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Cerebrovascular Disease

LISA R. ROGERS

Cerebrovascular disease is an important cause of neurologic morbidity and mortality in patients with cancer, and its presence must be considered in any cancer patient who experiences cerebral symptoms. It is the second most common cause of pathologically definable central nervous system (CNS) disease found in cancer patients at autopsy and is often symptomatic. An autopsy study from the Memorial Sloan-Kettering Cancer Center identified cerebrovascular disease in 500 (14.6%) of 3426 cancer patients at autopsy (Graus et al., 1985). Of those patients in whom cerebrovascular disease was identified, 51% had experienced clinical symptoms related to the disease.

Identifying cerebrovascular disease in the cancer patient is important because identification and treatment of the disorder can sometimes ameliorate neurologic symptoms and prevent subsequent episodes. Even when a stroke occurs in the setting of advanced cancer, treatment can improve the patient's quality of life. If a stroke occurs when cancer is limited, failure to identify and treat the cerebrovascular disease underlying the stroke may doom an otherwise successful outcome of the cancer treatment. In a small percentage of patients, stroke is the presenting sign of cancer, and identification of cerebrovascular disease in this subset may lead to the diagnosis of cancer.

Identifying cerebrovascular disease in the patient with cancer presents a challenge to the clinician, as the pathogenesis is often unique to this group of patients. In cancer patients, the common risk factors for stroke, such as systemic and cerebral atherosclerosis, hypertension, and advanced age, are overshadowed by the pathophysiologic effects of cancer and its treatment. Coagulation disorders, toxicity of antineoplastic treatment, and direct effects of cerebral tumor are the most common causes of stroke in this group. Neuroimaging studies are helpful in identifying the type and location of stroke, but the most important clues to its etiology in cancer patients are the type and extent of systemic cancer, the presence of CNS metastasis, and the type of antineoplastic therapy. This chapter reviews the cerebral hemorrhage and cerebral infarction syndromes that occur in cancer patients, with emphasis on the clinical settings in which they occur and current methods of diagnosis and treatment.

CEREBRAL HEMORRHAGE

Pathophysiology and Clinical Presentation

Table 21–1 lists the etiologies of the most common cerebral hemorrhage syndromes that occur in cancer patients. Hemorrhage is usually caused by coagulation abnormalities, brain metastasis, or a combination of the two. Hemorrhage typically occurs in the brain parenchyma, but associated intraventricular or subarachnoid hemorrhage may also occur, depending on the location of the primary hemorrhage. Primary subdural or subarachnoid hemorrhage is uncommon. Cerebral hemorrhage occurs more often in patients with leukemia than in those with lymphoma or solid tumors and is more common in acute than in chronic leukemias and in myelogenous rather than lymphocytic

Table 21–1. Pathophysiology of Cerebral Hemorrhage in Patients with Cancer

Etiology	*Pathology*	*Tumor Type and Setting*
Coagulopathy		
Disseminated intravascular coagulation	Intraparenchymal hemorrhage	Leukemia, especially early in the course of promyelocytic leukemia
Thrombocytopenia	Intraparenchymal hemorrhage	Leukemia, usually at relapse or the failure to induce remission
	Subdural or subarachnoid hemorrhage	Leukemia, often associated with disseminated intravascular coagulation or sepsis
Tumor related		
Hemorrhage into parenchymal brain metastases	Intraparenchymal hemorrhage	Melanoma, germ cell tumors, lung cancer
Ruptured neoplastic aneurysm	Intraparenchymal and subarachnoid hemorrhage	Cardiac myxoma, choriocarcinoma, lung cancer
Leukostasis, leukemic nodules	Intraparenchymal hemorrhage	Leukemia with hyperleukocytosis
Dural metastases	Subdural hemorrhage	Carcinoma, leukemia, lymphoma
Treatment related		
L-asparaginase	Intraparenchymal hemorrhage	Acute lymphocytic leukemia during induction therapy
Hemolytic uremic-like syndrome	Intraparenchymal hemorrhage	Adenocarcinoma treated with chemotherapy, especially mitomycin C
Miscellaneous		
Idiopathic thrombocytopenic purpura, platelet dysfunction, hyperviscosity, acquired von Willebrand's disease	Intraparenchymal hemorrhage	Lymphoma, multiple myeloma, or chronic myeloproliferative disorders
Hypertensive cerebrovascular disease	Intraparenchymal hemorrhage	Solid tumors

leukemias. The symptoms of intraparenchymal hemorrhage may be acute or gradual and include one or more of the following: headache, vomiting, reduced level of consciousness, seizures, focal neurologic signs, and confusion. The symptoms of subdural hematoma in cancer patients are typically confusion and lethargy, and these are usually acute. Rarely, there may be focal neurologic signs (e.g., hemiparesis, hemianopsia, monoparesis). Subdural hemorrhage is less often fatal than parenchymal hemorrhage (Graus et al., 1996). Subarachnoid or intraventricular hemorrhage usually produces rapid deterioration in the level of consciousness, resulting in coma.

Coagulopathy

In cancer patients, abnormal coagulation that predisposes to cerebral hemorrhage is typically due to *(1)* acute disseminated intravascular coagulation (DIC), *(2)* the presence of liver metastasis, *(3)* sepsis, and/or *(4)* thrombocytopenia induced by tumor invasion of the bone marrow or effects on the bone marrow of radiation or chemotherapy. Coagulation disorders are the most frequent cause of cerebral hemorrhage in patients with leukemia, and hemorrhages in these patients are usually symptomatic. In patients with acute promyelocytic leukemia, a subtype of acute myelogenous leukemia, DIC is triggered by release of procoagulant material from the granules in the progranulocytes. The coagulopathy worsens after the administration of chemotherapy. Cerebral hemorrhage occurs early in the course of this type of leukemia and is often fatal. In contrast, laboratory evidence of DIC is detected in as many as one-third of patients early in the course of acute lymphoblastic leukemia, but is rarely associated with clinically sig-

nificant hemorrhage (Higuchi et al., 1998). Disseminated intravascular coagulopathy may become symptomatic in these patients during induction chemotherapy, especially in the presence of very low levels of fibrinogen (Sarris et al., 1996). Cerebral hemorrhage is usually a late complication of other types of leukemia and occurs at relapse or when remission cannot be induced. In the late stages of those leukemias, the pathogenesis of hemorrhage is multifactorial. Disseminated intravascular coagulopathy may be present, but is often accompanied by infection, liver disease, and/or hematologic complications of chemotherapy.

Primary subdural hemorrhage occurs in leukemia patients when there is severe and refractory thrombocytopenia. In some patients, DIC, sepsis, and meningeal leukemia are contributing factors to hemorrhage (Pitner and Johnson, 1973). Subdural hemorrhage is more common in patients with acute myelogenous leukemia after autologous rather than allogeneic bone marrow transplant (Graus et al., 1996). An unusual cause of brain hemorrhage is venous infarction due to cerebral sinus thrombosis associated with coagulopathy, typically occurring in patients who have leukemia (Raizer and DeAngelis, 2000). Figure 21–1 shows a postmortem example of fatal bilateral hemorrhagic infarctions caused by superior sagittal thrombosis in a patient with adenocarcinoma and coagulopathy. In patients with solid tumors, symptomatic parenchymal brain hemorrhage resulting from coagulopathy is rare and it is usually a terminal event.

