Oncologic emergencies

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Objectives: **To provide an up-to-date review of current literature on the pathophysiology, diagnosis, and management of five key malignancy-related complications: superior vena cava syndrome, malignant pericardial effusion, malignant spinal cord compression, hypercalcemia, and acute tumor lysis syndrome.**

Data Sources: **Database searches and review of relevant medical literature.**

Data Synthesis: **Malignancy-related complications demand increased attention from intensivists due to their frequency and increasing cancer prevalence. Although such complications portend a poor prognosis, proper acute management can improve short-term outcomes by facilitating either definitive care of the underlying malignancy or the institution of appropriate palliative measures.**

Conclusions: **Knowledge of malignancy-induced complications in critically ill patients expedites the ability of the intensivist to properly manage them. Five complications commonly requiring emergency management are addressed in this review. Specifically, superior vena cava syndrome may warrant radiation, chemotherapy, vascular stenting, or surgical resection. Malignant pericardial effusion may require emergency pericardiocentesis if cardiac tamponade develops. Malignant spinal cord compression demands immediate spinal imaging, glucocorticoids, and either surgery or radiation. Hypercalcemia requires aggressive intravenous hydration and a bisphosphonate. Acute tumor lysis syndrome necessitates intravenous hydration, rasburicase, and management of associated electrolyte abnormalities. (Crit Care Med 2012; 40: 2212–2222)**

Key Words: adult; hypercalcemia; malignancy; spinal cord compression; superior vena cava syndrome; tumor lysis syndrome

Cancer is the second leading cause of death in the United States with over 500,000 deaths annually (1). Despite improvements in survival and decreased prevalence of certain malignancies (2), the overall prevalence of cancer is expected to rise (3). Individuals with malignancy may present with a cancer-related emergency; for many, this will be their initial manifestation of cancer (4). Efficient diagnosis and proper management of life-threatening complications may facilitate either definitive treatment of the underlying malignancy or palliation.

Five conditions frequently associated with malignancy that may require emergent treatment in an intensive care unit are reviewed. Some complications (e.g., febrile neutropenia) are too broad to be covered in this review, and have been recently covered (5, 6).

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Superior Vena Cava Syndrome

Scottish surgeon William Hunter in 1757 first described superior vena cava (SVC) obstruction from syphilic aortitis (7, 8). The syndrome resulting from the physiologic effects of obstruction is now associated more with malignancy than with mediastinal infection (8). Since the mid-20th century, malignancy has accounted for over 90% of cases of SVC syndrome (SVCS) (9, 10) (Fig. 1). However, implantable intravenous (IV) devices (e.g., tunneled central venous catheters, port catheters, pacemaker leads) have increased the prevalence of thrombosis-related SVCS and now account for up to 40% of cases of SVCS (11). Fibrosing mediastinitis due to histoplasmosis (11–14) and pulmonary tuberculosis (9, 15) still occur infrequently.

The SVC is a thin-walled vessel, about 4–6 cm in length and 1.5–2 cm in width in adults, extending from the confluence of the brachiocephalic veins and terminating in the superior right atrium. Confined by the chest wall and surrounding structures, a mediastinal mass impinging upon the SVC can easily obstruct blood flow (8). Over a period of 1–2 wks, the resultant high venous pressures and upstream vessel engorgement promote collateral vein dilatation to reduce this pressure (Fig. 2). In diseases associated with pleural thickening and adherence of the surfaces (e.g., tuberculosis), bridging veins can develop across the pleural space producing significant systemic-to-pulmonary venous shunting and hypoxemia (15).

Although the signs and symptoms of SVCS vary, the most common finding is facial edema (9–11, 16–18) (Fig. 3). The frequency of findings differ between malignant and benign etiologies, with dyspnea at rest, cough, chest and shoulder pain, and hoarseness more frequent in the former (19). This suggests some signs and symptoms of SVCS are due not solely to hydrostatic effects of venous obstruction but also direct effects of tumor compression or invasion of the airways or nerves. Similarly, neurological findings (which occur in a minority of SVCS cases) should not be assumed to result from increased venous pressure, but should raise suspicion for brain metastases (17).

Classically, SVCS has been considered an emergency requiring immediate treatment. Diagnostic procedures were assumed to be hazardous due to the risk of excessive bleeding or airway obstruction (16, 17, 20). Yet many diagnostic studies (e.g., cytology of sputum, bronchial washings, pleural effusion, palpable lymph node biopsy) are minimally invasive and have good

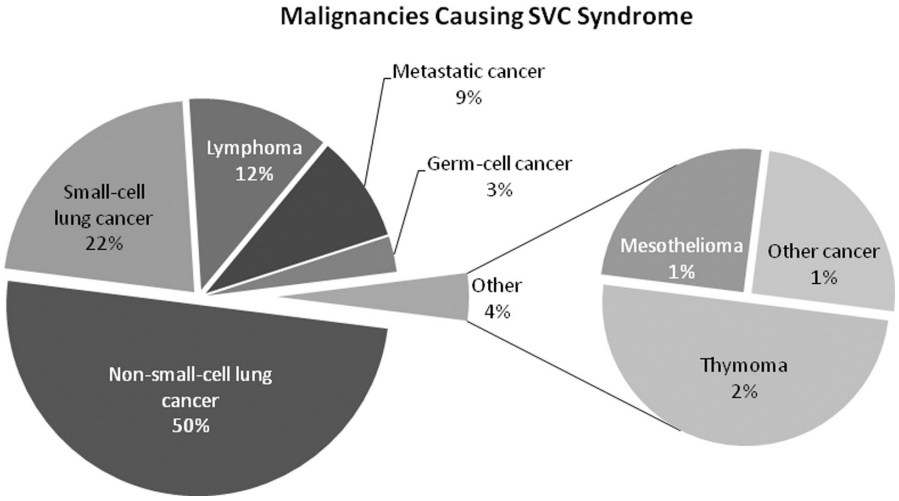

Figure 1. Distribution of malignancies causing superior vena cava syndrome. Data from Wilson et al (9).

