PERSPECTIVE

Oncologic emergencies embody an extensive range of illnesses that can occur at any time during the course of malignant disease. Some oncologic emergencies are insidious and develop during months; others are manifested in hours and can lead to paralysis and death. Prompt, accurate diagnosis and appropriate treatment of oncologic emergencies can improve the quality of life dramatically in patients with cancer. With timely intervention, many of these patients can return to their previous level of function and independence. In addition, a reversible life-threatening emergency can occur in a patient with an underlying malignant neoplasm that is otherwise highly treatable or even curable, making identification and management of the oncologic emergency a potentially lifesaving action.

Cancer remains the second leading cause of death in the United States. It is estimated that 1,529,560 men and women (789,620 men and 739,940 women) will be diagnosed with and 569,490 men and women will die of cancer of all sites in 2010. The most commonly diagnosed new cancer is prostate cancer in men and breast cancer in women. The second most commonly diagnosed new cancer in both sexes is lung cancer. The most common cause of cancer death for both sexes is lung and bronchial cancer. Worldwide, the most commonly diagnosed new cancer and most common cause of cancer death for both sexes is lung and bronchial cancer. Worldwide, the most commonly diagnosed new cancer and most common cause of cancer death is lung and bronchial cancer in men and breast cancer in women. The most common malignant neoplasm of childhood is leukemia, followed by brain tumors and lymphoma.

In 2003, it was estimated that the lifetime risk for development of cancer was 1:2 for men and 1:3 for women. Most cancer patients will experience at least one emergency during the course of their disease, and emergency physicians are increasingly managing complications related to cancer, although definitive therapy for an oncologic emergency is often multidisciplinary, involving surgeons, radiation oncologists, medical oncologists, and other medical and social specialists. Changing trends in cancer have produced an increased number of emergency department (ED) visits secondary to cancer and its complications (Box 123-1). In fact, a study reported that about 40% of cancer patients had visited the ED in the last 2 weeks of life. Therefore, the emergency physician should be well versed in oncologic emergencies. However, many factors can hinder the identification and management of oncologic emergencies in the ED (Box 123-2). This chapter focuses on the most common oncologic emergencies: fever and neutropenia, superior vena cava syndrome, acute tumor lysis syndrome, hyperuricemia, hypercalcemia, neoplastic cardiac tamponade, and spinal cord compression.

FEVER

Fever is defined as a single oral temperature in excess of 38.3°C (101.3°F) or a sustained temperature of 38°C (100.4°F) for more than 1 hour. Fever in the cancer patient can be caused by inflammation, transfusions, antineoplastics, antimicrobials, and tumor necrosis. Although fever can be secondary to malignant disease with a significant tumor burden, fever occurring in cancer patients more commonly has an infectious origin (55-70%). Neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/mm³ or less than 1000 cells/mm³ with predicted decrease to less than 500 cells/mm³, will assist in determining the need for empirical antibiotics and a more aggressive approach to treatment of a febrile cancer patient. ANC can be calculated from white blood cell (WBC) and polymorphonuclear (PMN) cell counts as follows:

\[
\text{ANC} = \text{WBCs} + \left(\frac{\text{PMNs}}{100}\right) + \left(\frac{\text{bands}}{100}\right)
\]

The risk of infection and morbidity are increased with an ANC of less than 1000/mm³ and are substantially higher when counts are less than 100/mm³. In addition to the ANC, the risk of infection is also increased with a more rapid rate of development and a longer duration of neutropenia. Fever in the neutropenic cancer patient is one of the most common complications related to chemotherapy treatment. It should be presumed to have an infectious origin and thus constitutes a medical emergency. Use of early empirical antibiotic therapy has resulted in a decrease in mortality in patients receiving chemotherapy.

Clinical Features

Because fever is often the first and occasionally the only sign of infection in the neutropenic cancer patient, a careful history and physical examination must be performed; this includes an evaluation of the fundi (looking for Candida endophthalmitisis), rectum, perineum and groin (for perirectal abscess), skin and mucous membranes (for any lesions suggesting malignant disease or cellulitis), axillae, and catheters. The oral cavity and the perianal area are inspected, although digital rectal examination is discouraged in that it may induce bacteremia. Common infections may be manifested atypically because of lack of neutrophils. In the absence of polymorphonuclear cells, traditional markers of inflammation such as erythema, warmth, and pyuria may be absent or minimal, making it essential to search for subtle signs of inflammation. For example, skin infections may be manifested as a subtle rash or erythema, meningitis may be present without nuchal rigidity,
Changing Trends in Cancer That Have Produced an Increased Number of Emergency Department Visits Secondary to Cancer and Its Complications

Box 123-1

More aggressive and broader use of chemotherapy regimens
Increasing use of bone marrow transplantation
More effective treatment options, increasing cure and survival rates
Increased number of elderly patients receiving chemotherapy
Increased survival for all cancers combined

Factors That Can Hinder Identification and Management of Oncologic Emergencies

Box 123-2

Patient or physician discomfort with the diagnosis of cancer
A voluminous and frequently changing database of chemotherapeutic agents and complex classification systems
Time constraints
Lack of an established physician-patient relationship
Inappropriate or premature labeling of the cancer patient as “terminal”
Failure to appreciate that effective treatments are available for oncologic emergencies and many of the cancers that cause them

Current Recommendations for Antimicrobial Therapy for Fever in Neutropenic Cancer Patients

Box 123-3

An antipseudomonal penicillin + an aminoglycoside ± vancomycin
Ceftazidime ± an aminoglycoside
Ceftazidime ± vancomycin
Cefepime ± an aminoglycoside
Cefepime ± vancomycin
Imipenem-clastatin
Meropenem

Overall, approximately 85% of the initial pathogens isolated in febrile neutropenic patients are bacterial, and of these, 60 to 70% are gram-positive pathogens. Gram-negative bacilli, particularly Pseudomonas aeruginosa, were the most common pathogens until the 1980s. However, the administration of prophylactic antibiotics primarily active against gram-negative pathogens during chemotherapy, the widespread use of indwelling venous catheters, and the newer chemotherapy regimens have led to an increase in gram-positive pathogens.

Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus epidermidis are the predominant gram-positive organisms. Once believed to be a skin contaminant, S. epidermidis has arisen as a major pathogen and may be resistant to antistaphylococcal penicillins and cephalosporins. Escherichia coli, P. aeruginosa, and Klebsiella pneumoniae remain the most common gram-negative pathogens.

Fungal, viral, and parasitic infections are also important primary and secondary complications. Fungal infections, especially with Candida albicans, can be a major problem in neutropenic febrile patients treated with broad-spectrum antibiotics for protracted periods. Although significant institutional variation has been noted, Histoplasma, Cryptococcus, Aspergillus, and Phycycomycetes are additional fungal pathogens encountered in the compromised host. In contrast to patients with acquired immunodeficiency syndrome (AIDS), parasitic infections are not a common source of infection in patients with solid tumors. Pneumocystis jiroveci (formerly carinii), however, may be seen when corticosteroid use or hematologic malignant disease has resulted in lymphocyte dysfunction. Herpes simplex, herpes varicella-zoster, and cytomegalovirus are common viral pathogens. The compromised host is at risk for infection from a large number of individual pathogenic agents, thus further complicating the diagnosis and treatment of these patients.

In an attempt to prevent these infections, oncologists may initiate antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (Bactrim) or quinolones for immunosuppressed patients before development of fever. In addition, recombinant human granulocyte colony-stimulating factor and granulocyte-macrophage...
colony-stimulating factor are used to stimulate rapid increase in granulocytes in neutropenic patients in an effort to decrease the duration and degree of neutropenia and immunosuppression.

Fever is occasionally without a source and is believed to arise from the underlying disease, although it is impossible to differentiate by clinical and demographic factors those patients with bacteremia-induced fever from those with unexplained fever. In addition, the absence of physical findings indicative of infection does not exclude a potentially life-threatening septic event. In addition to clinical and demographic factors those patients with bacteremia-induced fever from those with unexplained fever. In addition, the absence of physical findings indicative of infection does not exclude a potentially life-threatening septic event because at least 50% of septic patients lack any distinct physical findings.