Hemorrhage Associated with Cerebral Tumor

Hemorrhage into parenchymal metastatic brain tumor is the most common type of brain hemorrhage in patients with solid tumors. It occurs most frequently in patients with metastatic melanoma, germ cell tumors (especially choriocarcinoma), and carcinoma of the lung or kidney. It is caused by necrosis of tumor and the rupture of newly formed blood vessels or by invasion of blood vessels in the adjacent brain parenchyma (Kondziolka et al., 1987). In rare instances, especially with metastasis from malignant melanoma or choriocarcinoma, the metastasis underlying vascular invasion is microscopic. In more than one-half of patients, symptoms are acute and may be the first clinical sign of brain tumor metastasis

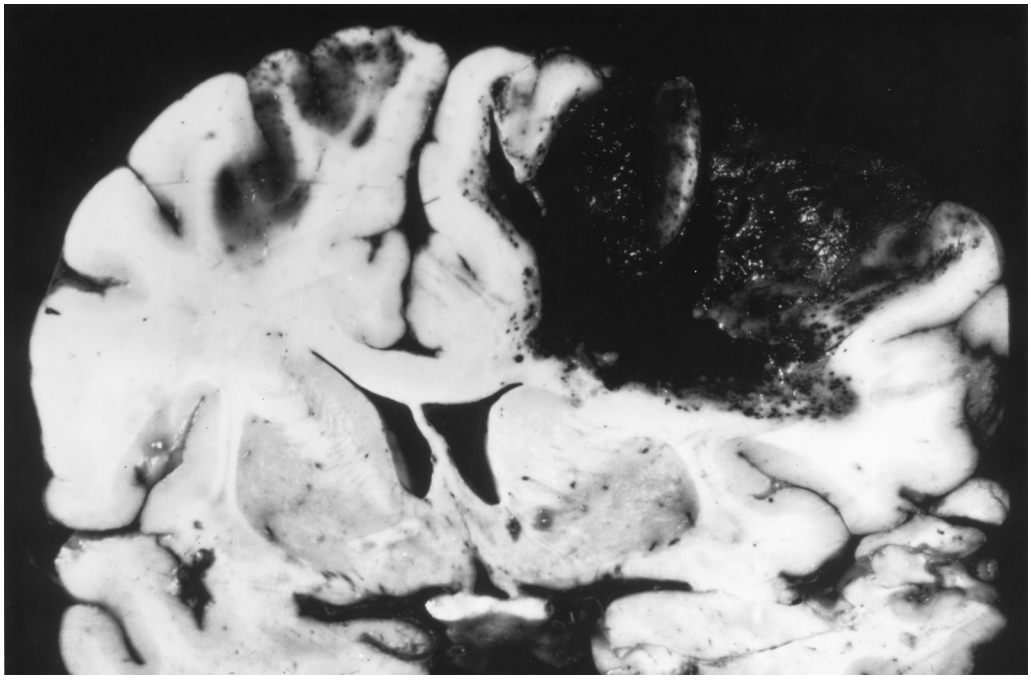

Figure 21–1. Bilateral cerebral hemorrhagic infarctions caused by nonmetastatic superior sagittal sinus thrombosis.

(Lieu et al., 1999). In other patients, the symptoms are superimposed on chronic or progressive symptoms of brain metastasis.

Ruptured neoplastic aneurysms are a rare cause of intracerebral hemorrhage and predominantly occur in patients who have cardiac myxoma, lung carcinoma, or choriocarcinoma (Kalafut et al., 1998). These aneurysms develop when tumor embolic material invades a cerebral vessel wall. After recanalization, the damaged wall dilates and ruptures (Murata et al., 1993). Rarely, aneurysms develop as a result of vascular invasion by a parenchymal metastasis. Neoplastic aneurysms are typically located in distal arterial branches, usually those of the middle cerebral artery.

Symptomatic subdural hemorrhage associated with tumor metastasis to the dura is uncommon. Dural metastasis develops from hematogenous spread of tumor to the dura or from skull metastasis that invades the dura. Figure 21–2 shows a subdural hematoma that was caused by dural metastasis of breast carcinoma. The subdural hemorrhage may be due to the rupture of vessels from vascular congestion by tumor or due to spontaneous hemorrhage of tumor. In some patients, there may be an effusion from tumor in the dura. The tumors that most commonly underlie subdural hemorrhage associated with dural metastasis are carcinomas (especially gastric, breast, or prostate); leukemia and lymphoma are less common (McKenzie et al., 1990). In some instances, a superimposed coagulopathy contributes to the hemorrhage (Minette and Kimmel, 1989). Signs of subdural hemorrhage usually develop gradually, and there may be focal neurologic signs in addition to headache. Epidural hematoma due to dural or skull metastasis is rare (McIver et al., 2001).

If DIC associated with acute promyelocytic leukemia is excluded, hyperleukocytosis (peripheral blast cell count in excess of 100,000/mm^3) is the most common cause of intracerebral hemorrhage at the time of diagnosis of leukemia. Hyperleukocytosis occurs most frequently in patients with acute myelogenous leukemia, especially the monocytic variant (Wurthner et al., 1999). Patients with hyperleukocytosis experience intracerebral hemorrhage in association with infiltration of cerebral capillaries by blast cells, but the pathogenesis of hemorrhage is controversial. In one series hemorrhage occurred while the white blood cell count was declining following chemotherapy administration (Wurthner et al., 1999). Postmortem studies reveal hemorrhage adjacent to dilated and thin-walled vessels that are filled with leukemic blasts (leukostasis) and adjacent to leukemic nodules (Freireich et al., 1960). Blast cells have less deformation than red blood cells; thus hyperviscosity, vascular endothelial damage, and competition with host cells to produce local hypoxia might result in hemorrhage.

Leukemic nodules enlarge and invade cerebral vessels. Leukostasis is more intense in the white matter, periventricular regions, and leptomeninges than in the cortex (Nowacki et al., 1995). Intracerebral hemorrhages associated with hyperleukocytosis are usually multiple and are located in the white matter. Intraventricular or subarachnoid hemorrhage may also occur. In contrast with patients who have hemorrhage caused by coagulopathy, only moderate thrombocytopenia is usually present, which would not be expected to cause spontaneous hemorrhage. A rare cause of intraparenchymal hemorrhage is cerebral perivascular infiltration of leukemic cells in leptomeningeal leukemia, resulting in the rupture of cerebral capillaries. Subarachnoid hemorrhage can also occur in patients with diffuse leptomeningeal tumor when there is thrombocytopenia.

Treatment-Related Hemorrhage

The use of L-asparaginase in induction therapy for acute lymphocytic leukemia results in cerebral hemorrhage or thrombosis in a small percentage of patients (Urban and Sager, 1981; Gugliotta et al., 1992). L-asparaginase is known to promote fibrinolysis and to deplete plasma proteins involved in coagulation, but the precise mechanism of thrombosis and hemorrhage is unknown. In some cases, cerebral hemorrhage is due to venous infarction from thrombosis of the superior sagittal sinus.

