CHAPTER 174 ONCOLOGIC EMERGENCIES

S. ANJANI D. MATTAI • JEFFREY S. GROEGER

Cancer is the second leading cause of death in the United States, surpassed only by heart disease. Approximately one million new cases of squamous and basal skin cancers and 1,445,000 new cases of all other cancers (excluding carcinoma in situ, with the exception of in situ bladder carcinoma) are likely to be diagnosed this year. When adjusted for normal life expectancy, a 5-year relative survival rate of 66% has been calculated for all cancers diagnosed between the period of 1996 and 2002, compared to 51% between 1975 and 1977 (1). New chemotherapy regimens, stereotactic radiosurgery (2), hematopoietic stem cell transplantation, including cord transplantation (3), and the expansion of biologic therapy with monoclonal antibodies (4) offer hope but may lead to complications rarely seen in the nononcologic patient. It is beyond the scope of this chapter to discuss all aspects of cancer that warrant admission to an intensive care unit, and such topics as infection in the immunocompromised host, shock, coagulation abnormalities, and multisystem organ failure are discussed elsewhere in this book. Herein, we focus on clinical conditions that arise either as a direct result of a neoplasm or antimetabolite therapy.

HYPERCALCEMIA

Hypercalcemia is one of the most common paraneoplastic syndromes, occurring in 30% of all patients with malignancy at some time during their disease course (5–7). Breast cancer, lung cancer, and multiple myeloma represent the most common malignancies associated with hypercalcemia (5). The presence of hypercalcemia in a patient with cancer portends an extremely poor prognosis, particularly when elevated parathyroid hormone-related protein (PTHrP) levels are detected (8,9), approximately 50% of cancer patients with hypercalcemia will die within 30 days (10).

Pathophysiology

Hypercalcemia of malignancy results from increased bone resorption and subsequent release of calcium from bone into the extracellular fluid (11). Classification is based on the mechanism by which the elevated calcium is generated, of which there are four recognized types:

1. Humoral hypercalcemia of malignancy (HHM)
2. Local osteolytic hypercalcemia
3. Tumor production of the active form of vitamin D
4. Ectopic parathyroid hormone (PTH) secretion

Humoral Hypercalcemia of Malignancy (HHM)

This is the most common cause of cancer-induced hypercalcemia, seen in 80% of cases (7,12). The mechanism is mediated by parathyroid hormone-related protein (PTHrP), which is secreted into the systemic circulation by malignant tumors (12)—most frequently squamous cell carcinoma, renal cell carcinoma, ovarian and endometrial carcinomas, human T-cell lymphoma/leukemia virus (HTLV)-associated lymphomas, and breast carcinoma (5). Normally, PTHrP is expressed in many
nonneoplastic adult and fetal tissues where it is involved in cell growth and differentiation but is not systemically secreted in significantly detectable levels. Because of its structural homology with parathyroid hormone at the amino terminal end, humoral PTHrP binds to PTH receptors in bone and kidney, causing an increase in bone resorption and distal tubular calcium resorption (5,13).

**Local Osteolytic Hypercalcemia**

Seen in about 20% of cases of malignant hypercalcemia, this form occurs when tumor cells present in bone metastases induce osteoclastic bone resorption by secreting cytokines—for example, tumor necrosis factor, interleukin-1, interleukin-6, macrophage inflammatory protein, and lymphotoxin—which, in turn, stimulate local macrophages within the tumor to differentiate into osteoclasts. Local osteolytic hypercalcemia occurs frequently in breast cancer, non-small cell lung cancer, and multiple myeloma (9).

**Tumor Production of the Active Form of 1,25-dihydroxyvitamin D**

Occurring in less than 1% of cases, this entity is seen in some lymphomas. The hypercalcemia is mediated by enhancement of both osteoclastic bone resorption and intestinal resorption of calcium.

**Ectopic Parathyroid Hormone (PTH) Secretion**

The final mechanism of hypercalcemia of malignancy is ectopic PTH secretion, which has been adequately described in only eight patients (5).

**Differential Diagnosis**

Malignancies and primary hyperparathyroidism account for approximately 90% of all cases of hypercalcemia and may coexist in the critically ill cancer patient (14). Among hospitalized patients, neoplastic disease is the most common cause, accounting for more than 65% of cases (15,16). Renal failure, rhabdomyolysis, granulomatous diseases such as sarcoid and tuberculosis, adrenal insufficiency, immobilization, vitamin A or D intoxication, milk alkali syndrome, familial hypercalcemic hyperparathyroidism, and medications such as thiazide diuretics, lithium, estrogens, and tamoxifen are also included in the differential diagnosis of hypercalcemia (16,17).

**Clinical Presentation**

There are multiple symptoms of hypercalcemia (Table 174.1), which are nonspecific and often attributed to coexisting chronic or terminal illness (9). In general, the symptoms correlate with the absolute concentration and the rapidity in rise of the serum calcium (18). Neurologic, gastrointestinal, renal, cardiac, and bone-related manifestations may be present. Neurologic symptoms may be mild at lower serum calcium levels or when the hypercalcemia has developed slowly. Mild drowsiness or fatigue may progress to weakness, lethargy, stupor, and eventually coma in hypercalcemic crisis or in acutely rising hypercalcemia (11). Psychotic behavior, visual and speech abnormalities, hypotonia, and occasionally localizing signs on neurologic exam, often thought to be secondary to metastatic disease, may be exhibited, and may resolve with therapy that lowers serum calcium (16,19). In older patients, neurologic dysfunction may be more pronounced even at lower concentrations of serum calcium (5). Gastrointestinal symptoms are related to smooth muscle hypotonicity and include anorexia, nausea, vomiting, constipation, and abdominal pain (11). Infrequently, hypercalcemia may present as peptic ulcer disease (18) and pancreatitis (20). Renal manifestations result from the impairment of renal water-concentrating ability because antidiuretic hormone (ADH) secretion is inhibited by hypercalcemia. Subsequent dehydration decreases the glomerular filtration rate and reduces renal excretion of excess serum calcium. To expand the extracellular volume, compensatory proximal tubular resorption of sodium and calcium occurs, leading to a paradoxical increase in

**TABLE 174.1**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>CLINICAL MANIFESTATIONS IN HYPERCALCEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUROLOGIC</td>
<td>Drowsiness, weakness, lethargy Stupor, coma Psychosis Visual and speech impairment Focal neurologic deficits</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>Anorexia Nausea, vomiting Constipation Abdominal pain Peptic ulcer disease Pancreatitis</td>
</tr>
<tr>
<td>RENAL</td>
<td>Nephrogenic diabetes insipidus Acute renal failure</td>
</tr>
<tr>
<td>CARDIAC</td>
<td>PVC interval prolongation QRS complex widening QT interval shortening T wave changes Bradycardia Bundle branch block AV nodal block Cardiac arrest</td>
</tr>
<tr>
<td>BONE</td>
<td>Pain Pathologic fractures</td>
</tr>
</tbody>
</table>
Cardiac symptoms of hypercalcemia include arrhythmias: (i) 50% is the ionized free fraction, (ii) 40% is protein bound (primarily to albumin) and is not renally filtered, and (iii) 10% is complexed to anions (18). Hypercalcemia is diagnosed by measuring the ionized calcium level, as this is the biologically active level that correlates with the signs and symptoms of hypercalcemia. Except in the presence of hypocalcemia, the ionized calcium level can be inferred from the total plasma calcium. In cancer patients, hypocalcemia is common, and the total plasma calcium must be corrected to reflect the calcium level that would have been measured as if the albumin were in the normal range. In general, for each 1 g/dL decrease in serum albumin, there is a 0.8 mg/dL decrease in serum calcium. This method of calculation is inaccurate in the presence of calcium-binding immunoglobulins, as seen in multiple myeloma. This circumstance warrants measurement of the ionized calcium level because the total serum calcium level may significantly overestimate the ionized fraction (11). Although ionized calcium concentrations increase with acidosis and decrease with alkalosis, these changes are relatively small and do not lead to clinically significant events (22).

Once the diagnosis of hypercalcemia is confirmed by obtaining corrected calcium levels, measurement of the intact PTH level—suppressed in hypercalcemia of malignancy and elevated in primary hyperparathyroidism—is often necessary to differentiate among the mechanisms of hypercalcemia. PTH lowers the serum phosphate and increases serum chloride concentrations (14). A low serum chloride (less than 100 mEq/L) suggests hypercalcemia of malignancy, whereas elevation of serum chloride is caused by hyperchloremic acidosis resulting from PTH-induced renal bicarbonate loss seen in hyperparathyroidism (9). Ectopic hyperparathyroidism is an extremely rare cause of malignant hypercalcemia, and elevations in PTH levels are more likely to indicate concomitant primary hyperparathyroidism in cancer patients with hypercalcemia (21). In contrast to PTH level measurement, determination of the serum PTH-P concentration is not routine. However, it may be useful in identifying the mechanism of hypercalcemia. For example, PTH-P levels are low in patients with primary hyperparathyroidism but high in patients with either HBM alone or concomitant primary hyperparathyroidism and malignant hypercalcemia (12,23). PTHrP has also been used in evaluating the response to bisphosphonate therapy; patients with PTHrP levels above 12 pmol/L were reported to be less responsive to pamidronate and more likely to develop recurrent hypercalcemia within 14 days (24).

**Diagnosis**

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TABLE 174.2

TREATMENT OF HYPERCALCEMIA OF MALIGNANCY

**DEFINITIVE TREATMENT**
Antitumor therapy to reduce tumor burden

**INITIAL TREATMENT**
Removal of exogenous calcium sources:
- Intravenous fluids
- Parenteral nutrition
- Oral calcium supplements
- Thiazide diuretics
- Vitamins A and D
- Calcitriol
- Lithium
- Estrogens
- Antiestrogens
- Weight-bearing ambulation
- Phosphate repletion
- Fluids and diuresis
- Loop diuretics
  - Judicious use in euvoledmic or hypovolemic patients; now less favorable because of hypokalemia, hypomagnesemia, volume depletion

**PHARMACOLOGIC TREATMENT**
Bisphosphonate therapy
Principal agents in hypercalcemic treatment
- Zoledronate: 15-min infusion
- Pamidronate: 2-h infusion
  - Bisphosphonate adverse effects: Acute and chronic renal failure, fever, arthralgias, ocular inflammation, electrolyte imbalance, osteonecrosis of the jaw

Other Agents
- Calcitonin: Useful in congestive heart failure or renal failure
- Glucocorticoids: Used in lymphomas with elevated levels of 1, 25-vitamin D
- Mithramycin: Use limited by adverse effects: Thrombocytopenia, anemia, leukopenia, renal failure
- Gallium nitrate: Use limited by 5-day continuous infusion, nephrotoxicity

**DIALYSIS**
For patients with renal failure or congestive heart failure


Loop diuretics inhibit calcium reabsorption at the loop of Henle, and, hence, also increase calcidiuresis. These agents should be used judiciously and only after euvoledmic is achieved in hypovolemic patients or in patients who present with vol-ume overload (5,9,16). Because of ensuing complications such as hypo-kaemia, hypomagnesemia, and volume depletion, and because of the availability of bisphosphonates, loop diuretics are used less favorably in clinical practice (26).

**Bisphosphonate Therapy**
Bisphosphonates inhibit osteoclastic bone resorption and are the principal agents used in the management of hypercalcemia of malignancy (27). When compared to saline and diuretics alone, and other antiresorptive agents including calcitonin, bisphosphonates are superior in treating hypercalcemia of malignancy (5). Because only 1% to 2% of oral bisphosphonates are absorbed, these drugs are administered intravenously (7). Pamidronate, and zoledronate are the most commonly used bisphosphonates, and are the two agents that have been approved by the Food and Drug Administration (FDA) for the treat-ment of hypercalcemia of malignancy. Clodronate and ibandronate are available in Europe and other countries. Patients respond to bisphosphonate therapy within 2 to 4 days, with a nadir in serum calcium occurring within 4 to 7 days; nor-mocalcemia may persist for 2 to 4 weeks (5,18). Compared to pamidronate, zoledronate is 850 times more potent and is more efficacious, although this increased efficacy is of un-clear clinical significance (9,28). In a pooled analysis of two randomized controlled trials comparing a single 4-mg dose of zoledronic acid to a 90-mg dose of pamidronate, serum calcium concentrations normalized within 10 days in 88% versus 70% of patients, respectively, and the duration of response was 32 days versus 18 days, respectively, within the two groups (28). Although pamidronate may be the less expensive of the two agents, zoledronate can be administered over a shorter interval of 15 minutes, making it advantageous in the outpatient setting; pamidronate requires a 2-hour infusion. Both zoledronate and pamidronate have been associated with acute and chronic renal
failure, with more adverse events reported with zoledronate. Dose reduction of zoledronate is recommended in patients with a creatinine clearance between 30 and 60 ml/min; however, the American Society of Clinical Oncology does not recommend changing the dose or infusion rate of pamidronate in patients with a serum creatinine of less than 3 mg/dl (2,39). Other complications of bisphosphonates include acute systemic inflammatory reactions such as fever and arthralgias, as well as osteonecrosis of the jaw (29).

