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Neurologic Complications of Cancer and its Treatment

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Abstract

The central nervous system (CNS) and peripheral nervous system (PNS) are very susceptible to cancer and its treatment. The most direct involvement of the nervous system manifests in the development of primary brain and spinal cord tumors. Many cancers exhibit a propensity toward spread to the CNS, and brain metastases are common problems seen in malignancies such as lung, breast, and melanoma. Such spread may involve the brain or spine parenchyma or the subarachnoid space. In the PNS, spread is usually through direct infiltration of nerve roots, plexi, or muscle by neighboring malignancies. In some cases, cancer has sudden, devastating effects on the nervous system: epidural spinal cord compression or cord transection from pathologic fractures of vertebra involved by cancer; increased intracranial pressure from intracranial mass lesion growth and edema; and uncontrolled seizure activity as a result of intracranial tumors (status epilepticus), which are neuro-oncologic emergencies. The best known indirect or remote effects of cancer on the nervous system are the neurologic paraneoplastic syndromes. Cancer can also result in a hypercoagulable state causing cerebrovascular complications. Treatment of cancer can have neurologic complications. The commonest of these complications are radiation-induced injury to the brain, spine, and peripheral nerves and chemotherapy-induced peripheral neuropathy. The suppressant effect of cancer and its treatment on the body's immune system can result in infectious complications within the nervous system.

Keywords

Cancer; Nervous system complications; Metastases

Introduction

Cancer often affects the nervous system and may result in significant neurologic morbidity and mortality. These effects may be direct—with direct cancer involvement of the brain, spine, or peripheral nervous system (PNS)—or indirect as in paraneoplastic neurologic syndromes. Treatment of cancer can also damage the nervous system. This article discusses the effects of systemic cancers and their treatment on the nervous system, although the complications of primary brain and spine tumors are not discussed.

Epidemiology

Cancer takes a huge toll on the human race. In 2009, it was estimated that almost 1.5 million new cases of cancer would be diagnosed in the United States, resulting in more than half a million deaths [1]. Many of these patients are expected to develop complications in sites distant to the original tumor location. The nervous system is very susceptible to such complications. In a prospective evaluation in a large cancer center, slightly less than half (45.2%) of more than 800 cancer patients seen in neurologic consultation during a 6-month period had metastases to the nervous system [2].

Direct Cancer Complications

Brain Metastases

Metastases to the brain from systemic malignancies are the most common direct form of nervous system involvement by cancer. It is estimated that in the United States as many as 200,000 cases of brain metastases (BMs) are diagnosed each year [3]. The most common cancers resulting in BMs are lung, breast, and melanoma. BMs are rare in prostate cancer [4] and quite uncommon in cancers of the female reproductive tract [5]. Gastrointestinal cancers and hematologic malignancies are less likely to result in parenchymal brain metastases. Leukemia and lymphoma are more likely to result in leptomeningeal metastases. Most brain metastases develop in the cerebral hemispheres (80%) in accordance with higher blood flow to the supratentorial compartment [6].

Clinical Presentation and Diagnosis—Seizures, headaches, and focal neurologic deficits, depending on location, usually lead to the diagnosis of brain metastases. Examination may reveal focal neurologic deficits such as focal weakness, numbness, or language problems. Head CT scans will reveal single or multiple discrete areas of contrast enhancement and associated vasogenic edema. Brain MRI may uncover metastases too small for CT resolution and prove more effective in defining size and location of lesions.

Treatment—Treatment of brain metastases includes symptomatic therapy for seizures and vasogenic edema. Although there are several anticonvulsants available, nonenzyme-inducing newer generation anticonvulsants are tolerated better and pose less risk of drug–drug interactions than older enzyme-inducing agents. Examples of nonenzyme-inducing anticonvulsants include levetiracetam, lacosamide, and pregabalin. Although seizure prophylaxis is still used, no evidence supports this practice. However, hemorrhagic metastases are more likely to cause seizures and prophylaxis may be prudent in these situations.

Vasogenic edema is treated with corticosteroids, usually dexamethasone. Depending on the degree of vasogenic edema and the presence or absence of mass effect, midline shift, and herniation of brain structures, high doses of corticosteroids (dexamethasone 12–24 mg daily) may be necessary. Short-term complications include hyperglycemia, psychoses, and weight gain.

Once patients are controlled on symptomatic therapy, more directed therapy for the metastatic lesions is planned. The most important modalities of treatment are surgery and radiation therapy. Chemotherapy has a modest role in the management of this cancer complication. Radiation therapy includes whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). The best treatment for patients with BMs depends on several factors. Age, performance status, and the presence of systemic metastatic disease emerged as the most important factors in a recursive partitioning analysis (RPA) of the

Radiation Therapy Oncology Group (RTOG) trials that demonstrated benefit from WBRT [7, 8].

The prognostic classes from this analysis were defined as follows. RPA class I is characterized by younger than 65 years old and Karnofsky Performance Status greater than 70; no extracranial disease and primary tumor not progressive; and median survival of 7.1 months. RPA class II is characterized by patients other than those in RPA class I or III and median survival of 4.2 months. RPA class III is characterized by Karnofsky Performance Status less than 70 and median survival of 2.3 months. Tumor histology and number of brain metastases are also important factors in determining treatment.

The following guidelines apply given current available data. WBRT is indicated in RPA class I and II patients with single metastasis after surgical resection and as palliative therapy in patients with a poor performance status (RPA class III). WBRT may also be used in RPA class I and II patients with multiple metastases but emerging data indicate that SRS alone as a first-line intervention may be preferable in these patients given the early development of cognitive dysfunction with WBRT [9•].