A hemolytic uremic–like syndrome is reported in patients with adenocarcinoma, sometimes developing after the administration of chemotherapy. The clinical manifestations are thought to be due to endothelial damage and include microangiopathic hemolytic anemia, thrombocytopenia, pulmonary edema, and renal insufficiency. Similar to the de novo hemolytic uremic syndrome, the neurologic signs include headache, confusion, hemiparesis, and coma. Originally reported as a complication of mitomycin C, it has now been associated with several antineoplastic agents, including bleomycin and cisplatin (Gordon and Kwaan, 1997). The onset after chemotherapy administration is highly variable and

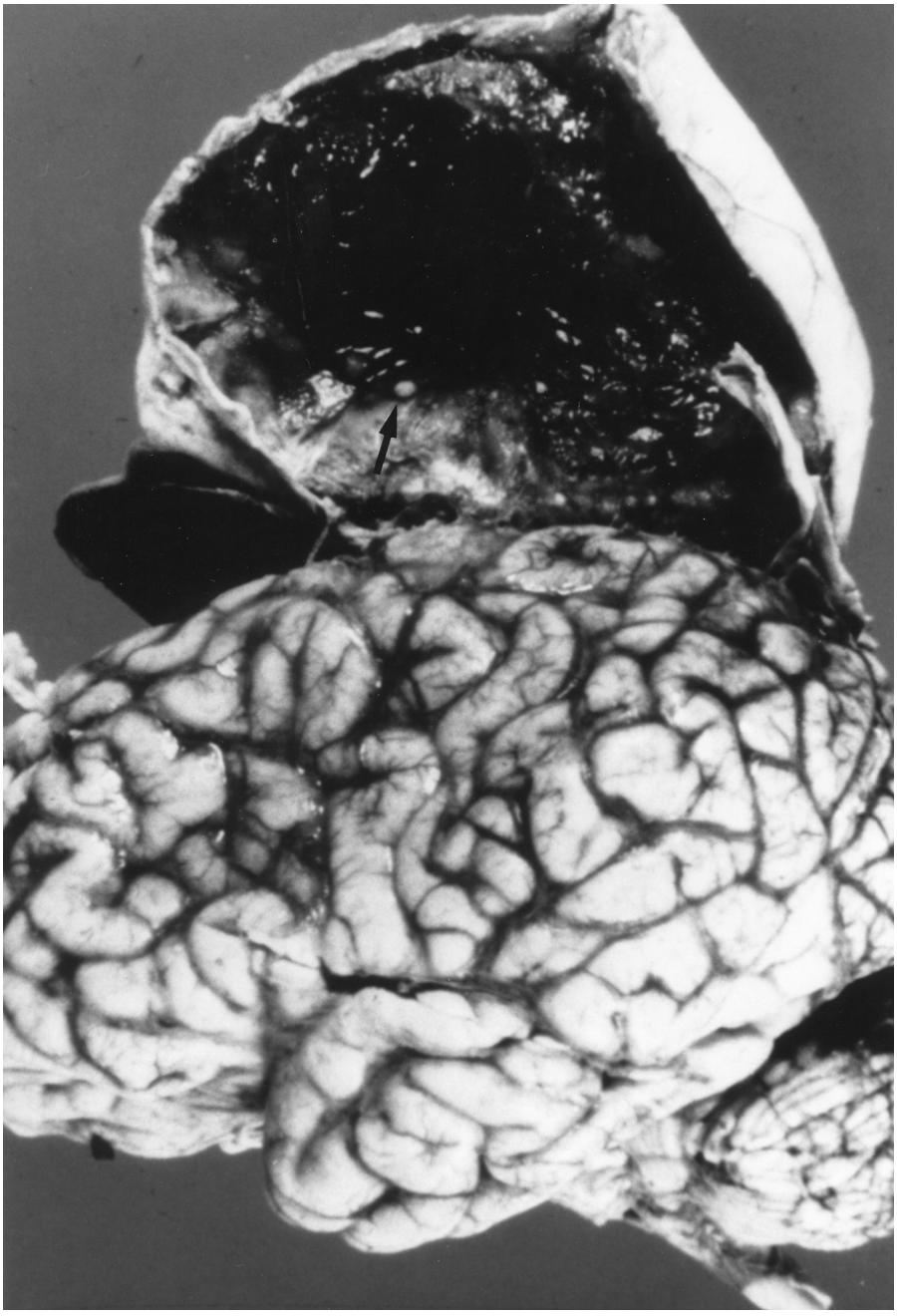

Figure 21–2. Postmortem examination of a subdural hematoma associated with nodular dural metastases (arrow) of breast carcinoma.

ranges from days to months. In other cancer patients, intracerebral hemorrhage occurs as a terminal event in the setting of severe thrombocytopenia induced by bone marrow failure from chemotherapy, radiation, or metastasis.

Miscellaneous

Hypertension is a rare cause of symptomatic intracerebral hemorrhage in cancer patients (Graus et al., 1985). It occurs primarily in patients with solid tu-

mors. A high percentage of patients with chronic myeloproliferative disorders, especially chronic myelogenous leukemia and osteomyelofibrosis, experience intraparenchymal hemorrhage. Hemorrhage may coexist with intracerebral thromboses (Buss et al., 1985), and these tend to occur early in the disease (Wehmeier et al., 1991). In patients with lymphoma, intracerebral hemorrhage may be related to severe thrombocytopenia from idiopathic thrombocytopenic purpura or to an acquired form of von Willebrand's disease. In patients with myeloma, intracerebral hemorrhage may be related to thrombocytopenia and serum hyperviscosity. Primary subarachnoid hemorrhage is sufficiently rare in cancer patients so that congenital aneurysms should be considered. Among 24 patients with cancer and primary subarachnoid hemorrhage in the series by Graus et al. (1985), 4 had ruptured congenital aneurysms.

Diagnosis

Coagulopathy

The stage of the leukemia and associated clinical factors such as degree of thrombocytopenia and the presence of sepsis can suggest the cause of brain hemorrhage in patients with leukemia. The diagnosis of intracerebral hemorrhage is established by MRI or CT scans of the brain that reveal single or multiple hemorrhages. Patients who have acute DIC may also have systemic thrombosis, including deep vein thrombosis, pulmonary embolism, or myocardial infarction, and systemic hemorrhage, including hemorrhage in the mucosal surfaces, retinae, skin, genitourinary and gastrointestinal tracts, and at the site of venipuncture or bone marrow aspiration. Laboratory studies to confirm acute DIC include measurement of platelets, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin split products, fibrinopeptide A, the D-dimer assay, and the presence of schistocytes on the peripheral blood smear. In many patients with cancer, laboratory tests reveal evidence of chronic DIC, but this condition is rarely symptomatic; results of laboratory tests of coagulation function in all patients must be carefully interpreted in their clinical context.

Hemorrhage Associated with Cerebral Tumor

Computed tomography or MRI scans of the brain reveal single or multiple hemorrhages when there is hemorrhage into parenchymal brain metastasis. Clues to intratumoral hemorrhage include a multiplicity of hemorrhages, brain locations other than those usually found with hypertensive hemorrhage, and early edema and enhancement adjacent to the hemorrhage (Atlas et al., 1987). If an intratumoral brain hemorrhage is suspected but the patient is not known to have cancer, biopsy of the hematoma wall is indicated to establish the diagnosis. Parenchymal hemorrhages associated with ruptured neoplastic aneurysms may be single or multiple. Cerebral angiography in neoplastic aneurysms can reveal filling defects, fusiform and saccular aneurysms, and occluded vessels, but the sensitivity of angiography is unknown; in some instances, the hematoma obliterates the aneurysm and angiographic findings are normal.