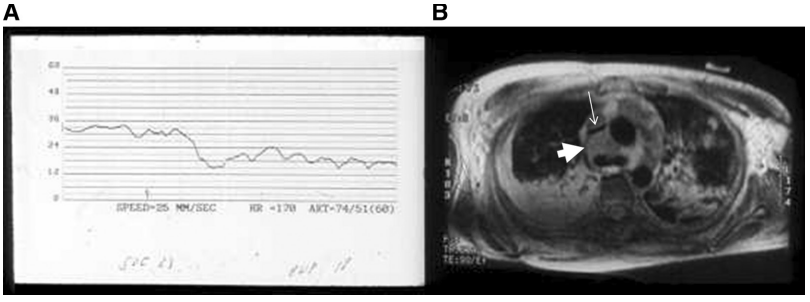

Figure 2. Case of an 18-yr-old man with relapsed acute T-cell lymphoblastic lymphoma and superior vena cava (*SVC*) syndrome. *A*, Diagnosis of SVC syndrome was first made by passing a pulmonary artery catheter through the obstruction with balloon deflated and measuring a drop in pressure from 33 to 18 mm Hg. *B*, Magnetic resonance imaging obtained the next day confirmed a large mediastinal mass (*thick arrow*) compressing the SVC (*thin arrow*). Courtesy of the Greenebaum Cancer Center and the Department of Radiology, University of Maryland School of Medicine.

yield (10, 11, 20). Furthermore, recent series have confirmed the safety of invasive procedures (16, 17, 20). Diagnosing underlying disease is essential before choosing a course of treatment because many causes of SVCS are benign. Additionally, some malignancies (e.g., small-cell lung cancer, non-Hodgkin lymphoma) require systemic chemotherapy (11, 21, 22). Radiation prior to biopsy causes tissue necrosis and can make histology uninterpretable. Consequently, SVCS becomes a true emergency requiring empiric treatment only in the setting of airway obstruction or cerebral edema.

Management of SVCS includes symptomatic relief, treatment of complications, and therapy for the underlying condition. Symptoms usually improve over a period of 1–2 wks with radiation or chemotherapy, although they can improve just as quickly without treatment. Furthermore, autopsy series suggest collateral venous blood flow provides most of the benefit (17). Elevation of the head of the bed and supplemental oxygen are standard. Although commonly prescribed, glucocorticosteroids are of unclear benefit except in the cases of lymphoma or thymoma where indicated for the underlying malignancy (9). Thrombosis-related SVC obstruction is treated with anticoagulation, intravascular device removal, and balloon dilatation or stenting if significant fibrosis remains (11).

In small-cell lung cancer and lymphoma, chemotherapy and external beam radiotherapy are equally effective in relieving SVC obstruction (21). Combination therapy is no more effective than either treatment alone (10). Radiotherapy only treats disease within the radiation fields, and is therefore best for patients with well-defined tumors that are less chemotherapy-sensitive, such as non–small-cell lung cancer and certain metastatic cancers causing focal obstruction (23). Chemotherapy is preferred for extensive chemo-sensitive tumors, such as small-cell lung cancer and lymphoma. Intravascular stenting provides symptomatic relief within 24–48 hrs and can safely precede tissue diagnosis. This may be the most appropriate initial therapy for patients with the most severe symptoms such as airway obstruction or cerebral edema (23). Stenting may provide the only treatment option in patients with recurrent obstruction (24). Patients with relatively chemo- and radiotherapy-resistant tumors such as thymoma and residual germ-cell mass may benefit from surgical resection (9, 23). Median survival of patients with cancer-induced SVCS is roughly 6 months after presentation, but many patients have survived over 2 yrs with treatment (9, 10, 20, 23, 24).

Malignant Pericardial Disease

Pericardial effusion is common in malignancy with up to 34% of cancer patients having involvement of pericardium (8, 25, 26). Neoplastic etiology was reported in 7% of all acute pericardial disease, and in roughly half of these cases it was the first manifestation of previously undiagnosed malignancy (27). Most malignant pericardial disease is due to metastasis from sites of disease outside of the heart and pericardium, primarily from lung, breast, and hematologic sources (8, 25–27).