Leptomeningeal Metastases

The largest autopsy series to date indicates that 8% of patients with cancer have leptomeningeal seeding at autopsy [10]. This complication is seen mostly in small cell lung cancer [11], breast cancer [12], and melanoma [13]. In hematologic and lymphoid malignancies, non-Hodgkin's lymphoma (NHL) [14] and acute nonlymphocytic leukemia [15] account for most cases.

Clinical Presentation, Pathophysiology, and Diagnosis—Patients present with evidence of spinal cord or nerve root involvement, cranial neuropathies, or symptoms and signs referable to the cerebral hemispheres [16•]. Patients may present with limb weakness, pain referable to the involved nerve roots or bladder, and bowel disturbances in spine and sacral root involvement. Examination confirms weakness, sensory loss, and changes in deep tendon reflexes. Cranial nerve VI, III, and IV dysfunction result in diplopia and optic nerve involvement causes visual blurring. The fifth cranial nerve is also involved in some cases. Extraocular nerve abnormalities or facial sensory deficits are present. Multiple cranial neuropathies in a patient with cancer are highly indicative of leptomeningeal metastases (LM).

Cerebral Symptoms—Cancer cells gain access to the cerebrospinal fluid (CSF) in three ways. The most common route is hematogenous, but direct extension from cancer sites contiguous to the central nervous system (CNS) and entry via perineural and perivascular spaces is also possible [16•]. The diagnosis of LM should be confirmed with CSF examination. This study also helps exclude other causes of cerebral, cranial nerve, and spinal/nerve root dysfunction in patients with cancer such as chronic (opportunistic) infections. The presence of malignant cells in the CSF is diagnostic; additionally high protein, low glucose, elevated opening pressures, and increased white cell count support the diagnosis when cytology is negative. A repeat CSF analysis increases the yield in such cases and should be performed [11]. Flow cytometry and polymerase chain reaction techniques are useful in cases of NHL with suspected lymphomatous meningitis [17]. Before CSF analysis, neuroimaging should be performed. MRI of the brain and entire spine is indicated in such cases to help stage the extent of LM and guide management. LM is often associated with increased intracranial pressure and concomitant parenchymal metastatic disease with mass effect. In such cases, a lumbar puncture (LP) for CSF analysis may be contraindicated. MRI imaging may demonstrate LM enhancement, which may be linear or more nodular (Fig. 1).

Cranial nerve enhancement, especially in the presence of cranial neuropathies, is highly indicative of LM disease. MRI sensitivity is low (<50%) although it is considered more sensitive than CT [18]. CSF flow analysis in patients with LM is another important diagnostic and prognostic tool. Abnormal CSF flow is common in LM and ¹¹¹indium-diethylenetriamine pentaacetic acid or ^{99m}Tc macroaggregated albumin tracers may be used to define the extent and location of such disturbances [19, 20].

Treatment—Treatment is palliative, and the patient and family should be made aware of this fact, as well as of prognostic implications. Surgery, radiation, and chemotherapy play a role, as the multidisciplinary care of these patients is very important. Patients with LM may require ventriculoperitoneal shunting for hydrocephalus. Surgery is also required for placement of Ommaya reservoirs for administration of intrathecal chemotherapy.

Radiation therapy may have significant palliative value in patients with LM. Radionuclide studies may demonstrate CSF flow abnormalities. Radiation therapy to areas of CSF block has been shown to be of benefit [21, 22]. Patients who have cerebral LM and concomitant brain metastases are treated with WBRT. Finally, focused radiation to bulky tumor involving the spine can help stabilize or improve neurologic function. Chemotherapy has shown activity in LM, especially lymphomatous and leukemic meningitis. The responses and palliation seen with chemotherapy in solid tumors are less robust but some benefit can also be derived in these cases. Most commonly, chemotherapy is administered via an Ommaya reservoir. DepoCyt (Enzon; New Brunswick, NJ) is considered the drug of choice for such administration. DepoCyt is sustained-release cytarabine (a liposomal formulation) and has shown benefit in patients with lymphomatous meningitis [23] and solid tumor LM [24]. In lymphomatous meningitis, Glantz et al. [23] demonstrated high response rates and better quality of life when liposomal cytarabine was compared with standard cytarabine. In solid tumors, the response rates noted to DepoCyt were similar to what had been reported for methotrexate administration [24]. However, the less-frequent administration of DepoCyt compared with methotrexate was felt to benefit the patient. This drug is also less toxic to the CNS than methotrexate. Direct spinal fluid injection of methotrexate, cytarabine, thiopeta, etoposide, topotecan, and rituximab have all been used in patients with LM. Chamberlain [16•] provided a very recent and comprehensive review on this subject.

Spine Metastases

Spine metastases are common in cancer patients. The most common form of involvement is metastases to the bone of the spine with or without encroachment on the epidural space. This represents up to 98% of cases of spine metastases [25]. Metastases to the parenchyma of the spinal cord are uncommon [26].

Epidural spinal cord compression (ECS) is a consequence of metastases to the vertebral bone with encroachment on the epidural space. Cancers most likely to result in ECS are breast, lung, and prostate cancer, but NHL, melanoma, and adenocarcinoma of unknown primary were also noted in ECS in a retrospective series of patients [27]. The pathophysiology mainly involves hematogenous dissemination of cancer cells to the vertebral body.

Clinical Presentation and Diagnosis—The presenting features of ECS depend on the level of involvement but pain is essentially universal in such patients. Pain may be reflective of nerve root involvement and have radicular or axial features. Thoracic spine involvement is most common so that mid-back pain, bilateral lower extremity weakness, and sensory disturbances tend to be the most common presenting symptoms. Patients may also develop

bowel and bladder symptoms. Such dysfunction may be very prominent in compression occurring at the level of the conus medullaris or cauda equina.