In patients with subdural hematomas, CT and MRI brain scans can show acute or chronic subdural fluid collections. If dural metastasis is present, there may be evidence of adjacent skull metastasis and dural enhancement after injection of a contrast agent such as gadolinium. However, histologic examination of the dural membrane or subdural fluid may be necessary to establish the diagnosis of dural metastasis. Leptomeningeal metastasis is suggested by leptomeningeal enhancement on neuroimaging studies after injection of a contrast agent such as gadolinium and proven by identification of malignant cells in cerebrospinal fluid or in leptomeningeal biopsy specimens.

Treatment-Related Hemorrhage

Cerebral hemorrhage can occur during or immediately after induction therapy with L-asparaginase in patients with acute lymphocytic leukemia. Brain MRI and magnetic resonance venography can be diagnostic of venous occlusion. Systemic signs of a hemolytic uremic–like syndrome in conjunction with severe hemolytic anemia and thrombocytopenia associated with the administration of chemotherapy for adenocarcinoma suggest this diagnosis.

Miscellaneous

Laboratory tests that reveal evidence of extreme thrombocytosis, impaired platelet function, or hyperviscosity can be helpful in identifying the cause of cerebral hemorrhage in patients with chronic myeloproliferative disorders, lymphoma, and multiple myeloma.

Treatment

Coagulopathy

Successful therapy for acute DIC is multifaceted and controversial. Evacuation of an intracerebral hemorrhage in the setting of coagulopathy is difficult, and in patients with cancer who have cerebral hemorrhage caused by DIC treatment should be directed at controlling the systemic tumor and the associated medical conditions that contribute to the coagulopathy, such as sepsis. Treatment with heparin and fresh-frozen plasma can control DIC in some patients. Other therapies include replacement of clotting factors with blood products such as cryoprecipitate and platelet concentrations and antifibrinolytic agents. In patients with acute promyelocytic leukemia and DIC, it is controversial whether prophylactic heparin as an adjunct to induction chemotherapy can reduce the incidence of intracerebral hemorrhage. Chemotherapy, however, can increase the lysis of blast cells and aggravate DIC. All-*trans* retinoic acid administered for remission induction therapy of acute promyelocytic leukemia can differentiate abnormal promyelocytes into mature granulocytes, which improves coagulation function and results in a slight decrease of early brain hemorrhage (Tallman et al., 1997). Most patients with subdural hematoma caused by coagulopathy can be successfully managed without surgery (Graus et al., 1996).

Hemorrhage Associated with Cerebral Tumor

Survival of patients with massive intratumoral parenchymal brain hemorrhage or ruptured neoplastic aneurysms is poor, especially for those who have an acute onset of symptoms (Graus et al., 1985). These patients may die as a direct result of the hemorrhage. In some patients, resection of a single large hematoma is life saving (Little et al., 1979). The clinical course in patients with hemorrhage into brain metastasis who have a stable neurologic condition is no different from that of patients with nonhemorrhagic brain metastasis. These patients should receive radiation therapy directed to the underlying brain metastasis. For patients with ruptured neoplastic cerebral aneurysms, therapy should be directed to the systemic tumor (appropriate antineoplastic therapy in the case of systemic cancer and removal of the cardiac tumor in the case of cardiac myxoma). Brain irradiation is indicated for neoplastic aneurysms that arise from systemic carcinoma.

Therapy for subdural hemorrhage associated with dural metastasis is generally palliative and includes brain irradiation and drainage of subdural fluid. The use of antimetabolites and leukapheresis reduces the frequency of brain hemorrhage in acute leukemia patients presenting with hyperleukocytosis (Wurthner et al., 1999).

Treatment-Related Hemorrhage

The chances for neurologic recovery in patients experiencing L-asparaginase–induced thrombosis or hemorrhage are generally good (Feinberg and Swenson, 1988), and cerebrovascular events do not usually recur after re-treatment. Fresh-frozen plasma may be beneficial for patients with venous thrombosis, but it is not known if anticoagulation is necessary. The prognosis for patients with the hemolytic uremic–like syndrome induced by chemotherapy is poor, but steroids and plasma exchange may prolong survival (Gordon and Kwaan, 1997).

Miscellaneous

Conventional cytoreductive therapy reduces the incidence of cerebral ischemic or hemorrhagic events in patients with chronic myeloproliferative disorders (Wehmeier et al., 1991).

CEREBRAL INFARCTION

As is the case with cerebral hemorrhage, the risk factors for cerebral infarction in patients with cancer are usually different from those in patients without cancer. Table 21–2 lists the causes of cerebral infarction in cancer patients. Coagulation disorders, infection, the direct effects of CNS metastasis, and complications of antineoplastic treatment are the most common causes. Symptomatic cerebral infarction is more common in patients who have lymphoma and carcinoma than it is in those with leukemia, in whom cerebral hemorrhage predominates.

Two clinical factors make the identification of cerebral infarction in cancer patients and the determination of its cause difficult. First, cerebral infarctions in cancer patients are often multifocal, and the resulting multifocal neurologic signs are difficult to distinguish from those caused by encephalopathy. Therefore, the possibility of cerebral infarction must be considered for all cancer patients who experience

Table 21–2. Pathophysiology of Cerebral Infarction in Patients with Cancer

Etiology	*Pathology*	*Tumor Type and Setting*
Coagulopathy		
Nonbacterial thrombotic endocarditis	Cerebral infarction	Adenocarcinoma, usually widespread
Cerebral intravascular coagulation	Cerebral infarction, petechial hemorrhage	Lymphoma, leukemia, breast cancer, in advanced disease and sepsis
Coagulopathy, etiology undetermined	Superior sagittal sinus thrombosis with or without adjacent cerebral infarction	Lymphoma and solid tumors, usually in advanced disease
Infection		
Fungal sepsis	Cerebral infarction	Leukemia
Tumor-related		
Skull or dural metastases	Saggital sinus thrombosis with or without adjacent cerebral infarction	Lung cancer, neuroblastoma, lymphoma
Tumor embolism	Cerebral infarction	Lung and cardiac tumors
Leptomeningeal metastasis	Cerebral infarction	Solid tumors
Radiation-induced vasculopathy	Cerebral infarction	Head and neck cancer, lymphoma
Chemotherapy	Superior sagittal sinus occlusion	Leukemia, during induction therapy with L-asparaginase
Chemotherapy	Cerebral infarction	Breast cancer during multi-agent chemotherapy and hormonal therapy; other solid tumors during cisplatin-based chemotherapy
Miscellaneous		
Atherosclerosis	Cerebral infarction	Head and neck and lung cancer
Granulomatous angiitis	Cerebral infarction	Hodgkin's lymphoma, leukemia
Thrombocytosis	Cerebral infarction	Chronic myeloproliferative disorders, particularly essential thrombocytopenia

encephalopathy. Second, proving a link between coagulation abnormalities and cerebral infarction can be difficult because many cancer patients have abnormalities of coagulation function that are revealed by laboratory tests but are not clinically significant. The most important clues to the etiology of cerebral infarction are the type of cancer, the extent of systemic metastasis, the presence of CNS metastasis, and the type of antineoplastic treatment.