The pericardium is composed of a visceral (or serous) layer formed by a single layer of mesothelial cells adhered to the surface of the heart and a fibrous parietal layer formed by the pericardium reflecting back on itself. The space between these two layers contains up to 50 mL of fluid serving as a lubricant (8, 28). Fluid filling the pericardial sac initially has a flat pressure response until reaching the pericardial reserve volume, i.e., the volume that begins to distend the pericardium. Pressure then begins to rise abruptly due to the relative inextensibility of the parietal pericardium (28, 29). The steep rise in pressure with minimal increment in pericardial fluid volume eventually leads to a critical intrapericardial pressure, which in turn results in impaired filling of the cardiac chambers and hemodynamic compromise. Thus, cardiac tamponade has been termed a "last drop" phenomenon (29). The amount of the pericardial fluid that causes tamponade is related to the rate of fluid formation. Rapidly accumulating effusions can cause symptoms with as little as 200 of pericardial fluid (28). However, if fluid accumulates

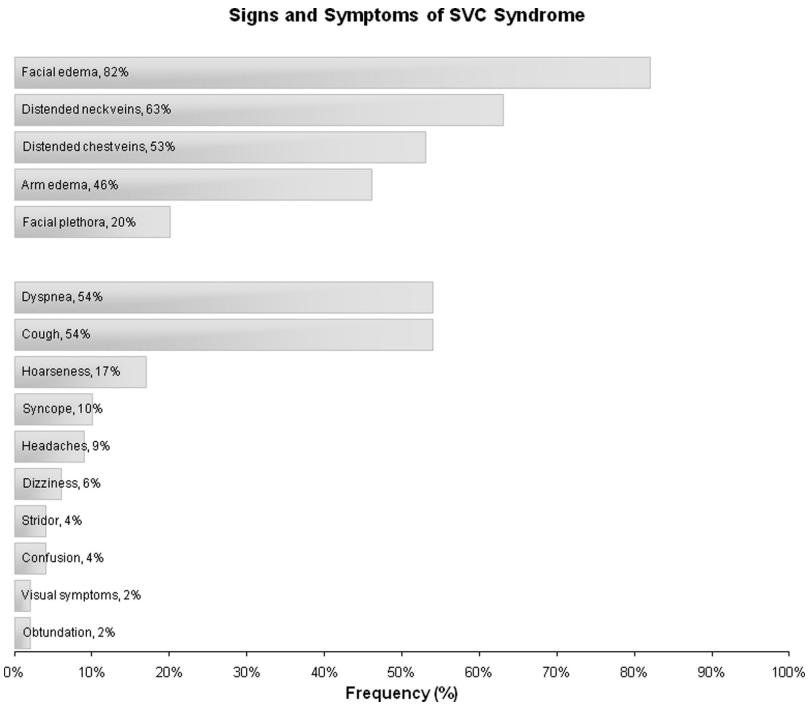

Figure 3. Distribution of signs and symptoms of superior vena cava (*SVC*) syndrome. Data from Wilson et al (9).

slowly (weeks to months), the parietal pericardial tissue can stretch. With this "stress relaxation" the pericardial sac becomes more compliant and can hold 2 L or more before tamponade develops (28, 29).

Exertional dyspnea is the most common presenting symptom in malignant pericardial effusion, observed in roughly 80% (25). The most common sign is pulsus paradoxus, occurring in about 30% of presentations of malignant pericardial effusion (25) and 77% of cases of acute tamponade (28). Tachycardia is frequent. Beck's triad of hypotension, increased jugular venous pressure, and decreased heart sounds is found mostly with rapidly forming effusion and acute tamponade, but only infrequently in patients with chronic pericardial effusion (28). The characteristic chest radiographic findings are that of enlarged cardiac silhouette and increase in transverse diameter (water bottle heart) (25, 28). Electrocardiogram findings include low amplitude waveforms (25, 28) and electrical alternans due to swinging heart (28). Cardiac catheterization demonstration of elevated and equalized right atrial, right ventricular diastolic, and pulmonary arterial occlusion pressures reflects tamponade physiology (28, 29). Reciprocation of cardiac pressures due to right atrial and right ventricular distention on inspiration impeding left-sided filling, with the converse on expiration, represents the same mechanism as pulsus paradoxus (29).

Echocardiography is the preferred diagnostic imaging technique in that it can define not only the size and location of pericardial effusion, but also hemodynamic significance and guide pericardiocentesis (28). Two-dimensional echocardiogram demonstration of right atrial collapse in late diastole lasting a third of the cardiac cycle and right ventricular collapse in early diastole are most characteristic of tamponade (28, 29) (Fig. 4). Respiratory reciprocation can be detected in the movement of atrial and ventricular septa (29).

Initial volume resuscitation may be indicated to stabilize the patient hemodynamically if hypovolemic, but in normovolemia or hypervolemia, additional fluid may be of no value or potentially detrimental (29). Patients with acute cardiac tamponade and shock may require bedside emergency pericardiocentesis. Echocardiographic guidance provides optimal placement of the needle and prevents lacerating the myocardium. Chronic pericardial effusion accumulates slowly, affording more time to plan treatment (28, 29). Fifty percent of malignant effusions recur, and it is therefore reasonable to place an indwelling drainage catheter at the time of pericardiocentesis (28). Reaccumulating fluid may require sclerosing therapy, balloon pericardotomy, or surgical window (28, 29). Surgical drainage may also be indicated for fluid unreachable by needle or catheter, bleeding into pericardial space, or clotted hemopericardium (29). Paradoxical hemodynamic instability, the unexpected development of vasopressor-dependent hypotension in the immediate postoperative period, has a poor prognosis, and over half of these patients do not survive the hospitalization (30).

Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) occurs in around 5% of terminal cancer patients within the last 2 yrs of life (31, 32). Despite a median survival of <6 months following diagnosis (33, 34), prompt treatment usually palliates pain and prevents paralysis (33). Intramedullary (intradural) (35) and leptomeningeal (dural) (36) malignancy are rare, and most MSCC is epidural (extradural) in origin.

