Cerebrovascular complications of cancer
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Introduction

Overview

Cerebrovascular disease (sinus thrombosis, cerebral infarction, or hemorrhage) is a common complication of cancer and of cancer therapy. In this article, the authors review the clinical milieu in which these disorders develop and summarize the methods of diagnosis, including characteristic abnormalities of clinical findings, coagulation function tests, and neuroimaging. The management of these vascular disorders can be challenging in this patient population because of comorbidities associated with cancer. Some vascular disorders are unique to the cancer patient, including radiation-induced carotid artery atherosclerosis and chemotherapy-induced vasculopathy. Until recently, reports of these latter conditions were anecdotal and infrequent.

Key points

• Cancer is a hypercoagulable state leading to an increased risk of venous and arterial thromboembolic events.
• Cancer therapies such as radiation and chemotherapy have a range of adverse effects upon the CNS vasculature.
• Patients with cancer are also at risk for intracranial hemorrhage from a variety of factors including thrombocytopenia, coagulopathy, hemorrhagic brain metastases, and hematological malignancies.

Historical note and terminology

In the mid-1800s, Armand Trousseau first drew attention to the clinical association between thrombophlebitis and cancer. Subsequently, clinicians observed that thrombophlebitis is only 1 manifestation of a coagulopathy associated with cancer, which represents a disruption of the delicate balance that normally exists between hemorrhage and coagulation. This coagulopathy is poorly understood, and its mechanism is controversial. Disseminated intravascular coagulation is generally defined as excess thrombin generation within the vasculature that overwhelms normal regulatory hemostatic mechanisms. This results in increased consumption of platelets, coagulation factors, and sometimes inhibitors of coagulation. Defibrination syndrome and consumption coagulopathy are alternate terms for disseminated intravascular coagulation.

Clinical manifestations

Presentation and course

The symptoms of cerebrovascular disease associated with cancer patients typically present acutely, as with patients without cancer. However, strokes in cancer patients are more often multifocal at the onset and may produce an encephalopathy rather than unifocal cerebral signs. In a retrospective observational study of critically ill patients with known malignancy who developed acute neurologic symptoms, hemiparesis was independently associated with ischemic stroke (Ryu et al 2016). Although cerebrovascular disorders occur in patients who are known to have cancer and who have been treated for cancer, in some instances, the cerebrovascular disease is the presenting sign of cancer. Recognition of the cerebrovascular disease can lead to the diagnosis of cancer. Cryptogenic stroke alone does not warrant a workup for occult malignancy, and should be considered as an etiology for acute ischemic stroke patients with a D-dimer greater than 3.7, a C-reactive protein greater than 27, older age, and a history of smoking (Selvik et al 2015).
Acute or chronic disseminated intravascular coagulation can result in hemorrhage, thrombosis, or a combination that involves the systemic or cerebral blood vessels. In addition to this type of coagulation abnormality associated with cancer, cerebral hemorrhage and thrombosis can occur in cancer patients due to altered hemostatic function induced by modern antineoplastic therapies. In other cancer patients, cerebral hemorrhage or thrombosis is a direct result of tumor on cerebral vessels.

Parenchymal brain hemorrhage in cancer patients produces headache, seizure, or obtundation that may be accompanied by focal cerebral signs (Graus et al 1985). However, in patients who experience hemorrhage into metastatic brain tumors, the acute symptoms of hemorrhage are superimposed on chronic cerebral symptoms caused by the brain metastasis. Brain hemorrhage can be the presenting sign of metastasis (Huang et al 2007). If the brain hemorrhage produces significant mass effect or if an uncontrolled coagulation disorder producing hemorrhage occurs, then the neurologic signs are progressive. Subdural hemorrhage in cancer patients usually presents acutely, typically with confusion and lethargy (focal cerebral signs are less common) (Graus et al 1985). Subdural hemorrhage can be fatal if caused by an uncontrolled coagulation disorder. Subarachnoid hemorrhage presents with headache, and may be accompanied by sudden deterioration of consciousness. When cerebral hemorrhage is due to a systemic coagulation disorder, there may be concomitant systemic bleeding, typically from the mucosal surfaces, retinæ, gastrointestinal and genitourinary tracts, skin, or venipuncture and bone marrow aspiration sites. Paradoxically, there may also be thrombosis, typically limb thrombophlebitis, pulmonary embolism, myocardial infarction, or limb arterial embolism. A syndrome similar to the hemolytic-uremic syndrome is associated with the administration of adjuvant chemotherapy for carcinoma (especially gastric adenocarcinoma) and may produce seizures, loss of consciousness, or confusion. It also typically produces dyspnea, hypertension, and peripheral edema (Gordon and Kwaan 1999).

Typically, cerebral infarction from nonbacterial thrombotic endocarditis produces focal cerebral signs; yet, because of the multiplicity of infarctions there may be a superimposed encephalopathy (Rogers et al 1987). In contrast, cerebral intravascular coagulation, unaccompanied by nonbacterial thrombotic endocarditis, commonly results in encephalopathy; although, there may be transient superimposed focal signs (Collins et al 1975). The clinical course of cerebral infarction caused by these coagulation disorders is progressive, but the severity of cerebral signs often fluctuates. Focal or diffuse cerebral signs caused by cerebral infarction from leptomeningeal metastasis may be accompanied by the more typical cranial nerve or spinal nerve root signs of this disorder.

The occlusion of large cerebral veins caused by a coagulation disorder generally presents with seizures (Bushnell and Saposnik 2014). The most frequently involved venous sinus is the superior sagittal sinus (Raizer and DeAngelis 2000). There may be accompanying focal or diffuse cerebral signs if cerebral edema, venous infarction, or hemorrhage occurs. In contrast, venous occlusion produced by skull or dural metastasis presents subacutely with signs of increased intracranial pressure (eg, headache, vomiting, papilledema) that may be accompanied by focal or diffuse cerebral signs (Raizer and DeAngelis 2000). Spontaneous recovery can occur when venous occlusion is caused by a coagulopathy, but the clinical course is progressive in untreated metastatic venous occlusion. Venous occlusion associated with L-asparaginase usually occurs during or after induction therapy to treat leukemia and can resolve spontaneously.

Fungal septic cerebral infarction can be seen in cancer patients treated with immunosuppressants. This produces acute focal signs, seizures, or encephalopathy. Focal signs and seizures are more common in aspergillosis, whereas encephalopathy is more common in candidiasis. Patients are usually febrile. Cerebral signs in septic fungal emboli are progressive, and the disorder is often fatal.