Management

Local resistance patterns are used to guide treatment. Patients are risk stratiﬁed and then treated accordingly. Patients with fever who appear in good condition are considered at low risk. Patients with fever who have severe neutropenia, appear ill, and are expected to have a protracted course are at high risk. In the initial evaluation and management of the febrile cancer patient, one must take into account the particular underlying malignant neoplasm, prior use of antimicrobial therapy, and how the degree of treatment has affected the host's immunologic compromise. For example, in acute leukemia, normal circulating neutrophils and monocytes are largely replaced by blast cells, which do not function well in the phagocytosis and killing of bacterial and fungal agents. Chemotherapeutic agents and irradiation exacerbate or potentiate the underlying defect in already compromised host defenses. Corticosteroids impair granulocyte and mononuclear cell mobilization in leukemic patients. Patients with severely compromised host defenses and those in whom fever is accompanied by an increase in respiratory rate, change in mental status, agitation or apprehensiveness, and hemodynamic instability should be urgently treated.

Once febrile neutropenia is diagnosed, broad-spectrum antibiotic therapy is indicated immediately after culture specimens are obtained regardless of evidence of infection. Afebrile patients with neutropenia and suspicion of infection should also be cultured and should be treated with broad-spectrum antibiotics.

The optimal antimicrobial regimen is synergistic, broad spectrum, and bactericidal with a low potential for toxicity and chosen for efficacy against the most likely causes of systemic and rapidly progressing infection: *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, and *Klebsiella* species. Traditionally, a two-drug regimen was selected because historical studies from the 1980s found that patients with gram-negative bacteremia had a higher survival rate when the isolate was sensitive to and treated with two antibiotics, compared with when the isolate was sensitive to only one of two antibiotics in the combined regimen.

Signiﬁcant advances in the antimicrobial armamentarium have been made in the past 10 years with the development of broad-spectrum single agents such as the carbapenems (imipenem–cilastatin, meropenem) and the third- and fourth-generation cephalosporins (cefazidime, cefepime). These agents, when investigated as monotherapy in neutropenic, febrile patients, have been found to be as effective as a dual-drug combination of an antipseudomonal penicillin (ticarcillin, carbenicillin, or piperacillin) plus an aminoglycoside (gentamicin or tobramycin). Furthermore, single-drug therapy is associated with fewer adverse effects. Amikacin is generally reserved as a second-line aminoglycoside for isolates that demonstrate aminoglycoside resistance. Antifungal and antiviral agents are not usually indicated during initial therapy, although they are becoming increasingly prevalent. Antifungal therapy is recommended if there is no improvement within 3 days of treatment. Box 123-3 summarizes current recommendations for antimicrobial therapy for fever in neutropenic cancer patients.

The drug most commonly used for treatment of gram-positive bacteria is vancomycin. Use of empirical vancomycin is indicated in the following circumstances:

- Clinically suspected catheter infections
- Known colonization with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant *S. aureus*
- Blood cultures positive for gram-positive bacteria before final identification and susceptibility testing
- Hypotension or other evidence of cardiovascular impairment

Neutropenic febrile patients are best admitted to an isolation room, and rapid movement out of a congested waiting room into a private space is a high priority. Handwashing and reverse isolation techniques should be used.

Several clinical trials validate the outpatient management of selected patients older than 16 years with neutropenic fever. These patients must be at low risk for serious infection and must have close follow-up and unrestricted access to healthcare professionals. The Multinational Association for Supportive Care in Cancer has introduced a prediction tool to assess patients suitable for outpatient therapy that accounts for burden of illness and social factors.

Contraindications to outpatient therapy are as follows:

- History of noncompliance
- Inability to care for oneself
- Lack of caregivers
- No telephone or lack of reliable transportation
- High risk of severe infection

The best-studied outpatient antibiotic regimen for neutropenic fever is a combination of ciprofloxacin (500 mg every 8 hours) and amoxicillin–clavulanate (Augmentin; 500 mg every 8 hours). Daily assessment by a healthcare professional is recommended for the first 3 days to ensure compliance and tolerability. All decisions involving disposition should be made in concert with the patient’s primary care physician, oncologist, or both.

Colony-stimulating factors are used in prophylaxis of neutropenic fever. However, their routine use as an adjunct to antibiotics in the treatment of neutropenic fever is controversial and currently recommended only in select, high-risk patients. Initiation of treatment should be made in consultation with the patient’s oncologist.

SUPERIOR VENA CAVA SYNDROME

Epidemiology

Superior vena cava syndrome (SVCS) is an acute or subacute process caused by the obstruction of blood flow through the superior vena cava (SVC) secondary to compression, infiltration, or thrombosis. It occurs in approximately 1500 persons in the United States annually. Malignant disease is the most common cause of SVCS and currently accounts for 60 to 85% of cases. It is estimated that 2 to 4% of all cancer patients will have SVCS; in fact, SVCS is often the initial presenting sign of the tumor, and it is a poor prognostic marker.

The most common cancers associated with SVCS are non–small cell lung cancer (50%), small cell lung cancer (25%), and lymphoma and metastatic lesions (10%). However, benign causes of SVCS, such as intrinsic thrombus, are gradually increasing, accounting for 20 to 40% of all cases owing to more frequent use of intravascular devices. Other common nonmalignant causes are goiter, pericardial constriction, primary thrombosis, idiopathic sclerosing aortitis, tuberculous mediastinitis, fibrosing mediastinitis (histoplasmosis and methysergide treatment), arteriosclerotic or (rarely) luetic aneurysm, nephritic syndrome, and indwelling central venous catheters. In contrast to SVCS in the adult population, SVCS in pediatric patients is most often...
iatrogenic secondary to indwelling catheters, ventriculoperitoneal shunts, and complications of cardiovascular surgical procedures.

**Clinical Features**

Knowledge of the unique anatomic relationship of the SVC in the anterior superior mediastinum is crucial to understanding of the clinical presentation of SVC obstruction. The SVC is easily compressed by any of its contiguous structures (trachea, heart, aorta, azygos vein, and paratracheal and bronchial lymph nodes). This compression can produce a constellation of symptoms that reveal the likely site of the pathophysiologic process (Fig. 123-1). The SVC arises from the innominate veins, which in turn arise from the internal jugular and subclavian veins. The azygos vein, the last main auxiliary vessel of the SVC, drains blood from the chest wall. As a consequence of this anatomic relationship, if the SVC is blocked above or at the entrance of the azygos, blood may bypass and decompress the obstruction through the chest wall collateral vessels and rejoin the SVC through the azygos. If the obstruction falls below or at the entrance of the azygos, blood must traverse in a retrograde manner down the azygos and other chest wall veins to reach the drainage area of the inferior vena cava and subsequently cause more prominent symptoms.

When the SVC is obstructed, blood flows through a collateral vascular network, but it generally takes weeks for these vessels to sufficiently dilate to accommodate the blood flow of the SVC. The severity of SVCS varies with the rate and degree of obstruction. When the obstruction occurs more slowly and the SVC is less compressed, there is more time for development of collateralization, which results in less severe symptoms.

Because the clinical features of the SVC are characterized by venous hypertension within the area ordinarily drained by the SVC, many of the findings are more noticeably evident in the recumbent or stooped-over position.