The diagnosis of ESCC is clinical. However, neuroimaging is required to confirm the level of compression, assess for the presence of other levels of bone and epidural involvement, and determine the presence of LM. Chamberlain and Kormanik [27] found involvement at more than one level in 29% of cases within their series. In the occasional patient who cannot undergo MRI, CT or CT myelography can also be diagnostic.

Treatment—Supportive care includes high-dose steroid therapy, usually with dexamethasone to reduce edema. This often helps with pain control and stabilization and improvement of neurologic function. We usually use immediate intravenous administration of 10 mg of dexamethasone followed by 6 mg every 4 hours. Pain control is very important and specific pain therapy besides corticosteroids is almost always necessary. For definitive therapy, early liaison with a radiation oncologist and a neurosurgeon are key to success. The neurosurgeon may use vertebroplasty or kyphoplasty for pain relief in collapsed vertebrae, corpectomy to resect tumor in the vertebral body and decompress the spine (anterior decompression), or a laminectomy (posterior decompression). Radiation therapy is the most common therapeutic modality available to patients with ESCC and may be the only source of palliation for patients who are not surgical candidates. The various radiation therapy modalities include stereotactic radiotherapy, intensity modulated radiotherapy (IMRT), and conventional external beam radiation therapy. Conventional fractionated external beam radiation therapy is most commonly administered. Radiation therapy is administered one level above and below the site of compression to reduce the risk of recurrence from epidural tumor extension. Success with radiation is highly dependent on tumor histology (eg, melanoma and renal cell carcinoma are radioresistant).

Peripheral Nervous System Metastases

The peripheral nervous system may be directly involved by cancer. Metastases to individual nerves is rare; more commonly noted is direct infiltration or compression of nerve roots, plexi (cervical, brachial, or lumbosacral), individual nerves, or muscles.

Clinical Presentation and Diagnosis—Cancer may infiltrate a nerve plexus causing pain and sensorimotor deficits in one limb. Examination in such cases may reveal evidence of partial or complete injury to the plexus. In the case of the lumbosacral plexus, injury to the entire plexus from infiltrating neoplasm is seen in 18% of cases, upper plexus involvement (L1-L4) is seen in 31% and the lower plexus (L4-S1) in 51% [28, 29]. Patients with extensive lumbosacral plexus involvement would have weakness of thigh flexion, eversion and adduction, as well as leg extension [30]. Sensory loss over the genitoinguinal region, thigh, and medial aspect of the lower leg as well as loss of the patellar reflex would also be expected signs in such cases [30]. Similarly, involvement of the cervical or brachial plexus by cancer may cause typical findings on examination; the reader is referred to comprehensive texts on this subject [30].

Weakness or numbness may also result from individual nerve involvement. Metastases to a nerve are rare but involvement of nerves from bone, soft tissue, or CSF metastases is not. The numb chin syndrome (NCS) caused by malignant infiltration of the mental or inferior alveolar nerve is one example. Patients present with orofacial numbness involving the chin or lower lip. The most common cause is bone involvement by cancer and nerve compression, although some cases are associated with leptomeningeal metastases [31]. Appropriate diagnostic studies such as a Panorax radiograph of the jaw and cerebrospinal analysis often determines the etiology.

Neuroimaging with MRI is the diagnostic modality of choice for most cases of tumor-related compression neuropathy or plexopathy. It may show direct infiltration of a nerve plexus or a mass compressing an individual nerve. Neuroimaging of plexus lesions may be difficult to interpret, especially when previous radiation therapy to the area (eg, brachial plexus) raises the possibility of radiation plexopathy. In such cases, electrodiagnostic studies with electromyography and nerve conduction studies may be very helpful. This differential is discussed later under nervous system complications from radiation therapy (see below).

Treatment of PNS involvement by cancer includes steroids and analgesics to reduce pain. Pain relief may be accomplished using tricyclic or other antidepressants such as duloxetine as well as anticonvulsants. Pregabalin and gabapentin are often the first choices. More definitive therapy includes both radiation and chemotherapy, depending on the underlying histology and site of involvement.

Indirect Complications of Cancer

Paraneoplastic Syndromes

Neurologic paraneoplastic syndromes (NPNS) are disorders caused by cancer without direct infiltration, metastases, or compression of the CNS or PNS structure involved as determined by clinical presentation. The mechanism is autoimmune and recognition of these syndromes is very important as it may lead to an early cancer diagnosis. Additionally, these syndromes are treatable by control of the underlying malignancy and immunomodulatory therapies. A classic paraneoplastic syndrome, Lambert-Eaton myasthenic syndrome, is discussed and summarized, along with other well-recognized syndromes, in Table 1.

Lambert-Eaton Myasthenic Syndrome—Patients with small cell lung cancer (SCLC) sometimes present with a neuromuscular syndrome consisting of fluctuating weakness, fatigue, and autonomic dysfunction caused by a defect in acetylcholine release from the presynaptic terminal at the neuromuscular junction. In turn, this is caused by antibodies to presynaptic voltage-gated calcium channels (VGCC). Examination confirms limb (especially lower extremity) weakness and hyporeflexia. Electromyography (EMG)/NCS show a decremental response to low-frequency repetitive nerve stimulation and an incremental response to higher frequency stimulation. Detection of VGCC antibodies in the presence of such findings should prompt an aggressive search for an underlying malignancy, usually SCLC. Treatment includes 3,4-diaminopyridine to improve acetylcholine release, pyridostigmine, and guanidine. Immunomodulatory therapy with intravenous Ig and plasmapheresis, as well as long-term steroid therapy, may also be necessary [32].