Cerebral tumor embolic infarctions present acutely (O'Neill et al 1987), and signs may progress in patients with systemic carcinoma because of cerebral tumor growth. In contrast, growth of tumor embolic material is rare in patients with atrial myxoma and papillary fibroelastoma. Intravascular lymphomatosis usually presents subacutely with progressive multifocal cerebral signs (Calamia et al 1999). Cerebral granulomatous angiitis complicating Hodgkin disease or leukemia may produce headache, fever, confusion, seizures, obtundation, or hemiparesis. Approximately 40% of patients with granulomatous angiitis may have transient ischemic attacks, and 25% may have seizures. Self-limited symptoms suggesting cerebral transient ischemic attacks can occur during therapy with interleukin-2. The reversible posterior leukoencephalopathy syndrome (PRES) is a recognized complication of systemic or intrathecal chemotherapy or antiangiogenic targeted therapies including bevacizumab, taxanes, platinum derivatives, and vinca alkaloids (Singer et al 2015). In addition, this syndrome has been observed in patients with lymphoproliferative disorders treated with stem cell transplantation and immunosuppressive treatments such as tacrolimus, cyclosporine,
everolimus, and sirolimus (Pruitt et al. 2013). PRES typically causes headaches, vomiting, confusion, seizures, cortical blindness, and motor signs.

Ischemic symptoms associated with the administration of chemotherapy do not recur when the medication is discontinued. In comparison, symptoms of carotid atherosclerosis associated with neck radiation can be recurrent and progressive. These include transient ischemic attacks, persistent focal cerebral signs, amaurosis fugax, and seizures (Murros and Toole 1989).

**Prognosis and complications**

Unfortunately, no prospective studies have taken place concerning cerebrovascular disorders in cancer patients that provide information about the duration and quality of survival specific to each syndrome. A D-dimer level greater than 5.50 mg/dL, systemic metastases, and diabetes are all independent predictors of poor survival in cancer patients with cryptogenic stroke (Shin et al. 2016). A confounding variable is that the duration of survival is often dictated by the underlying tumor or systemic thromboembolic or hemorrhagic complications. Retrospective studies indicate that the survival rate for patients with hemorrhage into metastatic brain tumor does not differ from those patients without tumoral hemorrhage, except for those with large hemorrhages that are life-threatening (Graus et al. 1985).

Independent factors associated with poor 30-day survival after intracranial hemorrhage in cancer patients include impaired consciousness, multiple foci of hemorrhage, hydrocephalus, no ventriculostomy, treatment of increased intracranial pressure, and absence of a primary brain tumor (Navi et al. 2010). Limited data are available regarding the survival rate for patients with ruptured neoplastic aneurysms from carcinoma. The prognosis for recovery and survival after brain hemorrhage associated with hyperleukocytosis early in leukemia or acute disseminated intravascular coagulation associated with acute promyelocytic leukemia has improved in recent years because of aggressive methods to treat the underlying tumor. The prognosis for many patients with parenchymal, subdural, or subarachnoid hemorrhage caused by coagulopathy is affected by systemic hemorrhage. Zhang and colleagues reported a retrospective comparison of the survival of patients hospitalized with cerebral infarction who did or did not have an associated cancer, and the overall survival was worse in the cancer patients (Zhang et al. 2006).

Survival in nonbacterial thrombotic endocarditis is usually short because many patients have advanced cancer; yet, death may also be a result of myocardial infarction or pulmonary embolus because of the associated coagulation disorder (Rogers et al. 1987). Survival in cerebral intravascular coagulation is brief (usually weeks) (Collins et al. 1975). Patients with nonmetastatic superior sagittal sinus occlusion can recover completely, especially if it occurs early in the course of cancer when the tumor is responding to treatment. The prognosis is poor, however, when the deep venous sinuses are involved (Santoro et al. 2005). When non-metastatic superior sagittal sinus occlusion occurs late, the prognosis is poor, especially if the tumor is not responding to treatment (Sigsbee et al. 1979). A study of cerebral venous occlusion in patients without cancer suggests that the long-term cognitive effects are less favorable than previously thought, even when anticoagulation is administered (DeBruijn et al. 2000). With metastases as the underlying etiology it may worsen, unless therapy is directed to the adjacent skull or dural tumor, and it can be fatal (Lopez-Pelaez et al. 2000). Fungal septic infarction is almost uniformly fatal, despite administration of antifungal therapy. This may reflect the severely immunosuppressed condition of patients who develop disseminated fungal infections in the setting of cancer. Infarctions from tumor emboli and leptomeningeal metastasis are rare, and the prognosis is directly related to the presence of metastatic disease. Subsequent embolization can be prevented in patients with cardiac myxoma by removing the tumor. However, aneurysm may develop as a delayed consequence of embolization. Successful surgical treatment of radiation-induced carotid stenosis may reduce ischemic symptoms, but data are limited regarding the survival rate and cause of death in such patients. In patients with radiation-induced stenosis, there appears to be a higher rate of in-stent restenosis (Yu et al. 2014). Carotid artery rupture is associated with high mortality. The prognosis in intravascular lymphomatosis is poor, often because the diagnosis is made late in the disease. It can stabilize with steroids, radiation, or chemotherapy (Calamia et al. 1999). The prognosis of granulomatous angiitis occurring with Hodgkin disease is more favorable if it occurs synchronously with, rather than later than, Hodgkin (Rosen et al. 2000). The probability for recovery from cerebral thrombosis caused by L-asparaginase is good. Survival in other cerebral infarctions related to chemotherapy covers a wide spectrum; the neurologic symptoms may be mild and transient, or fatal.

**Clinical vignette**

The patient was a right-handed, 63-year-old woman diagnosed with metastatic pancreatic cancer 2 months before experiencing neurologic symptoms. Her prior medical history was otherwise unremarkable, and there were no known
stroke risk factors. She received 1 cycle of investigational chemotherapy, and 2 days after the second dose of chemotherapy, she awoke with inability to speak. On examination a few hours later, she had marked reduction in speech output associated with paraphasic errors. She was unable to repeat. The remainder of the neurologic examination was normal. Her vital signs were normal; there was no cardiac murmur and no neck or ocular bruits. Table 1 shows the hematologic and coagulation studies performed that day (Day 1). There was a decrease in the platelet count compared to 2 weeks prior (Day -14) and the D-dimer was elevated. CT scan was unremarkable. However, MRI scan administered the next day showed abnormal tissue density in a gyriform pattern in the left tempoparietal area, consistent with infarction as well as ischemic changes in the periventricular regions of both cerebral hemispheres and in the left pons. Cranial MRA showed a loss of signal in the distal left middle cerebral artery. The extracranial MRA was normal aside from minimal atherosclerosis in the left internal carotid artery. Transthoracic echocardiography was normal aside from aortic sclerosis. Her neurologic symptoms improved considerably over the next 48 hours, but she was left with slight hesitancy in speech and occasional paraphasic errors.

