Malignant disease and its treatment may produce a variety of complications. Many of these complications are relatively specific to the disease (e.g., leukostasis in acute myeloid leukemia) or to a class of chemotherapeutic agents (e.g., chronic cardiomyopathy with the anthracyclines). However, life-threatening complications associated with malignancy are common to a variety of tumor types; in addition, many cytotoxic chemotherapeutic agents can produce potentially fatal toxicities, depending on the agent and its dosing schedule.

Cardiovascular Emergencies

Pericardial Disease and Tamponade

Neoplastic pericardial disease is usually associated with advanced lung cancer, breast cancer, leukemia, or lymphoma, with pericardial involvement occurring either by direct extension or by spread via the mediastinal lymphatic vessels. Pericardial disease with or without tamponade may also be caused by chemotherapeutic or radiotherapeutic toxicity. Patients who have neoplastic involvement of the visceral pericardium and those who receive mediastinal irradiation are at risk for effusive-constrictive pericarditis, a syndrome that is caused by pericardial effusion associated with constriction of the heart by the visceral pericardium. Patients who receive chemotherapy with anthracyclines or cyclophosphamide are also at risk for pericardial disease with tamponade, which may present as acute pericarditis or myocarditis syndromes. These syndromes occur primarily with very high dose chemotherapy regimens.

Diagnosis

The most common presenting symptoms of neoplastic pericardial disease with tamponade are progressive dyspnea, non-specific chest discomfort, and cough. Arterial blood pressure and heart sounds may be normal. Pericardial friction rubs frequently are not present. Although central venous pressure is always elevated in patients with tamponade, venous hypertension may be detected clinically in only about one half of cases because of anatomic variations in vasculature and body habitus and failure to observe venous pulsations.

A paradoxical pulse is the single most specific sign of pericardial tamponade. Because the signs and symptoms of pericardial tamponade in cancer patients are nonspecific, pericardial tamponade should be considered in any cancer patient who has dyspnea, nonspecific chest pain, elevations in jugular venous pressure, new and unexplained cardiomegaly on chest x-ray, or a paradoxical pulse. Electrocardiography is usually not helpful in the diagnosis of malignant pericardial disease.

Echocardiography is the single most helpful noninvasive method of evaluating pericardial disease or tamponade in cancer patients. Pericardial effusions secondary to neoplastic disease usually are large and do not produce internal echoes. The presence of tamponade is indicated by early diastolic collapse of the right atrial or ventricular wall or by Doppler echocardiography–documented changes in the respiratory variation of blood flow velocity through the tricuspid or mitral valves.

Measurements of pericardial fluid pressure during pericardiocentesis may help differentiate pericardial tamponade from superior vena cava (SVC) syndrome. In tamponade, pericardial fluid pressure is elevated initially but returns to normal as the fluid is withdrawn, whereas in SVC syndrome, pericardial fluid pressure is normal and jugular venous pressure is unaffected by pericardiocentesis. In patients with effusive-constrictive pericarditis, pericardiocentesis produces only partial improvement of the hemodynamic abnormality.

Treatment

Treatment of pericardial tamponade includes pericardiocentesis, pericardial window formation, or pericardiectomy. Pericardiocentesis with concurrent catheterization of the right side of the heart allows for definitive diagnosis of cardiac tamponade, removal of pericardial fluid to relieve the tamponade, cytologic and microbiologic analysis of the fluid, and placement of an intrapericardial catheter to prevent fluid reaccumulation. Frequently, catheter drainage for several days results in a decreased rate of pericardial fluid collection and may provide definitive long-term benefit. Intrapericardial instillation of bleomycin or tetracycline-doxycycline is a safe and effective method of sclerosing the pericardial space to prevent the recurrence of tamponade. Patients in whom effusions rapidly recur may benefit from a pericardial window, and those who have effusive-constrictive pericarditis may require partial pericardiectomy.

Systemic chemotherapy or hormone therapy may be beneficial. Limited cardiac irradiation may also provide palliation, especially in patients with radiosensitive tumors. However, the survival of patients with cancer and secondary pericardial involvement is usually short because of the systemic nature of their disease [see I: XIII Diseases of the Pericardium, Cardiac Tumors, and Cardiac Trauma].

Superior Vena Cava Syndrome

Extrinsic compression or intrinsic obstruction of the SVC [see Figure 1] may result in elevated venous pressures in the upper extremities, head, and neck and in increased intracranial pressure, soft tissue edema, venous distention, and venous collateral formation. Variations in the clinical presentation of SVC syndrome may occur if compression or obstruction occurs in a large upper mediastinal vein or a low cervical vein. The syndrome may develop rapidly over a period of days or slowly over a period of many months.

The most common cause of SVC syndrome is extrinsic compression of the thin-walled, low-pressure SVC by a malignant mediastinal mass, such as a bronchogenic carcinoma—especially small cell lung cancer [see Figure 2]—or non-Hodgkin lymphoma. Other malignant causes of SVC syndrome are thymic tumors, mediastinal germ cell tumors, and metastatic carcinoma. The differential diagnosis includes SVC thrombosis (especially in patients with central venous catheters), goiter, mediastinal fibrosis, tuberculoi mediastinitis, histoplasmosis, and ascending aortic aneurysm.

In the past, SVC syndrome was considered an oncologic emergency that required the immediate initiation of mediastinal irradiation. Irradiation was thought to be necessary because of the need to alleviate increased intracranial pressures, because
lung cancer was presumed to be the most likely diagnosis, and because of the erroneous belief that increased venous pressures would make diagnostic procedures hazardous. It is now recognized that in adults, SVC syndrome is usually not a true emergency and that a histologic diagnosis should be quickly established and treatment promptly initiated. Emergency treatment with mediastinal irradiation before a histologic diagnosis is established is warranted in children and in adults who have mental status alteration, other life-threatening manifestations of increased intracranial pressure, cardiovascular collapse, or evidence of upper airway obstruction.