Thecal sac impingement by spinal epidural metastases or locally advanced cancer originates directly from vertebrae (90% of cases) or via neural foramina (10% of cases) (37). The development and location of vertebral metastases correlate with degree of vertebral blood flow (38) and the prevalence, affinity for bone, and anatomic location of the tumor (39). The three most common cancers (lung, breast, and prostate) (40) each account for 15%–20% of MSCC, whereas multiple myeloma, non-Hodgkin lymphoma, and renal cell carcinoma each account for 5%–10% (37). Due to anatomic locations, breast and lung cancer most commonly metastasize to the thoracic spine, whereas abdominal malignancies typically metastasize to the lumbosacral vertebrae (41). Spread of pelvic cancers (e.g., prostate) is enabled by valveless venous communication with the lumbar spine (42).

Back pain, the first symptom in 95% of those with MSCC (43), precedes other symptoms by up to 2 months and offers the opportunity to intervene before incurring long-term morbidity (32, 44, 45). Because 40%–90% of afflicted individuals have sensory abnormalities (39) that correspond to nerve roots within four levels below or two levels above the compressed cord (46), spinal cord imaging is necessary to identify the site of obstruction and plan treatment. Approximately half of MSCC patients have bowel or bladder dysfunction (44) and postvoid residual aids diagnosis of cauda equina syndrome with

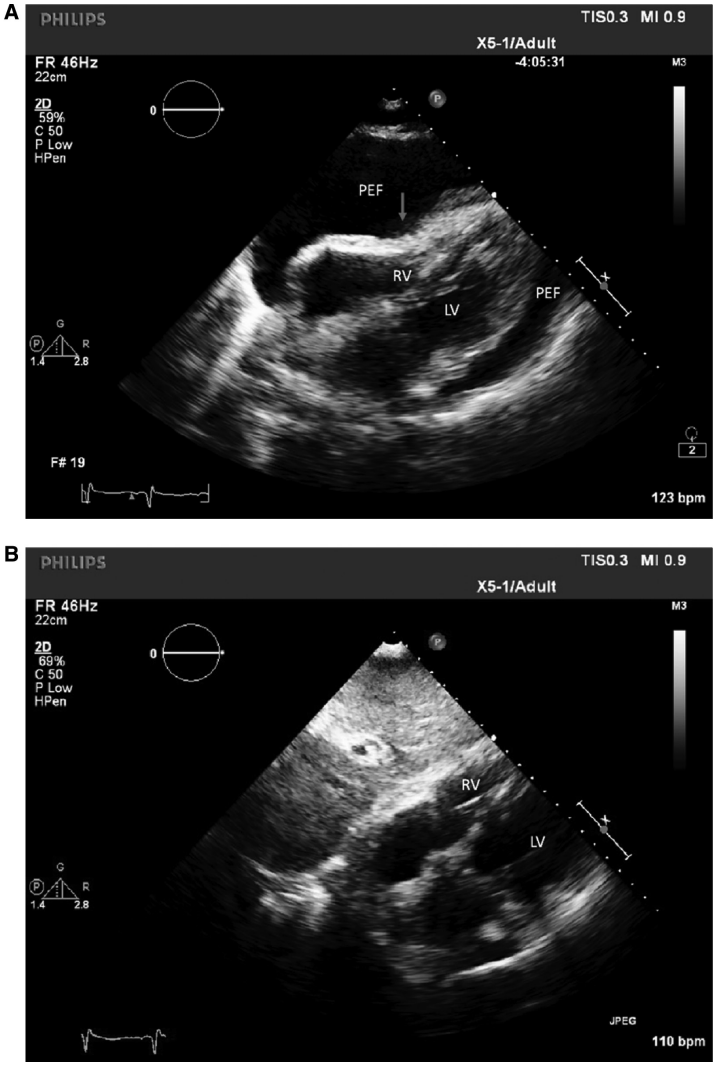

Figure 4. *A*, 2-D echocardiography subcostal view showing pericardial tamponade with diastolic compression of the right ventricle (*RV*) from a large pericardial effusion (*PEF*). B, 2-D echocardiography subcostal view after pericardial drain placement showing resolution of PEF and expansion of RV. *LV,* left ventricle. Image courtesy of Michael C. Reed, MD.

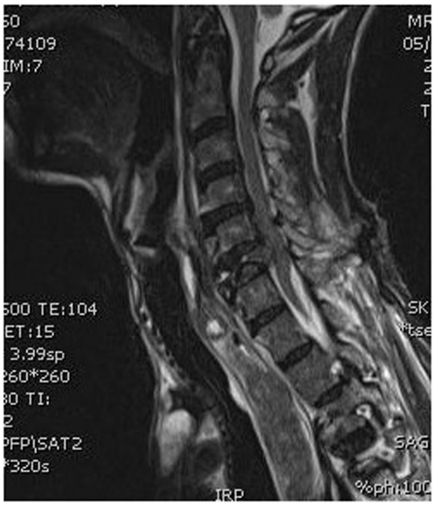

Figure 5. Magnetic resonance imaging showing spinal cord compression at C5. Reprinted with permission from EB Medicine, publisher of *EM Critical Care* and *Emergency Medicine Practice*, from McCurdy et al (8).

90% sensitivity and 95% specificity (47). About 75% have focal weakness, which, if untreated, progresses sequentially to ataxia and paralysis (44). Ambulatory status upon presentation is the most important prognostic factor for neurological function in MSCC patients (48).