Pathophysiology and Clinical Presentation

Coagulopathy

The majority of patients with advanced solid tumors have laboratory evidence of clotting activation that is usually asymptomatic. In a small percentage of patients, however, the coagulopathy results in thrombosis of arteries or veins in the systemic or cerebral circulation. There are multiple risk factors for coagulopathy and thrombosis, including a complex interaction between tumor cells and their products with host cells, cancer treatment including single- or multiple-agent chemotherapy, hormonal therapy, and hematopoietic growth factors. Nonbacterial thrombotic endocarditis is the result of a hypercoagulable state and is characterized by the development of sterile platelet-fibrin vegetations on cardiac valves.

Nonbacterial thrombotic endocarditis is the most common cause of symptomatic cerebral infarction in cancer patients (Graus et al., 1985). Figure 21–3 shows cardiac nonbacterial thrombotic endocarditis in a patient with lung adenocarcinoma. Patients with cerebral infarction caused by nonbacterial thrombotic endocarditis usually experience focal neurologic signs, and angiography in these patients typically shows multiple branch occlusions of the middle

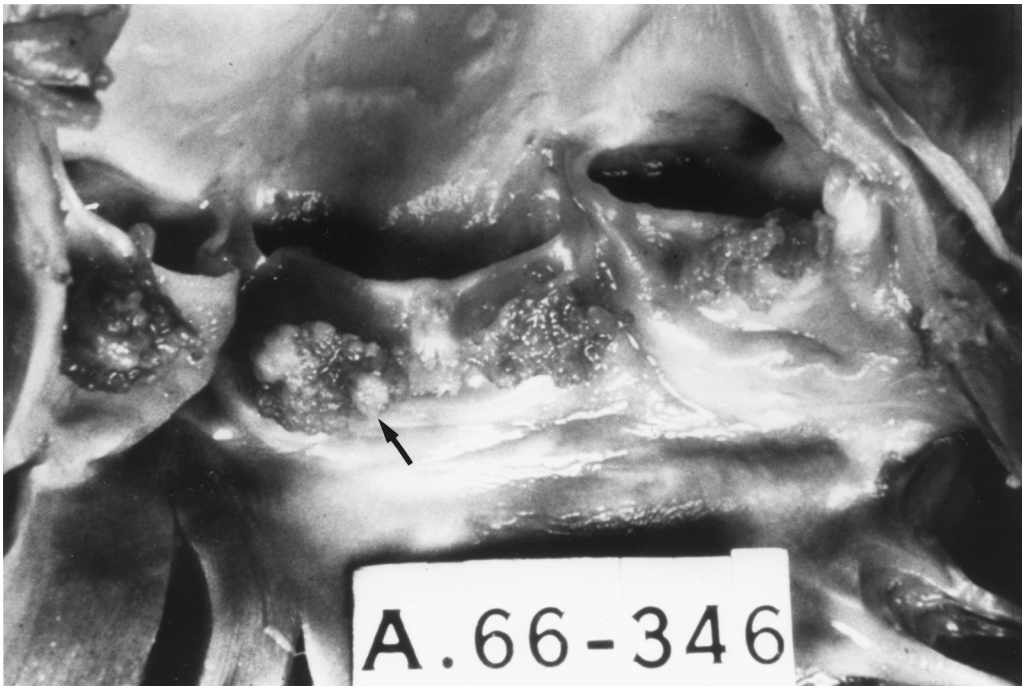

Figure 21–3. Postmortem examination demonstrating vegetations of nonbacterial thrombotic endocarditis attached to all cusps of the aortic valve. (The valve has been opened anteriorly.) The arrow indicates one area of vegetation.

cerebral artery. Focal signs may be preceded by transient ischemic attacks. Some patients also develop encephalopathy because of multifocal infarctions. Postmortem studies suggest that cerebral infarctions are caused by embolization of cardiac vegetations to the brain, cerebral intravascular thromboses that result from the associated coagulation disorder, or both (Reagan and Okazaki, 1974; Rogers et al., 1987). Nonbacterial thrombotic endocarditis occurs most commonly in patients with adenocarcinoma, especially mucin-producing carcinomas of the lung or gastrointestinal tract. It usually develops in patients with advanced cancer, but can occur in patients with early-stage cancer and can even be the presenting sign of cancer (Rogers et al., 1987). Evidence of systemic thrombosis or hemorrhage suggests the presence of nonbacterial thrombotic endocarditis.

Cerebral intravascular coagulation is due to thrombotic occlusion of small cerebral vessels caused by a coagulopathy unaccompanied by nonbacterial thrombotic endocarditis. It is the second most common cause of symptomatic cerebral infarction in patients with cancer (Graus et al., 1985). Patients with cerebral intravascular coagulation develop encephalopathy, and approximately one-half of patients have superimposed, sometimes transient, focal neurologic signs (Collins et al., 1975). The clinical course is progressive. Typically, multiple vessels in more than one major vessel territory of the brain and leptomeninges—usually small arteries, arterioles, capillaries, or venules—are occluded with fibrin. Figure 21–4 shows fibrin occlusions of leptomeningeal vessels in association with cerebral infarctions in a patient with breast cancer and cerebral intravascular coagulation. Cerebral intravascular coagulation is reported in patients with leukemia, breast cancer, and lymphoma, usually in the setting of advanced disease and sepsis. Amico et al. (1989) reported systemic and cerebral infarctions in six patients with mucinous cancers. At autopsy, mucin was present within vessels, macrophages, and areas of infarction. It is unknown whether mucin deposition results from metastasis or is associated with a cancer-related coagulopathy.

Nonmetastatic occlusion of large cerebral venous structures in cancer patients is caused by a coagulation disorder associated with cancer or with chemotherapy. The most common cerebral venous structure affected is the superior sagittal sinus, and the underlying tumor is usually leukemia (Raizer and DeAngelis, 2000). The incidence of this disorder is unknown