Other Agents
Calcitriol is a well-tolerated synthetic polypeptide analogue of salmon calcitriol, which reduces serum calcium levels by inhibiting bone resorption. When administered subcutaneously or intramuscularly, it produces a rapid but transient decrease in serum calcium levels within 12 to 24 hours (5,9). This agent is useful in patients with congestive heart failure or renal failure who have elevated serum calcium, and bisphosphonates may be contraindicated. Tachyphylaxis may occur with continued use (7). Glucocorticoids are effective in decreasing serum calcium in hypercalcemia of malignancy associated with some lymphomas, particularly Hodgkin lymphoma. Elevated levels of 1,25-vitamin D are present in Hodgkin's lymphoma (7); glucocorticoids, in addition to increasing renal calcium excretion, block vitamin D-mediated calcium absorption in the gastrointestinal tract (11). These agents have limited utility in the acute setting because a reduction in serum calcium may not be observed for 1 to 2 weeks (11). Mithramycin, an inhibitor of osteoclast RNA synthesis and formerly a first-line hypocalcemic agent, has serious adverse effects including thrombocytopenia, anemia, leukopenia, and renal failure (5). Gallium nitrate has the disadvantage of requiring continuous infusion over 5 days and has potential nephrotoxicity. Finally, dialysis may be used to treat patients with hypercalcemia complicated by renal failure or congestive heart failure (5,18).

ACUTE TUMOR LYSIS SYNDROME

Definition
Acute tumor lysis syndrome (ATLS) occurs as a consequence of the rapid and massive destruction of tumor cells resulting in the release of intracellular metabolites into the circulation in quantities sufficient to exceed renal excretory capacity (30,31). The four biochemical disturbances generated by this process that characterize the syndrome are life threatening (32): 1. Hyperkalemia 2. Hyperphosphatemia 3. Hypocalcemia 4. Hyperuricemia These metabolic abnormalities have widespread adverse effects on the cardiac, musculoskeletal, nervous, and renal systems.

Acute tumor lysis syndrome is most frequently observed after the administration of cytotoxic chemotherapy in patients with high-grade hematologic malignancies—classically, Burkitt's lymphoma and acute lymphocytic leukemia (ALL) (7,33,34). The incidence of clinically significant ATLS in non-Hodgkin's lymphoma and ALL has been reported as 6% (35) and 2.4% (7), respectively. Metabolic derangements in these patients may develop within a few hours to a few days after initiating chemotherapy (7,36). Other malignancies in which ATLS has been described include chronic leukemia, low-grade lymphoma, and, rarely, multiple solid tumors such as metastatic breast carcinoma, lung carcinoma, seminoma, thymoma, medulloblastoma, ovarian carcinoma, thymic carcinoma, dermatomyosarcoma, melanoma, vulvar carcinoma, and Merkel cell carcinoma (31). The syndrome can also occur after radiation therapy, immunotherapy (rituximab and interferon), and endocrine therapy (corticosteroids and tamoxifen) (7,31,33). Spontaneous tumor lysis syndrome (STLS) is a rare entity that develops primarily in Burkitt's lymphoma and leukemia in the absence of any treatment. The increased purine metabolism from high tumor cell turnover rates in these malignancies leads to hyperuricemia and consequent uric acid nephropathy (37,38). Prompt recognition of STLS is essential because it is associated with poor outcomes and high mortality rates (38).

Pathophysiology
Rapid dissolution of cells with aggressive cytotoxic therapy results in an increase in plasma uric acid, potassium, and phosphorous levels. The hyperphosphatemia, in turn, precipitates secondary hyperparathyroidism. Hypercalcemia occurs 6 to 72 hours after the administration of chemotherapy (36). Associated manifestations include lethargy, nausea, vomiting, diarrhea, muscle weakness, paresthesias, and electrocardiographic abnormalities such as peaked T waves, PR-interval prolongation, and QRS-complex widening. Ventricular arrhythmias may lead to sudden death (7,31).

Hyperparathyroidism is seen 24 to 48 hours following chemotherapy (36). Malignant cells may contain up to four times more phosphorous than nonneoplastic cells, and, as plasma phosphorous increases with cell lysis, the normal renal mechanism that excretes excess phosphate and prevents distal tubular reabsorption becomes overwhelmed, leading to hyperparathyroidism (39). Signs and symptoms of acute hyperparathyroidism are manifestations of secondary hyperparathyroidism, and range from no symptoms to anorexia, vomiting, confusion, neuromuscular irritability, tetany, carpopedal spasm, seizures, dysrhythmias, and cardiac arrest (7,31). Secondary hyperparathyroidism occurs in association with hyperparathyroidism because when the calcium phosphate product exceeds 60, calcium phosphate precipitates into tissues, including the renal interstitium and tubules, resulting in nephrocalcinosis (32). However, hyperparathyroidism may persist even after correction of hyperparathyroidism when an inappropriately low plasma calciotriol level is present (40). Hyperparathyroidism itself causes a rise in serum parathyroid hormone, which, in turn, increases phosphate reabsorption in the proximal tubule, leading to nephrocalcinosis and acute renal failure (7).

Hyperuricemia occurs 48 to 72 hours after chemotherapy (36). Patients may exhibit nonspecific symptoms such as...
nnae, vomiting, anorexia, and lethargy. Acute renal failure with associated oliguria, edema, hypertension, and altered sen-
soirum will be seen in untreated patients (33). Uric acid is generated from purine metabolites in the liver. Adenosine and guanosine nucleotides are degraded to hypoxanthine and xan-
thine, respectively, and xanthine oxidase converts these prod-
ucts to uric acid (7). Rapidly proliferating neoplastic cells have high turnover rates with accelerated purine catabolism from DNA and RNA degradation (41), and these cells contain large amounts of purine nucleotides; consequently, with cytotoxic therapy, there is a rapid rise in plasma uric acid (33). Uric acid is excreted by the kidneys through the processes of glomeru-
lar filtration, partial proximal tubular reabsorption, and distal tubular secretion (32). The clearance of uric acid is indepen-
dently proportional to intravascular volume status (31) and the urinary flow rate (32), and may be significantly reduced in the presence of dehydration or tubular obstruction from acute nephrocalcinosis or uric acid nephropathy. Uric acid nephropa-
yth develops when uric acid crystals deposit in the renal tubules and collecting ducts because of acidic conditions. The urinary pk₆ of uric acid is 5.4, and the luminal pH of the distal tubules and collecting ducts is 5.0, resulting in the poor solubility of uric acid in acidic urine (7). This poor solubility, coupled with the marked hyperuricosuria present in ATLs, leads to uric acid precipitation, intraluminal obstruction, oliguria, and acute re-
nal failure (7,42). Acute renal failure (ARF) in ATLs may also be mediated by renal calculi from phosphate and uric acid pre-
cipitation (31), as well as from ischemic acute tubular necrosis caused by renal hyperperfusion (33). Drug toxicity, sepsis, and tumor-associated obstructive urethral or renal parenchymal inflam-
mation may exacerbate ATLs-induced ARF (39).

Classification

Although no widely accepted definition of ATLs currently ex-
ists, Hande and Garrow (35) first classified ATLs into labora-
tory TLS and clinical TLS. Cairo and Bishop (39) have further developed this classification system into the Cairo-
Bishop definition, which uses laboratory and clinical data in conjunction with a grading scale to assess the severity of ATLs. Laboratory TLS (LTLS) is defined as two or more of the follow-
ing metabolic abnormalities occurring 3 days before or 7 days after chemotherapy: uric acid 8 mg/dL or greater, potassium 6 mg/dL or greater, phosphorous 6.5 mg/dL or greater, or a 25% increase in baseline levels of these metabolites, and calcium 7 mg/dL or less, or a 25% decrease from baseline level. Clinical tumor lysis syndrome is defined as LTLS in addition to one or more of the following findings: increased serum cre-
tinine (1.5 times the upper limit of normal), cardiac arrhyth-
mia/sudden death, or seizure. The grading of ATLs from 0 through 5 is determined by the presence or absence of LTLS, the degree of serum creatinine elevation, and the presence and severity of the cardiac arrhythmia and seizure (39).

Prevention and Treatment

Early recognition of patients at high risk for ATLs is an essential component of the management strategy so that appropriate prophylactic interventions can be instituted.

Fluids and Alkalization

Except in patients at risk for congestive heart failure, aggres-
sive intravenous hydration with isotonic or hypotonic saline (42) is the single most important intervention for both pre-
vention and treatment of ATLs. Cytotoxic therapy should be delayed whenever possible to administer appropriate hydration (7,42). Intravenous hydration should commence 2 days before and for 2 to 3 days after chemotherapy (31,33) at a rate of 3,000 mL/m² per day (7,39), or to two or four times the daily fluid maintenance requirement to achieve a urine output of 100 mL/m²/hr or greater (31,39). Aggressive administration of in-
travenous fluid increases the intravascular volume, renal blood flow, glomerular filtration rate, and urinary flow rate, result-
ing in correction of electrolyte derangements by dilution of the extracellular fluid and prevention of phosphate and uric acid precipitation by increasing urinary excretion of these metabo-
lites (31,33,39). Volume expansion alone may be insufficient to maintain adequate urine output, necessitating the administra-
tion of diuretics. Once euvaloria is achieved, and no signs of ac-
ute obstructive uropathy are present, a dose of furosemide—
0.5 to 1 mg/kg or 2 to 4 mg/kg for severe oliguria or anuria—
may induce or improve urine output (35). The effectiveness of furosemide is diminished in the setting of uric acid precipita-
tion in the renal tubules; in this circumstance, mannitol, at a
dose of 0.5 mg/kg, may be administered.

Alkalization of the urine to a pH 7.0 or greater remains contro-
versial (7,9,39). This practice is based on the biochemical prop-
erties of uric acid, that is, uric acid is 1.3 times more soluble at pH 7.0 than at pH 5.0 (32); maximal solubility of uric acid is attained at pH 7.5, and urine alkalization (pH 6.5 or greater) enhances renal excretion of uric acid (39). What limits this approach is that calcium phosphate precipitation in-
creases with systemic alkalization, exacerbating nephrocalci-
nosis (7,31). Additionally, hyperuricemia and xanthine solubil-
ity are substantially reduced, leading to xanthine nephropathy with concurrent allopurinol therapy (9,31,39).

Management of Hyperuricemia

Allopurinol reduces the risk of ATLs when administered 2 to 3 days prior to chemotherapy by inhibiting the production of uric acid (9). Allopurinol is both a synthetic structural analogue of the purine base, hypoxanthine, and a competitive inhibitor of xanthine oxidase (33), and, therefore, in the presence of allopurinol, xanthine oxidase cannot catalyze the conversion of hypoxanthine to xanthine and xanthine to uric acid (31). Allopurinol is administered orally at 300 to 800 mg daily (10 mg/kg per day or up to 400 mg/m² per day) in one to three divided doses, and should be titrated to uric acid level. Intravenous allopurinol was approved by the FDA in 1999 and can be administered in doses of 200 to 400 mg/m² per day (maximum 600 mg/day) in patients unable to tolerate oral medications, although the cost per day ranges between $400 and $1,000 (7,43). Dose adjustment of allopurinol is required for reduced creatinine clearance (7,43). There are several limitations with allopurinol therapy:

1. A reduction in serum uric acid level is not seen before 48 to 72 hours after initiating allopurinol because the drug in-
hhibits the synthesis of uric acid but does not affect the pre-
treatment uric acid concentration (7).