SVCS symptoms develop during a period of 2 weeks in about one third of patients and in a longer time in others. SVCS causes edema of the upper body, particularly of the head and neck. Early signs may include periorbital edema, conjunctival suffusion, and facial swelling, which will be most evident in the early morning hours and subside by midmorning. This edema may be significant enough to compromise the lumen of the trachea, causing stridor and dyspnea, or of the esophagus, causing dysphagia. One of the most common presentations in SVCS is dyspnea and swelling of the face, trunk, and upper extremities. Cough, dysphagia, and chest pain are less commonly reported, each occurring in approximately 20% of patients. With increasing impedance to blood flow, the full-blown syndrome begins to be manifested with thoracic and neck vein distention (67% and 59%, respectively), facial edema (56%), tachypnea (40%), tightness of the shirt collar (the Stokes sign), plethora of the face, edema of the upper extremities, and cyanosis. Other concerning symptoms are neurologic, such as headaches, confusion, and even coma, suggesting cerebral edema, ischemia, or both. Although cerebral edema is rare, it can be fatal. The usual course of SVCS is that collaterals develop, and symptoms improve when this occurs.

There is little evidence in the literature to substantiate the notion of untreated SVC obstruction as immediately life-threatening, as was once believed, except when it occurs with respiratory compromise or cerebral edema. Survival in patients with SVCS depends mainly on the course of the underlying disease.

SVCS can occur in conjunction with spinal cord compression (Rubin’s syndrome). Venous obstruction usually develops before the spinal cord compression, which is localized in most instances to the lower cervical or upper thoracic spinal cord. This syndrome is most commonly found with malignant neoplasms of lymphoma and lung cancer. Patients with venous obstruction and back pain or peripheral neurologic concerns should be evaluated with magnetic resonance imaging (MRI) of the vertebral spinal cord.

**Ancillary Evaluation**

The clinical diagnosis of SVC obstruction is mimicked by a few other clinical entities, most noteworthy of which are pericardial tamponade and heart failure; both can usually be excluded by physical examination and bedside cardiac ultrasound.
examination. The chest film is abnormal in 84% of patients with SVCS; the most common abnormalities are mediastinal widening (64%) and pleural effusion (26%).

CT of the chest with intravenous administration of contrast material is the most useful imaging study to evaluate the SVC. History and physical examination combined with the CT chest scan with intravenous contrast enhancement will help differentiate between intrinsic and extrinsic compression of the SVC. The presence of collateral vessels with compression of the SVC is a reliable indicator of SVCS. Venography is relatively contraindicated because of its concomitant bleeding complications. It is generally warranted only during placement of a stent or surgery. MRI may be useful in patients who cannot receive an intravenous contrast agent. Invasive diagnostic procedures, including bronchoscopy, mediastinoscopy, scalene node biopsy, and limited thoracotomy, are commonly used to establish the diagnosis and extent of the disease.

Morbidity secondary to excessive bleeding from puncture sites has been reported rarely with venous access procedures for SVC. Intravenous injections may be less reliable because of slowing of drug distribution. Low flow rates may result in local irritation with thrombosis or phlebitis. Venous access is preferable on the side contralateral to the obstruction.

Once SVC obstruction is suggested, the appropriate consulting services should be contacted and plans for prompt diagnosis undertaken.

**Management**

SVCS is considered an immediately life-threatening oncologic emergency only if CNS symptoms are present. If a true emergency exists, a stent can be emergetly placed in the SVC or radiation therapy can be used. In all other cases, once the clinical diagnosis is entertained, a tissue biopsy specimen should be obtained promptly before treatment decisions are made. Although supportive therapy may be instituted to alleviate symptoms, definitive therapy is dependent on the histologic diagnosis. The American College of Chest Physicians and the National Comprehensive Cancer Network both recommend consideration of radiation therapy, stent placement, or both. Historically, emergent radiation therapy was the treatment of SVCS. Currently, this is recommended only emergently for patients who present with stridor due to central airway obstruction or severe laryngeal edema. In an attempt to relieve the obstruction, current management uses radiation therapy for cancers responsive to this treatment and chemotherapy in other cancers because of the increased incidence of tumor sensitivity to newer antineoplastic agents. Complete relief of symptoms is achieved with chemotherapy in approximately 80% of patients with non-Hodgkin’s lymphoma or small cell lung cancer and in 40% of those with non–small cell lung cancer. However, temporizing measures that alleviate symptoms related to vascular compression should be rapidly instituted.

All management begins with attention to airway. Although no data exist to document its effectiveness, elevation of the head of the bed will theoretically decrease the hydrostatic pressure and thereby the edema with minimal risk. Glucocorticoid therapy (dexamethasone, 4 mg every 6 hours) is not well studied, but case reports do suggest benefit as a temporary measure. Loop diuretics have been used with transient symptomatic relief; they must be used judiciously to avoid hypovolemia, which may result in decreased blood flow. Other current management approaches include percutaneous transluminal stent placement and bypass surgery. Placement of an intravascular stent to bypass the obstruction is particularly useful in patients requiring urgent intervention before tissue diagnosis because of severe symptoms such as respiratory distress. Stent placement is also useful for patients whose cancer is minimally responsive to chemotherapy or radiation therapy and for those patients with a thrombus associated with an indwelling catheter. Surgical bypass grafting is infrequently used to treat SVCS but may be useful in cancers resistant to chemotherapy and radiation therapy.

The prognosis for patients treated for SVCS depends on the tumor type, with better survival rates in patients with lymphoma than in patients with bronchogenic carcinoma. Median life expectancy of patients with malignant causes of SVCS is 6 months, but this varies widely by the underlying malignant condition.

**ACUTE TUMOR LYSIS SYNDROME**

Acute tumor lysis syndrome (TLS) refers to the constellation of metabolic disturbances that result from ongoing cell death in a rapidly growing tumor. It also occurs frequently within a few hours to a few days after the initiation of chemotherapy or radiation therapy to treat bulky and treatment-responsive tumors. This syndrome is most commonly seen after chemotherapy of hematologic malignant neoplasms, including acute leukemias and high-grade non-Hodgkin’s lymphomas, particularly Burkitt’s lymphoma, in which the growth fraction often exceeds 90%. With advances in the effectiveness of chemotherapy, it has also been described after treatment of solid tumors, such as small cell lung carcinoma and germ cell tumors.22

The risk of acute TLS increases with the bulk of the tumor, with the presence of hyperuricemia, or with renal impairment before antineoplastic therapy (Box 123–4). Large numbers of neoplastic cells are killed rapidly, leading to release of intracellular ions and metabolic byproducts into the systemic circulation. A correlation between a very high level of blood lactate dehydrogenase and the development of TLS has been observed.

Biochemical hallmarks of this syndrome include hyperuricemia (DNA [nucleic acids—purine] breakdown), hyperkalemia (cytosol breakdown), and hyperphosphatemia (protein breakdown). Hypocalcemia develops secondary to hyperphosphatemia. Acute renal failure, cardiac dysrhythmias, neuromuscular symptoms, and sudden death may result from hyperkalemia or hypocalcemia, and lactic acidosis and metabolic acidosis from acute renal failure may ensue. Early aggressive treatment is crucial.

**Clinical Features**

Symptoms are related to the underlying malignant neoplasm and the degree of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia that develops. Hyperuricemia with resultant

**Box 123-4 Risk Factors for Acute Tumor Lysis Syndrome**

- Increased lactate dehydrogenase levels (>1500 U/L)
- Advanced disease with abdominal involvement
- Preexisting renal dysfunction
- Post-treatment renal failure
- Acidic urine
- Concentrated urine
- Young age
urate nephropathy is the most commonly recognized metabolic cause of renal insufficiency in patients with TLS. The kidney provides the primary mechanism for excretion of uric acid, potassium, and phosphate. Rapid proliferation of tumor cells exacerbated by the rapid destruction of the tumor cells during chemotherapy may exceed the kidney’s ability to remove these substances, resulting in toxicity. The integrity of renal function is a critical factor in determining the degree of metabolic derangements. In patients with preexisting renal insufficiency, the metabolic derangements of acute tumor lysis are more likely to be severe. However, even when renal function is normal at the start of treatment, the rapid lysis of certain tumors may overwhelm the excretory capacity of the kidney. Similar to hyperuricemia, hyperphosphatemia may also cause renal failure. A possible mechanism is precipitation of calcium phosphate within the kidney.