Magnetic resonance imaging is the gold standard for diagnosing MSCC (sensitivity 93%, specificity 97%, positive predictive value >95%) (46, 49, 50). The entire spine should undergo T1- and T2-weighted imaging in the axial, sagittal, and coronal planes because onethird of MSCC cases have multiple sites of metastases (51–55). Gadolinium-enhanced images improve both identification of leptomeningeal and intramedullary metastases and understanding of nearby anatomy but are not necessary to evaluate epidural spinal cord compression (55, 56) (Fig. 5). Computed tomography with myelography is a valuable alternative when magnetic resonance imaging is unavailable or contraindicated. If cerebrospinal fluid contrast flow is not obstructed, sensitivity and specificity are both >95% for MSCC (57, 58). However, lumbar puncture–induced neurologic decompensation does occur in 14% of those with complete spinal subarachnoid block (59). If magnetic resonance imaging and computed tomography myelography are unavailable, bone scintigraphy paired with plain radiography to diagnose MSCC has a sensitivity of 98%, but poor specificity (60). Non-contrast spinal computed tomography without myelography can still be useful (61).

Rapid treatment initiation improves short-term prognosis (62). Treatment goals include maintenance of neurological function, control of local tumor growth, spine stabilization, and pain control (63). Corticosteroids mitigate vasogenic edema resulting from compression-induced ischemia. High-dose dexamethasone (96 mg IV bolus, then 24 mg by mouth every 6 hrs × 3 days, then 10-day taper) had significantly increased preservation of ambulation at 3 months after radiation in a randomized controlled trial (64), but it can have serious side effects (65). High-dose steroids are recommended for patients with an abnormal neurological exam and moderate-dose steroids (10 mg IV bolus, then 4 mg qid with 2-wk taper) for all others (66).

Radiotherapy of radiosensitive tumors is fundamental in MSCC (Table 1). Nearly half of survivors are ambulatory at 1 yr following radiation (39). Older literature reported no improvement in neurologic outcomes when nonselective decompressive posterior laminectomy was added to radiation (45, 67, 68). Despite established indications for radiation (Table 2) (69), the ideal dose and schedule are uncertain. The older surgical technique of nonselective posterior laminectomy relieves pressure within the vertebral foramen but does not address the lesion, which is typically in the vertebral body. Patchell et al (70) reported significantly longer median duration of ambulation (122 vs. 13 days), maintenance of continence (156 vs. 17 days), and median survival (126 vs. 100 days) with direct, selective surgical decompression (anterior corpectomy for the 60% of cases involving only the vertebral body) followed

Table 1. Radiosensitivity of tumors

Sensitive
Lymphoma
Myeloma
Breast
Prostate
Small-cell lung cancers
Resistant
Melanoma
Sarcoma
Renal cell carcinoma

Table 2. Indications for radiation alone (48, 69)

Prior radical spinal decompression
No spinal compression or instability
Subclinical cord compression
Poor surgical candidate (e.g., anticipated survival <3 mos)

Table 3. Indications for surgery (71)

Spinal instability (e.g., spinal deformity, bony retropulsion into canal, pathologic fractures)
Previous radiation therapy to area
Disease progression despite radiation
Radioresistant tumor
Unknown primary tumor
Paraplegia for <48 hrs
Single area of cord compression

by postoperative radiation compared to radiotherapy alone, and this approach is generally recommended for patients meeting surgical criteria (Table 3) (71).

Malignancy-Associated Hypercalcemia

Malignancy-associated hypercalcemia (MAH) occurs in a quarter of cancer patients (72) and comprises over a third of all cases of hypercalcemia presenting to the emergency department (73). Antihypercalcemic therapy alone does not improve mortality, and half of all patients diagnosed with MAH die within a month of diagnosis (74). Yet temporizing clinical deterioration allows definitive cancer therapy or palliation.

Calcium homeostasis is maintained by intestinal absorption, bone resorption, and renal excretion. Parathyroid hormone (PTH) modulates calcium levels by increasing bone resorption, promoting renal calcium absorption and phosphate excretion, and converting calcidiol to calcitriol, the active form of vitamin D. Calcitriol promotes intestinal calcium absorption and, to a lesser extent, bone resorption. MAH results from: 1) PTH-related protein–induced humoral hypercalcemia of malignancy, 2) local osteolysis from bone metastasis, 3) lymphoma-associated calcitriol production, or 4) ectopic PTH secretion (75). The mechanism varies with each malignancy (Table 4). Humoral hypercalcemia of malignancy accounts for 80% of cases of MAH (72), and PTH-related protein is the most common mediator (76). Local osteolysis from bone metastasis (due to the cytokines interleukin-1, interleukin-6, interleukin-8, and locally produced PTH-related protein chemokines) accounts for nearly 20% of cases (72). Excess calcitriol production by activated mononuclear cells causes <1% of cases (72) but accounts for almost all Hodgkin and one third of non-Hodgkin lymphoma–induced hypercalcemia (77).

Table 4. Mechanism of hypercalcemia and type of malignancy (72)

Humoral hypercalcemia of malignancy
Squamous (head and neck, esophagus, cervix, lung)
Renal
Ovarian
Breast
Endometrial
Human T-lymphotropic virus-associated lymphoma
Local osteolysis from bone metastasis
Breast
Multiple myeloma
Lymphoma
Calcitriol production
Hodgkin lymphoma
Non-Hodgkin lymphoma
Ectopic parathyroid hormone secretion
Parathyroid
Ovary
Lung
Primitive neuroectoderm