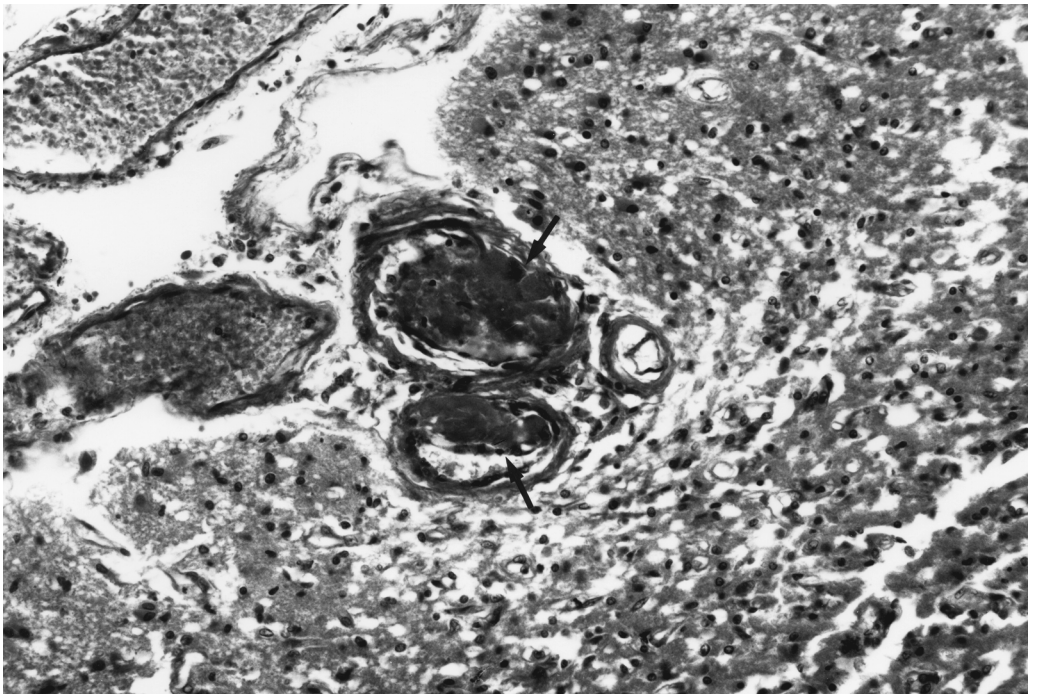

Figure 21–4. Organizing fibrin thrombi (arrows) in small leptomeningeal arteries overlying an area of cerebral infarction in a patient with disseminated breast carcinoma and cerebral intravascular coagulation. Hematoxylin and eosin; original magnification, ×50.

because the sinus occlusion can recanalize and is, therefore, underreported in autopsy series. The onset of symptoms from nonmetastatic superior sagittal sinus thrombosis is typically sudden headache; seizures, focal neurologic signs, or encephalopathy develop if there is brain hemorrhage or infarction. Superior sagittal sinus occlusion is associated with induction therapy that includes the administration of L-asparaginase to patients with acute lymphocytic leukemia (see "Treatment-Related Cerebral Infarction" in this chapter). In other patients with lymphoma or solid tumors, it usually occurs in the setting of widespread systemic metastatic disease.

Infarction Associated with Cerebral Infection

Cancer patients are predisposed to systemic infections because of immunosuppression caused by the tumor or by treatment with radiation, chemotherapy, broad-spectrum antibiotics, or immunosuppressants. Cerebral infarction associated with infection is most commonly caused by fungal septic emboli, typically of *Aspergillus* and *Candida* species. Fungal sepsis occurs more commonly in patients with leukemia than in those with lymphoma or carcinoma. Common sites of entry are the lower respiratory tract for *Aspergillus* and the gastrointestinal or genitourinary tracts or indwelling venous catheters for *Candida* species. Cerebral infarctions associated with cerebral infection are often multiple and may be hemorrhagic (Walsh et al., 1985). The neurologic signs usually consist of seizures, focal cerebral signs, or encephalopathy. Acute focal signs and seizures are more common in patients with *Aspergillus* infection, and encephalopathy is more common in patients with *Candida* infection. Meningitis is rarely present.

Infarction Associated with Cerebral Tumor

Skull or dural tumor that infiltrates or compresses the superior sagittal sinus can produce venous stasis and thrombosis. In contrast to patients with nonmetastatic superior sagittal sinus thrombosis, patients with the metastatic type of thrombosis develop subacute symptoms resulting from increased intracranial pressure (typically headache, vomiting, and papilledema). Focal neurologic signs or encephalopathy may be present if there is cerebral infarction. It occurs most commonly in patients with neuroblas-

toma, lung cancer, and lymphoma, but is reported in a variety of tumors.

Another mechanism for tumor-related cerebral infarction is embolism of a tumor fragment to the brain. This can produce focal or multifocal cerebral signs, sometimes preceded by transient ischemic attacks (O'Neill et al., 1987). Embolism of a tumor fragment to the brain is reported exclusively in patients with solid tumors, usually those with a primary or metastatic cardiac or lung tumor that is the source of the embolus. Cerebral embolism can occur at the time of manipulation of the lung in patients with lung tumor undergoing thoracotomy (Lefkovitz et al., 1986; O'Neill et al., 1987). It can be the presenting sign of cardiac tumor, especially cardiac myxoma. Leptomeningeal metastasis is a rare cause of cerebral infarction. Infarction may be the sole manifestation of this disorder, or there may be accompanying typical signs, including headache, cranial nerve palsies, and radiculopathies. Postmortem studies suggest that infarction occurs because tumor infiltrates the cerebral arteries in the Virchow-Robin spaces and causes vascular occlusion or spasm (Klein et al., 1989). The infarctions may be multifocal.

Treatment-Related Infarction

Neck radiation administered for head and neck cancer or lymphoma can produce delayed extracranial carotid stenosis or occlusion. In a prospective study of carotid duplex ultrasound performed in 240 patients with head and neck cancer who received radiation to the cervical region, a greater than 70% stenosis of the common and/or internal carotid artery was detected in 28 patients (11.7%) (Cheng et al., 1999). Histologic examination of the diseased artery suggests that radiation produces or accelerates atherosclerosis. Patients may develop transient ischemic attacks, including amaurosis fugax, or cerebral infarction. Murros and Toole (1989) reported a wide interval between radiation therapy and the development of this complication, with a mean interval of 19 years. Carotid artery rupture is a potentially fatal complication of head and neck tumor resection and neck irradiation. It is usually associated with orocutaneous fistulas, necrosis of the skin flap, and infection (McCready et al., 1983). Patients may die from exsanguination. If the carotid rupture is detected and the artery is ligated, there is a significant chance of cerebral infarction and death (Razack and Sako, 1982).

Potential mechanisms for abnormal coagulation function in patients receiving chemotherapy include alterations in coagulation factors or anticoagulant proteins and endothelial damage produced by these agents. Because of the small number of events occurring in individual treatment studies and the lack of uniform reporting of thromboembolism, including stroke, the evidence for a causal relationship with antineoplastic agents, regardless of other risk factors, is weak (Lee and Levine, 1999). The best-recognized cerebrovascular complication of chemotherapy is venous thrombosis caused by L-asparaginase used in combination induction chemotherapy for patients with acute lymphocytic leukemia (Lee and Levine, 1999; Gugliotta et al., 1992). L-asparaginase promotes fibrinolysis and causes a depletion of plasma proteins involved in coagulation. There may be promotion of thrombosis by a transient increase in unusually large plasma von Willebrand's factor multimers (Pui et al., 1987). There are also uncommon reports of systemic and cerebral venous and arterial thromboembolic complications in women with breast cancer receiving multiagent chemotherapy (Wall et al., 1989), especially when chemotherapy is combined with hormonal therapy (Saphner et al., 1991). Complications usually occur early in treatment.

A rare neurologic complication of chemotherapy is cerebral embolization from a ventricular mural thrombus that forms in association with cardiomyopathy resulting from chemotherapy with doxorubicin (Adriamycin) (Schachter and Freeman, 1982). Transient focal neurologic signs suggesting transient ischemic attacks can occur during interleukin-2 therapy (Bernard et al., 1990).