Cerebrovascular Complications of Cancer

Ischemic Stroke—Cancer patients are at risk for cerebrovascular complications for three reasons: 1) cancer and its treatment result in disorders of coagulation; 2) cancer may directly affect blood vessels; and 3) infections in individuals who are immunocompromised may result in secondary stroke [36•].

Cancer induces a hypercoagulable state. Tumors produce procoagulant factors, such as tissue factor and cancer procoagulant, and interaction of these with the host blood vessels result in abnormal clotting [36•]. Additionally, there is some downregulation of anticoagulant pathways, activated protein C resistance, or an imbalance between tissue factor expression and tissue factor plasminogen inhibitor [36•]. The normal coagulation balance tips in favor of a hypercoagulable state resulting in localized thrombosis or even a chronic disseminated intravascular coagulation (DIC) in cancer patients. As recently reviewed by Rogers [36•], there are two thrombotic syndromes in cancer that may result in

cerebrovascular disease: nonbacterial thrombotic endocarditis (NBTE) and cerebral intravascular thrombosis without NBTE. Graus et al. [37] described nonbacterial thrombotic endocarditis as the most common cause of stroke in cancer patients. This complication—often seen in patients with lung or gastrointestinal mucin-producing adenocarcinoma—results from cardiac vegetations that embolize to main cerebral arteries, often the middle cerebral [36•]. As a result, patients present with typical stroke symptoms such as aphasia, focal weakness, and numbness. Heparin has been recommended in such cases, as well as consideration for valve replacement if the patient is felt to have a reasonable prognosis [36•]. In non-NBTE cerebral thrombosis, the process of thrombosis is more widespread and affects smaller blood vessels than in NBTE cases; heparin is also recommended in such cases [36•]. Because the process is multifocal, more generalized presentations (eg, encephalopathy) than in NBTE are common.

There are also documented cases of embolic stroke from tumor cell embolization and tumors can cause direct compression of blood vessels, especially venous sinuses [38]. In such cases, direct management of the tumor is the only therapy possible [36•].

Venous sinus thrombosis occurring in cancer patients is yet another manifestation of hypercoagulability. Diagnosis is confirmed with magnetic resonance venography and this complication is treated with anticoagulation [39].

Hemorrhagic Stroke—Intracranial blood may be seen in patients with hemorrhagic metastases. Melanoma, lung cancer, and renal cell cancer are the most likely metastatic histologies to be hemorrhagic. Such cases may present with seizures, headache, and are diagnosed and managed in a similar manner to nonhemorrhagic metastases. The occurrence of a consumptive coagulopathy (DIC) may result in intracranial hemorrhage in hematologic malignancy.

Neurologic Complications of Cancer Treatment

Nervous System Complications from Radiation Therapy

The central and peripheral nervous system may be affected by radiation therapy. In the brain and spinal cord this is believed to be caused by a combination of vascular damage and damage to glia, mainly oligodendrocytes. The timing of radiation complications has led to a classification of such injury and this is helpful in predicting reversibility [40]. During or immediately after radiation therapy, patients may develop acute injury, usually manifest mainly by headache, nausea, and vomiting. Injury to capillaries and leakage with edema are the likely mechanism and this injury is steroid-responsive. Complications occurring beyond a month and up to 6 months from completion of radiation therapy are termed *early-delayed injury*. In these cases, patients may develop drowsiness, fatigue, and cognitive problems (somnolence syndrome). In addition, patients may also develop brain MRI changes suggestive of tumor progression. These changes are reversible and improvement may be hastened by steroids. Conversely, late injury is associated with permanent diffuse white matter changes (leukoencephalopathy), focal areas of necrosis, and cognitive impairment. This is irreversible and the most severe forms result in a severe dementia and, ultimately, death [41]. The most important risk factors in the development of leukoencephalopathy and cognitive impairment are older age, radiation dose, brain volume receiving radiation, and combination with chemotherapy [42]. The combination of radiation therapy with methotrexate for treatment of primary CNS lymphoma is the best example of this; very severe forms of leukoencephalopathy may be seen in patients treated with such combinations especially when methotrexate is administered concomitantly with radiation. Radiation-induced cognitive impairment presents a spectrum of severity ranging from mild impairment to frank dementia [42]. Neuroimaging shows white matter abnormalities and in

cases associated with dementia, significant atrophy may be noted. There are no effective therapies although psychostimulants have been advocated for the attention and memory problems associated with mild to moderate cognitive dysfunction [43]. Focal areas of necrosis in the brain raise concern about possible tumor progression because the appearance can be very similar with heterogeneous enhancement and lesional areas consistent with necrosis. Surgery may be necessary when such areas are symptomatic and to exclude tumor progression requiring further treatment.

Spinal Cord Injury—In the spinal cord, radiation-induced damage may be early-delayed, which is almost always reversible and late-delayed, which is more likely to be permanent [42]. Because the former improves spontaneously, specific treatment is not really necessary. Leung et al. [44] noted Lhermitte's sign in 121 (10.3%) of 1171 nasopharyngeal carcinoma patients treated with radiation. They also noted that median development time for such signs was 3 months and that it was more likely to happen when the dose to the cervical cord exceeded 48.9 Gy [44]. In rare instances, late-delayed radiation myelopathy has been noted to improve clinically and on imaging [45]. However, in most cases, deficits persist or progress. Patients may present with weakness and sensory loss in the legs and a paraparesis and sensory level are confirmed on examination; another presentation is with Brown-Sequard syndrome [45]. Problems with bladder and bowel control are also possible. MRI of the spinal cord may show increase signal at the level affected and even contrast enhancement [45]. Although anticoagulation and hyperbaric oxygen are used occasionally, corticosteroids are the most commonly used therapy that may result in improvement.