Table 1. Hematologic and Coagulation Parameters

Day -14
- Platelets (K/Cumm): 235
- Hematocrit (%): 36.8
- Fibrinogen (mg/dl): ---
- D-dimer (ug/ml): ---
- PT (sec): ---
- PTT (sec): ---
- Fibrin Monomers: ---
- Fibrin Split Products (ug/ml): ---

Day 1
- Platelets (K/Cumm): 147
- Hematocrit (%): 35.8
- Fibrinogen (mg/dl): 471
- D-dimer (ug/ml): .5-1
- PT (sec): 13.6
- PTT (sec): 25.4
- Fibrin Monomers: ---
- Fibrin Split Products (ug/ml): ---

Day 16
- Platelets (K/Cumm): 93
- Hematocrit (%): 34.4
- Fibrinogen (mg/dl): 379
- D-dimer (ug/ml): 1-2
- PT (sec): 14.4
- PTT (sec): 34.1
- Fibrin Monomers: positive
- Fibrin Split Products (ug/ml): 10-40

Day 21
- Platelets (K/Cumm): 67
- Hematocrit (%): 30.5
- Fibrinogen (mg/dl): 269
- D-dimer (ug/ml): 1-2
- PT (sec): 16.3
- PTT (sec): 37.3
- Fibrin Monomers: ---
- Fibrin Split Products (ug/ml): ---

She was difficult to rouse 1 morning approximately 2 weeks later (Day 16), and she was brought to the emergency
room. She was obtunded. She was able to open her eyes to a painful stimulus, but was unresponsive to commands. Her eyes were deviated to the right. She spontaneously moved all limbs. The deep tendon reflexes were symmetric, and the plantar reflex was flexor bilaterally. The brain MRI and MRA showed no change from the previous MRI and MRA. There was a further decrease in platelets and a further elevation of the D-dimer. In addition, fibrin monomers and fibrin split products were abnormal. EKG showed a possible septal infarct of indeterminate age. EEG showed diffuse slowing with triphasic waves. CT scan of the abdomen showed progression of hepatic metastases and decreased attenuation in the spleen consistent with an infarct. A clinical diagnosis of chronic disseminated intravascular coagulation was made, most likely in association with nonbacterial thrombotic endocarditis. As a result of the progression of her primary tumor, now considered incurable, anticoagulation was not administered.

The patient's level of consciousness waxed and waned over the first few days; at times she was alert and followed commands, and at other times was deeply obtunded. She became progressively more obtunded and could not be aroused. The right arm became spastic, and there was intermittent jerking of the right arm. She developed Cheyne-Stokes respirations. The left eye was slightly elevated above the right eye. Three days after the onset of the symptoms, she had a small amount of hematuria. Five days after admission, the left calf became swollen and warm. Table 1 shows further decrease in platelets and fibrinogen and increase in the prothrombin and activated partial thromboplastin times (Day 21). Her temperature rose to 101°F. She died 2 weeks after admission.

General autopsy revealed adenocarcinoma of the pancreas with diffuse abdominal metastasis and microscopic metastasis to the lungs and right adrenal gland. There was severe bilateral bronchopneumonia. Sterile platelet-fibrin vegetations were present that were consistent with nonbacterial thrombotic endocarditis on the mitral valve and multiple recent infarctions involving the spleen, both kidneys, and myocardium. Neuropathological examination revealed a large recent left frontal lobe infarction in the distribution of the proximal anterior and middle cerebral arteries, with organizing occlusive thromboemboli within the proximal left anterior and middle cerebral arteries, and organizing thromboemboli with partial recanalization of the distal middle cerebral artery. Thrombi were present in the subarachnoid arteries overlying the left inferior frontal lobe. In addition, there were recent infarcts involving the right parietal lobe, right superior cerebellar cortex, left basis pontis, and left basal ganglia. Old infarcts were present involving the left superior temporal and inferior parietal gyri, left paracentral cortex, and left thalamus associated with microscopic thromboemboli.

This case illustrates characteristic neurologic manifestations of nonbacterial thrombotic endocarditis, which in this instance were the presenting signs of this coagulopathy, prior to systemic manifestations. Nonbacterial thrombotic endocarditis typically presents with focal neurologic signs, most commonly aphasia. Most patients also develop encephalopathy that characteristically waxes and wanes but ultimately is progressive. Systemic findings and laboratory results that were consistent with a chronic coagulopathy include myocardial infarction, calf phlebitis, a progressive decrease in platelets and fibrinogen, elevated D-dimer and prothrombin, and activated partial thromboplastin times. Autopsy showed widespread systemic thromboemboli. The investigational drug that this patient received is not known to cause significant thrombocytopenia; thus, the progressive decrease in platelets was most likely related to the consumption of platelets from the coagulopathy. Occasionally, the drug is associated with systemic thromboembolic complications, such as clotting of indwelling venous catheters and deep vein thrombosis. It is possible that the drug contributed to the coagulopathy that resulted in nonbacterial thrombotic endocarditis, but a more likely cause is the underlying tumor; pancreatic cancer is commonly associated with clinically significant thromboembolic complications, even without therapy, and sometimes as the presenting sign of the cancer. The neuropathological examination showed infarctions of various ages in multiple vascular territories due to the coagulopathy. The likelihood is high that the left middle cerebral artery occlusions were due to embolization from the heart, and the remainder was due to in situ thrombosis from the coagulopathy.

**Biological basis**

**Etiology and pathogenesis**

The most common cause of symptomatic cerebral hemorrhage or thrombosis in cancer patients is altered coagulation function that is directly related to the tumor or its therapy. Direct spread of tumor to the brain, cerebral infection, and vascular toxicity of antineoplastic therapy are other important causes.

