Chapter 1
Neurologic Emergencies

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Chapter Overview

Neurologic complications of cancer and its therapy are varied and common, occurring in 30–50 % of cancer patients presenting to emergency departments or for neurologic consultations at teaching hospitals. However, a few true neurologic emergencies require rapid diagnosis and treatment to preserve neurologic function and, in some circumstances, save lives. A collaborative effort among the emergency room physician, the patient's oncologist, and consultants from neurology, neurosurgery, and radiation oncology services affords the best outcome. Even patients with advanced cancer and limited life expectancies can benefit from prompt therapy when it is appropriate for their circumstances.

Introduction

Malignant spinal cord compression, status epilepticus (SE), increased intracranial pressure (ICP), and intracerebral hemorrhage are neurologic conditions in cancer patients requiring urgent attention. This chapter details the clinical features of, possible etiologies of, diagnostic tests for, and treatment options for these complications.

Malignant Spinal Cord Compression

Malignant spinal cord compression is a grave oncologic emergency occurring in approximately 5 % of patients with terminal cancer during the last 2 years of life. It requires prompt intervention to prevent permanent paraplegia and reduced quality of life. Developments in oncologic and medical therapies have extended the life expectancy of patients with cancer, so this complication may be seen more frequently than in the past.

Metastatic spinal lesions are associated with primary breast, lung, and prostate malignancies in 60 % of cases. Renal cancer, non-Hodgkin lymphoma, and multiple myeloma each account for 5–10 % of cases. Colorectal cancer, primary cancer of unknown origin, and sarcoma account for most of the remaining cases. Men and women are affected equally. In 20 % of cancer patients, spinal cord compression is the initial manifestation of malignancy, with one third of these patients having lung cancer. The median survival duration after diagnosis of malignant spinal cord compression is only 3–6 months, and it depends on the patient's primary tumor type and ambulatory status at the time of diagnosis.

Etiology and Pathophysiologic Mechanisms

Spinal cord compression more often results from metastasis to vertebral bodies and adjacent structures than from direct metastasis to the spinal cord. These bony metastases subsequently erode into and encroach upon the spinal cord. The exact mechanism of this metastasis is not well understood. Most metastases occur in the thoracic spine owing to the bone volume or mass in this region. The clinical features of thoracic metastases are less well-defined than those of cervical or lumbosacral metastases. Also, thoracic metastases are far more dangerous than cervical or lumbosacral metastases because the blood supply in the thoracic region is vulnerable, as the width of the spinal canal relative to the width of the spinal cord is smaller than that in the other two regions. Additionally, the thoracic spine has small nerve roots that form the intercostal nerves, injury to which causes relatively innocuous symptoms. Band-like paresthesia, sometimes described as a feeling of being "squeezed, like a belt being pulled tight" or a "band of numbness about my waist," is a particularly ominous sign of epidural spinal-cord compression at the thoracic level (Fig. 1.1).

As a tumor invades the vertebral bodies, it induces activity of inflammatory mediators within the bone and soft tissue, which causes edema, venous stasis, and finally, ischemia at the level of compression. Once the tumor mass has expanded enough to cause venous congestion, an extensive inflammatory cascade ensues, causing edema of the spinal cord. If treated expediently using corticosteroids, this

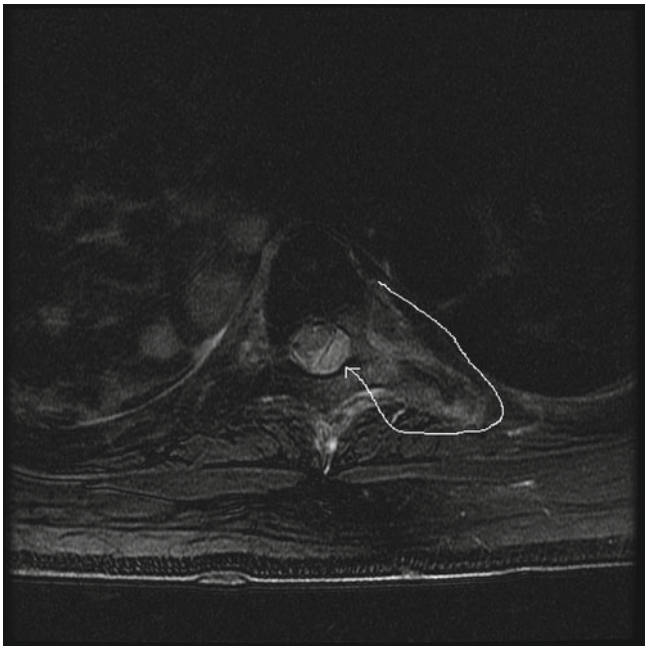

Fig. 1.1 MRI scan of the thoracic spine. At the T6 level, the epidural tumor (*outlined*) is causing impending compression of the spinal cord (*arrow*)

can be reversed. Corticosteroids are used to treat both the edema and the inflammation and, when used acutely, may ameliorate these processes. If they are left untreated, ischemia and demyelination are likely.