**Diagnosis**

SVC syndrome should be suspected in any patient who has a sensation of fullness in the face, plethora, dyspnea, facial swelling, distended neck veins, or venous collaterals in the neck or chest. In addition, many patients with SVC syndrome will acknowledge, if asked, that they have been sleeping fitfully and have been having nightmares. Headache, disturbance of vision, mental status alteration, cough, and chest pain may also be present. In almost all patients with SVC syndrome, a chest x-ray demonstrates widening of the superior mediastinum, a right hilar or an upper lobe mass, or pleural effusion. Computed tomography of the chest is the single most useful diagnostic tool. It confirms the clinical diagnosis, localizes the abnormality, provides information regarding biopsy sites, and identifies coexisting thrombosis. The diagnosis of SVC syndrome should be assumed if the patient has clinical manifestations of the syndrome and there is radiographic evidence of mediastinal disease.

In a patient without a history of cancer, an evaluation should be performed to identify any abnormality that is likely to provide a histologic diagnosis when a biopsy sample is taken. Procedures that will identify abnormalities include sputum cytology, fine-needle aspiration of pathologic lymphadenopathy, cytologic examination of pleural fluid, and bone marrow biopsy and aspiration. Because bronchogenic carcinoma is the most common cause of SVC syndrome, bronchoscopy is a high-yield procedure. Bronchoscopy can be performed safely in most patients with SVC syndrome. The combination of sputum cytology, bronchoscopy, and biopsy of palpable lymph nodes provides a definitive histologic diagnosis in approximately 70% of patients. Although the safety of biopsy procedures in patients with SVC syndrome has been well established, it is prudent to take biopsy samples from sites of disease outside the region of elevated venous pressures whenever possible.

**Treatment**

Treatment of SVC syndrome is based on the underlying etiology. Combination chemotherapy is preferred in patients with small cell lung cancer or lymphoma; in most patients, this treatment produces a positive disease response and improvement in the SVC syndrome. To prevent the increased risk of extravasation from veins with elevated pressure, chemotherapy should be administered into a vein in the lower extremity or a femoral vein. Mediastinal irradiation is generally the preferred therapy for patients with non-small cell lung cancer or other tumors that are relatively resistant to chemotherapy.

A newer treatment option for SVC syndrome is the placement of self-expanding stents in the SVC. Endovascular stenting can be combined with chemotherapy or radiotherapy, or it can be used on its own. Because it provides rapid relief of symptoms and is associated with a high success rate and low morbidity, endovascular stenting is increasingly being used as the initial treatment in SVC syndrome. The occurrence of SVC thrombosis in many patients who have SVC syndrome is seen by some clinicians as a reason for the routine use of anticoagulants. However, there are no convincing data to support routine use of these agents, and anticoagulation has been associated with a 10% fatality rate secondary to intracranial hemorrhage. SVC thrombosis should be suspected in the rare patient who fails to respond to chemotherapy or radiation therapy; in patients with documented thrombosis, treatment with anticoagulants or fibrinolytics is probably appropriate. Patients with stridor or significant airway compromise should be treated with glucocorticoids. Endotracheal intubation should be considered for acute airway management.

In 10% to 20% of patients, SVC syndrome will recur after radiation therapy and chemotherapy. The use of intravascular stenting devices may provide palliation in most of these cases. In patients with SVC syndrome secondary to malignancy, overall prognosis is determined by the underlying malignancy, not by the presence of the syndrome per se.

**Hematologic Emergencies**

disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) involves systemic activation of the coagulation process by tissue factor, impaired fibrinolysis, and deficiency in the physiologic anticoagulant system. In addition to malignancy, common causes of DIC...
include infection, obstetric complications, and trauma.\textsuperscript{14} The fibrinolytic system usually is activated secondarily; it is rarely activated primarily (primary fibrinolysis) without associated DIC. Patients with malignancy often have asymptomatic abnormalities of the coagulation system. These abnormalities include increased levels of factor VIII, fibrinogen, and platelets or evidence of increased fibrinolysis, as measured by increased levels of fibrin monomer, fibrinopeptide A, and fibrin degradation products.\textsuperscript{2} Patients with adenocarcinoma (especially carcinoma of the pancreas or prostate) or promyelocytic leukemia are particularly at risk. DIC may be either acute or chronic, and the coagulopathy may vary in severity, ranging from difficult to detect—even in the laboratory—to a fulminating bleeding diathesis. Thromboembolic manifestations are common.

\textbf{Diagnosis}

\textbf{Chronic DIC} Low-grade chronic DIC occurs in most patients with disseminated malignancy. The body typically compensates well, and laboratory measurements of coagulation may be normal or near normal. Some patients with low-grade chronic DIC, however, experience deep vein thrombosis, Trousseau syndrome, nonbacterial thrombotic endocarditis, or embolism without bleeding.\textsuperscript{25} Patients who have thrombosis and no evidence of bleeding should immediately be started on long-term anticoagulant therapy with heparin (either unfractionated or low-molecular-weight heparin). Warfarin provides inadequate protection against recurrent thrombosis in patients with chronic DIC.

\textbf{Acute DIC} Patients with acute DIC usually have clinical evidence of consumption coagulopathy, a low platelet count, and activation of clotting factors, which cause prolongation of the prothrombin, partial thromboplastin, and thrombin times; decreased fibrinogen levels; and elevated levels of fibrin degradation products. Common signs of acute DIC include bleeding from surgical wounds, venipuncture sites, the nose, the mouth, and the gastrointestinal tract; ecchymoses; petechiae; purpura; and stroke. In patients with malignancy, simultaneous blood loss from three or more sites usually is an indication of life-threatening acute DIC. The bleeding associated with DIC may be fulminating and may cause shock, end-organ dysfunction, and death.