2. The ATLS classification...
2. Inhibition of xanthine oxidase by allopurinol leads to increased plasma levels of xanthine and hypoxanthine, which may precipitate in the renal tubules (33).

3. Three percent of patients develop hypersensitivity reactions, including Stevens-Johnson syndrome.

4. Allopurinol interacts with many drugs, including chemotherapy agents such as cyclosporine and azathioprine (42).

Another agent that lowers uric acid concentration is urate oxidase. Urate oxidase converts uric acid to allantoin, which is five to ten times more soluble in urine than uric acid. Present in many mammalian species, urate oxidase is not expressed in human beings as a result of a nonsense mutation in the coding region during hominoid evolution (44). A nonrecombinant form of urate oxidase was first obtained from Aspergillus flavus and has been used in France (1975) and Italy (1984) for treatment of hyperuricemia. Subsequently, a recombinant urate oxidase, rasburicase, was developed because of the 4.5% of hypersensitivity reactions that occurred with the nonrecombinant form (7,31,32). Rasburicase was FDA approved in 2002 for use in pediatric patients at risk for ATLS (44). An injectable dose of 0.15 to 0.20 mg/kg normalizes uric acid levels within 4 hours of administration in children and adults (7,42). This dose may be repeated daily for a total of 5 days, and chemotherapy should be initiated 4 to 24 hours after the first dose. In addition to being more effective than allopurinol in reducing pretreatment uric acid levels, rasburicase does not generate increased xanthine and hypoxanthine levels, thereby minimizing the risk of uric acid nephropathy that may be seen with allopurinol use (7,31,42). Of note, rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Bronchospasms and anaphylaxis may rarely occur with rasburicase therapy (45). There is insufficient evidence that rasburicase reduces the incidence of dialysis in ATLS, and because a 5-day course of therapy is approximately 2,000 to 3,000 times more expensive than a 5-day course of oral allopurinol (7,43), cost-effectiveness must be considered in formulating a treatment plan.

**Correction of Electrolyte Abnormalities**

Because of the potential for life-threatening arrhythmias, prompt recognition of electrolyte derangements is imperative. Laboratory monitoring should be performed every 4 to 6 hours in the first 24 hours of chemotherapy in patients at high risk for ATLS, and then every 6 to 8 hours thereafter (42). A baseline electrocardiogram (ECG) should be obtained to assess for cardiac effects related to electrolyte abnormalities. Hyperkalemia is treated with calcium gluconate to stabilize the cardiac membrane and with intravenous insulin/dextrose and inhaled beta agonists to facilitate intracellular shift of potassium. Although sodium bicarbonate may also shift potassium intracellularly by improving the metabolic acidosis, its use may result in inappropriate volume expansion. Potassium binding resins such as sodium polystyrene sulfate increase potassium elimination in the gastrointestinal (GI) tract and have a delayed hypokalemic effect. Diuretics can be administered to reduce serum potassium. Asymptomatic hypocalcemia should be left untreated to preclude calcium phosphate precipitation; however, symptomatic hypocalcemia is managed with intravenous calcium gluconate. Treatment of hyperphosphatemia with oral phosphate binders such as aluminum hydroxide or aluminum carbonate will usually concurrently correct the hypocalcemia (7,33).

**Dialysis**

Dialysis is indicated in patients with marked elevations in serum uric acid, phosphate, and potassium that do not respond to aggressive treatment, and in patients with ARF with volume overload, severe uremia, or acidosis (31,33,39). Hemodialysis is used in ATLS because it is superior to peritoneal dialysis in the clearance of both uric acid and phosphorous (31,39).

**OBSTRUCTIVE SYNDROMES**

**Superior Vena Cava Syndrome**

**Definition**

Superior vena cava syndrome (SVCS) describes the set of signs and symptoms associated with obstruction of the superior vena cava, which may be caused by extrinsic compression, vascular invasion, or intraluminal thrombosis of the vein (46–48). The SVC is a thin-walled, compliant, low-pressure mediastinal vessel, rendering it easily vulnerable to disease processes in the adjacent right lung, the paratracheal and perihilar lymph nodes, the mainstem bronchi, the esophagus, and the thoracic spinal cord (48,49).

First described by William Hunter (50) in 1757 in a patient with an aortic aneurysm secondary to syphilis, SVCS was—prior to the widespread use of antibiotics—primarily a complication of infectious diseases, as seen in syphilitic aortitis, histoplasmosis-induced fibrosing mediastinitis, and tuberculous mediastinitis (51,52). Currently, malignancy is the most common cause of SVCS. The percentage of cases attributable to cancer varies widely in the literature from 78% (48,53) to as high as 90% to 97% (54–57). A more recent retrospective study, reviewing the outcome of 78 patients over 5 years, reported malignancy as the cause of SVCS in 60% of the patients, with an increasing proportion of benign causes related to the presence of intravascular devices, e.g., central venous catheters and pacemaker wires (71%) (58). Other benign causes of SVCS include fibrosing mediastinitis from prior irradiation or histoplasmosis, aortic dissection, and complications of surgery, such as aortic dissection repair (54,58). Bronchogenic carcinoma accounts for 85% to 90% of the malignancies in which SVCS presents (54,57). Overall, SVCS develops in 2% to 10% of lung malignancies (47,52,56,59,60), and the risk of SVCS is higher in small cell lung cancer, with an incidence of 6.6% to 12% (59) because it involves the central mediastinal structures. In addition, because of the anatomic location of the SVC, right-sided lung cancers cause SVCS four times as often as left-sided lung cancers (56). Other neoplasms include malignant lymphomas; although Hodgkin’s lymphoma more often involves the mediastinum, it rarely causes SVCS (48,54). Primary germ cell cancers, thymoma, mesothelioma (60), and metastatic disease (primarily breast carcinoma) constitute a small proportion of SVCS cases (54,58,60).

**Clinical Presentation**

SVCS may be the initial presentation of bronchogenic carcinoma and lymphoma, or may arise in patients with previously...
documented malignancy (53,58). The severity of signs and symptoms depends on the extent, location, and rapidity of onset of the SVC syndrome (55). In general, obstruction within or below the azygos vein results in more dramatic symptoms. Normally, azygos venous capacity increases from 11% to 35% to augment drainage of the head and neck (47), but impedance of flow from obstruction precludes this auxiliary function (47,54,60). With slowly developing SVCs, collateral vessels in the chest wall and upper extremities are recruited as a diversion for the existing SVC engorgement; hence, SVCS in this population is of insidious onset, as in fibrosing mediastinitis (55). The most commonly reported symptom in SVCS is dyspnea followed by head and facial swelling (48,58). Other cardiodi-
monary symptoms include cough, orthopnea, and chest pain. Associated signs are neck and arm vein distention, plethora or cyanosis of the head and neck (48), venous collateralization in the arms and upper chest wall (54), and chronic pleural effu-
sions (54,55). More extensive airway or vascular obstruction is predicted when postural maneuvers such as lying supine or leaning forward exacerbate respiratory or cardiac symptoms; for example, respiratory insufficiency in the supine position worsens as the weight of the mediastinal structures impinges on the tracheobronchial tree. In the substantially compromised patient with SVCS, cardiopulmonary arrest may ensue simply with the administration of sedatives and general anesthesia (54). Other head and neck signs and symptoms range from conjunctival and periorbital edema, nasal congestion, dyspha-
gia, and hoarseness due to laryngeal nerve compression (61) to proptosis, glossoedema, stridor secondary to laryngeal edema, and tracheal obstruction (54,55). Patients with central nervous system (CNS) manifestations may exhibit mild headaches, dizziness, and lethargy with progression to syncope (in rapidly developing or complete SVC obstruction) seizures, or coma (from cerebral edema due to increased intracranial pressure) (47,54). Bleeding complications such as epistaxis, hemothorax (54), and gastrointestinal hemorrhage from esophageal varices (in long-standing SVC) (55) may occur.

**Diagnostic Investigations**

**Imaging.** Once the clinical diagnosis of SVC syndrome is sus-
pected, confirmation can be obtained using both radiologic and nuclear techniques. Chest radiography reveals widening of the superior mediastinum in approximately 60% of patients (53,54,56) and pleural effusions, most frequently right-sided, in up to 25% of patients (48,54). A normal chest radiograph does not exclude the diagnosis. Contrast-enhanced helical comp-
tomed tomography (CT) accurately delineates the site, extent, and cause of the occlusion (56,60), as well as any associated thrombus and collateral vessel development (60). The radio-
logic diagnosis of SVCS is made by demonstrating both de-
creased or absent venous opacification below the level of ob-
struction and prominent collateral vessel opacification (56). MRI is an alternative imaging method in patients with su-
divided contrast allergy or without adequate venous access for contrast administration, but offers no distinct advantage over CT (48,54,62). Venography is most useful when plan-
ning bypass or stenting procedures (48,60). Although venog-
raphy is superior to CT in identifying the site and extent of obstruction and in mapping the collateral circulation, it does not elucidate the underlying cause of the SVCS (62), unless SVC thrombosis alone is the causative factor (52,56,60). Radiouclide technetium venography is a less invasive alter-
native to standard venography but lacks the image resolu-
tion of the latter (48). Although not a well-established di-
agnostic modality in clinical practice, helical CT phlebogra-
phy, which involves simultaneous bilateral venography with intravenous contrast, produces both detailed CT images of the mediastinum and a CT venogram that cor-
relates well with digital venography. Flow artifact (nonsig-
ificant contrast opacification) created by physiologic mixing of contrast-opacified and nonopacified blood may mimic intralu-
minal filling defects in patient vessels and remains the major limitation of this technique (62).

**Histologic Diagnosis.** Sputum cytology, thoracentesis, percu-
taneous needle biopsy, bronchoscopy, mediastinoscopy, or tho-
racotomy are all methods used to obtain pathologic speci-
mens. The diagnostic yields are as follows: bronchoscopic biopsy; 50% to 70%; transbronchial needle aspiration biopsy, 75%; medi-
astinoscopy or mediastinotomy, greater than 90% (63). His-
torically, the treatment practice was to administer emergent radiotherapy for SVCS without establishing a histologic di-
agnosis. This strategy was predicated on the following beliefs: SVCS was a life-threatening emergency necessitating immediate intervention; invasive diagnostic procedures were associated with a high risk of morbidity, including bleeding and anes-
thetic complications; and unresectable lung malignancy was the most probable cause of the SVCS (46,56,59). Presently, it is well established that in the absence of tracheal obstruction or severe laryngeal or cerebral edema, SVCS itself results in no life-threatening complications (59,60,64-66); that invasive investigative procedures such as percutaneous needle biopsy, bronchoscopy, mediastinoscopy, and thoracotomy can be per-
formed safely and with minimal morbidity and mortality; and that for going a pathologic diagnosis is unjustified, except in severe airway obstruction or cerebral edema (56,58,67,68), because identifica-
tion of the underlying condition guides appropriate treat-
ment of the SVCS in both benign and malignant disease.

**Treatment**

The primary goals of treatment are symptom relief and erad-
ication or palliation of the underlying malignancy. Initial symptomatic management involves bed rest, head elevation to reduce venous pressure, and supplemental oxygen administra-
tion. Diuretics and sodium restriction may decrease edema, but reports are anecdotal. Use of glaucoctocorticoids to minimize in-
flammatory responses to tumor or radiotherapy (XRT) is con-
troversial (48,56), but steroids are a mainstay of treatment in non-Hodgkin lymphoma (NHL) (54,56).

**Endovascular Stenting.** If these conservative measures are in-
effectual in controlling symptoms, a percutaneously placed en-
dovascular stent can be inserted with or without balloon an-
gioplasty (56). In recent studies, relief of symptoms occurred immediately after stent placement in 80% to 95% of patients with few complications (69,70). A systematic review of the lit-
erature found that morbidity increased with stent insertion if thromboctlytics were administered. One group advocates stent insertion as a first-line therapy for symptom relief because, after placement, symptoms were rapidly alleviated in 18/18 patients, enabling all to begin XRT the following day (71). In a study involving S2 patients with non-small cell lung cancer (NSCLC) and SVCS, immediate symptom relief permitted patients to re-
cieve the appropriate hydration required with full doses of platinum therapy (69). Recurrence of SVCS occurs in 10% to 30% of patients after primary therapy with chemotherapy.
In the head and neck, direct tracheal invasion is seen with locally advanced oropharyngeal tumors, laryngeal neoplasms associated with bulky or supraglottic lesions, and rarely, thyroid cancer and primary tracheal tumors (75). In thyroid cancer, tracheal invasion develops in 1% to 6.5% of patients, and UAO is the most common cause of death in this group (78). Bilateral thyroid cancer may cause glottic obstruction from bilateral laryngeal nerve paralysis and resultant bilateral vocal cord paralysis (75). Direct tumor extension into the trachea from adjacent structures by malignancies of the lung, esophagus, and mediastinum occurs more frequently than metastatic disease spread (79).