Cortical bone destruction in vertebral bodies does not occur until late in the disease process. The level of bone destruction must reach 30–70 % before it can be seen on plain X-rays. Bone destruction may cause a compression fracture of a vertebral body and retropulsion of bone fragments into the spinal canal, leading to mechanical compression of the spinal cord.

Clinical Manifestations and Findings

The presenting symptom of malignant spinal cord compression in about 90 % of cases is back pain. Although back pain is a common acute problem in the general population, in patients with a history of cancer, it must elicit a high degree of suspicion to ensure an early diagnosis. Pain associated with malignant spinal cord compression is often exacerbated by an axial load or associated with radicular symptoms. Pain that worsens while the patient is recumbent is unusual in those with degenerative disc disease and should raise the concern that the patient has epidural metastasis. Most often, the pain occurs at the area of vertebral compression. It is often described as gnawing or aching pain and is worse during the Valsalva maneuver. Palpation and percussion down the spine frequently help localize metastatic deposits. The pain is either unilateral or bilateral depending on the level of disease. Thoracic involvement frequently results in bilateral symptoms, whereas unilateral pain is seen with cervical or lumbosacral involvement. Complaints of thoracic pain should especially arouse suspicion, as disk herniation and spinal stenosis occur infrequently at this location. Pain while the patient is in the recumbent position worsens owing to lengthening of the spine and distension of the epidural venous plexus. Pain during motion usually is caused by vertebral body collapse and can be associated with spinal instability. Pain may precede neurologic symptoms by several weeks, so early intervention prior to the development of incontinence or inability to walk is one of the most important variables in a successful outcome aside from elimination of the primary tumor.

The second most common symptom of malignant spinal cord compression is weakness, which is present in 35–80 % of patients. Weakness is often associated with corticospinal tract signs such as hyperactive deep tendon reflexes, spasticity, and extensor plantar responses. Weakness is an ominous finding that, if not investigated, may lead to complete loss of spinal function below the level of the lesion.

Leg ataxia may be present before weakness arises and may occur without pain. Using a standardized strength scale (Table 1.1) during the initial evaluation greatly aids in monitoring the clinical course of the patient's disease. Each muscle group should be tested separately, and the results for both sides of the body should be compared. Rectal sphincter tone should be checked in all patients suspected of having malignant spinal cord compression. Patients who are immunosuppressed or

Table 1.1 Standardized muscle strength scale

Rating	Strength
0/0	No contraction
1/5	Muscle flicker, but no movement
2/5	Movement possible with gravity eliminated
3/5	Movement possible against gravity but not against resistance by the examiner
4/5	Movement possible against some resistance by the examiner
5/5	Normal strength

at risk for bleeding can be safely tested by placing a gloved finger adjacent to but not in the anal canal while the patient attempts to tighten the anal sphincter. A simple observation of the umbilicus can detect a spinal cord injury between the T10 and T12 levels. Known as the Beevor sign, this is done by having the recumbent patient flex his or her head against resistance. The umbilicus moves cephalad if the involvement is below the T10 level.

The Babinski sign is a sensitive, specific sign of corticospinal tract dysfunction, but interpretation of this valuable sign requires experience. Although most clinicians observe the great toe's movement during noxious stimulation along the lateral aspect of the bottom of the foot, the movement of the four smaller toes is a more reliable indicator. As Babinski observed, "The toes, instead of the flexing, develop an extension movement at the metatarsal joint."

Diagnosis

Diagnosis of malignant spinal cord compression begins with obtaining a thorough medical history and performing an appropriately focused physical examination coupled with a full central nervous system examination. New onset of back pain or neurologic symptoms, such as symmetric weakness and paresthesia, in a patient with known cancer should prompt further work-up for malignant spinal cord compression.

Magnetic resonance imaging (MRI) has a sensitivity rate of 93 %, specificity rate of 97 %, and overall accuracy rate of 95 % in revealing spinal cord compression. In the absence of contraindications or intolerance, MRI is usually sufficient in investigation of malignant spinal cord compression. Because one third of patients have multiple sites of compression, many researchers recommend imaging the entire spinal cord or, at minimum, the thoracic and lumbar spine. The study takes about 45 min and requires the patient to fit into an MRI scanner, lie flat, and be absolutely still.

Computed tomography (CT) myelography is a helpful technique for patients who cannot undergo MRI (e.g., those with pacemakers or extreme claustrophobia). It facilitates assessment of osseous integrity as well as the thecal sac contents and

has the added benefit of allowing for cerebrospinal fluid (CSF) sampling at the same time. Disadvantages of CT myelography include its overall greater cost than that of other available imaging tests, its invasive nature and inherent risk of contrast reaction, and postprocedure spinal tap-related headaches.