\textbf{Treatment}

Treatment of acute DIC includes elimination of the underlying cause, such as infection or malignancy, whenever possible. DIC in patients with promyelocytic leukemia may resolve with treatment with all-\textit{trans}-retinoic acid.\textsuperscript{16,18-20} The replacement of consumed platelets and clotting factors usually is appropriate, and red cell transfusions should be performed in patients who have significant blood loss. Recent evidence suggests a role for supraphysiologic doses of antithrombin III.\textsuperscript{19,21} The role of heparin administration remains controversial.\textsuperscript{21,22} Heparin may be valuable in inhibiting DIC and thereby in maintaining appropriate levels of clotting factors, but it carries a significant risk for increasing bleeding. When heparin is used, the lowest dosage of heparin (300 to 500 \text{U/hr}) or low-molecular-weight heparin that allows maintenance of the platelet count (\textgt 50,000 \text{U/mm}^3) and clotting factor level (a fibrinogen level \textgt 150 \text{mg/dl}) should be given. In patients with primary fibrinolysis, treatment consists of the vigorous replacement of consumed clotting factors by factors given in the form of cryoprecipitate or fresh frozen plasma. Early evidence suggests that the use of activated protein C may also be of benefit.\textsuperscript{22}

bleeding with thrombocytopenia

In patients with cancer, thrombocytopenia is most commonly caused by the underproduction of platelets secondary either to bone marrow infiltration by tumor or to the toxicity of chemotherapy or radiation therapy. Increased destruction of peripheral blood elements, as occurs in hypersplenism, DIC, and immune-mediated disorders, is also sometimes observed. In patients who are receiving myelosuppressive chemotherapy and in those with known thrombocytopenia, the use of agents that inhibit platelet function, such as aspirin and other nonsteroidal anti-inflammatory drugs, should be specifically avoided.

Bleeding time is increased when platelet counts fall below 100,000/mm$^3$, and the risk of spontaneous bleeding is significantly increased when platelet counts fall below 10,000/mm$^3$.\textsuperscript{23} Use of prophylactic platelet transfusions in patients with decreased platelet production without bleeding is controversial. One practice is to maintain the platelet count above 20,000/mm$^3$; another is to reserve prophylactic transfusion for patients with a platelet count below 5,000 to 10,000/mm$^3$.\textsuperscript{24} In patients with acute myeloid leukemia, the risk of major bleeding during induction chemotherapy is about the same with platelet counts of 10,000/mm$^3$ or greater and counts of 20,000/mm$^3$ or greater.\textsuperscript{24,25} To prevent allosensitization, prophylactic platelet transfusions should not be performed in patients with increased destruction of peripheral blood elements.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{(a) Shown is a chest x-ray of a patient with small cell lung cancer and superior vena cava syndrome. (b) Contrast-enhanced CT scan in the same patient is also shown. Note that the thin-walled, contrast-enhanced superior vena cava is compressed by the tumor mass to a crescentic shape (arrow).}
\end{figure}
Treatment of bleeding in patients with thrombocytopenia from underproduction of platelets consists of platelet and red cell transfusions and local control at the site of bleeding. Patients who become sensitized to transfused platelets may benefit from HLA-matched, single-donor platelet transfusions. Underlying DIC should also be considered and, if identified, should be treated as noted in the discussion of DIC (see above). In patients undergoing chemotherapy for solid tumors who are at high risk for thrombocytopenia, the use of recombinant human interleukin-11 (orelvekin) has been shown to reduce thrombocytopenia and the need for platelet transfusions.24

Thrombotic microangiopathy

Thrombotic microangiopathy is a rare syndrome that includes microangiopathic hemolytic anemia, thrombocytopenia, uremia, and neurologic dysfunction. The syndrome may present as thrombotic thrombocytopenic purpura (TTP) or the hemolytic uremic syndrome (HUS); TTP is typically diagnosed if neurologic symptoms predominate, whereas HUS is diagnosed if uremia predominates. Both TTP and HUS involve the intravascular hemolysis of red cells. Thrombotic microangiopathy occurs in a variety of situations, including malignancy (e.g., adenocarcinomas and squamous cell carcinomas) and chemotherapy.

The diagnosis of thrombotic microangiopathy is suggested by anemia and the presence of schistocytes on peripheral blood smears. The severity of disease varies widely, ranging from minimal anemia with few schistocytes to profound anemia with rapid hemolysis and large numbers of schistocytes. Patients with gastric carcinoma are particularly at risk. Many patients also have associated DIC. The differential diagnosis includes sepsis with DIC.

HUS (but not TTP) may occur in patients who have no evidence of active disease. HUS is most commonly observed after chemotherapy with mitomycin but also is seen after treatment with bleomycin, cisplatin, dacarbazine, fluorouracil, lomustine, vinca alkaloids, gemcitabine, and high-dose chemotherapy with autologous stem cell support.27,28 In one series, the syndrome developed in approximately 4% of mitomycin-treated patients.29

Mortality from thrombotic microangiopathy is high, and no consistently effective therapy is available. The mainstay of therapy is immediate plasma exchange with either fresh frozen plasma or cryosupernatant plasma.30-32 Prolonged courses of plasma exchange of one calculated plasma volume a day may be required. The use of extracorporeal immunoadsorption of plasma has produced improvement in 45% of treated patients.32 Prednisone, 1 to 2 mg/kg/day, has also been recommended.

Fever and neutropenia

Patients with cancer may experience transient or protracted periods of neutropenia related to the disease or its treatment. Patients with neutropenia (defined as counts of polymorphonuclear leukocytes plus bands < 500/mm²) experience an increase in the frequency and severity of a variety of infections. The increased susceptibility to infection is related both to the level and to the duration of the neutropenia. Patients are at particular risk for life-threatening infection if neutropenia is profound (counts of polymorphonuclear leukocytes plus bands < 100/mm³). Other factors that place patients with cancer at increased risk for infection include deficient phagocytic function secondary to cytotoxic therapy, the breakdown of skin and mucosal barriers secondary to chemotherapy, the presence of vascular access devices, and the high frequency of invasive procedures. Although some studies have demonstrated that patients who are at low risk for infection and who have fever and neutropenia may be managed in the outpatient setting, most patients should be managed in the hospital until further confirmatory studies are available.25-27