Miscellaneous

Atherosclerosis is the most common cause of cerebral infarction found at autopsy in patients with cancer, but it accounts for only 14% of symptomatic infarctions (Graus et al., 1985). The most common tumors associated with symptomatic cerebral infarction from atherosclerosis are head and neck cancers and lung cancer. A less common cause of symptomatic cerebral infarction is granulomatous angiitis occurring in patients with Hodgkin's disease or leukemia (Inwards et al., 1991; Lowe and Russell, 1987). Signs include headache, fever, confusion, seizures, obtundation, or hemiparesis. Patients with chronic myeloproliferative disorders who have extreme thrombocytosis can experience cerebral arte-

rial or venous thromboembolic events (Randi et al., 1998). These complications are most common in patients with polycythemia vera and essential thrombocythemia and occur more often in older patients (Jabaily et al., 1983; Wehmeier et al., 1991). Platelet thromboembolism is likely caused by inherent alterations of platelet function in addition to the excessively high number of platelets. Neurologic symptoms are most common before and shortly after the diagnosis of chronic myeloproliferative disorders, probably because cytoreductive therapy administered after the diagnosis is effective (Michiels et al., 1993). In patients with essential thrombocythemia, symptoms are usually transient and are poorly localized; they include unsteadiness, dysarthria, and scotomas. Focal symptoms such as transient monocular blindness or limb weakness are less common. They are of sudden onset and are often accompanied by headache. Systemic arterial or venous thrombosis may also occur. Patients with Hodgkin's disease who are in remission or cured can experience episodic neurologic dysfunction that resembles transient ischemic attacks (Feldmann and Posner, 1986). The cause of these symptoms is unknown.

Diagnosis

Coagulopathy

Patients with stroke caused by coagulation disorders may have evidence of systemic thrombosis or hemorrhage. Particularly, patients with nonbacterial thrombotic endocarditis may have systemic bleeding, limb thrombophlebitis arterial occlusion, pulmonary embolism, or myocardial infarction (Reagan and Okazaki, 1974; Rogers et al., 1987). Laboratory tests may reveal evidence of DIC in some patients (Rogers et al., 1987), but in many patients abnormalities on coagulation function tests are indistinguishable from the abnormalities commonly associated with cancer. These abnormalities include markers of clotting activation, such as abnormal thrombin–antithrombin complex, prothrombin fragment F 1 + 2, and D-dimer.

Cardiac murmurs are rare, and transthoracic echocardiography is usually nondiagnostic because of the small size of the cardiac vegetations. Transesophageal echocardiography can be diagnostic (Blanchard et al., 1992). Computed tomography or MRI scans of the brain may reveal cerebral infarction. In patients who experience focal neurologic signs, cerebral angiography is a sensitive test for the diagnosis of cerebral infarction from nonbacterial thrombotic endocarditis. In these patients, cerebral angiography typically shows multiple branch occlusions of the middle cerebral artery (Rogers et al., 1987). Many patients with cerebral intravascular coagulation have systemic bleeding, but results of laboratory tests of coagulation function are nonspecific. In a study by Collins et al. (1975), neuroimaging studies performed in a small number of patients were normal. There is no method currently known to diagnose this syndrome aside from postmortem examination.

Magnetic resonance imaging of the brain is the imaging procedure of choice to detect superior sagittal sinus thrombosis caused by coagulopathy. It can document the lack of normal flow void within the occluded sinus and can reveal enlarged collateral veins (Sze et al., 1988). Adjacent cerebral hemorrhage or infarction can also be visualized. When MRI is nondiagnostic, magnetic resonance venography can be diagnostic (Fig. 21–5).

Infarction Associated with Infection

Computed tomography and MRI brain scans can reveal infarctions in patients with septic cerebral embolism. Focal enhancement may appear later if the infarctions evolve into abscesses. Cerebrospinal fluid examination is generally nondiagnostic because usually only mild pleocytosis and protein elevation are present. Cultures are typically negative. Hemorrhagic cerebrospinal fluid can be a clue to *Aspergillus* infection (Walsh et al., 1985). Blood cultures are often negative, but clinical or radiographic evidence of pulmonary infection suggests systemic *Aspergillus* infection. *Aspergillus* can be isolated from respiratory secretions or open lung biopsy specimens, but open lung biopsy is potentially hazardous in many cancer patients because of coexisting thrombocytopenia (Walsh et al., 1985).

Infarction Associated with Cerebral Tumor

Brain MRI and magnetic resonance venography are the methods of choice to diagnose metastatic superior sagittal sinus occlusion and to reveal associated cerebral infarction. In patients with superior sagittal sinus occlusion due to skull or dural tumor, MRI may also reveal evidence of adjacent skull or dural metastasis. Dural or leptomeningeal metastasis will usu-

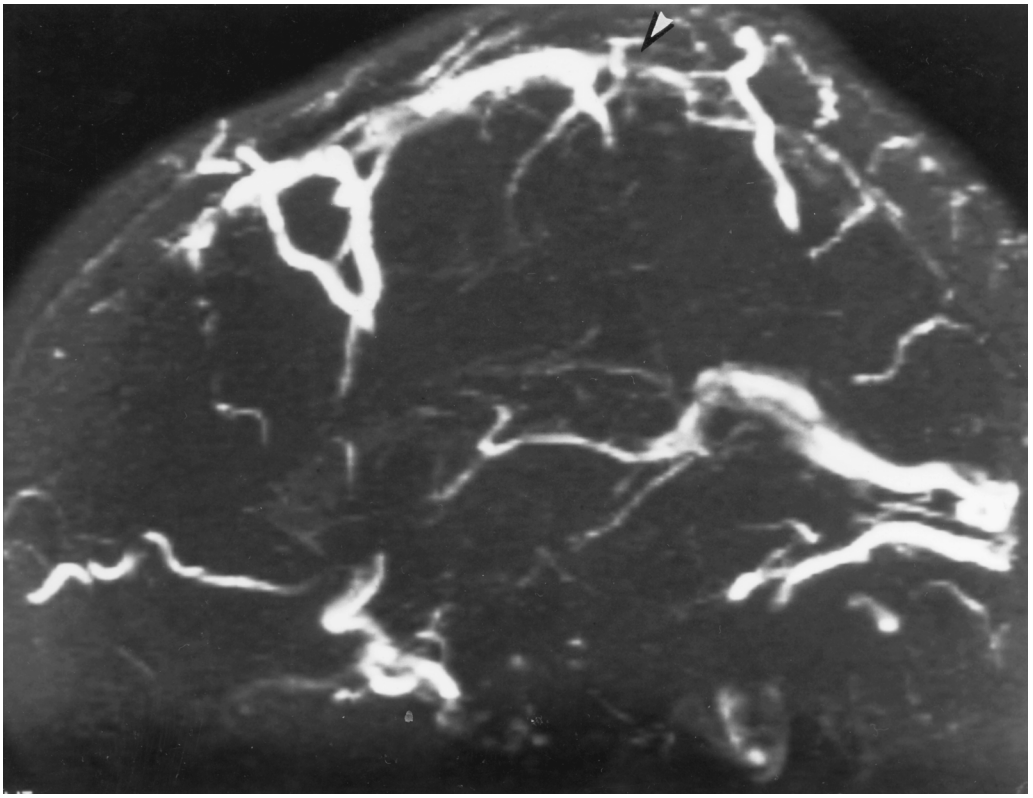

Figure 21–5. Nonmetastatic superior sagittal sinus occlusion (arrowhead) visible on two-dimensional time-of-flight magnetic resonance venogram.

ally enhance after injection of gadolinium. In patients with tumor embolic infarctions, the infarctions can be seen on CT or MRI scans, and angiography may reveal vascular occlusions (Marazuela et al., 1989; O'Neill et al., 1987); however, these findings are not specific, and a definitive diagnosis of tumor embolism can be established only if there is a simultaneous peripheral arterial embolism that can be examined histologically. Patients in whom tumor embolic infarction is suspected should undergo serial CT or MRI brain scans for evaluation of growth of the brain metastasis. Clinical clues to the presence of primary or metastatic cardiac tumor include a new onset of congestive heart failure, pericardial effusion, rapid cardiac enlargement, or arrhythmias that are difficult to control. Echocardiography is diagnostic.