Plain X-rays, although expedient and inexpensive, are not useful in the initial evaluation of suspected malignant spinal cord compression. They are not positive for compression until nearly 70 % of the bone is destroyed, which usually occurs at a late stage in the evolution of symptoms.

Bone scanning and positron emission tomography using [^{18}F]fluoro-2-deoxy-2-d-glucose are not useful in detecting cord compression, although both do demonstrate bony metastases.

Treatment

Because malignant spinal cord compression is associated with advanced-stage cancer, all treatments of it are palliative in nature and consist of pharmacotherapy, surgery, radiotherapy (RT), or a combination of them. The goals of therapy for malignant spinal cord compression should include (1) preservation of function and mobility, (2) pain relief, (3) local tumor control, and (4) spine stability.

Corticosteroid-based therapy should be administered in cases with a suspicion of cord compression and in which myelopathy is observed. Pain, which is difficult to control in the absence of neurologic symptoms, also may be an indication for steroid use. Steroids interrupt the inflammatory cascade, leading to a reduction in vasogenic edema. Pain and neurologic symptoms often improve afterward, which can be a prognostic indicator as to how well the patient's disease may respond to therapy.

Studies of acute spinal cord injury have suggested marked neurologic improvement with the use of steroids within 8 h after injury. In a randomized controlled trial, researchers compared high-dose (100-mg loading dose, then 96 mg daily) and moderate-dose (10-mg loading dose, then 16 mg daily) dexamethasone. They found no differences in efficacy; thus, most physicians give the lower dose. Tapering of steroids is begun as soon as feasible to avoid steroid-associated complications such as hyperglycemia, insomnia, and gastrointestinal irritability. The last of these side effects is common and should be treated with antacids. A lesser known but more serious complication is lower intestinal perforation, which can be minimized by preventing the patient from becoming constipated and using the lowest possible dose of steroids. In patients presenting with undiagnosed spinal masses and no history of cancer, especially young patients, steroid use should be avoided until diagnosis. Steroids have an oncolytic effect on some tumors, particularly lymphomas and thymomas, which may delay diagnosis.

Pain may be relieved by the administration of steroids, but often, additional analgesics are required. This can be a major focus of treatment. Using the World Health

Organization's analgesic ladder, a physician can choose the most appropriate medication on the basis of the severity of the pain.

In the absence of bony instability, RT has historically been the treatment of choice for malignant spinal cord compression, preferably started within 24 h of diagnosis. This requires a prompt consultation with a radiation oncologist. Radiation is usually fractionated over a few days to weeks to minimize its harmful effects on normal tissue. Pain is often improved with RT, and further tumor growth and neurologic damage are prevented. Neurologic outcome, with the goal of ambulation following RT, depends on the patient's ambulatory status at the time of diagnosis, timing of treatment (i.e., started within 12 h after presentation), presence of a single metastatic tumor, and severity of cord compression. Patients with radiosensitive tumors, such as lymphomas, myelomas, and breast and prostate cancers, are more likely than those with less radiosensitive tumors to regain neurologic function after RT. About 90 % of ambulatory patients retain ambulation after RT alone, but less than 30 % of patients who have lost the ability to walk by the time RT is initiated regain ambulation.

Anterior vertebral body resection with stabilization may offer the best chance for a good outcome, but the procedure is a major undertaking and requires (1) a good performance status, (2) uninvolved adjacent vertebral bodies for stabilization of the spinal canal, and (3) a skilled neurosurgical team.

Emerging treatment options such as stereotactic radiosurgery and vertebroplasty may provide some symptom relief for patients who are not surgical candidates.

Summary

Malignant spinal cord compression is a neurologic emergency frequently seen in cancer patients. Even patients with advanced disease and limited life expectancy can benefit from prompt therapy when it is appropriate for their circumstances. Prompt recognition and treatment of malignant spinal cord compression by a multidisciplinary team offer the best outcomes for these patients.

Seizures in Cancer Patients

Patients with cancer have a higher incidence of seizures than that in the general population (Fidler et al. 2002). Prolonged convulsive seizures in cancer patients can lead to brain injury, rhabdomyolysis, renal failure, and death. The discussion below focuses on definitions, evaluation, etiologies, and management of prolonged seizures in adult and pediatric patients with cancer presenting to the emergency center (EC).

Definitions

Early reports on SE defined it as "whenever a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur." Many authors have defined this length of time as 30 min because experimental studies demonstrated that irreversible neuronal damage occurs after this period (Sperduto et al. 2008). However, most physicians would agree that treatment of SE should begin before 30 min elapse. Lowenstein and Alldredge (1998) proposed a revised definition of SE as "either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness." This is the definition that is generally accepted today (DeAngelis and Posner 2009). This definition aims for rapid initiation of antiepileptic administration because controlling convulsive SE earlier rather than later is beneficial. Time is of the essence.