Prevention

The optimal dosages and schedules of antitumor chemotherapy for a number of malignancies produce neutropenia. Methods of minimizing infection in patients with protracted neutropenia include the maintenance of good hygiene, with aggressive treatment of abrasions and mucositis; careful hand washing by medical personnel between patient contacts; not placing fresh flowers or plants in the patient’s room; the use of low-microbial diets; the use of prophylactic antibiotics; and the use of colony-stimulating factors. However, the use of prophylactic antibiotics is of limited usefulness, is expensive, and increases the risk of drug-resistant infection. In addition, granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim, pegfilgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can decrease the duration of chemotherapy-induced neutropenia [see Colony-Stimulating Factors, below].26-28

Diagnosis

In patients with neutropenia, serious infection should be presumed after a single temperature measurement of 38.3°C (101°F) or higher or after recurrent temperature measurements of 38.0°C (100.4°F) or higher.28 In the neutropenic patient, even life-threatening infections may not be apparent on initial evaluation, and there may be an absence of localizing signs or symptoms of infection. When present, the signs and symptoms of infection may be subtle because of an inadequate inflammatory response; repeated daily examinations are therefore essential. Physical examination should focus on common sites of infection, including the sinuses, ears, mouth, oropharynx, skin, chest, abdomen, perianal region, and catheter sites. Cultures should be obtained from the blood and urine; in patients undergoing long-term venous catheterization, blood cultures from each catheter lumen should be obtained at the same time as peripheral venous blood cultures. Cultures of sputum, the pharynx, stool, pleural or peritoneal fluid, cerebrospinal fluid, and catheter sites should be obtained if signs or symptoms of localizing infection are present. A chest radiograph should be obtained, although it may be normal in neutropenic patients who have pneumonia because the development of an infiltrate requires the presence of neutrophils.

Despite careful and thorough evaluation, an infectious source is identified in only 30% to 40% of patients with fever and neutropenia. Gram-positive organisms are now the most commonly identified organisms, particularly in patients undergoing long-term catheterization; the most common organisms are Staphylococcus epidermidis, Streptococcus species, and S. aureus. Gram-negative organisms, especially Escherichia coli, Klebsiella species, and P. aeruginosa, are also commonly identified.29-31 Neutropenic hosts also have increased susceptibility to fungal infection, most commonly with Candida, Aspergillus, and Zygomycetes species [see 7:XXXVIII Mycotic Infections in the Compromised Host].

Treatment

Antibiotic selection Antibiotic therapy in the neutropenic patient with fever or other manifestation of infection should be initiated promptly and at full dosages (after adjustments are made for renal and hepatic function). If a specific infectious organism is identified, the antibiotic regimen should be modified...
to ensure coverage of that organism, ideally with two different antibiotics. However, the spectrum of coverage should not be narrowed. Neutropenic patients who have an identifiable source of infection should receive treatment for at least as long as nonneutropenic patients with a similar infection. The duration of antibiotic therapy in the patient who becomes promptly afibrile is controversial; if the neutropenia persists, therapy should be continued for at least 5 to 7 days, even if no source of infection is identified.29

The antimicrobial agents that are initially selected for patients with fever and neutropenia should provide broad-spectrum coverage against both gram-positive and gram-negative organisms (including P. aeruginosa) with consideration for the frequency of antibiotic resistance in the local patient population. A number of intravenous and oral antibiotic regimens are effective.34-41,43,44 One regimen is an antipseudomonal aminoglycoside combined with either an antipseudomonal penicillin or an extended-spectrum antipseudomonal cephalosporin. Alternatively, monotherapy with broad-spectrum agents (e.g., imipenem-cilastatin or an extended-spectrum antipseudomonal cephalosporin) may be used [see 7:XIV Chemotherapy of Infection]. The addition of vancomycin to the regimen should be considered in patients with a long-term vascular access device or in patients at centers with high rates of methicillin-resistant S. aureus infection.45,46 Recent randomized studies demonstrate that patients at low risk of infection may be treated effectively with oral antibiotics (ciprofloxacin plus amoxicillin–clavulanic acid).47-50 Limited studies also suggest that carefully selected low-risk patients may be managed on an outpatient basis with oral or parenteral antibiotics.35,36

Secondary infection, antimicrobial resistance, or inadequate initial coverage commonly necessitates ongoing modification of the antimicrobial regimen.35 To minimize toxicity, serum levels of the aminoglycosides and vancomycin should be monitored and the doses adjusted. There is evidence that the nephrotoxicity associated with aminoglycosides is increased in the elderly and in patients who have been or are being treated with cisplatin or amphotericin B.

Neutropenic patients who have persistent fever despite receiving broad-spectrum antibiotics for 5 to 7 days or who experience recurrence of fever after an initial response to antibiotics should be considered for empirical antifungal therapy with liposomal or conventional amphotericin B.35,36

**Indwelling catheters** Patients with indwelling catheters who experience fever with or without neutropenia present special problems. Indwelling catheters are associated with infections of the exit site, the catheter tunnel, and the catheter lumen. A variety of organisms cause catheter-related infections, the most common of which is S. epidermidis infection. Catheter lumen–related or exit-site infections caused by S. epidermidis may be effectively treated by administering antibiotics through the catheter lumen without removing the catheter. In patients with fungal infections, however, the catheter should be removed. Infections of the subcutaneous catheter tunnel usually necessitate catheter removal regardless of the causative organism. Antibiotics should be rotated through each lumen of multilumen indwelling catheters to ensure eradication of all organisms.