**Table 2. CNS Vascular Disorders Found at Autopsy in Patients with Cancer**
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebral hemorrhage</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td></td>
</tr>
<tr>
<td>Intratumoral</td>
<td></td>
</tr>
<tr>
<td>• Secondary to coagulopathy</td>
<td>42(35)</td>
</tr>
<tr>
<td>• Hypertensive</td>
<td>9(8)</td>
</tr>
<tr>
<td>• Primary subdural hematoma</td>
<td>28(9)</td>
</tr>
<tr>
<td><strong>Primary subarachnoid hemorrhage</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11(6)</td>
</tr>
<tr>
<td><strong>Cerebral infarction</strong></td>
<td>126(59)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>31(7)</td>
</tr>
<tr>
<td>Intravascular coagulation</td>
<td>15(13)</td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
<td>23(17)</td>
</tr>
<tr>
<td>Septic embolus</td>
<td>18(13)</td>
</tr>
<tr>
<td>Tumor embolus</td>
<td>6(3)</td>
</tr>
<tr>
<td>Venous occlusion</td>
<td>19(2)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>14(4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>244(139)</td>
</tr>
</tbody>
</table>

In acute disseminated intravascular coagulation, hemorrhages may coexist with thrombosis. The mechanisms involved in this paradoxical association are not fully understood. Cancer is associated with disseminated intravascular coagulation by a variety of mechanisms, including the release of procoagulant material or tissue cell enzymes into the systemic circulation, fibrinolytic activation, and neovascularization of tumor with abnormal endothelial lining. Acute promyelocytic leukemia is often complicated by acute disseminated intravascular coagulation caused by the release of procoagulant material from progranulocytes. This can result in cerebral and systemic hemorrhages. In other patients with leukemia who experience brain hemorrhage at relapse or at failure to induce remission, disseminated intravascular coagulation may be present; yet, thrombocytopenia, liver failure, and sepsis also contribute to the coagulopathy (Graus et al 1985). Hemorrhages caused by coagulopathy are usually located in the cerebral white matter and are more often single compared to hemorrhages caused by leukemic infiltration of brain.

Hemorrhage into metastatic brain tumors results from rapid tumor necrosis or from the rupture of neoplastic or adjacent cerebral blood vessels from rapid tumor growth (Lieu et al 1999). Malignant melanoma, germ cell tumors (especially choriocarcinoma), and papillary thyroid, hepatocellular, and lung cancers are the most common brain metastases to hemorrhage. In some tumors, particularly choriocarcinoma, the underlying metastasis may be microscopic. Intracerebral hemorrhages that result from a ruptured neoplastic aneurysm are caused by destruction of the arterial wall from a tumor embolus and subsequent restored blood flow. Brain hemorrhages may be multiple and usually rupture into the brain parenchyma. They occur most commonly in patients with cardiac myxoma, choriocarcinoma, and lung cancer. Parenchymal brain hemorrhages occurring in the setting of extreme elevation of the peripheral blast count in leukemia (hyperleukocytosis) are associated with cerebral leukostasis (plugging of thin-walled vessels) and parenchymal leukemic nodules. Hyperleukocytosis is most common in acute myelogenous leukemia (Wurthner et al 1999). The mechanism of hemorrhage is disputed, but is likely a combination of hyperviscosity and blood vessel damage from the leukostasis and rupture of blood vessels by the leukemic nodules. Hemorrhages associated with hyperleukocytosis are localized in the white matter, but may rupture into the ventricles or subarachnoid space, depending on the location.

In leukemia, acute subdural hematoma is most commonly due to thrombocytopenia or disseminated intravascular coagulation. Graus and colleagues (Graus et al 1996) reported a preponderance of subdural, rather than parenchymal, hematomas in leukemic patients undergoing allogeneic or autologous bone marrow transplant. Typically, the patients had acute myelogenous leukemia and severe refractory thrombocytopenia. In contrast, chronic subdural hemorrhage in leukemic patients is more often associated with dural leukemic infiltration (Pitner 1973). A possible association exists with subdural hematoma, hyperleukocytosis, and prior lumbar puncture in acute leukemia (Jourdan et al 1995).
Carcinoma (typically prostate and gastrointestinal malignancies) or lymphoma metastatic to the dura may also produce subdural hemorrhage from spontaneous hemorrhage of the tumor, from rupture of the inner dural vessels because the vessels in the external layer are obstructed by tumor, or from erosion of meningeal vessels by the tumor (Russell and Cairns 1934). Sometimes the tumor is microscopic at postmortem examination. Skull metastasis rarely underlies epidural hematoma (Hayashi et al 2000). Subarachnoid hemorrhages are usually caused by thrombocytopenia, and are rarely associated with leptomeningeal metastasis.

Cerebral hemorrhage can be a complication of chemotherapy if severe thrombocytopenia results. L-asparaginase, often used in the induction therapy of leukemia, can produce brain hemorrhage; the precise mechanism of altered coagulation function induced by this drug is not known, but it is known to produce fibrinolysis and to deplete plasma proteins involved in coagulation. A hemolytic-uremic-like syndrome that results from chemotherapy (particularly mitomycin) administered for carcinoma can produce brain hemorrhage. This syndrome can also occur in patients with carcinoma who have not received mitomycin, and the mechanism is unknown (Gordon and Kwaan 1999). Bevacizumab, a humanized monoclonal antibody that targets the vascular endothelial growth factor receptor, is typically used in the treatment of a variety of systemic and brain tumors. This drug carries a small risk of systemic or cerebral thrombosis or hemorrhage. Concomitant anticoagulation may increase the risk of cerebral hemorrhage (Nguyen and Abrey 2007); however, this has not held true in all studies (Norden et al 2012). In a series of children with systemic cancer and brain tumors, intracranial hemorrhage during treatment for cancer was associated with treatment for hydrocephalus, coagulopathy, thrombocytopenia, and hemorrhage into tumor. In patients who developed a brain hemorrhage after cancer treatment, brain radiation was a possible contributor (Kyrnetskiy et al 2005). Radiation-induced cerebral aneurysms are a rare complication of therapeutic radiation for skull base or nasopharyngeal cancers.