Also, a consensus on the definition of refractory SE is lacking. One suggested definition is failure of 2 or 3 anticonvulsants combined with a minimal duration of the condition of 1 or 2 h or regardless of the time elapsed since onset (Sperduto et al. 2008). Another definition is seizures lasting more than 2 h or recurring at a rate of 2 or more episodes per hour without recovery to baseline between seizures despite treatment with conventional antiepileptics (Groves 2010).

The definition of nonconvulsive SE (NCSE) is based on changes in behavior and/or mental processes from baseline that are associated with continuous epileptiform discharges on electroencephalograms (EEGs) (Groves 2010). Unfortunately, agreement regarding the duration that these alterations must be present is lacking, but most physicians would consider any abnormal epileptiform discharges on an EEG to warrant treatment.

Evaluation of a Cancer Patient with Seizures

When evaluating cancer patients with seizures, understanding the different etiologies of seizures is important. Most seizures in cancer patients are attributed to brain metastasis, but they can also be secondary to other abnormalities, such as intracranial hemorrhage and radiation necrosis. Cancers that commonly metastasize to the brain include breast and lung cancers and melanoma. Patients with primary brain tumors are also at risk for seizures. Other causes of seizures include metabolic abnormalities, infection, hypoxia, and medications that lower the seizure threshold.

Reversible posterior leukoencephalopathy syndrome can occur in cancer patients for a variety of reasons. It is associated with severe hypertension, altered mental status, and posterior cerebral T2 signals on MRI scans. Patients may present with headache, confusion, seizures, and visual impairment. Lowering the patient's blood pressure and discontinuing use of the offending agent often will prevent seizure reoccurrence. The agents most commonly associated with this syndrome include

cyclosporine, tacrolimus, sirolimus, rituximab, cytarabine, etoposide, cisplatin, oxaliplatin, gemcitabine, methotrexate, intrathecal chemotherapeutics, interferon-α, antiretroviral therapeutics, and high-dose methylprednisolone (Fidler et al. 2002).

Diagnostic Testing

Work-up for seizures should begin with a complete neurologic examination and history from a witness or family member of the patient. Laboratory values, including electrolyte, glucose, calcium, magnesium, phosphorous, and creatine kinase levels; complete blood count; and hepatic and renal function, should be obtained immediately. If indicated, arterial blood gas and antiepileptic medication levels may be measured, and echocardiograms, EEGs, and drug screens may be performed.

CT and MRI are indicated for patients with cancer who have seizures. MRI is preferred; however, CT is often performed because of its ability to quickly rule out intracranial hemorrhage. If possible, a contrast agent should be administered intravenously to help evaluate the patient for metastasis and abscesses. Lumbar punctures are indicated when an infection is suspected in the presence of fever or an elevated white blood cell count, which may be difficult to assess in cancer patients.

Management

Initial management of seizures should begin with assessing the patient's airway, breathing, and circulation. Intubation may be required if the patient has a compromised airway or severe hypoxemia. If the patient is hypoglycemic, he or she should receive 50 mL of dextrose 50 % in water. SE should be treated immediately with intravenous (IV) benzodiazepines. Studies have demonstrated lorazepam to be superior to diazepam, and pharmacokinetic studies have demonstrated that the anticonvulsant effect of lorazepam lasts much longer than that of diazepam (Groves 2010).

In addition, administration of a long-acting anticonvulsant should be started simultaneously. Phenytoin (PHT) or valproic acid is usually indicated; these two agents have the most evidence supporting their use. Unfortunately, these older generation medications may interact with chemotherapeutics and have unwanted cardiovascular side effects. This should not preclude their use given the patient's acuity and the need for controlling this unstable situation. Other agents, such as levetiracetam (LEV) and lacosamide, are frequently used, but data supporting their efficacy in patients with SE is lacking. In a recent retrospective study of 23 patients with primary or metastatic brain tumors who had SE, all of the patients were given IV PHT and LEV and oral pregabalin. SE was resolved in 70 % of the patients, with only one of the responders needing intubation. Although this study had many limitations, it provides insight into a regimen that may be safe and effective for seizures in patients with brain tumors.

LEV

Patients with primary brain tumors are unique in that they have expression of multidrug resistance proteins that may promote efflux of antiepileptic drugs from the brain. Interestingly, LEV does not appear to be a substrate for these efflux pumps (Fidler et al. 2002). In patients with brain tumors, both LEV and gabapentin are beneficial as add-on treatments of recurrent seizures and are well tolerated by most patients.

Small case series have demonstrated LEV to be effective against SE. However, only one retrospective study has compared LEV with other agents for this purpose. That study, which compared second-line treatment with PHT (70 episodes), valproic acid (59 episodes), and LEV (58 episodes) after failure of treatment with benzodiazepines, demonstrated that valproic acid was unable to control SE in 25 % of patients, PHT was unable to do so in 41 % of patients, and LEV was unable to do so in 48 % of patients. Of note, the researchers in this study did not report the incidence of cancer in the patient population.