Hyperkalemia, along with a contributing hypocalcemia, may result in life-threatening ventricular dysrhythmias. Hypocalcemia may also cause neuromuscular instability with muscle cramps and occasionally tetany. Confusion and convulsions also have been described.

Management

The main principles of TLS management are (1) identification of high-risk patients with initiation of preventive therapy and (2) early recognition of metabolic and renal complications with prompt supportive care, including hemodialysis. Most of the complications can be readily managed when they are recognized early; however, delay in recognition and in the initiation of treatment of TLS can be life-threatening.

Chemotherapy should be delayed, if possible, until metabolic disturbances, especially prerenal azotemia and hyperuricemia, are corrected. Initial management is aimed at the control of preexisting hyperuricemia with hydration, allopurinol, and alkalinization of the urine to a pH above 7. Diuretics are added if necessary, and frequent monitoring of electrolytes, calcium, and phosphorus is essential.

Hydration

Volume depletion is a major risk factor in TLS and must be corrected vigorously. Rapid intravenous hydration is the single most important intervention. Hydration not only helps correct electrolyte disturbances by diluting extracellular fluid but also increases intravascular volume. Increased volume enhances renal blood flow, glomerular filtration rate, and urine volume, which consequently decreases the concentration of solutes in the distal nephron and medullary microcirculation. Continuous infusion rates as high as 4 to 5 L/day, yielding urine volumes of at least 2 to 3 L/day, should be given unless the patient’s cardiovascular status indicates impending volume overload. Ideally, intravenous hydration in high-risk patients is started 24 to 48 hours before initiation of cancer therapy and continued for 48 to 72 hours after completion of chemotherapy.

Hyperuricemia

Allopurinol is a xanthine oxidase inhibitor that reduces the conversion of nucleic acid byproducts to uric acid. It is given in TLS to prevent urate nephropathy and subsequent oliguric renal failure. Because allopurinol inhibits the synthesis of uric acid but has no effect on preexisting uric acid, uric acid levels usually do not fall until after 48 to 72 hours of treatment. The dose of allopurinol is 300 to 600 mg/day orally for prophylaxis and 600 to 900 mg/day for treatment of TLS.

Rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches. It has been approved for the treatment of hyperuricemia in pediatric patients with acute leukemia, lymphoma, and solid tumor malignant neoplasms who are receiving anticancer therapies expected to result in tumor lysis. It works by catalyzing the conversion of poorly soluble uric acid to soluble allantoin, thus rapidly decreasing plasma and urinary uric acid levels. Unlike allopurinol, rasburicase does not increase the excretion of xanthine and other purine metabolites; therefore, it does not increase tubule crystallization of these compounds and decreases the risk of urate nephropathy. Although it is extremely effective in reducing serum uric acid to low levels within a few hours of administration, rasburicase is rarely initiated by emergency physicians because it has not been shown to have an impact on clinical outcomes. It is reserved for severe cases that have failed to respond to traditional prophylactic methods and in which the probability of acute renal failure is very high.

It is generally accepted practice to alkalinize the urine as a prophylactic measure in hyperuricemia to increase the solubility of uric acid. Caution is advised when hyperphosphatemia and hypocalcemia develop because alkalinization favors precipitation of calcium/phosphate complexes in the renal tubules. Furthermore, alkali therapy may aggravate manifestations of hypocalcemia, such as tetany. Although alkalinization may be beneficial, the primary means of uric acid control is hydration and diuresis to maintain adequate urinary flow.

The use of furosemide or mannitol for osmotic diuresis has no proven benefit as in front-line therapy for hyperuricemia. In fact, these modalities may contribute to uric acid or calcium phosphate precipitation in renal tubules in a volume-contracted patient. Instead, diuretics are reserved for the normovolemic patient with hyperkalemia or for the patient with evidence of fluid overload. If TLS develops and is refractory to the previously mentioned treatments, hemodialysis is considered a potentially lifesaving measure. This therapy is effective in lowering of uric acid, potassium, and phosphate levels as well as in control of uremic symptoms. See Box 123-5 for the criteria for institution of hemodialysis.

Aggressive management maximizes the outcomes of patients with TLS, and the prognosis is good in the absence of renal failure. If renal failure develops and hemodialysis is required, the prognosis becomes grave.

**HYPERVISCOSITY SYNDROME**

Hyperviscosity syndrome (HVS) refers to the clinical sequelae of increased blood viscosity. Viscosity is the resistance that a liquid exhibits to the flow of one layer over another. Excessive elevations in certain paraproteins (circulating immunoglobulins) or cellular blood components (leukocytosis, erythrocytosis, and thrombocytosis) result in elevated serum viscosity and the development of sludging, decreased perfusion of the microcirculation, and vascular stasis. The outcome of these pathophysiologic events leads to the development of HVS, which requires urgent medical therapy to forestall or to reverse the effects of sludging in the microcirculation of the CNS, visual system, and cardiopulmonary system.
Pathophysiology

HVS is most commonly associated with plasma cell dyscrasias (the paraproteinemias) and is due to the large size of the excess immunoglobulin M (IgM) paraproteins in these disorders. Waldenström's macroglobulinemia is the most common cause and accounts for 85 to 90% of cases of HVS. Less frequently, the disease can occur in multiple myeloma (especially with myeloma proteins of the IgA and IgG3 types). Other causes include cryoglobulinemia, a benign hyperglobulinemia of the IgM-IgG type, and leukemias.26

The blastic phase of chronic myelogenous leukemia, chronic granulocytic leukemia, and the blast cell crisis of acute lymphoblastic and nonlymphoblastic leukemias also commonly cause HVS. Other more benign causes are leukemoid reaction, polycythemia vera, and the accumulation of abnormal hemoglobins in sickle cell disease. The incidence of HVS in Waldenström's macroglobulinemia is found to be approximately 20%; in IgG myeloma, approximately 4.2%; and in IgA myeloma, as high as 25%.27

The inherent physicochemical properties of the dysproteinemias along with extremely high concentrations of these proteins predispose to the development of hyperviscosity. The etiologic factor most responsible for HVS in the leukemias appears to be leukocytosis with white blood cell counts in excess of 100,000, usually accompanied by blast forms exceeding 100,000 in the peripheral smear. The clinical manifestations of HVS become most apparent when the serum viscosity relative to water is greater than 4 to 5, normal serum viscosity relative to water being 1.4 to 1.8.

Clinical Features

The classic presentation of HVS is mucosal bleeding, visual disturbances, and neurologic manifestations. Visual disturbances and, on occasion, visual loss may occur with retinopathy characterized by venous engorgement (e.g., “sausage-link” or “boxcar” segmentation); other findings include microaneurysms, hemorrhages, exudates, and occasionally papilledema. Persistent bleeding diatheses from mucosal surfaces, especially nasal mucosa, the gastrointestinal tract, and sites of minor surgery or trauma, even in the presence of a normal platelet count, are common. Other clinical findings encompass myriad neurologic disturbances, including headache, dizziness, seizures, auditory disturbances (including hearing loss), hypotension, and coma. Constitutional symptoms of somnolence, fatigue, anorexia, and weight loss that are nonspecific early on are commonly associated with the underlying malignant neoplasm or with associated electrolyte disturbances related to the underlying malignant neoplasm. Cardiopulmonary findings include acute respiratory failure and hypoxemia, congestive heart failure, myocardial infarction, and valvular abnormalities. Renal insufficiency and failure may be a complication of the syndrome and will exacerbate existing clinical findings.

The laboratory evaluation of the patient with suggested HVS includes coagulation profile, creatinine and blood urea nitrogen concentrations, electrolyte values, and complete blood count with differential. Serum and urine protein electrophoresis should be done in all cases of suggested dysproteinemias; the diagnosis is supported by a large spike on the serum electrophoresis. A clue to the presence of hyperviscosity may be the inability of the laboratory to perform chemical tests on the blood because of clogging of the analyzers by serum stasis and increased viscosity. Significant hypercalcemia may also occur in multiple myeloma, and with high M-protein fractions, a factitious hyponatremia may be present. The diagnosis may also be entertained when a patient is brought to the ED in a stupor or coma and anemia and rouleaux formation are found on the peripheral smear.28

Because HVS is often a presenting characteristic of dysproteinemias and leukemias with blastic transformation and because a history of previously documented disease is often absent, this syndrome should be considered in patients with unexplained somnolence and coma.