Peripheral Nerve Involvement: Plexus and Individual Nerve Damage from Radiation Therapy—The brachial and lumbosacral plexi may also be involved in the radiation fields for treatment of breast and lung cancers and pelvic tumors respectively. As with CNS involvement, the tempo of the injury helps predict the prognosis. Thus, early-delayed brachial plexopathy occurring in the first few months after treatment usually improves whereas late-delayed injury is a progressive, disabling disorder [42]. In both cases, sensorimotor deficits in the limb supplied by the plexus are typical. EMG and nerve conduction studies are helpful, especially in helping distinguish brachial plexopathy of the late-delayed type from tumor recurrence with infiltration of the plexus. Myokymic discharges on EMG and the absence of severe pain favors radiation damage as the likely diagnosis. Neuroimaging with dedicated MRI of the plexus may show a mass involving the plexus; nonuniform, asymmetric diffuse, or focal enlargement especially eccentric masses with contrast enhancement favor neoplastic infiltration [46, 47, 48•]. In postradiation plexopathy, a more uniform symmetric swelling of the plexus is noted [49, 50]. In difficult cases, plexus biopsy may be necessary. Treatment of radiation-induced plexopathy includes steroids and pain management combined with physical therapy.

Nervous System Complications from Chemotherapy

Chemotherapy agents can result in toxicity to the nervous system. Peripheral neuropathy is the most common complication noted with a variety of chemotherapy agents. Table 2 presents examples of the neurotoxicity seen with conventional cancer therapies and some newer agents.

The following observations should be made as the reader refers to Table 2.

This table is not comprehensive of all neurotoxic agents used in cancer therapy and their complications. It is meant to provide examples of some of the most common neurologic toxicities seen with cancer therapy and the common agents causing such toxicity. The reader is referred to comprehensive texts on this subject [51, 52•, 53]. Some chemotherapy drugs

cause more than one type of neurotoxicity (eg, cisplatin may cause peripheral and cranial neuropathies, seizures, and myelopathy). Neurotoxicity may be seen with newer agents and is not restricted to conventional chemotherapy. Neurotoxicity may be exacerbated by the administration of more than one neurotoxic drug or by combination with radiation. The best example of the latter is methotrexate leukoencephalopathy, commonly seen as a delayed complication of high-dose or intrathecal methotrexate with radiation administered before or during such therapy. This syndrome has been seen in adults treated for primary CNS lymphoma and children treated for leukemia with such combinations. Gradual cognitive dysfunction and frank dementia may develop in such cases although neurologic stabilization is seen in some patients.

Peripheral Neuropathy—Conventional chemotherapy agents such as vinca alkaloids, platinum compounds, and taxanes are well known to cause neuropathy syndromes [53]. However, some newer agents such as bortezomib, a proteasome inhibitor, are also associated with this complication.

The presentation of chemotherapy-induced neuropathy depends on the offending agent and type of neuropathy induced, duration of treatment, and patient-related factors. In sensory neuropathies, numbness, tingling, and pain in the extremity is typical.

Investigation with EMG/NCS is not strictly necessary in most cases but is done occasionally when the presentation is atypical (eg, worsening of symptoms with withdrawal of chemotherapy). In axonopathies, a decrease in the amplitude of action potentials and prolonged latencies are noted. Demyelination results in delayed conduction velocities.

Among prevention strategies for chemotherapy-induced neuropathy, perhaps the most obvious is the limitation in cumulative drug dosing with drugs such as thalidomide or the vinca alkaloids. However, there are chemotherapy-specific strategies, such as the use of magnesium and calcium salt infusions to limit oxaliplatin neuropathy (Table 2). Other examples of specific treatments, as well as a list of nervous system complications of chemotherapy, are provided in Table 2.

Neurologic Complication of Stem Cell Transplantation—The regimen used in stem cell transplantation (SCT) for treatment of cancers such as leukemias and lymphomas has been associated with neurologic complications such as seizures, encephalopathy, and stroke. In addition, severe immunosuppression associated with this treatment may result in severe infections of the nervous system. Allogeneic stem cell transplantation was associated with neurologic complications in 18% of patients at day 100 after transplant in a series of patients treated for malignant and nonmalignant disease [54].

Seizures may occur with high-dose busulfan conditioning SCT regimens and benzodiazepine prophylaxis has been advocated in such cases [55]. The occurrence of seizures in this setting has been reported as high as 37% [54].

Encephalopathy may have multiple causes in SCT patients. The chemotherapy agents used are the commonest offenders and ifosfamide, melphalan, and etoposide may all be associated with this complication.

Stroke occurring as a complication of therapy for cancer has been discussed. The severe bone marrow suppression with thrombocytopenia in SCT makes this population high-risk for intracerebral hemorrhage. Hemorrhage can also be a result of septic emboli to the brain caused by opportunistic infections in this population.

Infections—Infections include opportunistic infections with bacteria, viruses, fungi, and parasites. *Aspergillus fumigatus* is the most common fungal infection in such cases and *Toxoplasma gondii* is the most common parasite to result in CNS infection. Viruses of the herpes group are very neurotropic and may result in skin eruptions from sensory nerve involvement, as well as encephalitis. JC virus reactivation, a consequence of treatment- or disease-related immunosuppression, results in progressive multifocal leukoencephalopathy with a very poor prognosis.