Lacosamide

Several case reports and case series documented that administration of lacosamide led to termination of seizures after several other therapies failed. However, many reports did not include the number of patients who did not have responses to lacosamide. The dosing in these trials varied widely from 100- to 400-mg IV boluses followed by 50–200 mg twice daily. Until more data are available, lacosamide should be reserved for patients who experience failure of more traditional therapies.

Alternative Routes of Administration

The IV route is preferred for the management of SE. If IV access cannot be obtained, intramuscular (IM) midazolam should be considered. Diazepam is poorly absorbed when administered intramuscularly, so its use should be avoided. In a recent study looking at control of SE in a prehospital setting, the researchers compared IM midazolam with IV lorazepam in children and adults. Patients who weighed more than 40 kg received 10 mg of IM midazolam or 4 mg of IV lorazepam, whereas those who weighed 13–40 kg received 5 mg of IM midazolam or 2 mg of IV lorazepam. The results demonstrated that seizures were absent without rescue therapy in 73 % of the midazolam group and 63 % of the lorazepam group. Therefore, IM midazolam is at least as safe and effective as IV lorazepam. In addition to benzodiazepines, fosphenytoin may be administered intramuscularly.

For patients with contraindications to IM administration (e.g., thrombocytopenia), meta-analyses have demonstrated that buccal midazolam is superior to rectal diazepam for treatment of SE in children and young adults. Buccal midazolam is

administered by squirting the IV formulation (1 mg/mL) onto the buccal mucosa in doses of 0.5 mg/kg or a 10-mg flat dose. If a patient is unable to tolerate buccal administration, intranasal administration can be considered. Midazolam can be administered intranasally (0.1–0.4 mg/kg) using a mucosal atomization device.

NCSE

For patients in a prolonged coma state following a seizure, EEGs should be performed to assess them for NCSE. Other clinical manifestations of seizures include blank staring; periorbital, facial, or limb myoclonus; and eye-movement abnormalities such as nystagmus and eye deviation. Patients may have rambling speech or be mute. A waxing and waning state alternating between agitation and obtundation can occur. Inappropriate laughing, crying, or even singing may occur. In a study of patients with cancer and altered mental status, 6 % of the patients had NCSE with no previous evidence of brain metastasis. Authors have also reported NCSE in patients with primary brain tumors. In non-cancer patients, the mortality rate for NCSE has been reported to be 18 %, but the rates in cancer patients are unknown. The gold standard for treating and confirming NCSE is clinical and EEG improvement following benzodiazepine administration. Treatment with 1–4 mg of IV lorazepam is given in incremental steps depending on the overall patient situation. Like in patients with SE, follow-up with administration of a long-acting IV antiepileptic agent (LEV, lacosamide, PHT, or valproic acid) is needed. Figure 1.2 shows an EEG of a patient with NCSE treated with lorazepam.

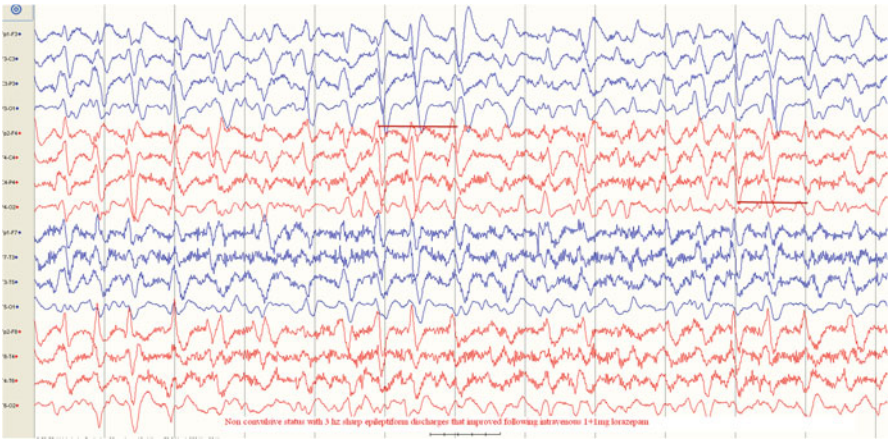

Fig. 1.2 EEG of a patient with NCSE treated with lorazepam

Refractory SE

Agents used for treatment of refractory SE include midazolam, propofol, high-dose thiopental, phenobarbital, pentobarbital, topiramate, tiagabine, ketamine, isoflurane, and lidocaine. Propofol is used most often because it is more effective and safer than the other agents.

Conclusion

SE is an emergency medical condition in patients with cancer. New therapies for it have emerged that are less toxic than previous therapies and have few or no drug interactions. Although data on these therapies are lacking, they have been effective in small case series. Prompt treatment and cessation of seizure activity in cancer patients are imperative to prevent long-term complications of seizures.