** Colony-stimulating factors** Colony-stimulating factors are hematopoietic growth factors that stimulate the growth and maturation of committed bone marrow progenitor cells. Two of these colony-stimulating factors are currently available: G-CSF and GM-CSF. Treatment with G-CSF before neutropenia develops reduces the duration of the neutropenia and decreases the frequency of infectious episodes in patients who are receiving highly myelosuppressive cytotoxic chemotherapy. However, the high cost of G-CSF and GM-CSF precludes their prophylactic use except in patients who are receiving highly myelosuppressive therapy or in those who have a history of fever and neutropenia.95 Prospective, randomized trials of both G-CSF and GM-CSF have demonstrated limited value in the treatment of fever and neutropenia. G-CSF and GM-CSF decrease the duration of neutropenia and hospitalization but not days with fever or mortality.50,52

**fever and actual or functional splenectomy**

The spleen is an important organ in antibody production and in the destruction of nonopsonized or poorly opsonized bacteria. Patients who have undergone surgical splenectomy or who are functionally asplenic after splenic irradiation are at increased risk for infection with encapsulated bacteria, including S. pneumoniae, Haemophilus influenzae, Neisseria meningitidis, group A streptococci, and Capnocytophaga canimorsus.40 Such patients who become infected with these organisms may experience rapidly overwhelming sepsis. Therefore, asplenic or functionally asplenic patients should have in their possession antibiotics that are active against the encapsulated bacteria. These antibiotics should be taken for any febrile illness, and the patient should receive prompt medical evaluation. The threshold for hospitalization should be low, and an antibiotic regimen such as cefotaxime or ceftriaxone should be urgently initiated. The use of vancomycin should be considered in situations in which penicillin or cephalosporin resistance is common or suspected.

**Metabolic Emergencies**

**HYPERCALCEMIA OF MALIGNANCY**

Hypercalcemia of malignancy occurs in 10% to 20% of patients with cancer at some time during their illness and may range from a mildly increased calcium level in asymptomatic patients to a life-threatening emergency. Hypercalcemia is usually a manifestation of advanced disease and is observed in patients with hematologic malignancies, solid tumors without bone metastasis, and solid tumors with bone metastasis.49

Non–small cell lung cancer, breast cancer, head and neck cancer, renal cell cancer, myeloma, and T cell lymphoma are the tumors most commonly associated with hypercalcemia. Patients with breast cancer metastatic to bone may experience hypercalcemia during the initiation of treatment with estrogens, androgens, progesterin, or antiestrogens.

**Pathophysiology**

Normal calcium homeostasis is a balance of intestinal absorption of calcium, bone resorption and formation, and renal excretion of calcium.49 In healthy persons, bone resorption and formation are closely balanced, so that renal elimination of calcium is primarily determined by intestinal calcium absorption. Intestinal calcium absorption occurs both actively and passively. Bone resorption is stimulated by parathyroid hormone (PTH) and inhibited by calcitonin. Active absorption of calcium by the intestine is subject to saturation and is regulated primarily by 1,25-dihydroxyvitamin D₃[1,25-(OH)₂D₃]. Other hormones, such as PTH and glucocorticoids, participate indirectly in regulation of the active intestinal absorption of calcium by modulating renal pro-
duction of 1,25-(OH)2D3. Renal calcium reabsorption is increased by PTH.

Both trabecular bone and cortical bone undergo a dynamic process: bone resorption by osteoclasts, followed by bone formation mediated by osteoblasts. Under normal conditions, the temporal and spatial balance of bone resorption and formation limits the ability of bone to participate in calcium regulation. The final pathway common to the mechanisms of hypercalcemia in malignancy is an uncoupling of the spatial and temporal balance of bone resorption and formation; as a result, bone resorption occurs more quickly than bone formation. Intestinal calcium absorption decreases, the extracellular volume contracts, and urinary excretion of calcium declines, producing hypercalcemia.

The mechanisms that underlie the uncoupling of bone resorption and formation are mediated by humoral factors released by tumors without bone metastasis and by paracrine factors released by metastatic deposits in bone. The mediators of humoral hypercalcemia of malignancy that have direct effects on the uncoupling of bone include parathyroid hormone–related protein (PTHrP), transforming growth factor–α (TGF–α), colony-stimulating factors, interleukin-1 (IL-1) and IL-6, tumor necrosis factor, and prostaglandins.55-56

PTHrP is a peptide that has homology to PTH at eight of 13 amino acids at the PTH receptor–binding domain. PTHrP is primarily associated with epithelium and is found in very high concentrations in milk. In humoral hypercalcemia of malignancy, PTHrP appears to activate the PTH receptor, which results in increased renal reabsorption of calcium and increased bone resorption. Unlike PTH, however, PTHrP does not stimulate new bone formation.55-57

A syndrome of increased levels of 1,25-(OH)2D3 may occur in patients with Hodgkin disease and non-Hodgkin lymphoma (especially patients with T cell lymphoma or leukemia who test positive for human T cell lymphotropic virus type I). In affected patients, elevations in the level of 1,25-(OH)2D3 result in increased intestinal absorption of calcium and increased bone resorption, leading to hypercalcemia.

Many patients with hypercalcemia of malignancy have widespread bone destruction secondary to metastatic lesions, a development that is especially common in patients with breast cancer and multiple myeloma. In these patients, local bone destruction appears to be the cause of the hypercalcemia. The metastatic cells either release directly or induce the surrounding normal cells to release paracrine factors such as TGF–α and prostaglandins, which uncouple bone resorption and bone formation by activating local osteoclasts.55

Hypercalcemia may arise in association with widespread osseous metastases, as occur with breast and prostate cancer; with the release of osteoclast-activating factor in such B cell malignancies as multiple myeloma and (less often) non-Hodgkin lymphoma; and with the release of a cytokine that interacts with the PTH receptor, as seen with some squamous cell carcinoma (e.g., cancer of the lung, cervix, anus, head and neck, and esophagus), renal cell carcinoma, or hepatocellular carcinoma. In patients with hepatocellular carcinoma, hypercalcemia may occur in the total absence of bony involvement; by contrast, in patients with breast and prostate cancer, hypercalcemia almost always occurs in the setting of bony involvement.

Diagnosis

Patients with hypercalcemia of malignancy have nonspecific symptoms. Early symptoms include polydipsia, polyuria, anorexia, fatigue, and constipation. Abdominal pain and bloating, nausea, and change in mental status are also seen. Late manifestations include coma and cardiac arrhythmia. Bone pain may or may not be present.