Conclusions

Cancer can involve the nervous system directly or through the toxic effects of treatment. Additionally, cancer can have effects on the immune system and the coagulation system that result in paraneoplastic syndromes and cerebrovascular disease, respectively. The immunosuppressant effect of cancer and its treatments may result in opportunistic infections of the nervous system.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. National Cancer Institute. [Accessed September 2009] Surveillance Epidemiology and End Results. Available at http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=1&page=sect_01_table_01.html
2. Clouston PD, DeAngelis LM, Posner JB. The spectrum of neurologic disease in patients with systemic cancer. *Ann Neurol*. 1992; 31:268–273. [PubMed: 1637135]
3. Gavrilovic IT, Posner J. Brain metastases: epidemiology and pathophysiology. *J Neurooncol*. 2005; 75:5–14.
4. Tremont-Lukats IW, Bobustuc G, Lagos GK, et al. Brain metastases from prostate carcinoma: The M.D. Anderson Cancer experience. *Cancer*. 2003; 15:363–368. [PubMed: 12872358]
5. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol*. 1978; 19:575–587.
6. Delattre JY, Krol G, Thaler HT, et al. Distribution of brain metastases. *Arch Neurol*. 1988; 45:741–744. [PubMed: 3390029]
7. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980; 6:1–9. [PubMed: 6154024]
8. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997; 37:745. [PubMed: 9128946]
9. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole brain irradiation: a randomized controlled trial. *Lancet Oncol*. 2009; 10:1037–1044. [PubMed: 19801201] In this very well-designed trial, the neurocognitive impairment from WBRT was so significant that the study was terminated prematurely.
10. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol*. 1978; 19:579–592. [PubMed: 570349]
11. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer*. 1982; 49:759–772. [PubMed: 6895713]
12. Kaplan JG, DeSouza TG, Farkash A, et al. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurooncol*. 1990; 9:225–229. [PubMed: 2086737]

13. Little JR, Dale AJ, Okazaki H. Meningeal carcinomatosis. Clinical manifestations. *Arch Neurol*. 1974; 30:138–143. [PubMed: 4272658]
14. Ersboll J, Schultz HB, Thomsen BL, et al. Meningeal involvement in non-Hodgkin's lymphoma: symptoms, incidence, risk factors and treatment. *Scand J Haematol*. 1985; 35:487–496. [PubMed: 4089528]
15. Chamberlain MC. Carcinomatous meningitis. *Arch Neurol*. 1997; 54:16–17. [PubMed: 9006407]
16. Chamberlain MC. Neoplastic meningitis. *Oncologist*. 2008; 13:967–977. [PubMed: 18776058]
This article offers a recent comprehensive review on the subject of neoplastic meningitis.
17. Rhodes CH, Glantz MJ, Glantz L, et al. A comparison of polymerase chain reaction examination of cerebrospinal fluid and conventional cytology in the diagnosis of lymphomatous meningitis. *Cancer*. 1996; 77:543–548. [PubMed: 8630963]
18. Chamberlain MC, Glantz M, Groves MD, Wilson WH. Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. *Semin Oncol*. 2009; 36:S35–S45. [PubMed: 19660682]
19. Chamberlain MC. Radioisotope CSF flow studies in leptomeningeal metastases. *J Neurooncol*. 1998; 38:135–140. [PubMed: 9696363]
20. Glantz MJ, Hall WA, Cole BF, et al. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. *Cancer*. 1995; 75:2919–2931. [PubMed: 7773943]
21. Chamberlain MC, Corey-Bloom J. Leptomeningeal metastases: ¹¹¹indium-DTPA CSF flow studies. *Neurology*. 1991; 41:1765–1769. [PubMed: 1944906]
22. Chamberlain MC, Kormanik P, Jaeckle KA, et al. ¹¹¹Indium-diethylenetriamine pentaacetic acid CSF flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. *Neurology*. 1999; 52:216–217. [PubMed: 9921888]
23. Glantz MJ, LaFollette S, Jaeckle KA, et al. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol*. 1999; 17:3110–3116. [PubMed: 10506606]
24. Jaeckle KA, Batchelor T, O'Day SJ, et al. An open trial of sustained-release cytarabine (DepoCyt) for the intrathecal treatment of solid tumor neoplastic meningitis. *J Neurooncol*. 2002; 57:231–239. [PubMed: 12125986]
25. Tubian-Hulin M. Incidence, prevalence and distribution of bone metastases. *Bone*. 1991; 12(Suppl 1):9–10.
26. Goetz, CG. Textbook of Clinical Neurology. edn 2. WB Saunders; Philadelphia: 2003. Direct metastatic disease; p. 1042–1051.
27. Chamberlain MC, Kormanik PA. Epidural spinal cord compression: a single institution's retrospective experience. *Neuro Oncol*. 1999; 1:120–123. [PubMed: 11550307]
28. Jaeckle KA, Young DF, Foley KM. The natural history of lumbosacral plexopathy in cancer. *Neurology*. 1985; 35:8–15. [PubMed: 2981417]
29. Jaeckle KA. Nerve plexus metastases. *Neurol Clin*. 1991; 9:857–866. [PubMed: 1722001]
30. Brazis, PW.; Masdeu, JC.; Biller, J. Cervical, brachial and lumbosacral plexuses. In: Brazis, PW.; Masdeu, JC.; Biller, J., editors. Localization in Clinical Neurology. Lippincott Williams & Wilkins; Philadelphia: 2001. p. 75–90.
31. Biasotto M. Numb chin syndrome as the presenting symptom in carcinomatous meningitis. *Ann Oncol*. 2008; 19:599–601. [PubMed: 18304968]
32. Pourmand R. Lambert-eaton myasthenic syndrome. *Front Neurol Neurosci*. 2009; 26:120–125. [PubMed: 19349709]
33. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol*. 2008; 7:327–340. [PubMed: 18339348] This article provides a very detailed comprehensive review on the subject with excellent discussion of pathophysiology.
34. Dalmau J. Limbic encephalitis and variants related to neuronal cell membrane autoantigens. *Rinsho Shinkeigaku*. 2008; 48:871–874. [PubMed: 19198103]