Space-Occupying Lesions

Brain Metastasis

Systemic cancer-related brain metastases are up to 10 times more common than primary malignant brain tumors. Metastatic lesions can affect the skull or several intracranial sites. Even though skull metastases are more common, intracranial metastases are more likely to be symptomatic in the involved structures (cerebral hemisphere, brain stem, pituitary gland, choroid, and meninges). Skull metastases may invade the epidural space and compress the brain from outside or involve the cranial nerves as they exit the skull. Intracranial metastasis can be the initial presentation in a small number of patients with no known cancer. Brain metastasis can also be asymptomatic (e.g., 11 % of patients with newly diagnosed lung cancer).

The estimated incidence of brain metastasis is 150,000–200,000 cases per year. The frequency of this metastasis is increasing owing to increased survival durations resulting from effective systemic treatment, improved imaging modalities, and the aging population. Common tumors of origin for brain metastases are lung cancer, breast cancer, and melanoma; others include renal cell carcinoma, colon cancer, and gynecologic malignancies. About 10 % of patients with metastatic brain lesions present with intraparenchymal hemorrhage, and the most common primary cancers associated with it are melanoma, renal cell carcinoma, thyroid cancer, and choriocarcinoma. Brain metastases from unknown primary tumors are well recognized, and the primary site may not be discovered, even at autopsy.

Clinical signs and symptoms of brain metastases result from destruction or displacement of normal brain tissue by growing lesions and associated edema.

Increased ICP and vascular injury may also ensue. Urgent evaluation in the EC is warranted for patients presenting with symptoms of new brain metastases or decompensation owing to known brain metastases. Acute management issues in the EC are related to control of medical problems resulting from these metastases (cerebral edema, elevated ICP, seizure, headache, nausea/vomiting, and control of coagulopathy). Requesting timely, appropriate consults (e.g., neurology, neurosurgery, radiation oncology) is warranted for patients with brain metastases.

Diagnostic Work-Up

Neuroimaging studies for brain metastases include brain CT and MRI. CT without contrast is useful for quick assessment of patients whose condition rapidly deteriorates. CT can identify hemorrhages, large brain lesions, and herniation. In less urgent situations or when other diagnostic modalities are being considered (for ischemic stroke, paraneoplastic conditions, or an infectious process), MRI with and without contrast should be performed. Use of CT or MRI without contrast may result in misidentification of tumors as strokes. Contrast enhancement is also important for detection and grading of tumors. For patients with persistent alteration of consciousness despite initial therapy or incomplete mental status improvement following a clinical seizure, EEGs are required to rule out subclinical electrographic seizure activity. Furthermore, electrolyte and glucose measurement, complete blood counts, coagulation profiling, and liver and renal function tests should be performed.

Clinical Presentation

Most patients present with brain metastasis after establishment of a diagnosis of primary cancer, often within 2 years. Five percent to ten percent of patients present with both systemic and intracranial disease at the time of initial diagnosis. Brain metastases may develop with overt symptoms or remain clinically silent.

Any patient with a history of cancer in whom new neurologic symptoms develop warrants careful examination. Common clinical presentations of brain metastases include headache, seizures, and focal neurologic deficits (focal weakness, focal sensory complaints, and cranial neuropathy). Signs and symptoms are generally insidious over a period of weeks to months. Occasionally, neurologic deficits have an acute onset secondary to vascular compromise. This may result from general hypercoagulability, disturbance of arterial flow, tumor embolization, or hemorrhage into the lesion. Tumor-related headaches are nonspecific, often resembling other types of headache and not necessarily accompanied by papilledema. The rare Foster Kennedy syndrome is a meningioma or plasmacytoma compressing the optic nerve, resulting in ipsilateral optic atrophy and papilledema in the contralateral eye. EC

policy should be that any new headache in a cancer patient requires work-up. Neurologic signs and symptoms of a brain metastasis can be progressive, reflecting local expansion and growth of the tumor. Vigilance for relatively uncommon sites of metastases, such as the pituitary gland, is important. Breast cancer is the most common tumor that spreads to the pituitary gland. Clinical symptoms of pituitary gland metastases include ocular palsies, hypopituitarism, bitemporal hemianopia, alteration in consciousness varying from confusion to coma, and severe headache should rare pituitary apoplexy occur. Recognition and treatment of diabetes insipidus and panhypopituitarism and neurosurgical consultation for pituitary apoplexy are urgently needed.