Tracheal impingement in lung cancer occurs when there is tracheal ingrowth of the primary tumor originating in a main-stem bronchus or from enlarging paratracheal or subcarinal lymph nodes. Bilateral vocal cord paralysis with recurrent laryngeal nerve paralysis may also be associated with lung malignancies (73,80). Extrathoracic malignancies may metastasize to mediastinal and endobronchial lymph nodes, causing airway obstruction. Renal cell carcinoma, sarcomas, breast cancer, and colon cancer are most commonly involved (81). Melanoma may arise as a primary tracheal tumor but more often is a metastatic lesion (79).

Tracheal compression, which is usually attributable to benign disease, is a secondary mechanism of UAO in neoplasic disease and is often the initial presentation of mediastinal tumors and extensive lymphoma (82).

**Clinical Presentation**

Patients may present with dysphagia, hoarseness, intractable cough, hemoptysis, dyspnea, or stridor (54,75). Important goals during physical examination are to determine whether impending airway obstruction is present and to localize the site of the lesion. Once stridor is apparent, the airway caliber has profoundly narrowed to approximately 6 mm, and without intervention, complete UAO is imminent. Inspiratory stridor implies an extrathoracic lesion at the level of the glottis or above, whereas expiratory stridor suggests an intrathoracic lesion. Bifocal stridor may be indicative of a subglottic or tracheal mass. Voice alteration, such as muffling and hoarseness, accompanies subglottic lesions and unilateral vocal cord paralysis, respectively (47).

**Diagnostic Investigations**

A chest radiograph may identify an obstructive neck mass and consequent tracheal deviation. Flexible oropharyngeal or nasopharyngeal endoscopy can be performed to assess the airway. Once the airway is stabilized, high-resolution CT of the head and neck provides comprehensive evaluation of the sites of narrowing and the size and extent of the tumor in relation to adjacent structures. Spirometry demonstrates a plateau in the inspiratory limb of the flow-volume loop if there is a fixed obstructive lesion in the extrathoracic trachea (83).

**Treatment**

Initial management includes head elevation and administration of cool humidified oxygen. Case reports have demonstrated that inhalation of a helium–oxygen mixture, consequent to its lower density compared to oxygen supplementation alone, reduces the work of breathing (34,84,85). Airway obstruction in patients with bulky oropharyngeal, laryngeal, or thyroid carcinomas will require emergent or elective tracheostomy. Endotracheal intubation is not recommended for patients with

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**Oropharyngeal and Tracheal Obstruction**

Sudden upper airway obstruction (UAO) of the larynx, pharynx, or extrathoracic trachea is uncommon with cancers of the head and neck. Tumors of the larynx, pharynx, base of tongue, and thyroid are primarily slow growing and, as they progressively enlarge, obvious signs and symptoms of airway compromise are usually evident prior to the development of acute obstruction (75); tracheal masses, which take years to be discovered, first become symptomatic when the airway lumen is narrowed by 75% (76). Mechanisms of UAO include direct tracheal invasion as well as extrinsic tracheal compression (77).
bulky, friable, laryngeal, and/or pharyngeal disease, as it may exacerbate existing airway edema and hemorrhage (75). For intrathoracic lesions, bronchoscopy with interventions such as laser therapy (86,87), brachytherapy, photodynamic therapy, or stenting may be performed to rapidly alleviate symptoms (87). Stents are also useful in palliating symptomatic extrinsic compression (54,88). Endotracheal intubation or stenting may be used to maintain the airway when there is extrinsic compression from lymphoma (88) or other highly radiosensitive or chemosensitive tumors with anticipation of rapid reduction of tumor mass. Surgical resection is indicated for primary airway tumors (54,89) and for lung cancers with- out mediastinal lymph node involvement. In lung and thyroid cancers that directly invade the trachea, surgery may be cura- tive (79); metastatic disease to the trachea requires palliative treatment.

### Infrathoracic Obstruction

Infrathoracic airway obstruction may be present with intrin- sic primary endobronchial tumors such as bronchogenic carci- noma and carcinoid, with metastatic tumors or their associated lymphadenopathy (lung, renal, breast, thyroid, and colon can- cers, and sarcoma or melanoma), or with bulky disease caus- ing airway compression. Symptoms often progress slowly over time, and patients may complain of dyspnea, wheezing, or chest discomfort, leading to the misdiagnosis of asthma or bronchitis prior to the development of fulminant airway obstruction (90).

Postobstructive pneumonia may be a finding on initial pre- sentation. With impending obstruction, patients may exhibit hypertension, tachycardia, tachypnea, and significant pulsus paradoxus. Poor air movement, use of accessory muscles, and mental status changes are indicators of severe obstruction. Progressive symptoms may result in negative pressure pulmonary edema and anoxic brain injury (83). Chest examination may reveal a prolonged expiratory time and wheezing. Respiratory symptoms are unilateral with lesions below the carina (90), and the chest radiograph reveals asymmetric lung fields, par- ticularly on end-expiration. Stable patients should have a flow- volume loop performed. An infrathoracic, mobile tracheal le- sion above the carina will demonstrate airway compression during the expiratory phase, producing flattening of the ex-piratory limb of the flow-volume loop, whereas a plateau in both inspiratory and expiratory limbs will be observed with fixed obstructive lesions (83). Chest CT defines tumor extent and location, but rigid bronchoscopy is usually necessary to evaluate the airway in impending obstruction. When airway obstruction is severe, flexible bronchoscopy is hazardous be- cause this technique does not permit ventilatory support, and, additionally, the bronroscope may obstruct the already nar-rowed airway lumen (90).

Treatment proceeds with the general measures of oxygen or helium/oxygen supplementation and, possibly, steroids. If endotracheal intubation is required, the clinician must recog- nize the potential for hemodynamic compromise associated with acute airway obstruction and significant increases in airway pressure distal to the obstruction (83). Bronchoscopy with var- ious interventions, including debridement, dilatation, endotra- cheal stent placement, laser ablation, photodynamic therapy, and placement of brachytherapy catheters may relieve symp- toms (90). External beam radiotherapy may also play a role. In lung cancer, tracheal and carinal resection is indicated in

patients without mediastinal lymph node involvement for a potential cure (54).

### NEUROLOGIC SYNDROMES

#### Spinal Cord Compression

**Etiology and Pathophysiology**

Malignant spinal cord compression (MSCC) is a profoundly debilitating, but usually nonfatal, manifestation of metastatic cancer, occurring in 5% to 10% of cancer patients (91–93). The term, MSCC, refers to epidural, intramedullary, and leptomeningeal disease; however, the focus of this section is on epidural spinal cord compression (ESCC) because the literature primarily discusses this population (93). Although any malignancy capable of metastatic spread may give rise to MSCC, prostate, breast, and lung cancers are most commonly involved, with each accounting for 15% to 20% of cases (91,94) or, in combination, 60% of cases (93,95). The cumulative inci- dence of MSCC is specific to tumor type, with the highest rates occurring in multiple myeloma (8%), prostate cancer (7%), and nasopharyngeal cancer (6.5%) (95). Other tumors include non-Hodgkin’s lymphoma and renal cell carcinoma, with each representing 5% to 10% of cases (96), and gastrointestinal cancers, sarcoma, melanoma, thyroid cancer (92,93), and un- known primary carcinoma (95,96). Enlarging meningiomas, nerve sheath tumors, and leptomeningeal metastases may also compress the spinal cord. Nonmalignant causes of MSCC in the cancer patient are epidural abscesses in the presence of immune compromise and hematoma with bleeding diatheses (97).

MSCC has a proclivity for the thoracic spine (92,96,98– 100) and is estimated to occur in this location in approximately 60% to 66% of cases (97,99). Twenty percent of cases involve the lumbar spine (92,97), and MSCC in the cervical spine is uncommon in 7% to 10% of cases (99,100). Prostate and col- orectal carcinomas favor the lumbarosacral spine (97). MSCC is the initial manifestation of malignancy in 20% of patients. One series found that carcinomas of the lung and unknown primary, multiple myeloma, and non-Hodgkin’s lymphoma accounted for 78% of patients with MSCC presenting with malignancy compared to 26% in patients with previously established ma- lignantancy (100).

The mechanisms by which MSCC occurs include vertebral body invasion by tumor with possible vertebral collapse caus- ing encroachment on the anterior spinal cord (85%), direct ex- tension into the intervertebral space by paraspinal lymphoma, sarcoma, or lung cancer, seen in 10% to 15% of cases (9,92); and epidural or intramedullary space invasion, seen in less than 5% of cases (92). The mechanism of injury to the spinal cord is mediated by white matter vasogenic edema and axonal swelling that result from cord compression. Venous hyperten- sion, decreased spinal cord blood flow, and cord infarction en- suring, results in ischemic hypoxic neuronal injury. Vascular endothelial growth factor (VEGF) is generated in association with spinal cord hypoxia, and it is thought that dexamethasone may down-regulate VEGF expression, resulting in the benefi- cial actions of steroids in MSCC (96).

**Clinical Presentation**

Pain, which may be characterized as localized, radicular, or re- ferred, is the primary presenting symptom in MSCC, occurring
in 83% to 95% (96,98,101) of patients for a median of 8 weeks prior to diagnosis (96,98). Focal bony pain is typically localized, dull or aching, and constant. Direct tenderness of the involved vertebral body may be evident with periosteal destruction (102). With time, radicular pain occurs in the dermatome of the affected nerve root and is severe, deep, and lancinating. Radicular symptoms occur most often in the lumbar sacral spine and may be unilateral or bilateral, the latter more frequent with thoracic spine involvement (97,103). Referred pain does not radiate, but appears in a region distal to the area of pathology; for example, sacroiliac pain may result from L1 compression (103). The pain of MSCC is typically worsened with recumbency secondary to distention of the epidural venous plexus (96,97). Coughing, sneezing, orValsalva maneuvers will also exacerbate the pain (103). Straight-leg raising identifies a lumbar sacral radiculopathy, and neck flexion reproduces symptoms of thoracic radiculopathy (97,101,103).

Motor weakness is present in 60% to 85% of patients on diagnosis of MSCC. Although only one third of patients complain of lower extremity weakness on initial presentation (97), two thirds are not ambulatory at the time of diagnosis (96,97). Motor deficits at the level of the conus medullaris or above generally have a symmetric distribution. Paraparesis is usually seen in the examiners of the upper extremities or the flexors of the lower extremities, depending on the location of the lesion in the spine. Upper motor neuron signs such as spasticity, hyperreflexia, and Babinski responses, may be present. Cervical lesions may lead to quadriplegia and respiratory collapse (102).

Sensory deficits, reported as varying degrees of paresthesias, are less common than motor deficits but can be found in 40% to 50% of patients. The level of hypesthesia on examination occurs one to five levels below the actual anatomic level of cord compression (96). The sensation of an electric shock radiating through the spine and extremities with neck flexion, termed the Lhermitte’s sign is seen infrequently with cervical or thoracic neoplasms. Perineal paresthesias may occur with cauda equina lesions. Gait ataxia may follow sensory loss impairment, but in the absence of sensory findings, impairment of the spinocerebellar tract should be considered.

Bowel and bladder dysfunction reflects autonomic dysfunction and is a late manifestation of MSCC (103). Patients report urinary incontinence and frequency, and both incontinence of urine, from poor sphincter tone or overflow of urine, and urinary retention may ensue. At the time of diagnosis, 50% of patients are incontinent or catheter-dependent (101). Patients may also exhibit erectile dysfunction and impotence. Constipation and incontinence of stool with diminished sphincter tone may be present (103). Narcotics are widely used in cancer patients and are capable of precipitating urinary retention and constipation; however, spinal lesions must be excluded in these patients before narcotic use is implicated.

