limbic dysfunction, and is frequently associated with prominent psychiatric symptoms. Most patients described so far have been middle-aged women, but the number of described cases with this variant of LE is small and the spectrum of clinical presentations continues to evolve. About 70% of these patients have an underlying tumor of the lung, breast, or thymus. More frequently than with anti-NMDA-LE, other autoimmune disorders are also present, including diabetes, stiff-person syndrome, and hypothyroidism, as well as Raynaud syndrome.

Anti-GABAb LE involves both sexes equally, with the median age being 62 years. Other autoantibodies may be present concomitantly, including anti-GAD antibodies. In about 40% to 50% of these patients, an SCLC or neuroendocrine cancer of the lung is found.

A lower occurrence of tumors has also been reported for 2 other LE syndromes previously ascribed to anti-VGKC that are now shown to be associated with antibodies targeting other specific synaptic function modulating proteins: anti-LGi1 and anti-CASPR-2. In anti-LGi-1 LE, memory disorder, confusion, and seizures dominate the clinical presentation. Short tonic seizures and rapid eye movement sleep behavior disorders, as well as hyponatremia, have been reported. Only 11% to 20% of patients have an underlying tumor, usually thymoma or SCLC. Mutations of LGi-1 have been associated with autosomal dominant lateral temporal lobe epilepsy. In anti-CASPR-2 LE, encephalitis and peripheral nerve hyperexcitability are usually present. Some patients concurrently suffer myasthenia gravis with either anti-acetylcholine receptor or MuSK antibodies, and increased titers of anti-CASPR-2 antibodies have been described in patients with thymoma. Some patients have presented with predominantly peripheral neuromuscular symptoms prompting the differential diagnosis of variant forms of motor neuron disease.
Diagnosis and Management

Compared with other paraneoplastic syndromes, LE may be one of the more treatable paraneoplastic disorders. Removal of the underlying neoplasm is usually more effective than immunosuppression. LE associated with anti-Ma2 antibodies seems to have a better prognosis with orchiectomy and aggressive treatment of residual disease, and patients with NMDAR-LE may improve with removal of teratoma.

Diagnosis of specific variants of LE is based on finding increased titers of specific autoantibodies in the serum and CSF. Additional testing should include investigations of possible mimics of paraneoplastic LE (especially CNS infections), and neuroimaging studies and EEG should be considered as well.

In NMDAR-LE, neuroimaging findings are usually nonspecific, and MRI may be normal in up to 50% of cases. Functional neuroimaging with MR spectroscopy, PET, and single-photon emission computed tomography may show fluctuating multifocal abnormalities involving cortical and subcortical structures that may change during the course of the disease. EEGs are usually abnormal, and EEG may reveal underlying NCSE. However, most often EEG shows only nonspecific slowing.

As with other paraneoplastic disorders, CSF analysis in paraneoplastic LE is usually abnormal with mild lymphocytic pleocytosis, normal or mildly increased protein, and CSF-specific oligoclonal bands being found in approximately 60% of patients. Most patients with NMDAR-LE have evidence of intrathecal synthesis of anti-NMDAR antibodies and, in patients who had a protracted course or who had been treated with plasma exchange or intravenous immunoglobulin (IVIG), anti-NMDAR antibody was detected only in CSF. Persistence of antibody titers in CSF seems to correlate with ongoing symptomatic disease activity, but persistent serum antibody without evidence of intrathecal synthesis may be found in patients who have been successfully treated. The most useful screening studies for ovarian teratoma include MRI, CT scan, and pelvic and abdominal ultrasound. Serologic tumor markers seem unhelpful.

Management of paraneoplastic LE is based on the combination of tumor removal, immunotherapy, and symptomatic treatment (eg, treatment of seizures). Results of immunotherapy with corticosteroids, chemotherapy, plasma exchange, and biologic agents are frequently unsatisfying. However, LE associated with anti-NMDAR antibodies seems to be more responsive and treatment should include both immunotherapy and the search for an underlying tumor. Treatment options include corticosteroids, IVIG, or plasma exchange as the first phase of treatment, and this may be sufficient in some patients when an underlying teratoma is identified and removed. In patients without a tumor, or with long-delayed diagnosis and severely symptomatic disease, second-line therapy with rituximab or cyclophosphamide is usually used. Approximately 75% of patients recover with minimal sequelae, and the other 25% remain neurologically incapacitated or die. The experience of Dalmau and colleagues in 105 consecutive cases suggests that patients without a diagnosed tumor more frequently require second-line therapy, and second-line therapy may result in substantial improvement in 65% of treated patients.

The association of the LE syndromes with seizures has led Dalmau to propose preliminary clinical criteria for the recognition of antibody associated encephalitides in patients with refractory seizure disorders. In the setting of other psychiatric, autonomic, peripheral nervous system, sleep, or movement disorders, autoantibody-associated encephalitic syndromes should be considered in the differential diagnosis of refractory seizures. Identifying the diagnostic antibodies in serum and CSF would lead to specific immunotherapies and the search for the appropriate associated...
neoplasms. At present, the antibody testing is performed by a limited number of reliable laboratories, and, for some of these syndromes, the antibody testing is not yet commercially available. In many patients, the decision to institute immunotherapy is based on the clinical, imaging, and CSF abnormalities before definitive diagnosis of the identification of specific autoantibody-associated syndrome.

SUMMARY

Neurologic emergencies are common in patients who have cancer and are associated with significant morbidity and mortality. Timely recognition and treatment may improve symptoms and outcome in some patients. A previously established diagnosis of cancer simplifies diagnostic algorithms and narrows differential diagnosis, but neurologic emergency may be the first clinical manifestation of undiagnosed neoplastic disease with potentially catastrophic outcome. After diagnosis is made, an interdisciplinary team approach including neurology, hematology/oncology, neurosurgery, and radiation oncology team members allows more flexible and effective treatment options.

REFERENCES