Management

Emergency leukapheresis or plasmapheresis is the definitive treatment of HVS. Temporizing measures provided by the emergency physician focus on adequate rehydration and diuresis. An immediate temporizing measure in a patient with frank coma and an established paraproteinemia is a two-unit phlebotomy with replacement of the patient’s red blood cells with physiologic saline.26 Once plasmapheresis or leukapheresis has adequately alleviated the clinical findings, chemotherapeutic modalities can be used.

HYPERURICEMIA

Hyperuricemia is a serious and well-known consequence of certain malignant disorders; its complications can be avoided if it is recognized and treated early. The major source is cell breakdown, and its major excretory pathway is through the kidneys.

Pathophysiology

The pathogenesis of hyperuricemia results from either the increased production or the decreased excretion of uric acid, or both. Uric acid is produced by metabolism, and hyperuricemia results from the rapid dissolution of neoplastic tissues (cell death) after chemotherapy or radiation therapy. It is often seen in the treatment of undifferentiated lymphomas, lymphoblastic lymphomas, and acute lymphoblastic leukemias. In addition, hyperuricemia may be seen with multiple myeloma and occasionally with disseminated metastatic carcinoma. With massive release of precursors, uric acid levels rise precipitously and may reach levels as high as 15 to 20 mg/dL. As a result, uric acid crystals form in the highly concentrated and acidified urine of the distal tubules; intrarenal obstruction follows, leading to acute renal failure.29

Chronic, moderately elevated levels of the serum uric acid may result in renal colic, obstructive uropathy, or chronic renal failure. Either uric acid renal calculi or interstitial deposits of sodium urate may develop. This situation is associated with neoplastic overproduction of uric acid precursors. Polycythemia vera, myeloid metaplasia, mast cell disease, and chronic granulocytic leukemia are often associated with this type of hyperuricemia.

Decreased excretion of uric acid may be a result of underlying renal insufficiency or a consequence of urate precipitation in the renal tubules, parenchyma, or ureters. Three types of renal diseases are attributable to hyperuricemia: acute hyperuricemic nephropathy, uric acid nephrolithiasis, and gouty nephropathy.

Clinical Features

Hyperuricemia can occur with or without symptoms. Hyperuricemia precipitated or aggravated by therapy may occur as an isolated metabolic disturbance or may be accompanied by other manifestations of the TLS (see previous discussion of TLS). If an underlying neoplastic disease has been diagnosed, the possibility of hyperuricemia should be investigated before, during, and after chemotherapy or radiation therapy. In patients with urate stones and hyperuricemia, examination of the peripheral blood may provide evidence of an underlying myeloproliferative disorder. Acute oliguria after chemotherapy or radiation therapy suggests the diagnosis of hyperuricemia, and the uric acid level in the blood often far exceeds that associated with acute renal failure.
A number of relatively benign diseases associated with hyperuricemia may coexist with neoplasia. These include hereditary gout, hyperparathyroidism, psoriasis, sarcoidosis, and renal failure of any cause. The long-term administration of certain drugs may lead to elevation of the serum uric acid level. Those most commonly encountered are thiazide diuretics and furosemide. Acute therapy is the same regardless of the etiology.

Management

When possible, hyperuricemia should be treated before chemotherapy or radiation therapy, especially with bulky tumors or if the serum uric acid level is borderline or increased. If a uric acid elevation of more than 9 mg/dL is found, allopurinol, fluids, and alkalization of the urine should be initiated.

Patients with a history of gouty arthritis are treated with colchicine (0.6 mg orally twice a day) to avoid the acute attacks that can be associated with allopurinol administration. Patients should be kept well hydrated. In patients with acute distal tubular uric acid obstruction, treatment includes the administration of allopurinol together with the fluid and electrolyte management used in other forms of acute renal failure.

If hyperuricemia is secondary to malignant disease, cytotytic therapy is generally stopped. Allopurinol in dosages of 300 to 600 mg/day decreases the serum uric acid level in approximately 3 days, so its administration is started 2 or 3 days before cytotytic therapy, if time permits. Hydration is vital, with a goal of maintaining a urine output above 2 L/day. As discussed before, rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches.

Alkalization to keep the urine pH above 7 is accomplished by the administration of sodium bicarbonate. Acetazolamide (Diamox) usually alkalizes the urine temporarily until allopurinol becomes effective. If oliguria occurs, intravenous mannitol may be started with 12.5 g of a 20% solution given during 3 minutes to keep urine output more than 250 mL/hr. The dose of mannitol is limited to avoid clinical features resembling water intoxication. If these measures fail, peritoneal dialysis or hemodialysis or flushing of the ureters through retrograde catheters may be considered. Clearly, prevention of this complication is far better than the need for treatment.

The cancer patient who comes to the ED with renal colic warrants careful evaluation for hyperuricemia. The prognosis depends on the underlying malignant neoplasm and degree of renal failure.

HYPERCALCEMIA

Hypercalcemia occurs in approximately 20 to 40% of cancer patients and is the most common life-threatening metabolic disorder associated with cancer. It affects multiple organ systems and induces a variety of pathophysiologic events that may be more immediate threats to life than the cancer itself. For the purpose of this discussion, we discuss non–parathyroid hormone–mediated hypercalcemia that is associated with malignant disease.\(^{30}\)

Pathophysiology

Two mechanisms have been proposed to explain the development of hypercalcemia associated with malignant disease. The first mechanism involves patients with metastatic bone involvement, in which case hypercalcemia is associated with the release of calcium and phosphate by increased osteoclastic activity within the bone. The second mechanism involves those patients with no bone disease but who have tumor-produced hormone-like substances that affect bone turnover (e.g., parathyroid hormone, prostaglandins, steroids, and peptides).

Hypercalcemia is a common feature of many malignant neoplasms but most commonly breast, lung, head, and neck cancers as well as multiple myeloma and leukemia. Bone metastases are not a prerequisite for hypercalcemia and are not necessarily the cause of the hypercalcemia. For example, in patients who are hypercalcemic from squamous cell lung cancer, only one in six has bone metastases, whereas in small cell lung carcinoma, hypercalcemia is almost never seen, despite the presence of bone marrow metastases in 20 to 50% of cases. Entities that cause hypercalcemia are listed in Box 123-6.

Clinical Features

The symptoms of hypercalcemia are nonspecific. There is little correlation between serum calcium levels and the presence and severity of symptoms. Acute hypercalcemia results in marked CNS effects ranging from personality changes (depression, paranoia, lethargy, and somnolence) to coma. With chronic hypercalcemia, symptoms include a history of anorexia, nausea, vomiting, constipation, polyuria, polydipsia, and memory loss. The signs, symptoms, and complications of hypercalcemia are summarized in Box 123-7.