In the differential diagnosis of hypercalcemia of malignancy, the most common competing diagnosis is primary hyperparathyroidism. Primary hyperparathyroidism is associated with a slight elevation in the serum calcium level (11 to 12 mg/dl) and a decrease in the serum phosphate level (2 to 3 mg/dl). In contrast, the hypercalcemia of malignancy is usually associated with a more dramatic increase in the serum calcium level (often greater than 14 to 15 mg/dl) with a normal serum phosphate value. Immunoradiometric assays for intact PTH appear to distinguish between patients with hypercalcemia and elevated PTH levels (hyperparathyroidism) and those with depressed PTH levels (hypercalcemia of malignancy).

Treatment

Hypercalcemia of malignancy is usually a manifestation of advanced cancer. In the patient with symptomatic hypercalcemia and for whom there are no effective anticancer treatment options, median survival is approximately 35 days; for the patient with anticancer treatment options, median survival is less than 90 days.55 For this reason, in patients for whom there are no anticancer treatment options, withholding active treatment of the hypercalcemia may be the most humane, compassionate, and appropriate course of action.55 In the patient for whom effective anticancer therapy is available, treatment of the hypercalcemia is appropriate and includes volume and electrolyte repletion, inhibition of bone resorption, and treatment of the underlying malignancy.

Extracellular volume deficits exist in all patients with symptomatic hypercalcemia of malignancy. The single most important and urgent treatment is the infusion of normal saline to correct the extracellular volume deficit, increase glomerular filtration rate (GFR), and, secondarily, increase renal calcium excretion. Hypokalemic metabolic alkalosis commonly is observed in patients with hypercalcemia of malignancy despite the coexisting decrease in GFR. Therefore, attention should also be directed to the correction of any coexisting potassium deficit, especially in patients who are taking digitalis preparations.

Diuretics should not be used until the volume deficit has been fully corrected. The loop diuretics cause calciuresis and therefore may be effective in acutely decreasing calcium levels—but again, only after volume repletion. The thiazide diuretics decrease renal calcium excretion and should be specifically avoided.

The bisphosphonates offer an improved and simplified treatment of hypercalcemia of malignancy. The bisphosphonates have a high affinity for areas of high bone turnover, such as the areas of bony involvement with malignancy, where they block osteoclast attachment to bone matrix and osteoclast recruitment and differentiation.55 Zoledronate (4 mg given in a 15-minute intravenous infusion) is the preferred bisphosphonate in the treatment of hypercalcemia of malignancy, with a complete response rate of 88% at day 10.55 The toxic effects of the bisphosphonates include transient fever, local reactions at the infusion site, hypomagnesemia, hypophosphatemia, decreased renal function, and occasionally a flu-like syndrome.

Other agents used in the second-line treatment of hypercalcemia of malignancy include plicamycin, calcitonin, and the glucocorticoids.
Immobilization leads to a rapid increase in bone resorption. Mobilization is therefore an important but frequently neglected component in the treatment of hypercalcemia of malignancy. Except in the rare case of hypercalcemia of malignancy secondary to increased levels of 1,25-(OH)2D3, intestinal absorption of calcium is depressed in patients with hypercalcemia of malignancy. Therefore, efforts to decrease intestinal absorption of calcium by dietary restriction are of limited therapeutic value.

A reasonable approach to the treatment of hypercalcemia of malignancy includes rapid saline rehydration, with correction of any coexisting electrolyte deficiency; inhibition of bone resorption with zoledronate; and initiation of active treatment of the underlying malignancy.

**Tumor lysis syndrome**

Patients with a large tumor burden or rapidly proliferating tumors may experience a spontaneous or treatment-related tumor lysis syndrome that includes the rapid discharge of intracellular electrolytes and nucleic acids. The syndrome usually occurs within 6 to 72 hours after the initiation of therapy and is characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia with secondary hypocalcemia. Tumor lysis syndrome is most often seen in patients with lymphoma or leukemia but also in patients with a variety of solid tumors. A large tumor burden, a high growth fraction, an increased pretreatment lactate dehydrogenase level, an increased pretreatment uric acid level, or preexisting renal insufficiency increases the risk of tumor lysis syndrome. Increased levels of uric acid, xanthine, and phosphate may result in precipitation of these substances in the kidney. Renal sludging and acute renal insufficiency or failure further aggravates the metabolic abnormality.

The hyperkalemia associated with tumor lysis syndrome may be accentuated by associated renal insufficiency or renal failure and may cause electrocardiographic alterations and potentially fatal cardiac arrhythmia. The major manifestation of hyperphosphatemia is secondary hypocalcemia caused by precipitation of calcium phosphate in the soft tissues and the kidney. Hypocalcemia may lead to alterations in mental status, neuromuscular irritability, carpopedal spasm, and seizures.

**Treatment**

Anticipation and controlled management of tumor lysis are the keys to preventing the syndrome. Patients who are at risk should be hospitalized and fully hydrated, with ongoing diuresis before, during, and after treatment, and they should undergo frequent electrolyte monitoring. Diuresis minimizes the renal sludging caused by high urinary loads of uric acid, xanthine, and phosphate. Pretreatment with allopurinol blocks the conversion of hypoxanthine and xanthine to uric acid and minimizes the uric acid sludging in the kidney caused by xanthine crystals. Alkalization of the urine with sodium bicarbonate infusion increases the solubility of urinary uric acid and decreases the risk of urate nephropathy but may increase risk of calcium phosphate precipitation.

Patients at risk for tumor lysis syndrome should not receive supplemental potassium and should be monitored for development of hyperkalemia. Life-threatening hyperkalemia should be treated aggressively with diuresis, potassium-binding salts, and renal dialysis. Patients who have either symptomatic hypercalcemia or the electrocardiographic changes associated with hypocalcemia should be treated with an infusion of calcium gluconate. The hypocalcemia may persist beyond the period of observed hyperphosphatemia.

In its most severe form, tumor lysis syndrome may result in the rapid onset of profound and life-threatening fluid and electrolyte abnormalities and acute renal failure. The rapid lysis of tumor usually is iatrogenic and transient; therefore, aggressive supportive care is appropriate. Such care includes meticulous monitoring of fluid and electrolyte balances, cardiac monitoring, and hemodialysis as necessary.