The majority of patients with advanced solid tumors have laboratory evidence of clotting activation at diagnosis that is generally asymptomatic. The mechanism for this remains poorly understood, and its relationship to subsequent thromboembolic episodes is uncertain. The third-generation breakpoint cluster-Abelson tyrosine kinases inhibitors (BCR-ABL TKIs) ponatinib and nilotinib used to treat chronic myelogenous leukemia were found to have an increased incidence of stroke compared to imatinib. It is proposed these medications may exacerbate traditional risk factors and increase smooth muscle proliferation (Gopal et al 2016). Surgery, hormone therapy, and chemotherapy appear to increase the risk of thromboembolism in the systemic circulation (Sutherland et al 2003). Their role in cerebral thromboembolism has not yet been adequately investigated. Cerebral infarction in patients with nonbacterial thrombotic endocarditis is due to a combination of embolization of valvar platelet-fibrin vegetations to the brain and cerebral intravascular coagulation, both of which are related to an underlying coagulopathy (Rogers et al 1987). Medium and small vessels may be affected. The resulting infarctions are single or multiple, and may be hemorrhagic. Nonbacterial thrombotic endocarditis is most commonly associated with adenocarcinoma, especially mucin-producing carcinoma of the lung or gastrointestinal tract, and lymphoma (Edoute et al 1997). Another cardiac mechanism of ischemic stroke in cancer is via atrial fibrillation. Intravenous bisphosphonate is often used in patients with bone metastases and appear to impart an increased risk of atrial fibrillation and stroke (Wilkinson et al 2010). Mucinous adenocarcinomas can also be complicated by intravascular mucinosis and thrombosis with brain infarctions. The hallmark of cerebral intravascular coagulation is fibrin occlusion of multiple small arteries, veins, or capillaries resulting in multiple infarctions or petechiae. Usually these occur in the white matter more than in the gray matter (Collins et al 1975; Nowacki et al 1985). Cerebral intravascular coagulation is reported most commonly with leukemia, lymphoma, and breast cancer. Spontaneous occlusion of the superior sagittal sinus occurs in patients with solid tumors, lymphoma, or leukemia. In a retrospective review of stroke in children treated for acute lymphoblastic leukemia, a prevalence of 0.47% was found, all due to venous thrombosis (Santoro 2005). It is likely to be related to a coagulation disorder associated with the tumor or chemotherapy. Many of these occlusions may compress or infiltrate the superior sagittal sinus and lead to stasis and thrombosis. This type of venous occlusion is found more often at autopsy. Venous infarction from superior sagittal sinus occlusion is typically hemorrhagic. Septic cerebral infarction results from embolization of septic material to the brain, and is typically caused by fungal organisms complicating immunosuppression in patients with leukemia or those who have undergone bone marrow transplantation (Coplin et al 2001; Kawanami et al 2002). Candida and aspergillus species are most common. The infarctions are usually multiple and may be hemorrhagic. If left untreated, they will evolve into an abscess. Aspergillus, in addition, can have an angioinvasive presentation characterized by progressive stenosis of the large cerebral vessels which left untreated, can progress rapidly and precipitate cerebral infarction (Li et al 2015).
addition, some species can disrupt the vascular elastic lamina leading to cerebral aneurysmal formation and hemorrhage. Cerebral tumor emboli usually gain access to the systemic arterial circulation via the pulmonary circulation; therefore, cerebral tumor emboli are most common in patients with primary or metastatic lung cancer. In some patients with lung cancer, the embolization occurs during manipulation of the lung at thoracotomy. Embolization can occur even with small peripheral lung tumors (Brown et al 2004). Tumor emboli may obstruct large or small cerebral vessels. In intravascular lymphomatosis, multiple cerebral vessels become occluded by intraluminal proliferating lymphoma cells. The mechanism of infarction in leptomeningeal metastasis is tumor cell invasion of the Virchow-Robin spaces, producing occlusion or spasm of the penetrating arteries. Treatment-related cerebral infarctions result from direct damage to intracranial or extracranial cerebral vessels or by other speculative mechanisms, including platelet activation, perturbation of hemostasis, vasculitis, and vasospasm. The mechanism for posterior leukoencephalopathy syndrome after chemotherapy administration is not known.

The precise role that systemic chemotherapy and hormonal therapy for cancer treatment play in cerebral ischemia is uncertain. Women with breast cancer have an increased risk of cerebral infarction compared to the general population (Nilsson et al 2005). It is unclear if the infarctions are due to tamoxifen therapy. In a meta-analysis of breast cancer patients, Bushnell and Goldstein (Bushnell and Goldstein 2004) found that tamoxifen administration was associated with a small risk of ischemic stroke. However, in a case control study, no association with tamoxifen was found (Geiger et al 2004). Cisplatin, particularly when used in combination chemotherapy, carries a small risk of systemic and cerebral thrombosis (Li et al 2006; Etgen et al 2009). In rare instances it causes reversible posterior leukoencephalopathy syndrome, which has also been described with bevacizumab (Glusker et al 2006; Ozcan et al 2006), as well as other targeted therapies, including pazopanib (Chelis et al 2012), sunitinib (Padhy et al 2011), cetuximab (Palma et al 2011), sorafenib (Govindarajan and Adusumilli 2006; Dogan et al 2010), and trastuzumab (Kaneda et al 2012). It appears that the therapies targeting the vascular endothelial growth factor pathway are particularly linked to reversible posterior leukoencephalopathy syndrome (Tlemsani et al 2011). In a retrospective study of 1559 patients with advanced lung or prostate cancer, 28 cerebral ischemic events (transient ischemic attack or cerebral infarction) were identified. No association between these events and the administration of a matrix metalloprotease inhibitor, with or without platinum-based chemotherapy, was found. The events were, however, predicted by the presence of distant metastases in the liver or lungs (Behrendt and Ruiz 2005). In some patients, a hemolytic, uremic-like syndrome develops after combination chemotherapy with cisplatin or the sole use of mitomycin. Neck radiation administered for head and neck cancers and lymphoma produces or accelerates carotid artery atherosclerosis (Dorresteijn et al 2002).

Radiation-induced extracranial vasculopathy produces ischemia by atherosclerotic embolization to the brain or by hemodynamically significant arterial stenosis (Atkinson et al 1989). Dorresteijn and colleagues (Dorresteijn et al 2005) reported an increase in intima-media thickness of irradiated carotid arteries detected on ultrasound in patients treated for parotid tumors as compared with non-irradiated arteries. The changes were more significant with longer post-radiation intervals. Histologically, it is indistinguishable from typical atherosclerosis, but the distribution is usually more extensive and involves the common carotid artery, localized to the field of radiation. A report identified that long-term survivors of childhood Hodgkin disease who received mantle radiation are at increased risk for stroke, presumably related to carotid artery vascular injury or cardiac valvular disease (Bowers et al 2005). Stereotactic radiosurgery is rarely complicated by cerebral infarction. Moyamoya syndrome can result from cranial irradiation in childhood (Kikuchi et al 2007; Manion and Sung 2011). Emergency carotid artery ligation to treat carotid artery rupture complicating head and neck cancer therapy can result in extensive cerebral hemisphere infarction and death. The biological basis for the association of cerebral granulomatous angiitis with Hodgkin disease or leukemia is unknown. Some experts consider it an antibody negative paraneoplastic syndrome (Mauermann 2017).