35. Rosenfeld, MR.; Dalmau, J. Paraneoplastic syndromes of the nervous system. In: Schiff, D.; Kesari, S.; Wen, PY., editors. *Cancer Neurology in Clinical Practice*. Humana Press; New Jersey: 2008. p. 237-255.
36. Rogers LR. Management of stroke in cancer. *Curr Oncol Rep*. 2008; 10:72–77. [PubMed: 18366963] ***This article provides an excellent recent review in an area of neuro-oncology that is lacking strong data, especially in terms of management recommendations.
37. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine (Baltimore)*. 1985; 64:16–35. [PubMed: 3965856]
38. Navi BB, Kawaguchi K, Hriljac I, et al. Multifocal stroke from tumor emboli. *Arch Neurol*. 2009; 66:1174–1175. [PubMed: 19752313]
39. Razier JJ, DeAngelis L. Cerebral sinus thrombosis diagnosed by MRI and MR venography in cancer patients. *Neurology*. 2000; 54:1222–1226. [PubMed: 10746588]
40. Giglio P, Gilbert MR. Cerebral radiation necrosis. *Neurologist*. 2003; 9:180–188. [PubMed: 12864928]
41. DeAngelis LM, Delattre YP, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology*. 1989; 39:789–796. [PubMed: 2725874]
42. Chi, D.; Behin, A.; Delattre, J-Y. Neurologic complications of radiation therapy. In: Schiff, D.; Kesari, S.; Wen, PY., editors. *Cancer Neurology in Clinical Practice*. Humana Press; New Jersey: 2008. p. 259-286.
43. Meyers CA, Weitzner MA, Valentine AD, et al. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *J Clin Oncol*. 1998; 16:2522–2527. [PubMed: 9667273]
44. Leung WM, Tsang NM, Chang FT, et al. Lhermitte's sign among nasopharyngeal cancer patients after radiotherapy. *Head Neck*. 2005; 27:187–194. [PubMed: 15627248]
45. Uchida K, Nakajima H, Takamura T, et al. Neurological improvement associated with resolution of irradiation-induced myelopathy: serial magnetic resonance imaging and positron emission tomography findings. *J Neuroimaging*. 2009; 19:274–276. [PubMed: 18681929]
46. Thyagarajan D, Cascino T, Harms G. Magnetic resonance imaging in brachial plexopathy of cancer. *Neurology*. 1995; 45:421–427. [PubMed: 7898688]
47. Wittenberg KH, Adkins MC. MR imaging of nontraumatic brachial plexopathies: frequency and spectrum of findings. *Radiographics*. 2000; 20:1023–1032. [PubMed: 10903692]
48. Bowen BC, Seidenwurm DJ. Plexopathy. *AJNR*. 2008; 29:400–402. [PubMed: 18272570] This article provides expert consensus guidelines for neuroimaging in plexopathy.
49. Bowen BC, Verma A, Brandon AH, et al. Radiation-induced brachial plexopathy: MR and clinical findings. *Am J Neuroradiol*. 1996; 17:1932–1936. [PubMed: 8933882]
50. Wouter van Es H, Engelen AM, Witkamp TD, et al. Radiation-induced brachial plexopathy: MR imaging. *Skeletal Radiol*. 1997; 26:284–288. [PubMed: 9194228]
51. Wolf S, Barton D, Kottschade L, et al. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer*. 2008; 44:1507–1515. [PubMed: 18571399]
52. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol*. 2009; 6:596–603. [PubMed: 19707193] ***This article provides a very recent review of neurotoxicity caused by targeted and newer therapies.
53. Harati, Y.; Bosch, EP. Disorders of peripheral nerves. In: Bradley, WG.; Daroff, RB.; Fenichel, GM.; Jankovic, J., editors. *Neurology in Clinical Practice*. Butterworth-Heinemann; Philadelphia: 2008. p. 2249-2356.
54. Siegal D, Keller A, Xu W, et al. Central nervous system complications after allogeneic hematopoietic stem cell transplantation: incidence, manifestations, and clinical significance. *Biol Blood Marrow Transplant*. 2007; 13:1369–1379. [PubMed: 17950923]
55. Chan KW, Mullen CA, Worth LL, et al. Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplant*. 2002; 29:963–965. [PubMed: 12098063]
56. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol*. 2009; 63:761–767. [PubMed: 19034447]

Fig. 1. MRI imaging may demonstrate leptomeningeal metastases enhancement, which may be linear or more nodular