### Diagnostic Investigation

The imaging study of choice in evaluating MSCC is magnetic resonance imaging (MRI) because it is a noninvasive test that provides high resolution of the soft tissues, including bone metastases and intramedullary pathology. One study found that MRI had a sensitivity, specificity, and overall accuracy of 93%, 97%, and 93%, respectively, in detecting MSCC in patients with known primary extramedullary tumors (104). It is fundamental to recognize that when the entire spine is imaged beyond the area of clinically determined cord compression, multiple epidural metastases (MEMs) are found in 30% of patients. Because the presence of MEMs may alter treatment strategy, several studies have purported using whole-spine MRI in all patients before initiating dexamethasone (94,104,105). With the relative paucity of cervical spine metastases, if the clinical presentation does not suggest cervical disease, it may be acceptable to image the thoracoabdominal spine alone (106).

Myelography with or without CT myelogram is a more invasive tool than MRI and is used in imaging MSCC when MRI is contraindicated. CT alone does not adequately define the soft tissues and spinal cord, and plain radiographs and radionuclide testing have low sensitivity and specificity for demonstrating MSCC. Plain films detect vertebral metastases at the site of known cord compression only 80% of the time (9,97), and many metastases are missed because the ability to visualize these lesions requires that 30% to 40% of the bone be eroded (107). Bone scintigraphy is the most cost-effective and sensitive technique in imaging vertebral metastases.

### Treatment

The goals of therapy are pain control and preservation of neurologic function to improve quality of life. Narcotic and corticosteroid administrations, XRT, and surgery may all be used.

#### Corticosteroids

In a randomized trial that established the efficacy of corticosteroids in cord compression, patients were assigned to XRT with or without dexamethasone. At the conclusion of the study, 81% of those receiving corticosteroids and XRT versus 63% of those receiving XRT alone remained ambulatory. At 6 months, the percentages were 59% and 49%, respectively (108). With time, radicular pain occurs in the dermatome of known cord compression only 80% of the time (9,97), and many metastases are missed because the ability to visualize these lesions requires that 30% to 40% of the bone be eroded (107).

#### Surgery and Radiation

A recent randomized trial demonstrated that direct decompressive surgery followed by radiotherapy is superior to radiotherapy alone for patients with MSCC. Patients were assigned to either surgery followed by XRT or to XRT alone. The study was stopped early because the primary end point had been satisfied, and a therapeutic advantage of surgery plus XRT was observed: 84% of the surgery group versus 57% of the XRT group were ambulatory after surgery. Additionally, those in the surgery group were ambulatory for 122 days compared to 13 days in the XRT group after treatment. Furthermore, of the patients unable to ambulate on entering the study, 62% of those receiving surgery and radiation versus 19% receiving XRT alone regained the ability to ambulate (110). Therefore, radiotherapy alone should be used for patients who are not surgical candidates. Radiotherapy may also be useful in preserving neurologic function in subclinical MSCC (94). Most tumors causing MSCC are not chemosensitive.
The cardiac pericardium is a fibroserous sac composed of two layers that surround the heart. The outer layer is the fibrous pericardium, which attaches to the diaphragm and securely anchors the heart within the thoracic cavity. The serous pericardium is a single layer of mesothelial cells and its underlying connective tissue, which lines the fibrous pericardium. During embryonic development, the heart invaginates the walls of the serous pericardium, creating a potential space between an inner serous layer that is adherent to the heart (visceral pericardium) and an outer serous layer that lines the fibrous pericardium (parietal pericardium). The pericardial space is formed between the two serous layers, and it normally contains 15 to 50 mL of fluid for lubrication. The fluid is drained from the right pleural space into the right lymphatic duct, and from the parietal pericardium into the thoracic duct (119,120). Any interruption in this flow will result in accumulation of fluid and pericardial effusion. The mechanisms by which malignant disease generates MPEs include direct invasion of the pericardium or myocardium, and disruption of lymphatic flow from lymph node metastases or from prior radiotherapy to the chest or mediastinum (113,117). The parietal pericardium functions as a barrier to the spread of cancer cells. Malignant pericardial effusions may be the initial presentation of cancer, but in any patient, it is important to rule out another cause of pleural effusion, such as infection or heart failure (118). Pericardial effusions in some cancer patients may be attributable to comorbid conditions rather than to malignant disease, and other causes must be considered, such as radiation-induced pericarditis, infection, uremia, myocardial infarction, congestive heart failure, and pneumonia (113).

Pathophysiology

Primary neoplasms of the myocardium and pericardium are uncommon, but metastatic disease to the pericardial space is frequently seen (112). Primary pericardial tumors, of which mesothelioma represents the largest proportion, are 40 times less common than metastatic disease. Secondary malignancies include, most frequently, lung, breast, and ovarian carcinoma, and melanoma, lymphoma, and leukemia (113). Malignancy is a primary cause of pericardial effusion in the United States (114), and pericardial tamponade resulting from malignant pericardial effusion (MPE) represents at least 50% of reported cases of pericardial fluid collection requiring intervention (115,116). Autopsy series have reported, with varying estimates, that MPE is seen in 2% to 22% of cancer patients (47,114,115,117), and that these effusions are clinically quiet, remaining unrecognized (47). In some patients, MPE may be the initial presentation of cancer, but in any patient, it signifies a dismal prognosis, with most patients dying within 1 year (118). Pericardial effusions in some cancer patients may be attributable to comorbid conditions rather than to malignant disease, and other causes must be considered, such as radiation-induced pericarditis, infection, uremia, myocardial infarction, congestive heart failure, and pneumonia (113).

Prognosis

The median survival in MSCC patients receiving XRT is 3 to 6 months (96). Patients who initially present with paralyzable or became paralyzed after treatment have a shorter life expectancy than those who are ambulatory (94). Multiple studies have shown that the ambulatory function on diagnosis of MSCC is the most important predictor of outcome of ambulatory function after irradiation. This finding underscores the need for education of both the clinician and the patient to ensure prompt recognition of MSCC. In one study, delay in diagnosis was attributed to the patient’s failure to identify symptoms and diagnostic delays by the generalist and hospital practitioner, leading to deterioration in motor or bladder function (111).
Electrical alternans in the P wave and QRS complex is a rare finding, noted in 0% to 10% of patients (120), in which every other QRS complex has a lower voltage and/or reversed polarity (121). The echocardiogram precisely localizes the pericardial fluid, discerns the quality of the effusion (homogeneous versus heterogeneous), determines whether loculations or bulky tumor are present, assesses right and left ventricular function, and ascertains whether right atrial and right ventricular diastolic collapse are present. On echocardiography, the heart may be seen to swing in a pendular fashion within the pericardial fluid. Right heart catheterization is the definitive standard for further defining the pericardial effusion. Classically, there will be equalization of diastolic pressures across all cardiac chambers (115).

**Treatment**

Treatment strategy should be individualized to each patient based on age, comorbid conditions, malignancy type, and overall prognosis (118). Cardiac tamponade is a class I indication, as designated by the European Society of Cardiology Task Force, for performing pericardiocentesis, and the initial emergent intervention in malignant cardiac tamponade is to drain the effusion, usually in conjunction with echocardiographic guidance (113). Fluid should be sent for chemical analysis, microbiology, and cytology; the effusion is removed successfully in 97% of patients (123). The guidelines recommend that in the absence of tamponade, systemic chemotherapy be administered as baseline treatment (113), thereby precluding reaccumulation in 67% of cases (123). Systemic chemotherapy is effective in controlling malignant effusions when the tumors are chemosensitive, as in lymphoma, leukemia, and breast cancer. Notably, ERT is highly effective (93%) in controlling malignant pericardial effusions in patients with lymphoma and leukemia, although radiation myocarditis or pericarditis is, in itself, a complication of radiotherapy (113). Pericardiocentesis should be performed in MPCs, especially when these are large, for symptomatic relief and to establish a cause. Because fluid reaccumulates within 88 hours of the initial pericardiocentesis (124), intrapericardial sclerosing or cytostatic agents, selected according to tumor type, should be administered to prevent recurrence. The mechanism of action of sclerosing agents is to effect synphysis of the visceral and parietal pericardia (113). A surgical approach to MPCE management is subxiphoid pericardiectomy to create a pericardial window. An advantage of this technique is that it is performed using local anesthesia and has a low recurrence rate. Additionally, tissue can be obtained for pathologic review. However, there is a small risk of myocardial infarction, pneumothorax, and mortality with this procedure. One study showed a 12% recurrence at 1 year and a 4% reaccumulation rate for subxiphoid pericardiectomy (114). Pleuropericardiodiomy and pericardiectomy, which require general anesthesia, have higher morbidity and mortality rates, and are rarely used in MPCE management (113). Percutaneous balloon pericardiectomy may become the procedure of choice in the future. Requiring only local anesthesia, it facilitates passage of pericardial fluid into the left pleural or peritoneal spaces, which have greater resorptive capacity. The major side effect is asymptomatic pleural effusion in most patients (47,125). Percutaneous balloon pericardiectomy appears to be a safe and effective technique in patients with large MPCEs and recurrent tamponade (90% to 97%) (125,126). Reaccumulation rates with this method are 0% to 6%. Reaccumulation rates for other therapies that are administered after initial pericardiocentesis is performed are radiotherapy, 33%; systemic chemotherapy, 30%; sclerotherapy with tetracycline, 15% to 30%; and mechanical therapies, including indwelling pericardial catheter placement, balloon pericardiectomy, and thoracotomy with pericardiostomy, 0% to 15% (47).

Even if there is no reaccumulation of fluid, cardiac function may remain impaired in the presence of epicardial inflammation by tumor. Diastolic dysfunction occurs because of the constriction effect of a diseased epicardium surrounding the heart. Effusive-constrictive pericarditis results in a combination of tamponade and cardiac restriction. This entity must be considered in the differential diagnosis when a patient develops hemodynamic collapse a few days after pericardiocentesis. Pericardectomy may be useful in alleviating the constrictive component; irrespective of this procedure, mortality is extremely high (47,127,128).

**Prognosis**

Survival after the development of a malignant pericardial effusion is extremely poor (124,128). The pericardial lesions either contribute to or directly cause death in 86% of untreated patients with symptomatic MPCE (128). In one series of 275 patients with MPCE, the median survival was 135 days, and the chance of surviving the first year was 26%. The findings of male gender, lung cancer, positive fluid cytology for malignant cells, and the clinical presentation of cardiac tamponade or hemodynamic collapse were independently associated with poor survival (124). In another series, which concluded that a poor prognosis was associated with positive fluid cytology, median survival was 7.3 weeks versus 29.7 weeks in the positive cytology and negative cytology groups, respectively. MPCE and abnormal cytology were found to be independent predictors of death (129). Taken together, these prognostic factors can be used to make practical and realistic treatment decisions.

**GASTROINTESTINAL EMERGENCIES**

**Neutropenic Enterocolitis**

Neutropenic enterocolitis (NE) is also known as necrotizing enteropathy, ileoscecal syndrome, or typhlitis (130), from the Greek derivation of the word “typhlon,” or cecum (131). Necrotizing enteropathy was first described in adult patients with leukemia and lymphoma more than four decades ago (132), and typhlitis was recognized as an equivalent entity involving the cecum in children undergoing induction therapy for acute leukemia in 1970 (133). The disorder is a life-threatening inflammatory syndrome in the immunocompromised patient that involves the terminal ileum, ascending colon, and cecum (134). Because the disease affects both the small and large bowel, the term, neutropenic enterocolitis, is most commonly used (135). The cardinal features that define the syndrome are fever, abdominal pain, and bowel wall thickening in a patient with neutropenia (134,136), where neutropenia is defined as...
Neutropenic enterocolitis (NE) occurs primarily in patients following aggressive cytotoxic therapy for acute leukemia (134,139) and other hematologic malignancies such as lymphoma (134,136), chronic leukemia (134), multiple myeloma (134–136), and rarely in solid tumors, such as colon, breast, testicular, lung (130,140), and pancreatic cancer (140). In leukemia, administration of drugs toxic to the bowel mucosa, such as cytosine arabinoside (141), which cause cellular atypia to frank ulceration, increases the risk of NE (140). Other agents include cytarabine, cisplatin, fluorouracil, vincristine, doxorubicin, 5-fluorouracil, thioguanine, and mercaptopurine (141). NE is rare in solid tumors, but there are case reports identifying the syndrome in breast cancer patients receiving taxanes (142–144). Interestingly, there are also case reports of acute leukemia patients presenting with NE in the absence of chemotherapy (136), indicating that drug toxicity is a predisposing factor rather than a prerequisite in the disease pathogenesis (136). Other immunocompromised patients in whom NE occurs include cases of aplastic anemia (134,136,139,145), cyclic neutropenia (146,147), agranulocytosis (148), Felty syndrome, thalassemia minor, systemic lupus erythematosus (134), and HIV disease (134,149). Patients receiving immunosuppressive therapy for bone marrow (150) or renal transplantation (151) are also at risk.