Treatment-Related Infarction

Carotid angiography in patients with radiation-induced carotid artery disease usually reveals occlusion or extensive stenosis of the common carotid artery that is confined to the field of irradiation. The length of stenosis in these patients is typically greater than it is in patients with atherosclerosis not associated with irradiation (Fig. 21–6). Little information is available on neuroimaging abnormalities in patients who experience cerebral infarction related to chemotherapy administration except for patients with superior sagittal sinus occlusion. There are no laboratory tests that can diagnose chemotherapy-induced coagulation abnormalities.

Miscellaneous

Atherosclerotic brain infarction is suggested by the patient's age and the presence of typical risk factors for atherosclerosis. Granulomatous angiitis is suggested by the presence of cerebral infarctions, hemorrhages, or contrast-enhancing masses on CT or MRI brain scans in patients with lymphoma or leukemia. Angiography may show a classic beading pattern but

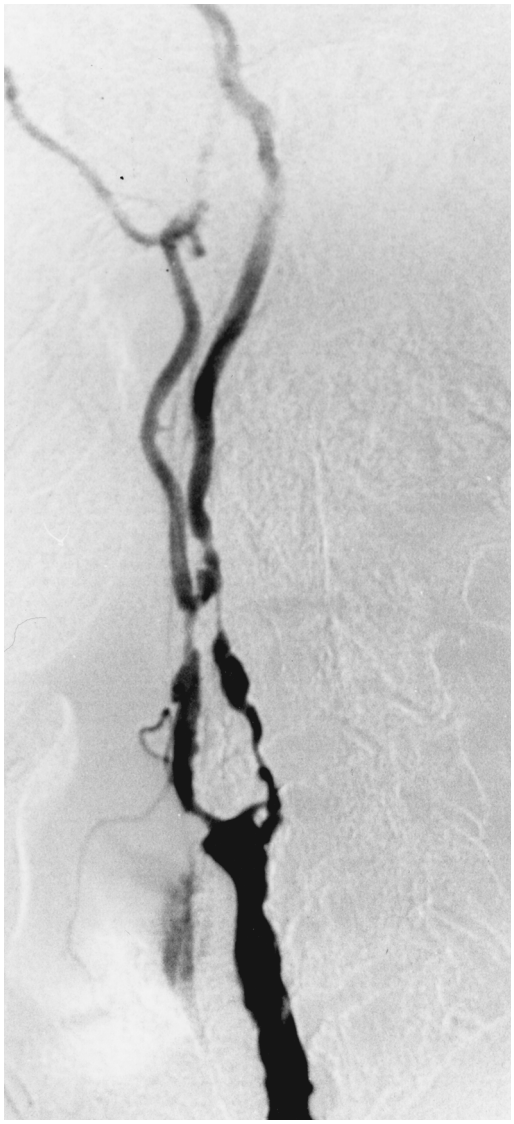

Figure 21–6. Cerebral angiography in a patient with laryngeal cancer and radiation-induced carotid atherosclerosis reveals irregularity and moderate stenosis of the distal left common carotid artery. There is a long segment of diffuse irregularity and severe stenosis alternating with zones of dilatation in the proximal internal and external carotid arteries. The area of involvement of the common, internal, and external carotid arteries corresponds to the field of radiation.

may be nonspecifically abnormal or normal. The most definitive method for diagnosis of granulomatous angiitis is biopsy, but its sensitivity is low (Inwards et al., 1991). The association of cerebral infarction with thrombocythemia can be determined by measuring the platelet count.

Treatment

Coagulopathy

Effective therapy for coagulation disorders must be directed to the underlying tumor, to associated medical conditions such as sepsis that predispose the patient to the disorder, and to the coagulation disorder itself. Management decisions for coagulopathy are still controversial, and therapy must be individualized. Low-molecular-weight heparin or low-dose warfarin can reduce the risk of systemic venous thromboembolism in cancer patients (Levine and Lee, 2001), but their role in the prophylaxis of stroke is unknown. Patients who experience cerebral infarction from nonbacterial thrombotic endocarditis may benefit from anticoagulation therapy. In the series by Rogers et al. (1987), heparin therapy was effective in reducing ischemic symptoms in some patients with cerebral infarction, and the incidence of hemorrhagic infarction and cerebral hemorrhage, possible side effects of this therapy, was no greater than in patients who were not anticoagulated. However, anticoagulation must be undertaken judiciously because of the risk of systemic and cerebral hemorrhage in patients with this disorder. Appropriate therapy for cerebral intravascular coagulation is not known. Heparin and urokinase are reported to be beneficial in reducing the morbidity of superior sagittal sinus thrombosis in patients without cancer (Einhaupl et al., 1991; De Bruijn and Stam, 1999; Philips et al., 1999), but no prospective studies have been performed in patients with cancer.

Infarction Associated with Infection

Patients with fungal septic cerebral infarction should be treated with antifungal therapy, but the prognosis for recovery and survival is poor (Walsh et al., 1985).

Infarction Associated with Cerebral Tumor

Patients with metastatic superior sagittal sinus occlusion should be treated with irradiation of the brain. It is not known whether anticoagulation therapy is effective in treating this disorder. In patients with embolic infarction from malignant tumors, the brain should also be irradiated. In those patients with cardiac tumors, removal of the cardiac tumor will prevent subsequent embolization. Patients with leptomeningeal metastasis should be treated with radiation to the symptomatic areas of the neuraxis and with systemic or intraventricular chemotherapy.

Treatment-Related Infarction

Patients with symptomatic or high-grade radiation-induced carotid stenosis can be effectively treated with endarterectomy; the long-term patency rates are similar to those in nonirradiated patients (Kashyup et al., 1999). Endovascular occlusion is a safe and effective method to avoid carotid artery ligation and prevent cerebral infarction in patients with carotid artery rupture (Citardi et al., 1995). If carotid ligation is required, low-dose heparin may reduce the risk of cerebral infarction (Leikensohn et al., 1978). There is no effective therapy known for the vascular complications of chemotherapy, although Feinberg and Swenson (1988) suggest that prophylactic fresh-frozen plasma be administered to patients receiving L-asparaginase. In other situations, the benefits of chemotherapy must be carefully weighed against the risk of recurrent thromboembolic events.

Miscellaneous

Granulomatous angiitis can respond to treatment directed to the underlying cancer (Hodgkin's disease or leukemia) or to steroids and cytotoxic drugs administered for vasculitis (Inwards et al., 1991). Aspirin and cytostatic reduction of the platelet count are effective in preventing recurrence of thrombotic events in patients with essential thrombocythemia (Michiels et al., 1993). The clinical course of patients with Hodgkin's disease who experience transient neurologic symptoms of unknown etiology is benign, and no treatment is indicated (Feldmann and Posner, 1986).

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