**Neurologic Emergencies**

**Brain metastasis**

Intracranial metastases occur in 20% to 30% of patients with systemic cancer. The most common primary cancers that result in intracranial metastases are lung cancer, breast cancer, GI cancer, genitourinary cancer, and melanoma. Most metastases are to the cortical-medullary junction, are associated with vasogenic edema, and occur with approximately equal frequency as a single metastasis or multiple metastases.

**Diagnosis**

Intracranial metastases compress the adjacent brain parenchyma and increase intracranial pressure. The increased intracranial pressure is associated with nonspecific symptoms, including headache that is frequently retro-orbital, nausea, and vomiting, all of which may be most severe in the morning. Cranial nerve abnormalities, including blurred vision, diplopia, and visual-field defects, also are common. Finally, localized mass effects and edema may produce localized neurologic signs and symptoms, including motor and sensory abnormalities, dysphasia, ataxia, personality change, and seizures.

CT with contrast enhancement and magnetic resonance imaging with contrast enhancement are both relatively sensitive methods of diagnostic imaging in patients with suspected intracranial metastasis. Contrast-enhanced MRI is generally preferred, because it is more sensitive.

When multiple intraparenchymal metastases develop in a patient who has a known primary neoplasm, histologic diagnosis of the metastases usually is not warranted. However, intraparenchymal metastasis may be the presenting manifestation in some cases of neoplastic disease. In such cases, a focused evaluation for the primary tumor is appropriate, with special consideration of lung cancer, breast cancer, and melanoma. If the primary tumor is identified, it should be biopsied. Should no primary tumor be identified, biopsy of the intracranial disease is appropriate. Biopsy or excisional biopsy is particularly appropriate to help differentiate between a primary CNS tumor and a metastatic tumor in patients with no known primary malignancy who have a solitary intracranial lesion.

**Treatment**

Factors to be considered when deciding on a treatment regimen for intracranial metastasis are the age of the patient, whether there is control of the disease at other systemic sites, the patient’s performance status, and the number of intraparenchymal metastases. The survival of patients with untreated intraparenchymal metastases is approximately 1 month. Treatment usually provides substantial palliation and may prolong survival.

Glucocorticoids should be administered to patients with newly diagnosed intraparenchymal metastases. In most patients,
Dexamethasone, administered at a dosage of 4 to 16 mg/day in divided doses, is associated with improvement of symptoms within hours to days. Higher doses may improve the rates of response, but toxicity is also increased. The optimal duration of glucocorticoid administration is not known, but doses should be tapered gradually as therapy is completed.

Patients who have seizures should receive antiepileptic drugs. Erythema multiforme major (Stevens-Johnson syndrome) may occur in patients treated with phenytoin, cranial irradiation, and glucocorticoids.

Randomized studies document the superiority of surgical resection followed by radiation therapy over the use of radiation therapy alone in the treatment of patients who have surgically resectable solitary intraparenchymal brain metastasis. However, patients with uncontrolled systemic disease experience no benefit from the addition of initial surgery. Thus, patients who have solitary brain metastasis and controlled systemic disease should undergo initial surgical resection when possible, followed by whole brain irradiation. Patients who have a solitary brain metastasis that is unresectable or who have uncontrolled systemic disease should undergo whole brain irradiation.

Whole brain irradiation provides substantial palliation and increased survival in patients who have multiple intraparenchymal metastases. A few studies have suggested that initial surgery provides some benefit in patients with multiple surgically resectable intraparenchymal metastases, but other studies have found no advantage.

Techniques now exist for the delivery of high doses of stereotactically directed ionizing radiation to defined tumor volumes with relative sparing of surrounding normal tissue. These techniques have been used successfully to treat solitary and multiple brain metastasis with or without whole brain irradiation. In the primary treatment of intraparenchymal metastasis, the benefit of whole brain irradiation after stereotactically directed radiation therapy is still being defined.

epidural spinal cord compression

Epidural compression of the spinal cord or cauda equina occurs in 5% to 10% of patients with malignancy. Patients with breast cancer, lung cancer, prostate cancer, lymphoma, renal carcinoma, or sarcoma are at particular risk. The site of epidural compression is thoracic in 70% of patients, lumbar in 20%, and cervical in 10%. More than 30% of patients experience multiple levels of epidural compression.

Pathophysiology

The epidural space lies between the dura mater of the spinal cord and the bony spinal canal. Mass lesions in the epidural space may cause injury to the spinal cord or cauda equina by direct mechanical distortion or by vascular compromise with edema and ischemia or infarction.

Almost all epidural masses occur as the result of extension of metastasis from the bony spine, especially from the vertebral bodies. Involvement of the epidural space also may occur by extension through the intervertebral foramina or through Batson venous plexus in patients with increased intra-abdominal pressure [see Figure 3].

Diagnosis

Because the prognosis for recovery of neurologic deficits from spinal cord compression is related to the duration and the severity of the deficits at the start of treatment, early diagnosis is crucial. More than 95% of patients with epidural compression caused by malignancy have pain, either local or radicular, both as the first symptom and at the time of diagnosis [see Table 1]. It usually is constant and progressive and increases with the Valsalva maneuver or straight leg raising. Unlike the pain of spinal disk disease, the pain of epidural compression typically is worsened by recumbency. Local vertebral tenderness to percussion often is present. Sensory loss in a distribution distal to the site of epidural compression is common and may be rapid.
because its ability to scan the entire spinal axis efficiently and its resource intensive. CT of the spine should not be performed, as one cannot compass the entire spinal axis and thus may be time consuming and sometimes impossible in its interpretation may not be available. MRI of the spine, especially with gadolinium enhancement, is highly sensitive. Dexamethasone and local radiation therapy. An initial surgical approach is considered in patients who do not have a histologic diagnosis of malignancy, in patients who have an unstable bony spine, in patients whose symptoms progress during radiation therapy, or in patients whose symptoms progress after a maximally tolerated dose of radiation to the spinal cord.