In patients with carcinoma, any of these symptoms should suggest the diagnosis of hypercalcemia, but the emergency physician should be particularly alert to the possibility of hypercalcemia in any cancer patient with lethargy or a change in mental status. Many may also have electrolyte abnormalities, such as

<table>
<thead>
<tr>
<th>Box 123-6 Non-neoplastic Causes of Hypercalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Renal insufficiency (diuretic phase of acute renal failure, after transplantation, secondary hyperparathyroidism)</td>
</tr>
<tr>
<td>Drugs (thiazide diuretics, lithium, and calcium carbonate)</td>
</tr>
<tr>
<td>Hypervitaminosis (A and D)</td>
</tr>
<tr>
<td>Acute adrenal insufficiency</td>
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<tr>
<td>Immobilization (Paget's disease, fracture, paraplegia)</td>
</tr>
<tr>
<td>Acromegaly</td>
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<tr>
<td>Myxedema</td>
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<tr>
<td>Milk-alkali syndrome</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Benign monoclonal gammopathy</td>
</tr>
<tr>
<td>Rarer still are factitious hypercalcemia, idiopathic hypercalcemia of infancy (with elfin facies), familial hypocalcic hypercalcemia, and hypercalcemia from pheochromocytoma or periostitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box 123-7 Common Signs and Symptoms of Hypercalcemia in Malignant Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Fatigue, muscle weakness, hyporeflexia, lethargy, apathy, disturbances of perception and behavior, stupor, coma</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Polyuria, polydipsia, renal insufficiency</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Anorexia, nausea, vomiting, constipation, abdominal pain</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Hypertension, dysrhythmias, digitalis sensitivity</td>
</tr>
</tbody>
</table>
hypothesis and dehydration. Thus evaluation of serum electrolytes should accompany the measurement of serum calcium, phosphorus, albumin, and alkaline phosphate. In general, a serum calcium level above 14 mg/dL constitutes a medical emergency. In chronic hypercalcemia, patients with blood calcium levels as high as 15 mg/dL may be seen with only mild symptoms. With an acute onset, patients may present comatose with a level of only 12 to 13 mg/dL.31

Many benign conditions can result in hypercalcemia. The most common are hyperparathyroidism and Paget’s disease of bone. Clinical features include a long history of hypercalcemia symptoms, particularly renal stones. Chronic changes on bone films, such as subperiosteal reaction and cysts or a “ground-glass” appearance of the skull, suggest hyperparathyroidism. Diagnosis of Paget’s disease rests in biopsy results. Vitamin D excess, milk-alkali syndrome, and adrenal insufficiency are other common causes in the differential diagnosis of hypercalcemia.

The acute onset of severe hypercalcemia or chronic exposure of the renal tubules to elevated calcium levels may reduce the glomerular filtration rate and renal blood flow, resulting in acute renal failure.

Management

The therapeutic modalities for hypercalcemia are numerous, but they should always be used in conjunction with treatment of the underlying malignant disease. The exception to this is breast cancer, in which hormone therapy is generally stopped until hypercalcemia is regulated.

The treatment depends on the clinical status of the patient and on the calcium level in the blood, but the general principles include treatment of the cancer when possible, encouragement of ambulation, correction of dehydration, increase of urinary calcium excretion, inhibition of osteoclastic activity (calcium removal from bone), and reduction of calcium intake.

If serum calcium levels are below 14 mg/dL, oral rehydration and ambulation may suffice. Normal saline solution can be administered if the oral intake is not sufficient. If the serum phosphate level is not elevated, oral phosphates may be used cautiously. Phospho-Soda (5 mL by mouth, two or three times daily) is usually tolerated with mild or no diarrhea. Intravenous phosphates are able to effectively lower the serum calcium level through precipitation of inorganic calcium phosphate salts in bone. This modality of treatment is usually not recommended in view of its serious complications, which include widespread visceral calcifications, shock, and renal failure. However, if it is needed, it is best done in consultation with a nephrologist or oncologist and reserved for hypercalcemia unresponsive to other agents.

Prednisone (60–80 mg) or other corticosteroids may be effective within a few days to a week. They are more useful for long-term treatment than for acute control. Corticosteroids are particularly valuable in breast carcinoma, myeloma, and lymphoma. If the serum calcium level is greater than 14 mg/dL or significant symptoms are present, a more vigorous management should be undertaken. Continuous cardiac monitoring in the ED is necessary, and central venous or pulmonary artery pressure monitoring may be required.

Saline rehydration stimulates renal tubular excretion of calcium and is the most important initial component of the emergency management of hypercalcemia. Dehydration should be corrected within 1 to 2 hours with normal saline solution. When urine flow is adequate, furosemide (40–60 mg intravenously) may be given to increase excretion of calcium. Although the calciuric effect of furosemide is modest, it is also useful in preventing fluid overload in patients predisposed to cardiac failure. Careful attention to fluid input and output to ensure that the patient remains euvoletic is necessary.

Calcitonin is a naturally occurring hormone that inhibits bone resorption and increased excretion of calcium. Calcitonin may be effective in doses of 4 to 8 IU/kg intramuscularly or subcutaneously. This treatment, although relatively safe when renal function is normal, is not generally part of the initial emergency management of hypercalcemia.

Fifty percent of hypercalcemic cancer patients also have hypokalemia. Serum potassium levels should be monitored every 4 hours and potassium chloride (20–40 mEq intravenously or orally) supplemented as necessary to prevent severe hypokalemia.31

In the past 10 years, after approval by the Food and Drug Administration, bisphosphonates have become the treatment of choice for management of cancer-induced hypercalcemia, supplanting all other pharmacologic approaches except corticosteroids. Bisphosphonates act by binding to hydroxyapatite in bone and thereby inhibiting the dissolution of crystals. These agents prevent osteoclast attachment to bone matrix and interfere with osteoclast recruitment without inhibiting bone formation and mineralization.

Several agents are now available; pamidronate, etidronate, alendronate, and zoledronate are currently available in the United States, and other more potent bisphosphonates are in development. Pamidronate (90 mg, given as an infusion during 4-24 hours) effectively and safely achieves normocalcemia within a few days (mean 4 days) in more than 90 to 95% of patients.31 Risedronate is another bisphosphonate that is being evaluated in oral form for the treatment of hypercalcemia. Because of the lag in onset of effect, bisphosphonates should be combined with faster-acting therapeutic modalities mentioned earlier.

NEOPLASTIC CARDIAC TAMPOONADE

Although cardiac tamponade resulting from neoplasm is uncommon, it can occur abruptly and result in death if it is not treated quickly. In most cases, neoplastic cardiac tamponade is observed in patients with a previous diagnosis of cancer, typically at late stages of the disease. It is rarely seen as the initial manifestation of an extracardiac malignant neoplasm.

The decompressed state of cardiac function comes from a marked rise in intrapericardial pressure caused by accumulation of fluid within the pericardial sac due to malignant disease or pericardial thickening with scar formation, which results in a thick constrictive neoplastic encasement. This condition, if it is not recognized and decompressed promptly, can lead to circulatory compromise and death. Signs and symptoms are partially affected by the rapidity of development. In the era before diagnostic ultrasonography, this medical-oncologic emergency was often unrecognized in a timely manner. In most instances, pericardial effusion is accompanied by signs and symptoms that presage the development of the clinical picture of tamponade, including dyspnea, apprehension, anxiety, and chest pain. In rare instances, tamponade may be the first manifestation of the malignant disease, solid tumor, or leukemia. Any patient in the ED with a history of cancer, shortness of breath, and hypotension should be suspected of having pericardial tamponade. The diagnoses of pulmonary embolism, congestive heart failure, and anxiety can be mistakenly made in this setting.

Etiology

The most common cause of neoplastic pericardial tamponade is malignant pericardial effusion, often associated with postirradiation pericarditis, fibrosis, and effusion. Only rarely does a tumor or radiation fibrosis cause a neoplastic constrictive pericarditis with resultant tamponade. In most reported cases, cardiac
tamponade represents a clinical progression of neoplastic or post-irradiation pericarditis.

Neoplastic pericarditis can result from any number of benign, malignant, primary, or secondary tumors of the pericardium or mediastinum. The most common benign tumors of the pericardium or mediastinum are fibromas, angiomas, and teratomas. Pericardial mesothelioma can have a clinical course characterized by rapid accumulation of massive quantities of bloody pericardial fluid, eventually leading to tamponade. Secondary involvement of the pericardium may result from either direct invasion from structures or metastases from a distant primary tumor. These metastases are usually multiple rather than solitary lesions. The tumors most commonly associated with pericardial involvement are those of the lung and breast, leukemia, Hodgkin's and non-Hodgkin's lymphomas, melanomas, gastrointestinal primary tumors, and sarcomas. Clinically recognizable symptoms or signs of pericardial disease are difficult to appreciate before death. Less than 30% of patients with autopsy-proven malignant pericardial disease were diagnosed ante mortem.