The incidence of NE in adults varies widely in the literature, ranging from 0.3% to 26%. In a recent systematic review, the pooled incidence rate for adults hospitalized for treatment of hematologic malignancies and solid tumors and for aplastic anemia was 5.3%. The incidence of NE in the acute leukemia group receiving myelosuppressive therapy, with the exclusion of transplant patients, was 5.6%. Extrapolating from these findings, the authors concluded that neutropenia rather than acute leukemia is the primary risk factor for NE (134). In another study, 88 (6%) of 1,450 consecutive patients treated for leukemia had clinical manifestations of NE (152). Although the incidence may be low, it is the high mortality rate associated with NE that underscores its designation as an oncologic emergency. Initial studies reported mortality rates ranging from 50% to 100% (153). The above systematic review stated that several authors observed a rate of 50% or higher, with other published figures ranging between 40% and 50% (154).

Pathogenesis

NE has a predilection for the terminal ileum, cecum, and appendix (154). One factor that may explain this predisposition is the overall decreased blood supply to the colon (136). Also, inherent to the cecum is decreased vascularity and increased distensibility compared to other colonic segments (140,142), and progressive distention in the cecum may cause increasing intraluminal pressure and exacerbation of submucosal edema (140). The pathogenesis of NE is multifactorial and remains unclear (130,136). Drug-induced cytotoxic mucosal injury (130,131,140) initiates the process by limiting cellular proliferation and generating glandular epithelial atypia and necrosis (cytotoxic arabinoside), and by producing myenteric plexus degeneration (vincristine) (140). Subsequently, mucosal barrier integrity is breached because cells cannot rapidly regenerate to replace damaged superficial epithelial cells. Once mucosal damage develops, bacterial translocation occurs, resulting in microbial infection and sepsis (130,140). Marked neutropenia impairs host defense and promotes further microbial invasion; bowel flora becomes altered (136). Blood cultures are often positive for Clostridium septicum, C. difficile, Escherichia coli, Pseudomonas, Klebsiella, Enterobacter, and Staphylococcus (135,140). Candidiasis, primarily Candida albicans, which colonizes mucosal surfaces, is the most common fungal infection in neutropenic patients and is associated with a high morbidity and mortality (155). These microbial infections lead to inflammation and edema. With sustained profound neutropenia, bacterial invasion is unconstrained, resulting in transmural necrosis, hemorrhage, ulceration, and perforation (135,136,140,156). In addition to drug-induced mucosal injury, infiltration of mucosa with leukemic and lymphoproliferative cells and mucosal ischemia from sepsis-related hypotension may also participate in initiating and perpetuating mucosal injury (140,154).

Symptoms

The onset of NE is 7 to 10 days after treatment when neutropenia is evident. The clinical presentation includes fever, occurring in 90% of all hospitalized neutropenic patients at any time (140), nausea and vomiting, abdominal pain, and watery or bloody diarrhea. Physical examination may reveal stomatitis with diffuse mucositis, abdominal distention, abdominal dis- tenion, and peritoneal signs suggestive of bowel perforation (140,141,157). In 60% to 80% of patients, right lower quadrant (RLQ) tenderness is elicited. Palpation of a mass in the RLQ usually indicates a thickened, dilated, fluid-filled cecum (140).

Differential Diagnosis

Neutropenic enterocolitis must be included in the differential diagnosis whenever a neutropenic patient presents with fever and abdominal pain, particularly RLQ pain. Other entities that may mimic NE are pseudomembranous colitis, acute appendicitis, acute cholecystitis, acute pancreatitis (152), diverticulitis (158), ischemic colitis, Ogilvie’s syndrome (colonic pseudo-obstruction) (159), chemotherapy-induced abdominal pain (130), and ileus secondary to vincristine toxicity (152). Gastrointestinal bleeding may occur in 35% of typhlitis cases, and hemorrhage should suggest NE rather than appendicitis (157).

Diagnostic Investigation

On laboratory analysis, in addition to neutropenia, thrombocytope尼亚 may be seen. Blood cultures are positive in 50% to 82% of cases for bowel organisms as described above (135). Stool studies may be notable for absence of C. difficile toxin A because C. difficile is not the primary pathogens in NE (134,142).

Plain radiographs of the abdomen are usually normal or nonspecific. Findings may include a decrease in right lower quadrant gas with dilated small bowel loops and air fluid levels.
consistent with a distal bowel obstruction. Free intraperitoneal air after perforation, pneumatosis colii, or localized or diffuse “thumb-printing” characteristic of mucosal edema may be exhibited (130,140).

Sonography assists in confirming the diagnosis of NE and in excluding other differential diagnoses by detecting bowel wall thickening. Additionally, ultrasound is useful in following the clinical course of the disease (136,152). Sonographic manifestations of NE include a rounded mass with dense central echoes and a wider hyperechoic periphery (130), pseudopolyloid changes of the Cecal mucosa, and pericolonic fluid collections (140). One study of neutropenic enterocolitis demonstrated that patients with sonographically detected bowel wall thickness of greater than 10 mm had a significantly higher mortality rate (60%) than did those with bowel wall thickness less than or equal to 10 mm (4.2%) (152).

Computed tomography is a more accurate modality for assessing cecal wall thickening and evaluating the extent of the colitis (130,136). It also has utility in differentiating NE from appendicitis, appendical abscess, or pseudomembranous colitis (159). CT findings include diffuse submucosal thickening and edema of the terminal ileum and ascending colon, mural hemorrhage, pericolonic fluid collections, abscess formation, pneumatosis colii, and intraperitoneal free air (136). The false-negative rates in identifying NE for CT, ultrasound, and plain radiographs are 15%, 23%, and 48%, respectively (139).

Barium enema is unsafe because it may result in bowel perforation in the presence of severely damaged, necrotic bowel (131,160). Endoscopic evaluation is generally avoided because it involves a high risk of perforation in addition to hemorrhagic and infectious complications, whose fevers may precipitate fulminating mural necrosis (130). Colonoscopy has been performed in a paucity of patients and will reveal irregular nodular mucosa, ulcerations, hemorrhagic friability, and a maslike lesion resembling carcinoma (131).

Histopathology

With the difficulty of obtaining biopsy specimens, a tissue diagnosis is not required to confirm NE. On gross examination, striking bowel wall thickening is evident. Scattered serosal echymoses give the bowel a dusky appearance. Microscopy demonstrates pronounced transmural submucosal edema, vasculitis, stromal hemorrhage, and patchy or complete epithelial necrosis, resulting in mucosal ulceration and pseudomembrane formation. With further damage, transmural necrosis leads to muscularis propria degeneration. Vascular injury affects intramural and intraluminal hemorrhage, and fibrin thrombi may be seen in the submucosal vessels. Polymicrobial infiltration with bacteria and fungi is observed in 53% of postmortem cases (134). Very few inflammatory cells are observed, and rarely, leukemic or lymphoproliferative infiltrates invade the bowel wall. Neutrophils are absent, and anaeutrophilia in the setting of marked cell injury is pathognomonic for NE (134,154).

Management

Prospective trials or case control studies evaluating therapeutic interventions in NE are lacking (134). Management strategy remains controversial regarding the decision to proceed with early surgical intervention versus a conservative approach (161). Conservative management of NE involves bowel rest, intravenous fluid and blood product resuscitation, broad-spectrum antibiotics, granulocyte colony-stimulating factor (G-CSF), and frequently, parenteral nutrition (130,141). Use of omeprazole and gastric decompression is not advocated by some authors because these interventions facilitate bacterial migration from the bowel into the respiratory tract, predisposing the patient to pneumonia (134). Medications that inhibit bowel motility, such as antiadhesive and narcotic agents should be avoided since they perpetuate ileus and promote bacterial overgrowth (141). Patients with chemotherapy-induced NE may suffer from repeated episodes with future treatment; therefore, further chemotherapy should be withheld until NE has completely resolved. Bowel decontamination may be helpful before subsequent chemotherapy, although this is not well-studied (131).

Selection of broad-spectrum antibiotics should incorporate the Infectious Diseases Society of America (ISDA) 2002 recommendations for febrile neutropenia (137) as well as the 2003 ISDA guidelines for complicated intra-abdominal infections (162). Without prompt antibiotic therapy, neutropenic patients with Gram-negative bacteremia have a mortality rate approaching 40% (163). The antibiotic(s) of choice in NE must demonstrate activity against both Gram-negative and anaerobic organisms. Options include the following: monotherapy with a carbapenem or piperacillin-tazobactam; duotherapy with another antipseudomonal beta-lactam plus an aminoglyco- side; or duotherapy with cefepime or ceftazidime plus metronidazole (134,141,162). Antifungal therapy with amphotericin B therapy should be considered for empiric therapy in those with unexplained fever. The Infectious Diseases Society of America (ISDA) 2002 recommend monotherapy with another antipseudomonal beta-lactam plus an aminoglycoside for patients with Gram-negative bacteremia who have a high risk for infection-associated complications and poor prognostic factors. Without prompt antibiotic therapy, neutropenic patients with Gram-negative bacteremia have a mortality rate approaching 40% (163). The antibiotic(s) of choice in NE must demonstrate activity against both Gram-negative and anaerobic organisms. Options include the following: monotherapy with a carbapenem or piperacillin-tazobactam; duotherapy with another antipseudomonal beta-lactam plus an aminoglycoside; or duotherapy with cefepime or ceftazidime plus metronidazole (134,141,162). Antifungal therapy with amphotericin B therapy should be considered for empiric therapy in those with unexplained fever (134,141,162). Without prompt antibiotic therapy, neutropenic patients with Gram-negative bacteremia have a mortality rate approaching 40% (163). The antibiotic(s) of choice in NE must demonstrate activity against both Gram-negative and anaerobic organisms. Options include the following: monotherapy with a carbapenem or piperacillin-tazobactam; duotherapy with another antipseudomonal beta-lactam plus an aminoglycoside; or duotherapy with cefepime or ceftazidime plus metronidazole (134,141,162). Antifungal therapy with amphotericin B therapy should be considered for empiric therapy in those with unexplained fever (134,141,162).

Granulocyte colony-stimulating factor (G-CSF) increases cell division in myeloid precursor cells, decreases bone marrow transit time, and modulates activity and function of developing and mature neutrophils (156). The current American Society of Clinical Oncology (ASCO) guidelines recommend G-CSF administration in febrile neutropenic patients with a high risk for infection-associated complications and poor prognostic factors, such as profound neutropenia (less than 100 cells/μL), sepsis, pneumonia, hypotension, invasive fungal infection, and uncontrolled primary disease (164). NE undeniably meets these criteria. G-CSF administration in chemotherapy-related febrile neutropenia reduces hospitalization time and time to neutrophil recovery, and may have an impact on infection-related mortality that warrants further study (163). Clinical improvement in NE patients is usually seen after normalization of the neutrophil count with discontinuation of chemotherapy. It has been observed that symptoms commence as the white blood cell count (WBC) declines after chemotherapy, and recovery begins after the nadir when the WBC is increasing (130).