Table 1

Pathology and clinical presentation of the paraneoplastic syndromes

Paraneoplastic Syndrome	Antibody	Clinical presentation	Usual cancer association	Pathology	Treatment ^a
Paraneoplastic cerebellar degeneration [33]	Anti-Hu, anti-Yo, anti-Tr, anti-Ri	Gait disturbance, nausea, dizziness, diplopia	SCLC, ovarian, breast, Hodgkin's lymphoma	Purkinje cell loss, dentate, and olivary nuclei degeneration	Plasmapheresis and IVIg
Paraneoplastic limbic encephalitis [34]	Anti-Hu, anti-Ma-2, anti-NMDAR	Seizures, memory loss, insomnia	SCLC	Loss of neurons, limbic microglial proliferation, perivascular and interstitial inflammation	Corticosteroids and IVIg or plasma exchange
Paraneoplastic encephalomyelitis and associated paraneoplastic phenomena [33]	Anti-Hu, anti-CV-2/CRMP5, anti-Ma proteins, anti-NMDAR	Brainstem: diplopia, dysphagia, dysarthria; autonomic: orthostatic hypotension, arrhythmias	SCLC, thymoma, testicular (germ cell), non-SCLC, ovarian teratomas		Plasma exchange, IVIg or cyclophosphamide (for anti-CV2/CRMP5 and anti-NMDAR)
Paraneoplastic stiffman syndrome [35]	Anti-amphiphysin	Generalized rigidity	Breast, SCLC	Motor neurons and interneurons anterior horn cell loss	IVIg, benzodiazepines
Paraneoplastic sensorimotor neuropathy [35]	?	Motor and sensory loss in extremities	Multiple, usually advanced	Axonal degeneration or demyelination	Corticosteroids, IVIg
Paraneoplastic sensory neuronopathy [35]	Anti-Hu	Sensory loss (limbs, trunk, face)	SCLC	Neuronal degeneration	Steroids
Paraneoplastic opsoclonusmyoclonus [33]	?	Falls, ataxia, opsoclonus,	Neuroblastoma (children), SCLC (adults)		Corticosteroids, IVIg, ACTH; adults: IVIg
Lambert-Eaton myasthenic syndrome [32]	Anti P/Q-type VGCC	Weakness, fatigue, autonomic dysfunction	SCLC	P/Q type VGCC antibody	Immunotherapy, 3,4-DAP, pyridostigmine, guanidine
Polymyositis and dermatomyositis [35]	?	Proximal myopathy, neck flexion weakness, eyelid rash in DM	Ovarian, breast, lung, gastrointestinal	Immune-mediated vasculopathy, muscle necrosis with elevated creatine kinase	Corticosteroids, IVIg and chemotherapy (eg, azathioprine)
Myeloma associated sensorimotor neuropathy [35]	?	Neuropathy (sensory, sensori-motor)	Multiple myeloma		None specific

^aRefers to specific treatment modalities. In most cases treatment of the underlying tumor is usually the most effective treatment of the paraneoplastic syndrome.

ACTH—adrenocorticotropic hormone; CRMP5—collapsin response mediator protein 5; IVIg—intravenous immunoglobulin; NMDR—N-methyl-D-aspartate receptor; SCLC—small cell lung cancer; VGCC—voltage-gated calcium channel.

Table 2

Nervous system complications from chemotherapy

Complication	Typical drugs causing complication	Clinical syndrome	Treatment and prevention	Prognosis
Peripheral and cranial neuropathy	Vinca alkaloids (tubulin binding) vincristine, vinblastine	Sensorimotor neuropathy (axonal)	Drug withdrawal	Usually good with discontinuation [53]
	Platinum compounds (DNA crosslink formation) (cisplatin, carboplatin, oxaliplatin) [53]	Sensory neuropathy; vestibulo-cochlear toxicity with cisplatin (hearing loss, dizziness, ataxia, vertigo)	Amifostine, carbamazepine to treat oxaliplatin neuropathy; calcium gluconate, magnesium sulfate, and oxcarbazepine prophylaxis for oxaliplatin neuropathy [51]	Variable for cisplatin; good with treatment for oxaliplatin [52•]
	Taxanes: paclitaxel, docetaxel (inhibition of microtubule function) [53]	Sensory neuropathy (numbness, tingling)	Vitamin E and N-acetyl carnitine	Good with drug discontinuation
	Macrolide antibiotic: ixabepilone (tubulin binding) [52•]	Sensory neuropathy (numbness, tingling)	Discontinue drug or reduce dose	Good with treatment
	Thalidomide (antiangiogenesis) [53]	Sensory neuropathy		
Stroke	Bortezomib (proteasome inhibitor) [52•]	Distal sensory axonal neuropathy	Discontinue drug/reduce dose	Good with treatment
	Bevacizumab [52•]; imatinib [52•]	Hemorrhagic or ischemic stroke (rare)	Discontinue drug	Variable
Seizures	Cisplatin (DNA crosslinks); cytosine arabinoside (pyrimidine antimetabolite) [56]	Seizures	Discontinue drug/reduce dose	Good with drug discontinuation
	Cyclophosphamide	Seizures	Discontinue drug/reduce dose	Good with drug discontinuation
	Nelarabine (purine nucleoside analog) [52•]	–	Discontinue drug/reduce dose	Good with drug discontinuation
Myelopathy	Cisplatin (DNA crosslinks); Ara-C (pyrimidine antimetabolite); MTX (dihydrofolate reductase inhibitor) [56]	Lhermitte's sign with cisplatin; motor, sensory and bowel/bladder dysfunction with Ara-C and MTX.	Discontinue drug/reduce dose	Good with treatment (drug discontinuation)
Aseptic meningitis	MTX (dihydrofolate reductase inhibitor) [56]	Headache, neck stiffness, back pain and fever following intrathecal injection.	Discontinue drug and reduce dose; corticosteroids	Usually good
Encephalopathy	Ifosfamide (alkylating agent) [56]	Confusion, hallucinations, drowsiness	Discontinue drug; benzodiazepines may hasten recovery	Good with drug withdrawal
	Methotrexate (dihydrofolate reductase inhibitor) [56]	Acute mental status change, seizures within 24 hours of high-dose i.v administration	Discontinue drug	Good with drug withdrawal
Cerebellar syndrome	Cytosine arabinoside (pyrimidine antimetabolite)	Ataxia, nystagmus, and dysarthria	Prevention with avoidance of high-dose	Variable; may or may not reverse completely

Ara-C—cytosine arabinoside; MTX—methotrexate.