**Epidemiology**

Few population-based studies of cerebrovascular disorders in cancer patients have been performed. However, in a study of 100 critically ill patients with cancer, 20 were found to have cerebrovascular disease (Legriel et al 2010). A prospective population based study using 327,389 pairs of cancer patients and matched controls from the Surveillance, Epidemiology, and End-Results Medicare linked database demonstrated an association between incident cancer and stroke in the following 3 months (Navi et al 2015). They concluded there was an increased short-term risk of stroke, particularly in patients with lung, pancreatic, and colorectal cancer, after diagnosis. In both treated and untreated cancer patients a critical lack of prospective studies have been executed correlating neurologic evaluation with coagulation function and evidence of systemic thromboembolic or hemorrhagic complications. Most clinical
reports are retrospective or anecdotal. One retrospective clinical review (Chaturvedi et al 1994) determined the cause of cerebral ischemic events in 33 patients with cancer. The most common cause identified was atherosclerosis, followed by a hypercoagulable state. However, less than one third of patients had complete laboratory investigation for disseminated intravascular coagulation, and many others did not undergo complete evaluations for the cause of infarction. A retrospective study of cerebral infarction in cancer patients found embolic strokes to be slightly more common than non-embolic ones. Atherosclerosis was an uncommon cause of infarction. Lung cancer was the most common underlying cancer (Cestari et al 2004). Lung cancer patients that have received surgery plus irradiation appear to have a 2-fold increase of ischemic stroke over patients treated with surgery alone (Hung et al 2014). A population-based study of patients with cervical cancer in Taiwan found an increased risk of ischemic stroke particularly in younger patients (Tsai et al 2013). In a large population-based study, the additional risk of ischemic stroke associated with ovarian cancer was particularly prominent in women under the age of 50 (Kuan et al 2014). Small vessel ischemic changes in the brain may actually be protective against the development of brain metastases in lung cancer patients (Mazzone et al 2009). A precise diagnosis of the cause of infarction or hemorrhage is often established only at autopsy. The most comprehensive study of cerebrovascular disease in cancer patients is an autopsy study conducted by Graus and colleagues that documented the frequency and type of CNS vascular disorders in 3426 patients dying with cancer who underwent neuropathologic examination (Graus et al 1985). Five hundred patients had cerebrovascular disease, and 255 of the 500 patients (7.4% of the entire population) were symptomatic. This study may overestimate the frequency of cerebrovascular disease because a likelihood exists that patients who experienced cerebral symptoms underwent neuropathologic examination more often than those who did not. Yet, this study provides the most reliable data currently available associating the types of cerebrovascular disease with cancer and its treatment.

**Prevention**

The risk for stroke in cancer patients varies depending on the type of cancer, the extent of systemic and CNS metastasis, and the type of antineoplastic treatment. In cancer patients, the risk factors considered significant for symptomatic cerebrovascular disease in patients without cancer (eg, hypertension, diabetes, coronary artery disease, and age) are not as significant as the pathophysiologic effects of cancer and its treatment.

Hyperleukocytosis, usually occurring at the presentation of acute leukemia, is a risk factor for intracerebral hemorrhage. Emergency administration of antime tabolites and leukapheresis are the standard treatments to reduce the risk of brain hemorrhage by lowering the peripheral blast count. A retrospective study documents that leukapheresis is effective in reducing early mortality due to systemic or CNS hemorrhage, though not long-term survival (Bug et al 2007). Increased cerebral blood flow has been reported following leukapheresis in acute myelogenous leukemia (Kasner et al 2007). This study is contradicted by a larger retrospective review by Chang and colleagues, which focused on the rate of CNS hemorrhage in acute myeloid leukemia patients with hyperleukocytosis who were pretreated or not with cranial irradiation and leukapheresis (Chang et al 2007). No difference in early mortality was identified. The reason for these disparate findings is not clear. Acute disseminated intravascular coagulation, accompanying acute promyelocytic leukemia, is also a risk factor for intracerebral hemorrhage. Prophylactic heparin, chemotherapy, and all-trans retinoic acid are effective in reducing the risk of brain hemorrhage in this setting (Lengfelder et al 2005). However, cerebral venous thrombosis has been reported with the use of all-trans retinoic acid as treatment for promyelocytic leukemia (Ciccone et al 2008). Although no prospective studies to document this have taken place, it would seem rational that prompt therapy of coagulation disorders, with attention to replacing clotting factors or administration of anticoagulation, along with therapy of the tumor and sepsis would reduce the cerebral hemorrhagic complications of other cancer patients with acute or chronic intravascular coagulation. Prophylactic heparin or low-dose oral anticoagulants are effective in reducing some systemic thromboembolic complications of cancer (ie, deep vein thrombosis and indwelling catheter thrombosis), but they have not been studied in cerebrovascular disease. The administration of anticoagulants and head trauma may be risk factors for subdural hemorrhage in some patients with solid tumors (Minette and Kimmel 1989). The use of antibiotics, steroids, and other immunosuppressants are risk factors for fungal infection in patients with leukemia or those undergoing bone marrow transplant. Irradiation, infection, and unintentional oorocutaneous fistulas are risk factors for carotid artery rupture after head and neck tumor resection. Some authors suggest routine carotid duplex ultrasound screening in patients who have received neck radiation in order to detect carotid stenosis (Lam et al 2001). The administration of low-dose heparin may reduce the risk of cerebral infarction in patients undergoing carotid ligation to treat a ruptured carotid artery. In many other conditions, cerebrovascular complications related to cancer are not preventable because the underlying disease or coagulation disorder is difficult to control. However, prompt recognition
of the disorder will help to distinguish it from other neurologic complications of cancer, and can lead to therapy to ameliorate symptoms or prevent additional cerebrovascular events.

**Differential diagnosis**

In patients with solid tumors, sudden focal neurologic signs from cerebrovascular disease may be confused with the acute presentation of cerebral metastasis. Cerebral metastasis may present acutely because of a seizure or rapid expansion of the tumor. In many cancer patients, cerebral hemorrhages or infarctions are multiple and, thus, present in an atypical fashion compared with the more typical unifocal hemorrhages or infarctions in patients without cancer. In addition, cancer patients with cerebrovascular disease often show progressive neurologic deterioration rather than early recovery. In this setting, the most important differential is encephalopathy, which in cancer patients is usually due to metabolic abnormalities, hypoxia, or sepsis.