The protean symptoms and signs of hypercalcemia include lethargy, confusion, constipation, hypovolemia, and cardiac dysrhythmias. The degree of hypercalcemia can be classified by total serum calcium level as mild (10.5–11.9 mg/dL), moderate (12.0–13.9 mg/dL), or severe (≥14.0 mg/dL) (72, 78). Clinical effects of hypercalcemia are related more to the rate of rise in serum calcium and the underlying volume depletion resulting from osmotic diuresis than the absolute serum calcium value (72, 78, 79). Half of serum calcium is protein-bound, and formulas to correct for hypoalbuminemia are imprecise; therefore, ionized calcium more accurately represents true serum calcium levels (80–82). Notably, due to competition between hydrogen and calcium ions for serum protein binding sites, ionized calcium levels decrease 1.44 mg/dL with every pH unit increase (83). Serum phosphorus, magnesium, and potassium are often low and should be monitored (84). Intact PTH level should be obtained to rule out primary hyperparathyroidism, which has an increased prevalence in cancer patients (85, 86). An elevated PTH-related protein confirms a diagnosis of humoral hypercalcemia of malignancy and monitors treatment response (87, 88), but is unnecessary for acute management (89).

Electrocardiographic findings in clinically significant hypercalcemia include prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, Brugada syndrome (in predisposed individuals) (90), and bradydysrhythmias leading to cardiac arrest when serum calcium exceeds 15 mg/dL (91) (Fig. 6).

Restoring adequate intravascular volume is fundamental to improve glomerular filtration rate and decrease passive sodium–calcium reabsorption from the proximal tubule (92). Normal saline infusion is recommended at 200–500 mL/hr (72) and adjusted for a urine output of 100–150 mL/hr, absent any contraindications. However, fluids only modestly decrease serum calcium levels, and <30% of patients achieve normocalcemia with fluids alone (93). Loop diuretics to inhibit calcium reabsorption in the ascending loop of Henle (72, 94) risk worsening electrolyte abnormalities and volume loss, and should only be used in volume overload (95). Hemodialysis is generally indicated for congestive heart failure, severe kidney injury (glomerular filtration rate <10–20 mL/min), clinically significant neurological findings, or calcium concentration >18 mg/dL (72, 96).

Management of calcium metabolism includes eliminating medications (e.g., thiazides) that increase intestinal absorption of calcium and glucocorticosteroids (Prednisone, 40–100 mg PO; or hydrocortisone, 200–400 mg IV daily for 3–5 days) to decrease extra-renal calcitriol production in lymphoma (97, 98) or myeloma (79, 95, 99), increase renal excretion (100), and inhibit osteoclastic resorption from bone (101). However, effects may not be realized for >4 days, and glucocorticosteroids may precipitate tumor lysis syndrome (TLS) in these malignancies.

The bisphosphonates, pamidronate and zoledronate, are first line therapy for MAH. These pyrophosphate analogues bind to hydroxyapatite and inhibit bone crystal dissolution and osteoclastic resorption (102).

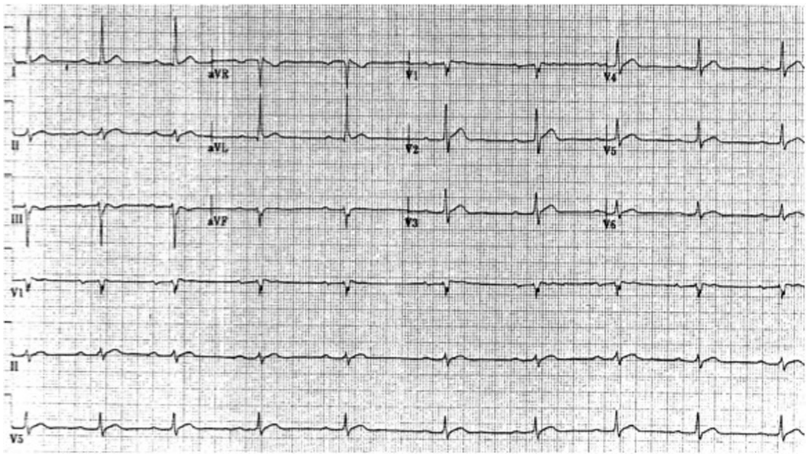

Figure 6. Short QT interval; Ca 16 mg/dL. Courtesy of Amal Mattu, MD, Department of Emergency Medicine, University of Maryland School of Medicine.

Calcium levels decrease 2–4 days after administration, reach their nadir between 4 and 7 days, and usually normalize for 1–4 wks, affording time to treat the underlying malignancy (72). Potential side effects include hypophosphatemia, hypomagnesemia, hypocalcemia, influenza-like symptoms, nephrotoxicity (103), and jaw osteonecrosis (104). Zoledronate, either 8 mg or 4 mg given over 5 mins, has been proven more effective than pamidronate (90 mg given over a 2-hr period) at normalizing and maintaining serum calcium within 10 days (105). However, the higher dose of zoledronate is associated with slightly increased risk of kidney injury and is only recommended for relapsed or refractory MAH.

Calcitonin has negligible toxicity and rapid onset of action, but short duration of action and potential for tachyphylaxis (106) has caused it to be mostly abandoned for newer drugs. Less commonly used agents include gallium nitrate and plicamycin (mithramycin). Gallium nitrate lowers serum calcium by inhibiting osteoclastic bone resorption (107, 108), and particularly benefits patients with epidermoid cancers, calcium levels >13.5 mg/dL, or a poor response to bisphosphonates (108). Prolonged administration time (5 days) and side effects (e.g., nephrotoxicity) preclude its widespread acceptance. Plicamycin, an antineoplastic antibiotic formerly used for hypercalcemia, has less efficacy and tolerability than newer alternatives (109).