There are no standard recommendations, but rather, general guidelines in the literature regarding surgical intervention in NE; however, most patients are unlikely to be surgical candidates. Early reports recommended aggressive and early surgical resection of involved bowel, anticipating that in the natural history of NE, bowel perforation is inevitable (134). Recent series demonstrate successful nonsurgical management (134,161,166). More recent publications support surgery with laparotomy alone for patients with perforation and ileus (134). Some advocate that patients who fail to improve or develop bowel perforation and peritonitis after 2 or 3 days of
TOXICITY OF CHEMOTHERAPY

Most antineoplastic agents exert their therapeutic actions by targeting rapidly proliferating malignant cells. Because these agents interrupt fundamental cellular processes such as DNA, RNA, and protein synthesis, they are not completely specific to malignant cells and will also act on normal tissues, causing multiple toxicities. Rapidly regenerating cells, such as the hematopoietic lineage, gastrointestinal mucosa, spermatogenesis, and hair follicles may suffer transient toxicity compared to cells that have limited regenerative capacity, including those of the myocardium, and nerves (169–171). This section focuses on the major life-threatening toxicities that occur with commonly used chemotherapeutic agents.

Pulmonary Toxicities

Pulmonary toxicity, both acute and chronic, is seen increasingly with numerous antineoplastic agents (172). Chemotherapy-induced lung disease (CLD) describes lung injury with multiple etiologic agents and varying pathophysiologic mechanisms. These major mechanisms include direct lung toxicity, immunologic response, and increased capillary permeability. The corresponding clinical presentations are interstitial pneumonitis/fibrosis, hypersensitivity syndrome, and capillary leak syndrome, respectively, and each may eventuate in fulminant respiratory failure. Symptoms can appear immediately or months after termination of therapy (173).

Antitumor Antibiotics

Bleomycin. Bleomycin is an antitumor antibiotic used in the treatment of lymphoma, germ cell tumors, cervical carcinoma, and head and neck squamous cell carcinoma. The absence of bleomycin hydrolyase in the skin and lungs prevents deactivation of the drug, accounting for its selective toxicity. Bleomycin interstitial pneumonitis is the most ominous toxicity, associated with a 3% mortality rate (174) and occurring in 0% to 46% of patients receiving bleomycin-containing regimens, either during treatment or up to 6 months after discontinuation (175). Toxicity is mediated by the mechanism of direct lung injury via generation of cytokines and free radicals, the sequelae of which are endothelial damage, inflammatory cell infiltration, fibroblast activation, and fibrosis (173,175). There is conflicting evidence in the literature as to whether peroperative oxygen supplementation exceeding a concentration of 24% fractional inspired oxygen causes synergistic toxicity with bleomycin through the production of free radicals (176,177).

Mitomycin C. This is an antibiotic used in treating solid tumors, primarily breast and lung carcinomas. The mechanism of injury is alkylation of endothelial cell DNA, precluding cell division. This agent is associated with the development of an interstitial pneumonitis/fibrosis (178,179), usually 3 to 12 months after therapy (179,180), with a 3% to 14% incidence. Mortality is as high as 14% to 50% (178,179,181). Risk factors include oxygen exposure, prior irradiation, and other cytotoxic drug administration, such as bleomycin, cisplatin, the vinca alkaloids, cyclophosphamide, and doxorubicin. Drug withdrawal, steroids, and avoidance of supplemental oxygen may be helpful (180).

Mitomycin–vinca alkaloid syndrome is a unique entity occurring with a 6% incidence after the vinca alkaloid is administered to patients receiving combination therapy with mitomycin and vinblastine but not with the vinca alkaloid alone. Severe hypoxemia ensues with development of interstitial infiltrates on chest radiograph. Most patients show acute improvement within 24 hours with oxygen, diuretics, and occasionally, mechanical ventilation, although chronic lung damage occurred in 60% of patients in one study (178).

Alkylating Agents

Carmustine (BCNU). This is a nitrosourea used in the management of central nervous system tumors and in induction therapy for bone marrow transplantation (BMT). Its cytotoxicity is mediated by alkylation of guanine in DNA (172). Cancer causes dose-dependent pulmonary fibrosis and carries the highest incidence of fibrosis among the nitrosoureas. The mortality rate ranges from 24% to as high as 90% in some reports (180,181). In 1% and 30% of the patients receiving high- and low-dose carmustine, respectively, early-onset fibrosis and alveolitis will occur. In up to 40% of the patients undergoing induction for BMT, pulmonary fibrosis will develop within 2 years. Late fibrosis can be observed up to 17 years after exposure. Concomitant radiotherapy, chronic obstructive pulmonary disease (COPD), and pneumoconioses increase the risk of carcinomatous toxicity. Sixty percent of patients will respond dramatically to steroids (180).

Microtubule-targeting Agents

Taxanes. Paclitaxel inhibits microtubule disassembly (182), and has activity against solid tumors such as non-small cell lung carcinoma, breast carcinoma, and ovarian carcinoma (173); it is prepared in Cremophor, a castor oil-based solution (173,182). A type I hypersensitivity reaction, characterized by urticaria, bronchospasm, angioedema, and hypotension, occurs within 2 to 10 minutes of infusion of paclitaxel (182,183) with a 3% to 10% incidence (180), and is attributable to the Cremophor vehicle rather than paclitaxel itself (173). Premedication with steroids and H1 and H2 blockers can curtail this reaction (182).

Antimetabolites

Cytosine Arabinoside. Ara-C is a substituted nucleoside antimetabolite that disrupts DNA replication and is used in the
therapy of leukemia and non-Hodgkin's lymphoma. One of its toxicities is the abrupt onset of endothelial inflammation and capillary leak syndrome (173), causing noncardiogenic pulmonary edema, acute dyspnea, and a diffuse interstitial and alveolar pattern. Management is supportive and includes oxygen, diuretics, and mechanical ventilation when needed (180).

Gemcitabine. This is a pyrimidine analogue, structurally similar to ara-C (183), that has activity against tumors of the pancreas, lung (NSCLC), breast, and ovaries. Recent large series report an incidence of lung toxicity of less than 1% to 1.4% (184). The proposed mechanism of injury involves pulmonary endothelial cell damage resulting in capillary leak syndrome (173,183). The symptoms of gemcitabine pulmonary toxicity range from mild dyspnea to a fatal acute respiratory distress syndrome. Increasing age, pulmonary neoplasm, and prior radiotherapy may be contributing risk factors (173,185). Patients respond rapidly to corticosteroids (173), but fatalities do occur (173,181,183,185,186).

Differentiation Agents

All-trans-Retinoic Acid. ATRA is a differentiation agent used for the treatment of acute promyelocytic leukemia (APL). It is associated with retinoic acid syndrome, developing in 20% to 50% of APL patients receiving ATRA (187) a median of 7 days (range 0–35 days) after induction therapy (188). The clinical presentation includes fluid retention, weight gain, fever, and musculoskeletal pain, with progression to respiratory distress, pulmonary infiltrates, pleural (187) and pericardial effusions (180), renal insufficiency, skin infiltrates, hypotension, and death (187). Corticosteroids are highly effective when the syndrome commences but have limited utility once pulmonary symptoms are apparent. The putative mechanism of the pulmonary toxicity of ATRA is a capillary leak syndrome (180).

Monoclonal Antibodies

Trastuzumab. This is a humanized monoclonal antibody that targets the epidermal growth factor type 2 (HER2) receptor (189). In approximately 25% of breast cancers, the HER2 receptor is overexpressed (183) and is associated with a poor prognosis (190), a finding that provides the rationale for use of trastuzumab in HER2 receptor-positive metastatic breast cancer. A retrospective analysis of 25,000 patients identified bronchospasm as the only manifestation of pulmonary toxicity. Nine cases (0.04%) attributable to trastuzumab infusion were fatal; most serious reactions commenced within 2 hours of infusion, and most fatalities were observed in patients with poor performance status and severe underlying pulmonary disease (191).

Bevacizumab. This is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) that inhibits binding of VEGF to its receptors, hence impairing angiogenesis. The drug is approved for first-line treatment of advanced colorectal cancer in combination therapy (183). In a phase II randomized trial of 99 patients with advanced or recurrent NSCLC, the incidence of hematopoiesis in patients with NSCLC was demonstrably higher in patients treated with bevacizumab, carboplatin, and paclitaxel (20%) than in those treated with carboplatin and paclitaxel alone (6%). Four patients in the bevacizumab group had severe hemoptysis, which occurred with an incidence of 9.1% and was associated with squamous cell pathology, tumor necrosis and cavitation, and centrally located tumors in close proximity to major blood vessels (192). A recent study excluded patients with pre-existing hemoptysis and squamous cell pathology based on the premise that squamous carcinomas, as a consequence of their location and ability to cavitate, are more prone to bleeding. With these exclusions, a 1.9% incidence of life-threatening hemorrhage with bevacizumab was observed (193).

Alemtuzumab. This is a monoclonal antibody to the lymphocyte and monocyte cell surface antigen CD52 and is used as a salvage therapy for chronic lymphocytic leukemia (194). In a series of 16 patients with B-cell chronic lymphocytic leukemia (B-CLL), the associated pulmonary toxicity in one patient was severe bronchospasm that responded to corticosteroids (195).

Chapter 174: Oncologic Emergencies

Cardiac Toxicities

Antitumor Antibiotics

Anthracyclines. These are red-pigmented antibiotics (rhodomycins), which include doxorubicin, daunorubicin, idarubicin, and epirubicin (196). They are active against a broad spectrum of tumors, such as breast and esophageal carcinomas, Hodgkin’s and non-Hodgkin’s lymphomas, osteosarcomas, Kaposi’s sarcoma, and soft-tissue sarcomas. Three mechanisms that lead to oxidative stress (197) contribute to the cardiac toxicity of these agents: mitochondrial dysfunction and consequent adenosine triphosphate depletion; free radical lipid peroxidation by iron–doxorubicin complexes; and glutathione peroxidase depletion (196). Histopathology demonstrates myofibril dropout, vacuolization of myocardial cells, and sudden death. The cardiomyopathy is dose dependent, and is classified as subacute and late. Subacute cardiomyopathy presents within 8 months of therapy, with a peak onset of 3 months, whereas late cardiomyopathy is observed after 5 or more years. A continual decline in left ventricular function results in congestive heart failure (CHF) (196); liposomal doxorubicin may play a role in reducing cardiotoxicity (199). Dexrazoxane, an iron chelator with cardioprotective properties, has been demonstrated to substantially reduce toxicity (197,200). Toxic effects may be compounded by other therapies, including trastuzumab, cyclophosphamide, dacarbazine, mithramycin, mitomycin, etoposide, melphalan vincristine, bleomycin, daicarbazine (196), and taxanes (201,202).

Mitoxantrone. This agent has structural similarity to the anthracyclines, and is used in managing metastatic breast cancer, acute myeloid leukemia, and non-Hodgkin’s lymphoma (202). The mechanism of cardiac injury, like that of the anthracyclines, may involve iron chelation complexes (203); arrhythmias and dose-dependent heart failure are toxicities. The incidence of a moderate to severe decrease in left ventricular ejection fraction (LVEF) and of CHF is 13% and 2.6%, respectively, with a cumulative dose of less than or equal to 140 mg/m². Doses below 110 mg/m² decrease the incidence of heart failure, whereas incidence increases with doses greater than 160 mg/m² (196).
Mitomycin C. In addition to its lung toxicity, mitomycin is cardiotoxic, resulting in an increased incidence of cardiac failure with cumulative doses exceeding 30 mg/m² (196,204). Additive cardiotoxicity occurs when mitomycin is used in conjunction with anthracyclines (204); supratherapeutic free radicals may mediate this toxicity (196).

Alkylating Agents

Cyclophosphamide. This agent is a nitrosourea mustard alkylating agent effective in treating leukemia, lymphoma, multiple myeloma, mycosis fungoides, neuroblastoma, and ovarian cancer. Acute cardiotoxicity may develop with doses of 120 mg/kg to 170 mg/kg given over 1 to 7 days in preparation for bone marrow transplantation. Electrocardiogram may reveal decreased QRS amplitude, nonspecific T-wave abnormalities, poor R-wave progression, supraventricular and ventricular tachyahrrhythmias, and second-degree atrioventricular block (203). Acute fulminant CHF may occur in up to 28% of patients treated with high-dose cyclophosphamide (196), but CHF is usually short lived and reversible (203). The drug is metabolized to its active form in the liver by the cytochrome P-450, and more rapid metabolism amplifies the risk of CHF (205). Another cyclophosphamide-related cardiotoxicity is hemorrhagic myocarditis, putatively mediated by endothelial capillary injury, which results in pericardial effusion, tamponade, and death; most effusions are treatable with corticosteroids and analgesics. When the purine analogue pentostatin (198) is used in bone marrow conditioning regimens in combination with cyclophosphamide, there is an increased incidence of fatal cardiac toxicity (196) that includes myocardial infarction, CHF, and arrhythmias (198). There may be an additive effect of cyclophosphamide and anthracycline-induced cardiomyopathy, but the data are conflicting (196).