Radiation pericarditis has been a well-known complication of radiation therapy since the introduction of modern megavoltage techniques. The cardiac effects of radiation therapy may be manifested immediately with acute pericarditis or delayed for months to years, although the majority develop effusion within the first year. The acute forms are inflammatory or effusive, usually self-limited, and subside without residual constriction; the chronic effusive and constrictive types may lead to tamponade and death.

Neoplastic constrictive pericarditis, although rare, may be caused by the invasion of the pericardium by metastatic lesions or indirectly from the complications of radiation therapy with resultant fibrous thickening of the pericardium. Each of these entities can progress to cardiac tamponade because of thickening by tumor or radiation fibrosis, resulting in a decrease in the distensibility of the pericardium, thus reaching the critical point of cardiopulmonary decompensation earlier, despite smaller volumes of slowly accumulating effusion.

The symptoms and signs of neoplastic and radiation pericarditis mimic pericarditis from other causes. Because of the usual insidious onset of the effusion of fibrous pericardial thickening, the condition might be attributed to the underlying malignant disease and not considered until the full-blown picture of cardiac tamponade develops.

**Pathophysiology**

The severity of cardiac tamponade and eventual cardiopulmonary decompensation increases with more rapid pericardial fluid accumulation, larger fluid volumes, and worsening cardiac function. Clinically, the progressive elevation of intracardiac pressure interferes with ventricular expansion and results in a decrease in the cardiac volume. Intracardiac chamber pressures rise rapidly with subsequent transmission of this pressure peripherally in pulmonary and venacaval beds. In an effort to maintain cardiac output, various compensatory mechanisms come into play (tachycardia, peripheral vasoconstriction, decrease in renal flow with resultant increase in blood volume by sodium and water retention), all to maintain arterial pressure and venous return. When these compensatory mechanisms fail to maintain cardiac output, ventricular end-diastolic pressure increases and subsequent circulatory collapse is impending. The signs and symptoms parallel these pathophysiologic changes. The most common symptoms include extreme anxiety and apprehension, a precordial oppressive feeling, and actual retrosternal chest pain with dyspnea of varying degrees. True orthopnea and paroxysmal nocturnal dyspnea are uncommon; when they occur, the patient assumes a variety of positions to obtain relief from the chest pain and the dyspnea. Other prominent symptoms include cough, hoarseness, hiccups, and occasional gastrointestinal manifestations, such as dysphagia, nausea, vomiting, and epigastric or right upper quadrant abdominal pain that is probably the result of visceral congestion.32

**Clinical Features**

Patients with severe tamponade are acutely ill and may appear ashen, pale, or markedly diaphoretic with an impaired consciousness ranging from mildly confused to unresponsive. Rapid, shallow, and occasionally labored breathing may be present along with peripheral cyanosis and distended jugular veins. Seizures have been reported. Striking facial plethora and a full neck secondary to edema (Stokes collar) can also be seen in SVCS. Pulses are soft and easily compressible. The systolic blood pressure is usually low, with a decreased pulse pressure, although normal systolic, diastolic, and pulse pressures have been reported with moderate degrees of tamponade. Kussmaul’s signs (muffled heart sounds, an enlarged cardiomedialstinal silhouette, tachycardia, and, most notably, pulsus paradoxus) are extremely useful findings in the physical evaluation of tamponade (Box 123-8). Ascites, hepatomegaly, peripheral edema, and mottling are other findings that reflect the elevation in venous pressure and decrease in cardiac output.33

**Box 123-8  Physical Evaluation of Neoplastic Cardiac Tamponade**

**Beck Triad or Acute Compression Triad**

Described in 1935, this complex of physical findings refers to increased jugular venous pressure, hypotension, and diminished heart sounds. These findings result from a rapid accumulation of pericardial fluid. However, this classic triad is usually observed in patients with acute cardiac tamponade.

**Pulsus Paradoxus or Paradoxical Pulse**

This is an exaggeration (>12 mm Hg, or 9%) of the normal inspiratory decrease in systemic blood pressure. For measurement of the pulsus paradoxus, patients are often placed in a semirecumbent position; respirations should be normal. The blood pressure cuff is inflated to at least 20 mm Hg above the systolic pressure and slowly deflated until the first Korotkoff sounds are heard only during expiration. At this pressure reading, if the cuff is not further deflated and a pulsus paradoxus is present, the first Korotkoff sound is not audible during inspiration. As the cuff is further deflated, the point at which the first Korotkoff sound is audible during both inspiration and expiration is recorded. If the difference between the first and second measurement is greater than 12 mm Hg, an abnormal pulsus paradoxus is present.

The paradox is that while listening to the heart sounds during inspiration, the pulse weakens or may not be palpated with certain heartbeats, while S1 is heard with all heartbeats. A pulsus paradoxus can be observed in patients with other conditions, such as constrictive pericarditis, severe obstructive pulmonary disease, restrictive cardiomyopathy, pulmonary embolism, rapid and labored breathing, and right ventricular infarction with shock.

**Kussmaul’s Sign**

This was described by Adolph Kussmaul as a paradoxical increase in venous distention and pressure during inspiration. This sign is usually observed in patients with constrictive pericarditis but occasionally is observed in patients with effusive-constrictive pericarditis and cardiac tamponade.
Ancillary Evaluation

Low voltage and the nonspecific findings of pericardial effusion, sinus tachycardia, ST elevation, and nonspecific ST-T wave changes may occur. Electrical alternans is the sinusoidal variation in QRS size—usually in a 2:1 ratio—secondary to the pendular effect of the heart’s swinging in the fluid medium of the pericardial sac. It may be observed in patients with myocardial ischemia, acute pulmonary embolism, and tachyarrhythmias. Electrical alternans with 1:1 total atrial-ventricular complexes is an uncommon yet pathognomonic sign of cardiac tamponade.

Radiographic signs of tamponade suggestive of pericardial effusion include an enlarged cardiac silhouette with clear lung fields and normal vascular pattern, although a normal chest radiograph does not exclude tamponade. The typical “water-bottle” appearance of the heart on a plain radiograph is often present. Echocardiography is the simplest and most sensitive of diagnostic tests and can be done at the bedside for confirmation of pericardial effusion. Thoracic CT has also become an important diagnostic tool in diagnosis of pericardial effusions in more clinically stable patients.

Cardiac tamponade should be considered in any cancer patient with dyspnea. Highly suggestive symptoms include clouded sensorium, thready pulse, pulsus paradoxus exceeding 50% of the pulse pressure, low systolic pressure, engorged neck veins with a rising peripheral venous pressure above 130 mm H₂O, falling pulse pressure below 20 mm Hg, and electrical alternans. In this setting, sudden death may occur and emergent pericardiocentesis is indicated.

Management

In the ED, bedside, blind, percutaneous pericardiocentesis resulting in immediate removal of the pericardial effusion is a lifesaving treatment of cardiac tamponade. The procedure carries some risk, including induction of cardiac dysrhythmias and hemorrhage from an injured coronary vessel. Aspiration of as little as 50 to 100 mL of fluid will temporarily alleviate the pathologic process.34

Echocardiographically guided pericardiocentesis can also be performed in the ED, but the cardiac catheterization laboratory is a more controlled setting and is preferable. Removal of the maximal amount of fluid is advisable, along with insertion of an indwelling catheter because fluid may reaccumulate during the first 24 hours. Once the pericardial fluid has been obtained, it must be sent for biochemical and cytologic analysis. Neoplastic cardiac tamponade accounts for at least 50% of all reported cases of pericardial effusion. Other types of supportive therapy may be needed during the evaluation process while preparing for pericardial fluid collection. Other types of supportive therapy may be performed in the ED, but the cardiac catheterization laboratory is a more controlled setting and is preferable. Removal of the maximal amount of fluid is advisable, along with insertion of an indwelling catheter because fluid may reaccumulate during the first 24 hours. Once the pericardial fluid has been obtained, it must be sent for biochemical and cytologic analysis. Neoplastic cardiac tamponade accounts for at least 50% of all reported cases of pericardial effusion. Other types of supportive therapy may be needed during the evaluation process while preparing for pericardiocentesis, such as intravascular hydration with normal saline and oxygen therapy. Once the patient has been stabilized, additional therapeutic intervention is planned and initiated by the appropriate admitting services in that reaccumulation of effusion in neo-plastic tamponade is not easily managed on a short-term basis. Pericardial windows, radiation therapy, intrapericardial chemotherapy, and pericardiectomy may be justified.