**Diagnostic workup**

In addition to a careful neurologic examination, a careful systemic examination to search for evidence of peripheral thromboembolism or hemorrhage is essential in evaluating the cancer patient who presents with stroke. Brain MRI and CT scans are most useful in identifying cerebral hemorrhage or infarction. Clues to hemorrhages from coagulation disorders or brain metastasis are multiple hemorrhages in an atypical location. In addition, intratumoral hemorrhage is often accompanied by edema and enhancement early in its course, and evolution of the hematoma is delayed. Chou and Singhal described multifocal punctuate intraparenchymal hemorrhages in a patient with blast crisis from acute myeloid leukemia (Chou and Singhal 2007). Subdural hemorrhage can be detected on CT or MRI scans, which may also reveal skull or dural tumor if these underlie the hemorrhage. CT scans can initially be normal in patients subsequently shown to have subdural hematoma due to a coagulation disorder (Graus et al 1996). Dural enhancement on neuroimaging studies is suggestive, but not diagnostic, of dural tumor. Neoplastic subdural hemorrhage is usually acute but when chronic, it can be difficult to distinguish on neuroimaging studies from effusion of dural tumor.

In patients who experience cerebral infarction, the CT or MRI scan may show single or multiple lesions, depending on the etiology. Some infarctions are hemorrhagic because of an associated coagulation disorder or because the infarction is due to an arterial embolus or venous occlusion. Only a small number of CT scans have been reported in patients with cerebral intravascular coagulation, and they were normal (Collins et al 1975). It is possible that MRI is more sensitive in detecting the small infarctions that complicate this disorder. Diffusion-weighted MRI in cerebral infarction from nonbacterial thrombotic endocarditis typically shows numerous infarctions of varying sizes in multiple territories (Singhal et al 2002). Serial CT and MRI scans can reveal abnormalities additional to infarction, such as contrast-enhancing lesions in evolving abscesses in patients with septic embolic infarction, tumor growth following tumor embolic infarction, and granulomatous angiitis. Gabelmann and colleagues reviewed the MRI findings in 9 patients with CNS aspergillosis (Gabelmann et al 2007). Single or multiple abscesses were seen in 4 patients, and 4 patients had single or multiple infarctions. Each area of infarction was positive on diffusion-weighted imaging. A dural or vascular infiltration pattern was also observed in patients with infection extending from the paranasal sinuses or orbital region. One patient developed a mycotic aneurysm of the internal carotid artery. Computerized axial tomography or MRI scans in the posterior reversible encephalopathy syndrome associated with chemotherapy typically show edema in the parietal or occipital regions, but edema may be seen in other regions as well (Bartynski and Boardman 2007). Cerebral angiography, MRA, and MR perfusion findings may also be supportive of the diagnosis and are summarized elsewhere (Bartynski and Boardman 2008).

MRI is the procedure of choice to detect cerebral venous occlusion. However, if venous flow is slow or if the occlusion is acute, the signal intensity can be difficult to interpret and magnetic resonance venography is diagnostic (Raizer and DeAngelis 2000). MRI and CT scans can also detect skull or dural tumor associated with the metastatic variety of superior sagittal sinus occlusion.

Cerebral angiography is useful in detecting several diseases that cause hemorrhage or ischemia. Cerebral angiography is a sensitive test for detecting vascular occlusions in patients with focal cerebral symptoms from nonbacterial thrombotic endocarditis. Typically, multiple branch occlusions of the middle cerebral artery are found (Rogers et al 1987). Vessel occlusion(s) can also be detected in patients with tumor embolic infarction (O'Neill et al 1987). In leptomeningeal metastasis, angiography may be normal or may show focal narrowing of arterioles at the base of brain or over the cerebral convexities. The sensitivity of
angiography in cerebral intravascular coagulation is not known. Angiography in radiation-induced atherosclerosis typically reveals occlusion or extensive stenosis of the common carotid artery confined to the field of radiation (Murros and Toole 1989). In patients with granulomatous angiitis, angiography may be normal or may show typical changes of vasculitis. The sensitivity of angiography in detecting neoplastic aneurysms is not known. FDG-PET identified patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease (Rominger et al 2009).

CSF examination is rarely helpful in patients with cancer who experience cerebrovascular complications. In suspected septic fungal infarction, the CSF is usually normal or nonspecifically abnormal. CSF examination may show mildly elevated protein, decreased or normal glucose, or moderate pleocytosis, but cultures are most often negative. The CSF in granulomatous angiitis may reveal pleocytosis and elevated protein. Most patients (75%-90%) with CNS angiitis will have elevated CSF WBCs and protein. CSF cytologic examination can be diagnostic in patients with leptomeningeal metastasis.

Patients suspected of septic infarction should have blood cultures drawn, but these may be normal in fungal sepsis. Patients with suspected aspergillosis should undergo a chest x-ray to look for pulmonary infiltrates, but the x-ray may be normal early in the illness. A chest CT scan may be more sensitive. Transbronchial biopsy should be considered for diagnosis, but it is often contraindicated because of coexisting thrombocytopenia. Echocardiography should be performed in patients with suspected tumor embolic infarction from an atrial myxoma, septic infarction from infective endocarditis, or infarction associated with nonbacterial thrombotic endocarditis. The valvular lesions of nonbacterial thrombotic endocarditis are generally too small to be detected on standard transthoracic echocardiography, but they can be detected by transesophageal echocardiography. Echocardiography can identify structural risks for paradoxical embolism such as patent foramen ovale. Comprehensive tests of coagulation and hematologic function should be performed in patients with a suspected coagulation disorder. Useful tests to diagnose acute disseminated intravascular coagulation include the activated partial thromboplastin time, prothrombin time, D-dimer assay, fibrinogen, platelet count, and peripheral blood smear examination. One large-scale study identified that the hemostatic markers thrombin-antithrombin complex, soluble fibrin monomer, and D-dimer are predictive of acute or chronic disseminated intravascular coagulation (cutoff values differ depending on the tumor type) (Wada et al 1999). As clinically indicated, limb venous duplex studies or venography, pulmonary ventilation perfusion scans, and electrocardiograms can be useful in patients with suspected systemic thromboembolic complications.

Histologic examination of the hemorrhage and hematoma wall should be performed in patients who experience a brain hemorrhage from suspected metastatic tumor when the patient does not have cancer. In patients with suspected metastatic subdural hemorrhage, biopsy of the hematoma wall or cytologic examination of the subdural fluid is necessary to establish the diagnosis. Biopsy of contrast-enhancing lesions, visible on CT or MRI, is the most sensitive way to establish the diagnosis of cerebral granulomatous angiitis, although given the irregular nature of the affected tissue it has a low specificity. In patients with suspected tumor embolic infarction, examination of a simultaneous peripheral arterial embolus is the only way to confirm this diagnosis. Visualization of a cardiac tumor on echocardiography can strongly suggest the diagnosis. All patients with suspected tumor embolic infarction should undergo follow-up CT or MRI brain scans for evidence of tumor growth. Intravascular lymphomatosis can be identified on biopsy of the brain, leptomeninges, or an active systemic site of lymphoma.