The receptor activator of nuclear factor-κB ligand induces osteoclast differentiation, activation, and survival. Denosumab is a monoclonal antibody that binds receptor activator of nuclear factor-κB ligand and has been approved for prevention of skeletal-related events in patients with bone metastases from solid tumors (110–112). Denosumab for MAH is experimental.

Acute TLS

Acute TLS is a potentially life-threatening emergency characterized by metabolic derangements resulting from the death of malignant cells and release of intracellular contents (113). The subject has been recently reviewed (114). TLS is primarily associated with aggressive hematologic malignancies due to the large tumor burden and rapid cell lysis with treatment, particularly high-grade non-Hodgkin lymphomas and acute lymphocytic leukemia (115, 116). Acute TLS has been also been reported with low- and intermediate-grade hematologic malignancies (e.g., multiple myeloma, acute myeloid leukemia, chronic lymphocytic leukemia), solid tumors with high proliferative rates and rapid response to cytotoxic therapy (e.g., testicular cancer, small-cell lung cancer) (116), neuroblastoma, and breast cancer, but is otherwise uncommon in solid tumors (117, 118). Preexisting renal dysfunction and elevated serum lactate dehydrogenase, commonly associated with lymphoid malignancies, are risk factors for TLS (113, 116, 119, 120).

Almost all types of cancer treatment can cause TLS, including systemic chemotherapy (115, 119–122), intrathecal methotrexate, glucocorticosteroids for lymphoma, biological agents (e.g., rituximab, interferon α), ionizing radiation, and tamoxifen (115). However, spontaneous TLS in the absence of treatment is well-recognized in rapidly proliferating tumors, especially Burkitt lymphoma (119), large T-cell lymphoma (123), and acute lymphocytic leukemia (115, 124).

Metabolic derangements of TLS include hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia (Table 5). Coiffier et al (124) published consensus definitions, grading its severity based upon laboratory derangements and clinical manifestations, and guidelines for management of TLS. Hyperkalemia, the most serious manifestation of acute TLS, occurs 6–72 hrs after the initiation of cytotoxic therapy and can be exacerbated by acute kidney injury (AKI) (115). Hyperphosphatemia occurs 24–48 hrs after chemotherapy. Malignant cells contain up to four times the amount of inorganic phosphorus as normal cells (115, 124), and chemotherapy prevents phosphate reutilization (125). Hypocalcemia results from binding of excess phosphate to ionized calcium when the calcium phosphate solubility product of 70 is exceeded (115, 116, 124). Acute phosphate loads can cause AKI from calcium phosphate crystalluria and obstructive uropathy, followed by intratubular nephrocalcinosis (126).

Hyperuricemia results from the catabolism of purine nucleic acids to hypoxanthine, xanthine, and then uric acid by xanthine oxidase (Fig. 7). Most uric acid is renally excreted, but poor solubility in urine (pKa_1 of 5.4–5.7) (116) can cause uric acid crystal precipitation in the collecting tubules. The resultant obstructive nephropathy and uric acid–mediated glomerular and tubular injury from oxidant stress and inflammation can further injure the kidneys (117).

Management of acute TLS consists of prophylactic measures to reduce the risk of renal impairment and treatment of metabolic abnormalities. Although metabolic abnormalities may be more immediately life-threatening, AKI in the setting of acute TLS independently and significantly increases the risk of mortality (127). Volume depletion predisposes AKI (117). The primary intervention for high-risk patients is volume loading with fluid at roughly twice the maintenance rate to increase glomerular filtration rate, urine flow, and uric acid and calcium phosphate solubility (113, 124). The practice of alkalinizing urine to increase the solubility of uric acid (115) is no longer supported because of the nephropathy risk resulting from xanthine (116, 128) and calcium phosphate crystal precipitation (124, 126, 128).

Hyperkalemia can usually be managed with enteral sodium polystyrene. Because

Table 5. Metabolic abnormalities in acute tumor lysis syndrome (115, 124, 126)

Metabolic Abnormality	Value or Change From Baseline[124a]	Clinical Implications	Management
Hyperkalemia	≥6.0 mmol/L or 6 mEq/dL or 25% increase	Muscle cramps Paresthesias Dysrhythmias Ventricular fibrillation Cardiac arrest	Polystyrene sulfonate 1 gm/kg Insulin 0.1 unit/kg with dextrose 25% 2 mL/kg Sodium bicarbonate 1–2 mEq/kg IV push Calcium gluconate 100–200 mg/kg slow IV infusion
Hyperphosphatemia	≥2.1 mmol/L for children or ≥1.45 mmol/L for adults or 25% increase	Nausea Vomiting Diarrhea Lethargy Seizures Acute kidney injury	Volume loading Removal of phosphate from IV fluids Oral phosphate binders Hemodialysis
Hypercalcemia	≤1.75 mmol/L or 25% decrease	Muscle cramps Tetany Hypotension Dysrhythmia	Calcium gluconate 50–100 mg/kg slow IV infusion with electrocardiogram monitoring. Give only if symptomatic.
Hyperuricemia	≥476 μmol/L or 8 mg/dL or 25% increase	Acute kidney injury	Volume loading Rasburicase (see text for dosing) Allopurinol by mouth or IV

IV, intravenous.

[a]Cairo–Bishop definition requires two or more laboratory abnormalities within 3 days prior to or 7 days after initiation of cytotoxic therapy (124).