Table 1 Signs and Symptoms Associated with Epidural Spinal Cord Compression

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>First Symptom (%)</th>
<th>Symptoms at Diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Weakness</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>Autonomic</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>Dysfunction</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Sensory loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Flexor spasms</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Weakness, usually bilateral and symmetrical, is present in more than 75% of patients at the time of diagnosis and may be rapidly progressive. Autonomic dysfunction of the bladder or bowel is a late sign of epidural compression. The duration and severity of neurologic dysfunction before the initiation of treatment are strong predictors of whether neurologic function can be maintained or restored.

Radiographs of the spine and radionuclide bone scans are usually abnormal in patients with epidural compression but are not specific enough to be diagnostic or localize. The current recommendation for the radiographic evaluation of patients with possible epidural compression is gadolinium-enhanced MRI of the entire spinal axis. Myelography is also sensitive and specific for detecting epidural compression, but myelography is invasive, it may be uncomfortable for the patient with severe bone pain, and radiologists experienced in its interpretation may not be available. MRI of the spinal cord, especially with gadolinium enhancement, is highly sensitive, noninvasive, and more sensitive than myelography in detecting intramedullary metastasis. The MRI of the spinal cord should encompass the entire spinal axis and thus may be time consuming and resource intensive.

Intramedullary spinal metastasis is unusual and occurs primarily in patients with lung cancer, breast cancer, colon cancer, or lymphoma. Presenting manifestations are similar to those of epidural spinal cord compression except that the associated motor weakness is commonly unilateral. Intramedullary metastasis must be distinguished from epidural cord compression, leptomeningeal metastasis, radiation myelopathy, primary intramedullary tumors, and necrotizing myelopathy. Myelography may reveal a fusiform swelling of the spinal cord, but myelographic results are frequently normal. High-resolution CT or MRI with gadolinium enhancement is superior to myelography in identifying intramedullary metastasis. Treatment is similar to that of epidural spinal cord compression.

Leptomeningeal metastasis

Leptomeningeal metastasis occurs rarely. It is observed chiefly in patients with lung cancer, breast cancer, melanoma, or lymphoma.

Diagnosis

The signs and symptoms of leptomeningeal metastasis may be referable to the brain, cranial nerves, or spine. In patients with malignancy, the presence of signs or symptoms that are referable to more than one location within the craniocaudal axis always raises the possibility of leptomeningeal metastasis. Headache, changes in mental status, ataxia, nausea, vomiting, diplopia, facial weakness, lower extremity weakness, paresthesia, reflex asymmetry, and spinal pain are particularly common. Results of cerebrospinal fluid examination are almost always abnormal, with elevated protein levels and positive cytology the most common abnormalities. Pleocytosis in the CSF may be seen as a manifestation of leptomeningeal involvement in patients with leukemia or lymphoma. Contrast-enhanced CT or gadolinium-enhanced MRI may be abnormal, but false negative results are common.

Treatment

Treatment of epidural cord compression should be initiated immediately, especially in patients with recent onset of neurologic dysfunction or whose neurologic dysfunction is progressive. Dexamethasone provides pain relief for many patients and may decrease edema that is localized to the area of compression. One evidence-based guideline recommends 24 mg of dexamethasone every 6 hours. Regardless of the dexamethasone dosage, dosages should be tapered to minimize toxicity.

The mainstay of treatment is radiation therapy to the level of epidural compression and to a margin of normal tissue above and below it. Spinal cord tolerance to radiation is related both to the fraction size and to the cumulative dose. The frequent occurrence of multiple synchronous or metachronous levels of epidural compression necessitates careful planning to minimize the need for serial treatment of adjoining areas of the spine. With serial treatment, it is particularly difficult to match adjoining radiation therapy fields to avoid overlapping.

A surgical approach to epidural compression may provide pain relief, halt the progression of the neurologic deficits, allow for stabilization of the spine, and provide a histologic diagnosis of malignancy in patients without a known primary tumor. However, most patients with epidural compression have widespread disease and are assessed at increased operative risk. Because the rate of local recurrence after surgery alone is high, local irradiation is still warranted. Recent studies conducted on the treatment of epidural cord compression with an aggressive surgical approach reported encouraging results, especially when the spine was unstable, pathologic compression fracture caused impingement of the cord by bone fragments, or the tumor was resistant to irradiation. However, most studies of surgery plus radiation therapy versus radiation therapy alone have not demonstrated meaningful differences in the return of neurologic function and survival.

The typical patient who has a known malignancy and epidural cord compression should receive immediate treatment with dexamethasone and local radiation therapy. An initial surgical approach is considered in patients who do not have a histologic diagnosis of malignancy, in patients who have an unstable bony spine, in patients whose symptoms progress during radiation therapy, or in patients whose symptoms progress after a maximally tolerated dose of radiation to the spinal cord.

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Treatement

Systemic administration of chemotherapy usually results in very low levels of drug in the CSF. However, therapeutic levels of methotrexate, cytarabine, and thiotepa may be safely achieved in the CSF by lumbar puncture or by intraventricular instillation. The use of subcutaneous reservoirs attached to a catheter that is inserted into the lateral ventricle (Ommaya reservoir) is a safe and convenient method of delivering intrathecal chemotherapy and provides a uniform distribution of drug throughout the CSF in many patients. A sustained-release formulation of cytarabine is commercially available. In one study comparing sustained-release cytarabine with methotrexate for intrathecal treatment of neoplastic meningitis, onset of neurologic progression was slower with cytarabine (50 mg once every 14 days) than with methotrexate. Radiation therapy may be administered to patients with leptomeningeal metastasis who have particularly severe symptoms or in whom the sites of involvement threaten neurologic function.

The response to therapy for leptomeningeal metastasis is strongly dependent on the underlying tumor type, previous therapy, extent of disease, and presence or absence of blockage of CSF flow. Patients who have leptomeningeal involvement from leukemia, lymphoma, or breast cancer may experience substantial palliation and increased survival after prompt and aggressive therapy.

As is the case with the other CNS emergencies, the extent of neurologic dysfunction when therapy is initiated predicts the degree of neurologic function that will be achieved after therapy. In general, however, patients with leptomeningeal metastasis have a poor prognosis.

The author has no commercial relationships with manufacturers of products or providers of services discussed in this subsection.

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