Management

The therapy for cerebrovascular disorders associated with cancer is largely empiric. No controlled studies have been reported, aside from the management of leukemia complicated by hyperleukocytosis or disseminated intravascular coagulation. Therapy of hemorrhagic brain metastasis should be directed to the underlying brain tumor(s), typically radiation therapy. This is often delayed until after the acute issues are controlled. There are no strong arguments for emergent radiation in this setting. Some patients with a single neoplastic hemorrhage benefit from surgical removal. Patients with a ruptured neoplastic aneurysm should receive brain radiation. To date, no evidence stipulates that resection of the aneurysm is beneficial. Patients who have systemic cancer resulting in a neoplastic aneurysm should also undergo aggressive therapy of the tumor to prevent subsequent embolization. Patients with cardiac myxoma should undergo removal of the cardiac tumor. Subdural hemorrhage caused by dural metastasis should be treated with drainage of the subdural fluid if it is symptomatic and with brain irradiation. Patients who develop cerebral hemorrhage from a coagulation disorder should be treated with replacement of blood clotting factors, platelets, heparin, and anti-edema measures, as indicated. Most patients with subdural hematoma caused by a coagulopathy can be successfully treated without surgery (Graus et al 1996; Colosimo et al 2000). The therapy for treatment-related cerebral
hemorrhages is the discontinuation of the offending drug. The microangiopathic hemolytic anemia syndrome is best treated with plasma exchange, control of hypertension, and use of a Staph aureus column (Gordon and Kwaan 1999).

The management of systemic and cerebral thromboembolic disorders caused by activated coagulation in cancer patients is controversial. Attempts should be made to control the underlying tumor, when possible. In general, heparin is more effective than warfarin in treating these disorders. In a randomized trial comparing low-molecular-weight heparin and warfarin in cancer patients with systemic venous thromboembolism, there was a 50% relative risk reduction in recurrent thromboembolism with heparin (Lee et al 2003). Heparin reduces cerebral ischemic symptoms in some patients with nonbacterial thrombotic endocarditis (Rogers et al 1987). Subcutaneous heparin may be attempted to reduce the need for hospitalization, but often high doses are required to reverse the coagulation abnormality. No known effective therapy for cerebral intravascular coagulation exists. The effect of anticoagulation in cancer patients with metastatic or non-metastatic superior sagittal sinus occlusion has not been rigorously studied. In children with acute leukemia and cerebral venous thrombosis Santoro and colleagues reported that there were no bleeding complications from heparin (Santoro et al 2005). Anticoagulation, urokinase, and endovascular thrombolysis are useful treatments when sinus occlusion occurs in patients without cancer (DeBruijn and Stam 1999; Soleau et al 2003) and should be considered for cancer patients. Patients with cancer (Casado-Naranjo et al 2011) and extraxial brain tumors (Neil and Ovbiagele 2011) have received thrombolytic agents; however, there are no controlled studies for these patient populations. Anticoagulation with heparin appears safe, even in the presence of intracerebral hematoma (Fink and McAuley 2001). Patients with metastatic venous occlusion should be treated with brain radiation. Patients with fungal sepsis and embolic infarction should be treated with antifungal therapy, although it is rarely successful in eradicating the infection. The most effective treatment for radiation-induced carotid artery disease is not known. Surgical revascularization is as effective and safe as in nonirradiated patients (Leschke et al 2003), although there is risk of restenosis. Angioplasty and stent placement is effective (Al-Mubarak et al 2000) with a low rate of complication and restenosis (Harrod-Kim et al 2005). A direct comparison with surgery has not been performed. No prospective trials of antiplatelet or anticoagulant therapy have been reported for this disease. The proper method to treat the stenosis should be evaluated after a careful screen for recurrent malignancy, as the major risk for death in a clinical cohort was the underlying cancer (Marcel et al 2005). Low-dose heparin administration may reduce the risk of cerebral infarction in patients undergoing ligation to treat carotid rupture. A variety of endovascular techniques can be used to treat threatened or acute carotid blowout syndrome (Chang et al 2008). Intravascular lymphomatosis should be aggressively treated with steroids and chemotherapy, with or without brain radiation (Ponzoni et al 2007).

Leptomeningeal metastasis may be treated with radiation, systemic therapy, intraventricular chemotherapy, or a combination of these approaches. Granulomatous angitis can respond to successful therapy of the associated Hodgkin disease or leukemia or to cytotoxic drugs administered for the vasculitis.

Outcomes

In a retrospective study of 49 patients diagnosed with acute ischemic stroke and cancer, 9 patients were treated with intravenous tissue plasminogen activator and 3 patients were treated with mechanical thrombectomy, all of whom had poor functional outcomes at 3 months (Cutting et al 2017). Four patients who received tissue plasminogen activator had asymptomatic hemorrhagic transformation. Three of these patients had post thrombolysis coagulopathy, and the fourth had elevation of the INR to 1.4. The most common stroke etiology in this group was hypercoagulability of malignancy, and the authors postulate that the underlying coagulopathy may be responsible for the number of asymptomatic hemorrhagic transformations. Overall, the 3-month mortality among all patients was 46.9%, and a quarter of survivors had poor functional outcomes at 3 months. In a prospective study at a single medical center comparing acute ischemic stroke patients with no malignancy, prior malignancy, and active malignancy, Karlinska and colleagues demonstrated that alteplase can be used safely in active malignancy patients (Karlinska et al 2015).

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**References especially recommended by the author or editor for general reading.**

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**Profile**

**Age range of presentation**

02-05 years  
06-12 years  
13-18 years  
19-44 years  
45-64 years  
65+ years  

**Sex preponderance**

male=female

**Family history**

none

**Heredity**

none

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

acute presentation of cerebral metastasis  
progressive neurologic deterioration  
encephalopathy

**Associated disorders**

Carcinoma  
Disseminated intravascular coagulation  
Leukemia  
Lymphoma  
Radiation-induced atherosclerosis  
Radiation-induced vasculopathy  
Sepsis

**Other topics to consider**

Brain abscess  
Brain metastases  
Calvarial, skull base, dural, and nasopharyngeal metastases  
Cancer pain  
Chemotherapy: neurologic complications