Location-Related Symptoms

By being aware of the following symptoms, a physician can match them with brain masses at specific locations. (1) A dominant frontal lobe mass may manifest with expressive speech difficulty. Frontal lobe syndrome symptoms can vary, including loss of vitality, slow thinking, odd behavior, inappropriate remarks, irritability, trouble with executive planning that can be covered up by euphoria, platitudes in speech, and robotic behavior. Of note, a large frontal lobe mass (nondominant) can be clinically silent or accompanied by symptoms similar to those described above. (2) A dominant temporal lobe mass may cause receptive speech difficulty, depression, and/or apathy. A nondominant temporal lobe mass may manifest with visual field deficits and inability to recognize daily familiar sounds, such as a loud clap. A dominant parietal lobe mass may impair arithmetic skills and cause right-left confusion and inability to copy 3-dimensional constructions. (3) A nondominant parietal lobe mass may result in neglect owing to the patient being unaware of his or her deficits. (4) Occipital lobe masses cause visual field deficits, cortical blindness, and trouble identifying colors.

Differential Diagnosis

A clinical history along with MRI may establish the diagnosis of brain metastasis, although biopsy is warranted at times. A brain lesion is not necessarily a tumor. In one study, 6 of 54 patients with known cancers and single brain lesions did not have metastasis according to biopsy; 3 patients did not even have neoplastic lesions. Other diagnostic entities include intracerebral hemorrhage, brain abscesses, viral infections, cerebral radiation necrosis, paraneoplastic syndromes, and brain demyelination (tumefactive multiple sclerosis). Cerebral radiation necrosis occurs most often after stereotactic radiosurgery rather than whole-brain RT. MRI may demonstrate a “Swiss cheese/soap bubble” appearance with spreading wavefront margins.

Cerebral Edema and Elevated ICP

Cerebral edema is a potentially devastating complication of brain metastasis. The two main types of cerebral edema are (1) vasogenic edema, which is increased fluid in the extracellular space, and (2) cytotoxic edema, which is increased cellular fluid. Brain tumors cause vasogenic edema. Potentiating factors that worsen tumor-associated edema are seizures, use of chemotherapeutic agents (e.g., interleukin-2), and RT. Radiation necrosis following stereotactic radiosurgery can mimic brain tumors, with accompanying cerebral edema. Cerebral edema can be focal (from a lesion) or diffuse (hepatic postanoxic-ischemic swelling). Brain edema is predominantly cleared through the CSF. Brain edema displaces brain tissue, impairs consciousness, and causes buckling of and irreversible damage to the brain stem.

The mainstay of treatment of cerebral edema is corticosteroid use, as it is effective in reducing perilesional edema resulting from brain metastasis or a primary brain tumor. General dosing recommendations are 10 mg of dexamethasone in an IV bolus followed by 4–6 mg of IV dexamethasone every 6–12 h depending on the patient's clinical status. Use of corticosteroids improves CSF dynamics, predominantly, the outflow over the convexity.

If cerebral edema results in elevated ICP, reducing the ICP to maintain adequate cerebral blood flow is imperative. Interventions can include mechanical ventilation with a partial pressure of arterial carbon dioxide goal of 35–40 mm Hg and partial pressure of arterial oxygen goal of 80–120 mm Hg, maintenance of euvolemia, prevention of hypotension, maintenance of appropriate sedation and analgesia, elevation of the head end of the patient's bed to 30°, and CSF drainage. Use of osmotic diuretics should be considered in combination with these interventions. Options for this include mannitol (initial dose of 1 g/kg) and hypertonic saline (3.0–23.4 %), the doses of which can be titrated to a serum osmolality of 320 mOsmol/L or serum sodium concentration of 145–155 mmol/L. Administration of hypertonic saline requires using a central line. Three percent saline has an osmolality similar to that of 20 % mannitol. A single bolus of 250 mL of 3 % saline or 30 mL of 23.4 % saline can be given. Mannitol may induce hypovolemia and renal failure. Both agents have been associated with acute heart failure, pulmonary edema, and rebound increases in ICP. Two recent meta-analyses demonstrated hypertonic saline to be superior to mannitol in decreasing ICP; however, they demonstrated no clear benefit in neurologic outcome.

The efficacy of acute hyperventilation is lost after 6 h. Also, hypocapnia (partial pressure of arterial carbon dioxide less than 25 mm Hg) may induce severe cerebral vasoconstriction, causing ischemia.

CSF diversion (via ventriculostomy, sometimes urgent at bedside) is warranted for management of hydrocephalus, particularly in patients with intraventricular or pineal region tumors. A ventriculostomy tube is connected to a manometric CSF drainage system draining at 10–15 cm of water. If the CSF is bloody, drainage at no more than 0 cm of water should be considered to reduce clotting in the catheter.

If the patient already has an Ommaya reservoir, tapping of the reservoir can be considered after careful evaluation of the patient's neuroimages and measurement of the opening pressure. Lumbar puncture is contraindicated in patients with significant cerebral edema, hydrocephalus, or frank or impending herniation.

Urgent craniotomy and tumor debulking can be considered when the measures described above are unsuccessful and aggressive management is considered to be warranted (e.g., unknown tumor for diagnosis, relatively controlled primary tumor status, single large metastases, resectable lesions, potentially reversible situations [hemorrhage]).