Ifosphamide. This is an alkylating agent, with similar properties to cyclophosphamide, used to treat lymphoma, leukemia, and testicular and bladder tumors. Arhythmias and transient, reversible, dose-dependent CHF—as with cyclophosphamide—may be seen (203,206).

Cisplatin. This agent cross-links interstrand DNA. It is used in treating cancers of the testes, bladder, ovaries, and other tumors. Bradycardia, supraventricular tachycardia (196), acute ischemia (207), myocardial infarction, and ischemic cardiomyopathy may be observed (196). Acute chest pain and palpitations may be associated with cisplatin infusion. Late complications can occur 10 to 20 years after therapy. Hypokalemia and hypokalemia generated by cisplatin-induced tubular defects (196) may exacerbate arrhythmias (198).

Microtubule-targeting Agents

Vinca Alkaloids. Vinca alkaloids include vincristine and vinblastine, which are used for management of hematologic malignancies and solid tumors, and vinorelbine, a semisynthetic derivative used in NSCLC therapy. These agents exert their toxicity by inhibiting microtubule assembly, and all possess vasoconstrictive properties. Hypertension, vasoepathic myocardial ischemia, and myocardial infarction may be seen (198). Vinorelbine toxicity is more common in women than men (208).

Taxanes. (See also Pulmonary Toxicities, above.) Hypertension (196) and cardiac arrhythmias, most commonly transient asymptomatic bradycardia (182), are observed with paclitaxel. In a large series, the incidence of more significant bradycardia—Mobitz type I and II heart block and complete heart block—was 0.1% (209). Rarely, atrial and ventricular tachycardias, myocardial ischemia, and myocardial infarction occur, often in patients with underlying cardiac disease or electrolyte derangements (196). Docetaxel may lead to the potentiation of anthracycline cardiomyopathy (202).

Antimetabolites

5-Fluorouracil and Capecitabine. 5-Fluorouracil (5-FU) is a synthetic pyrimidine antimetabolite used in regimens for managing multiple solid tumors including gastrointestinal, breast, ovarian, and head and neck malignancies. Myocardial ischemia, possibly triggered by coronary vasospasm, is a well-known cardiac toxicity that occurs with increased frequency in combination with cisplatin. In one study, silent ischemic ECG changes were identified during 24 hours of observation in up to 65% of patients receiving a continuous 5-FU infusion (210). Other cardiac manifestations include chest pain, angina, atrial and ventricular arrhythmias, myocardial infarction, persistent ventricular dysfunction, sudden death, and cardiogenic shock (196,203) requiring inotropic support (196). Pre-existing cardiac morbidity significantly increases the risk of cardiotoxicity compared to no prior cardiac disease (15.1% vs. 1.5%) (203). Given the potential for severe cardiotoxicity, infusions should be terminated when chest pain occurs. The oral equivalent of infused 5-FU is capecitabine, which exhibits a similar cardiotoxicity profile to 5-FU (211).

Topoisomerase Inhibitors

Etoposide. This agent is a topoisomerase II inhibitor used primarily for treatment of refractory testicular tumors and small cell lung carcinoma. Hypotension is the most common side effect (198). Myocardial infarction (198,212) and vasospastic angina (196) may also occur. Prior chemotherapy or mediastinal irradiation may increase the risk of myocardial infarction after etoposide therapy (196).

Biologic Response Modifiers

Interferons. These are glycoprotein biologic response modifiers classified according to their respective derivations: interferon-alfa (leukocytes), interferon-beta (fibroblasts), and interferon-gamma (lymphocytes) (196). They are used to treat various tumors including renal cell carcinoma, metastatic melanoma, multiple myeloma, Kaposi sarcoma, and some leukemias and lymphomas. Cardiovascular toxicities include hypertension or hypotension (198), ischemia in patients with coronary artery disease, myocardial infarction, arrhythmias (20% incidence) (213), sudden death, and cardiomyopathy characterized by resolution with termination of the infusion (214).

Interleukin-2 (IL-2). This is a glycoprotein biologic response modifier derived from helper T-lymphocytes, and is approved for the treatment of metastatic renal cell cancer. Most patients develop capillary leak syndrome and hypertension associated with decreased peripheral vascular resistance necessitating vasopressors (196). In a study of 423 treatment courses with IL-2, 65% required pressor support for hypotension (215). In patients with coronary artery disease, direct myocardial toxicity precipitates ischemia, myocardial infarction, arrhythmias, and...
death. IL-2 may also predispose patients to ventricular and supraventricular arrhythmias, which are seen in 14% to 21% of patients (196).

**Differentiation Agents**

**All-trans-Retinoic Acid.** (See also Pulmonary Toxicities.) Pericardial effusions, cardiac tamponade, myocardial ischemia (196), fatal infarction, and thrombosis (198), in addition to pulmonary toxicity, may occur with the retinoic acid syndrome as described above (196).

**Arsenic Trioxide.** Arsenic trioxide is a differentiation agent effective in treating relapsed acute promyelocytic leukemia. Like all-trans-retinoic acid, it may also cause the retinoic acid syndrome. Prolongation of the QT interval is another complication seen in up to 63% of patients, leading to torsades de pointes (196) and sudden death. The degree of QT prolongation is higher in the presence of hypokalemia (216); therefore, careful monitoring of electrolytes and maintaining levels in the high normal range is prudent.

**Monoclonal Antibodies**

**Trastuzumab.** (See also Pulmonary Toxicities.) There is an increased risk of cardiotoxicity associated with trastuzumab, which is highest in patients receiving concurrent anthracycline plus cyclophosphamide (227%) compared to concomitant trastuzumab and paclitaxel (13%) or trastuzumab alone (3%–7%) (217). The mechanism of cardiac toxicity of trastuzumab is not well understood, but cardiac erbB2 is essential for myocyte function, and trastuzumab targets both HER2 and erbB2 receptors (203,218). Early following initial treatment, there may be an asymptomatic decline in LVEF with late progression to dilated cardiomyopathy (203). Risk factors for cardiovascular toxicity include older age, cumulative doxorubicin dosage increased to 0.4% over 5 years and 1.4% to 1.7% over 5 years, compared to those receiving tamoxifen, the incidence is increased risk of VTE with tamoxifen. The following data are from a study of patients receiving estramustine, venous thrombosis (VTE) associated with thalidomide, occurring at a mean of 2 months of therapy (227). Lower extremity deep venous thrombosis (DVT) is the most frequent thrombotic complication occurring with thalidomide treatment, and approximately 50% of these patients will develop PE. The mechanism of thalidomide-induced DVT is not well defined. Thalidomide may exert a direct effect on endothelial cells that have been injured by other chemotherapy agents such as doxorubicin (226). In one study, VTE rates with thalidomide monotherapy, thalidomide–dexamethasone–doxorubicin, and thalidomide–dexamethasone–doxorubicin were less than 5%, 9%, 12%, and 22%, respectively (228). These findings suggest a role for VTE prophylaxis, and further investigation is warranted.

**Hormones**

**Estramustine.** Estramustine phosphate has hormonal properties because it contains nor-nitrogen mustard linked to 17 beta-estradiol. It is used in the treatment of prostate cancer. In up to 10% of patients receiving estramustine, venous thrombosis, pulmonary emboli, and myocardial and cerebrovascular ischemia may occur (196).

**Tamoxifen and Aromatase Inhibitors.** Tamoxifen and the aromatase inhibitors—anastrozole, letrozole, and exemestane—are used as adjuvant therapy for early-stage estrogen receptor-positive breast carcinoma (229). It is well known that there is an increased risk of VTE with tamoxifen. The following data clearly quantifies the risk: the incidence of VTE in the general population is 0.12% per year and 0.09% per year in women. In women with early-stage breast cancer and no adjuvant treatment, compared to those receiving tamoxifen, the incidence increases to 0.4% over 5 years and 1.4% to 1.7% over 5 years,
respectively. This incidence escalates to 10.8% over 5 years in the same population of women who receive concurrent tamoxifen and chemotherapy. Aromatase inhibitors (AI) are generally associated with a lower risk of VTE than tamoxifen. In the ATAC trial (Arimidex, Tamoxifen, Alone, or in Combination) at 5 years, the incidence of VTE with anastrozole was 1.6% versus 2.4% with tamoxifen (230).

### Gastrointestinal Toxicities

**Bevacizumab**

This agent is associated with both bowel perforation and gastrointestinal hemorrhage. In a randomized controlled trial in patients with metastatic colon cancer, subjects received either irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, or IFL alone. Gastrointestinal perforation was observed in six patients (1.5%) treated with IFL plus bevacizumab with one fatality compared to no patients in the control group (231). A more recent phase II trial adding bevacizumab to bolus 5-FU and leucovorin reported bowel perforation in 2% of cases (223). In a phase II trial of bevacizumab in combination with fluorouracil and leucovorin in advanced refractory colorectal cancer, severe to life-threatening gastrointestinal hemorrhage (grades 3 and 4) was seen in 3.8% of patients (232).

### Genitourinary Toxicities

**Cyclophosphamide and Ifosfamide**

Cyclophosphamide and ifosfamide induce an early (within 72 hours of administration) hemorrhagic cystitis via their metabolite acrolein, that causes denudation of the bladder mucosa and bleeding (233,234). In the past, early hemorrhagic cystitis was observed in over 40% of bone marrow transplants, but that rate has dramatically declined to 5% with aggressive hydration regimens and administration of the thiol mesna. Mesna is a type of thiol that inactivates acrolein in the bladder after itself being converted to the active form in the kidney. It must be administered prior to cyclophosphamide infusion and continued after the infusion is terminated consequent to its shorter half-life. Acrolein irritation and cystoscopy with clot extraction and fulguration may be necessary to intractable or profuse bleeding, bladder irrigation and cystoscopy with clot extraction and fulguration may be necessary to treat. Late occurring hemorrhagic cystitis commences 72 hours after administration of preparatory regimens in bone marrow transplantation, with risk factors including viral infections, busulfan use, pelvic irradiation, older age at transplantation, allogenic transplantation, and graft versus host disease (235).

### Mitomycin C

Mitomycin C has been discussed with reference to its pulmonary and cardiac toxicities. Another life-threatening manifestation associated with mitomycin C is the thrombocytopenic purpura-hemolytic uremic syndrome (TPP-HUS). This entity is a distinct multiorgan disorder distinguished by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and tissue ischemia precipitated by platelet agglutination in the arterial microvasculature (236). The classic pentad—fever, thrombocytopenia, MAHA, renal failure, and neurologic dysfunction—is no longer required to make the diagnosis. Instead, the new definition encompasses a broad spectrum of conditions in which unexplained thrombocytopenia and MAHA are present (237). Of the chemotherapeutic agents associated with TTP-HUS, mitomycin is the most common, but bleomycin, cisplatin, and gemcitabine are also causes of the syndrome (238). The pathogenic mechanism of mitomycin C-induced TTP-HUS may involve chemotherapy-induced endothelial cell injury (238,239) and circulating immune complexes against tumor-related antigens (239). In some cancer patients, it may be difficult to attribute TPP-HUS to mitomycin, because malignancy-induced TTP-HUS is clinically indistinguishable from mitomycin-induced disease. TTP-HUS is typically seen 4 to 8 weeks following the final dose of mitomycin. Patients usually present with dyspnea from noncardiogenic pulmonary edema, which may progress to adult respiratory distress syndrome, and may mimic mitomycin lung toxicity. Renal failure is generally present, whereas neurologic symptoms are infrequent (237). Unfortunately, patients with mitomycin-induced TTP-HUS do not respond to plasmapheresis. Immunoabsorption of plasma over a thioloplocar protein A column to remove immune complexes may be effective in these patients (240). The prognosis of mitomycin-induced TTP-HUS is poor, with most patients succumbing to pulmonary or renal failure or to their underlying malignancy within 4 months (237).

### References

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