The prognosis after neoplastic cardiac tamponade depends on the underlying type and extent of cancer. The presence of total atrial-ventricular complexes is an adverse prognostic sign, even when the alternans disappears with pericardiocentesis. Despite a poor prognosis for patients with cancers such as melanoma and non–small cell lung cancer, some patients with treatment-responsive lymphomas have survived long term after neoplastic cardiac tamponade.

NEUROLOGIC EMERGENCIES

Of all patients with cancer, 15 to 20% have neurologic complications.35 Neurologic symptoms are occasionally the presenting complaint in patients with systemic cancer, but more often symptoms develop in patients known to have cancer. Neurologic emergencies in cancer patients include malignant spinal cord compression, cerebral herniation, seizures, CNS infections, and reversible toxic or metabolic encephalopathies.

Malignant Spinal Cord Compression

Principles of Disease

Malignant spinal cord compression (MSCC) from metastatic cancer is common, serious, and potentially treatable. It occurs in approximately 1 in 12,700 cancer patients in the United States annually.35 Pretreatment neurologic status is the most significant predictor of function after treatment.35

MSCC most commonly occurs when malignant disease metastasized to the spine extends into the epidural space, causing compression of the spinal cord, but it can also occur with direct metastasis of the epidural or dural tissue. Of all osseous sites, the spinal column is the most common site of metastatic deposits.35 Acute compression causes occlusion of the epidural venous plexus, compromising the blood–spinal cord barrier, resulting in inflammation and vasogenic edema. At this stage, corticosteroids may mitigate the damage. Untreated, spinal cord ischemia, infarction, and irreversible damage result.

Although all tumors can potentially cause MSCC, it is most often caused by breast, prostate, and lung carcinoma.34 Less common causes of spinal cord compression in patients with cancer include non-Hodgkin’s lymphoma, melanoma, myeloma, renal cell carcinoma, vertebral subluxation, spinal epidural hematomas and abscesses, and intramedullary metastasis. Acute myelopathy in patients with cancer may also be caused by radiation, paraneoplastic necrotizing myelitis, ruptured intervertebral disk, and meningiceal carcinomatosis with spinal cord involvement. Most cases (68%) of epidural cord compression occur in the thoracic spine, 15% in the cervical spine, and 19% in the lumbosacral spine.35

Clinical Features

Back pain, either local or radicular, is the initial symptom in 95% of patients with epidural metastasis and is usually reported to be worse at night.36 It may be acute in onset or develop insidiously during weeks to months and usually predates other symptoms. The pain may increase during physical examination with spinal percussion, neck flexion, Valsalva maneuver, or straight leg raising; it is usually located at the level of the tumor, although radicular pain is reported if the tumor compresses or invades the nerve roots.37

Motor deficits are the second most commonly reported symptoms associated with MSCC, followed by sensory deficits.36 Other symptoms are usually present at the time of diagnosis and may include weakness (75% of patients) and autonomic or sensory symptoms (50% of patients). Fifty percent of patients are not ambulatory at the time of diagnosis. The neurologic examination usually reveals symmetrical weakness with either flaccidity and hyporeflexia (if the diagnosis is made very early) or spasticity and hyper-reflexia (if the diagnosis is made later). The severity of MSCC can be scored according to several grading systems, some of which include assessment of bowel and bladder function. These are useful in assessing predicted response to therapy.

Diagnostic Strategies

Plain films show evidence of tumor in the vertebral body in 70 to 90% of patients with vertebral metastases.37 They have a false-negative rate of 10 to 30%, so they should not be used to rule out
compression, nor should obtaining plain films delay MRI or myelography, the study of choice when compression is a consideration. In cases with questionable findings on plain films of the spine, tomograms, coned-down views, or CT may reveal bone metastases not otherwise appreciated.

The “gold standard” for the diagnosis of MSCC is MRI, with a sensitivity of 93%, a specificity of 97%, and an overall accuracy of 95%. If MRI is not available, CT myelography can be used. Lack of neurologic deficits should not inhibit further investigation but may affect the urgency of evaluation. For those patients with back pain only and normal findings on neurologic examination, the spine can be imaged within 72 hours. Those with neurologic deficits need urgent evaluation before nerve damage becomes permanent. Many patients have compression in more than one site of the spine, and therefore the entire spine needs to be imaged. When myelography is used, it can demonstrate a complete or nearly complete obstruction of contrast dye flow at the level of vertebral body involvement.

Management

Because minimal weakness at the time of presentation may progress to profound, irreversible weakness in several hours, rapid initiation of treatment is indicated. Corticosteroids are first-line treatment of most patients with MSCC. Steroids decrease the vasogenic edema and inflammation. In the ED, a loading dose of dexamethasone is recommended. There is still no consensus on the optimal dose, but it is typically given as an intravenous bolus of 10 to 16 mg, followed by 4 to 6 mg every 4 hours with a taper during or immediately after completion of radiation therapy. Immediate oncology and radiation oncology consultations should be obtained. High-dose corticosteroids (e.g., dexamethasone 100 mg) are occasionally administered by an oncologist; however, this is associated with complications, and their use is controversial.

Palliative radiation therapy has been the standard of care for patients with malignant MSCC since the 1950s and is generally initiated after steroid treatment. The prognosis depends on the radiosensitivity of the tumor, the location of the compression, the pretreatment performance status, and the rate of decompensation. The role of surgical decompression has evolved since the 1980s with the advancement of surgical techniques and spinal instrumentation. In 2005, Patchell and colleagues published the first randomized trial that compared direct decompressive and reconstructive surgery, followed by postoperative radiation therapy with radiation therapy alone. This landmark study demonstrated the advantage of a surgical approach in the management of MSCC. However, surgery is not appropriate in all patients, particularly if the patient is not a surgical candidate or has a life expectancy that might be less than necessary for recovery.

Intramedullary metastases are similar in presentation and treatment to epidural cord compression but are associated with a very poor prognosis. A rapidly progressive paraparesis and back pain are seen. MRI or myelography can establish the diagnosis; the treatment is surgical decompression. In cases of thrombocytopenia, platelet transfusions may limit progression of this process.

Encephalopathy

Toxic and metabolic encephalopathies are considerations when patients with cancer have an acute or subacute alteration in mental status. Toxic and metabolic causes should be routinely excluded even when infection or a metastatic complication is suggested. Signs of encephalopathy include confusion, aberrant behavior, and decreased level of consciousness. These may develop acutely or insidiously during days to weeks. Patients with cancer are particularly susceptible to toxic and metabolic encephalopathy because the disease can have multiple organ system involvement and can cause electrolyte and nutritional abnormalities, and the drugs used to treat the disease (especially chemotherapeutic agents and narcotics) can cause encephalopathy even in therapeutic doses. In the ED, encephalopathic patients should first be evaluated carefully for a possible infection or mass lesion, and when these are ruled out, evaluation for toxic and metabolic causes must be pursued. The metabolic workup includes electrolytes; blood urea nitrogen, creatinine, glucose, and calcium levels; arterial blood gas analysis; and liver function tests. Toxicology screens are recommended in possible ingestions and in patients who are unable to give a history. Naloxone and 50% dextrose should be given while the workup is proceeding. Specific treatment is indicated for any abnormalities found during the workup. Hospital admission is usually required unless the cause is easily and rapidly reversible and is unlikely to recur.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.
References


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