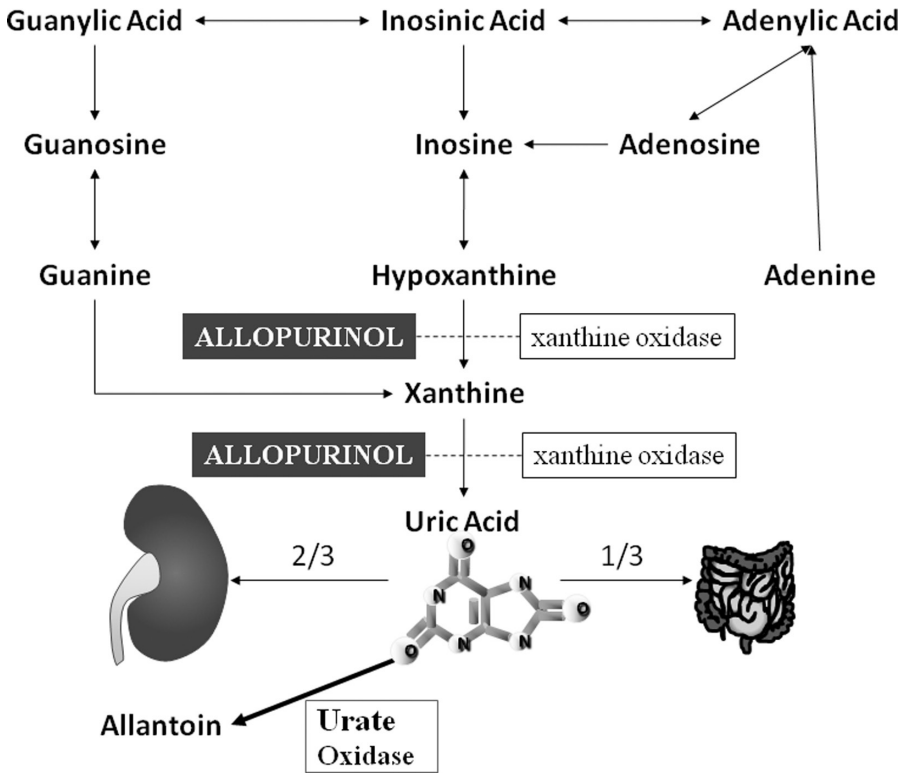

Figure 7. Diagram of purine catabolism. Purine nucleotides are catabolized to hypoxanthine, xanthine, and then uric acid by xanthine oxidase, which is inhibited by allopurinol. Uric acid is excreted two thirds by the kidney and one third in the intestine. Urate oxidase lyses uric acid to allantoin, which is 5–10 more soluble in urine.

ion exchange resins work slowly, symptomatic patients require more rapid treatment such as insulin and dextrose or sodium bicarbonate to shift potassium intracellularly, and calcium gluconate to stabilize cardiac cell membranes (115, 124). Sodium bicarbonate should be administered cautiously to avoid inadvertent hypervolemia (115), metabolic alkalosis (124), or precipitation of calcium either in the IV tubing (124) or in the kidney (115, 117). Primary prevention of hyperphosphatemia includes phosphate removal from fluids, volume loading, and phosphate binders. For more severe cases, and when medical management has failed, renal replacement therapy has been employed (124). Hypocalcemia is treated only if symptomatic because of the risk of nephropathy (124).

Recombinant urate oxidase (rasburicase) works by catabolizing uric acid to more soluble allantoin (113, 116, 121, 122, 124, 129–132). Whether given therapeutically or prophylactically, this agent is highly effective at rapidly normalizing uric acid levels (121, 122, 130–132), and has greater efficacy than allopurinol (133). It is recommended as first line treatment for high-risk patients with tumors prone to rapid lysis or the presence of preexisting kidney injury and elevated uric acid levels (113, 124). Because hydrogen peroxide is a byproduct of uric acid catabolism to allantoin, rasburicase can cause hemolytic anemia or methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency, and is therefore contraindicated in these patients (129). The recommended dose (0.2 mg/kg IV daily given for 5 days) is based on predicted body weight even in patients with morbid obesity (134). Because of the drug's expense, alternative dosing regimens using single doses or shorter courses have been reported (135–142). Our institution has published its experience with 6 mg fixed-dose

rasburicase in patients with high-risk disease or serum uric acid levels >8 mg/dL (142). Although hyperuricemia contributes to TLS-induced renal dysfunction, no prospective, randomized controlled trial demonstrates that urate oxidase reduces the prevalence of AKI or mortality (143).

Allopurinol prevents formation of uric acid by inhibiting xanthine oxidase (115, 116, 144). It is typically started before administration of chemotherapy (113, 116, 124). Drawbacks include hypersensitivity reactions to the medication (144), inability to clear uric acid already formed, accumulation of xanthine with potential nephropathy (116, 124, 128), and inhibition of purine drug metabolism (e.g., 6-mercaptopurine, azathioprine) (116). Evidence that it lowers elevated creatinine levels is lacking (144). Allopurinol is therefore not recommended as first line prophylaxis of patients at high-risk for TLS (113).

Renal replacement therapy for acute TLS is indicated for significant AKI, poor response to medical management, or symptomatic life-threatening metabolic derangements. Hemodialysis more effectively clears solutes than peritoneal dialysis, but it is unknown if continuous renal replacement is more effective than intermittent therapy in TLS (115).

CONCLUSIONS

As the number of cancer patients grows (3), the prevalence of malignancy-related complications will increase. Often the stage of malignancy carries a poor prognosis (34, 74). Yet diagnosis and management of oncologic emergencies can usually improve the duration or quality of patients' lives.

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