Cerebral Herniation Patterns

Cerebral edema increases the size of a brain tumor and symptoms related to displacement of the thalamus as well as lateral, upward, and downward displacement of the brain stem, all of which can have major consequences.

Cingulate herniation occurs when the cingulate gyrus in the frontal lobe herniates under the falx and compresses both frontal lobes, leading to urinary incontinence and bilateral extensor plantar responses. The ipsilateral anterior cerebral artery may be compressed, causing frontal lobe ischemia.

Temporal lobe (uncal) herniation at the tentorium cerebelli causes ipsilateral III cranial nerve compression with the resulting sudden appearance of wide pupils with loss of light reflex. Lateral displacement of the brain stem with compression of pyramidal long tracts against the tentorial edge results in ipsilateral hemiparesis. As herniation progresses with further brain stem buckling, the pupils contract, which may be falsely mistaken as improvement of the patient's condition.

Central herniation occurs when a medially located mass forces the thalamus-midbrain through the tentorial opening (central displacement). This causes shearing of the penetrating basilar artery branches with irreversible brain stem damage. Central displacement results in poorly responsive midposition pupils, Cheyne-Stokes breathing, extensor or flexor posturing, and loss of oculocephalic reflexes.

Posterior fossa lesions can be displaced upward with pupillary and eye-movement abnormalities accompanied by significant changes in consciousness level. Downward displacement of these lesions (tonsillar herniation through the foramen magnum) can compress the brain stem and cause apnea. This is why patients with cerebellar metastases may present with cough and syncope.

Intracranial Hemorrhage

Certain tumor types (melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma) are known to be associated with spontaneous hemorrhage. Intracerebral hemorrhage (subdural, epidural, or subarachnoid) can occur in cancer

patients, with thrombocytopenia as a risk factor for it. Subdural metastases may exude fluid into the subdural space, with a resulting subdural hematoma or effusion.

Prompt evaluation and management of intracranial hemorrhage in the EC are critical. Neurosurgical consultation should be performed immediately. Supportive measures such as blood pressure control, correction of coagulopathy, and management of elevated ICP may improve outcomes.

Blood Pressure Management

A recent study demonstrated that interventions such as rapid lowering of blood pressure (systolic blood pressure goal, 140 mm Hg) can reduce hematoma growth in patients with intracerebral hemorrhage (Delcourt and Anderson 2012). One agent recommended for blood pressure management is labetalol because of its ability to preserve cerebral blood flow and its minimal effect on ICP. Labetalol should be administered in a 10- to 20-mg IV bolus followed by infusion at 2–8 mg a minute. Another option is nicardipine owing to its ability to improve cerebral perfusion pressure and lack of effect on ICP. Nicardipine administration should be started as a continuous infusion at a rate of 5 mg an hour and titrated to a maximum dose of 15 mg an hour. Nicardipine may be preferred over labetalol for its quick onset of action and short half-life.

Correction of Coagulopathy

Platelet transfusion is warranted if the patient is thrombocytopenic. Depending on the clinical situation, other treatments to be considered include fresh frozen plasma (2 U), vitamin K (5–10 mg IV), protamine sulfate (1 mg per 100 U of heparin), prothrombin complex concentrate (25–50 U/kg), and recombinant factor VIIa.

Central Nervous System Infections

Antibiotics are recommended if a brain abscess or meningitis is part of the initial differential diagnosis of a brain lesion. In nonimmunocompromised patients, coverage with cefotaxime, metronidazole, and vancomycin is recommended. Immunocompromised patients, transplant recipients, and hematologic cancer patients may need broader coverage for fungal (amphotericin), parasitic (toxopyrimethamine, sulfadiazine, leucovorin), and/or atypical bacterial ([*Nocardia* species] imipenem) infections. An in-depth review of central nervous system infections is outside the scope of this chapter.

Conclusion

Neurologic complications of cancer are common and result in devastating consequences if not managed early. In collaboration with specialized neurology services, emergency room physicians can act quickly to prevent further deterioration and permanent neurologic sequelae.

Key Practice Points

- Neurologic events, including malignant spinal cord compression, SE, cerebral edema, and intracranial hemorrhage, are true emergency conditions in patients with cancer, and prompt treatment of them is imperative to prevent long-term complications.
- The complaint of back pain in a patient with cancer should elicit a high degree of suspicion of spinal cord compression.
- Prolonged convulsive seizures in cancer patients can lead to brain injury, rhabdomyolysis, renal failure, and death.
- Lung cancer, breast cancer, and melanoma are the most common tumors of origin for brain metastases.
- Incomplete mental status improvement following a clinical seizure necessitates an EEG.
- Administration of 10 mg of IV decadron is the mainstay of initial treatment of cerebral edema and suspected malignant spinal cord compression.

Suggested Readings

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