Oncologic Emergencies
Endocrinologic/Metabolic, Hematologic, Renal/Urologic, Dermatologic/Immunologic, GI, and Pain

Last month's discussion concludes as the authors consider six additional types of emergent conditions related to cancer and/or its treatment.

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ENDOCRINOLOGIC/METABOLIC EMERGENCIES
Adrenal Insufficiency

Adrenal insufficiency may be related to adrenal gland destruction by metastases; it can also be caused by adrenal suppression from corticosteroid administration. Ninety percent of the adrenal gland must be nonfunctional before adrenal function is detectably impaired. The most common cancers to metastasize to the adrenals are those of the lung and breast and melanoma.[1] Patients with adrenal insufficiency are unable to tolerate stress from infection, metabolic disruption, or surgery. Acute adrenal crisis with resulting vasomotor collapse can be sudden and fatal. Signs of adrenal insufficiency include mild hypoglycemia, hyponatremia, hyperkalemia, metabolic acidosis, and eosinophilia. Any steroid-dependent patient with signs of stress should empirically be given IV steroids with both glucocorticoid and mineralocorticoid effects. Emergency stress doses of hydrocortisone hemisuccinate are 100 to 200 mg IV. In cases of suspected adrenal insufficiency in hemodynamically stable patients, serum cortisol levels should be measured prior to initiation of steroids.[1]

Syndrome of Inappropriate ADH

Syndrome of inappropriate antidiuretic hormone (SIADH) is caused by ectopic secretion of ADH due to malignancies or by stimulation of ADH release from pharmacologic agents such as chemotherapeutics, narcotics, carbamazepine, or SSRIs.[2] The absorption of free water at the collecting-duct level due to SIADH results in worsening hypotonicity and inappropriately concentrated urine. Clinically, the result is hyponatremia in an apparently euvolemic patient.[3] SIADH is the most common cause of euvolemic hyponatremia in clinical medicine. Signs and symptoms are primarily neurologic. Anorexia, nausea, and malaise are the earliest findings, followed by headache, confusion, obtundation, seizures, and coma. Seizures are tonic-clonic and, if recurrent, require treatment with hypertonic saline. Focal seizures are atypical and require a more in-depth evaluation. Life-threatening symptoms are almost always present with sodium concentrations below 105 mEq/L.[2]

ED management is guided by symptom severity and serum sodium level. For stable patients, water restriction is the mainstay of treatment. Patients with sodium levels above 125 mEq/L are generally asymptomatic and can be managed on an outpatient basis with water restriction of 500 mL per day and close follow-up. More severe symptoms require administration of furosemide (0.5 to 1.0 mg/kg), along with IV administration of normal saline to maintain euvolemia and a net free-water clearance. Demeclocycline (300 to 600 mg PO twice daily) is a tetracycline derivative that induces a state of diabetes insipidus, which allows continued water intake and improvement in sodium level. Hypertonic saline (51 mEq sodium/dL) can be given, with or without furosemide, for rapid correction of hyponatremia; however, this is reserved for previously healthy patients who become symptomatic and present with seizures, coma, or focal symptoms. The hypertonic saline amount must be carefully calculated to avoid

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correction that is too rapid, which can result in an osmotic demyelination syndrome (formerly known as central pontine myelinolysis) that can produce a locked-in type of neurologic syndrome. The rate of correction of hyponatremia is controversial, but a rate of 0.5 mEq/L per hour, with no more than a 10- to 12-mEq increase in the first 24 hours, is recommended. A simple approach is to infuse 3% saline at a rate of 1 mL/kg per hour, which results in a serum sodium increase of 1 mEq/L per hour.[4] Concomitant hypokalemia requires correction as well because plasma potassium elevation can raise the serum sodium concentration.[2]

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) is a constellation of metabolic derangements resulting from acute destruction of cancer cells and release of their intracellular contents into the circulation. The body's homeostatic mechanisms are overwhelmed and rapidly rendered useless, and potassium, calcium, phosphorus, and uric acid levels go unregulated. TLS occurs more commonly with hematologic malignancies and may occur spontaneously at any point during the disease course or soon after chemotherapy treatments. TLS is also seen in patients receiving chemotherapy for solid tumors. Renal failure may rapidly ensue and is dependent on the type and extent of tumor, the treatment type, and premorbid renal function. The institution of prophylaxis with IV fluids and allopurinol prior to chemotherapy has greatly reduced the incidence of TLS.[5]

Hyperkalemia (potassium level >5.5 mEq/L) is the most life-threatening metabolic derangement of TLS. In patients with potassium levels of 6.5 to 7.5 mEq/L, ECG shows peaked T waves in precordial leads, prolonged PR intervals, and shortened QT intervals. With levels of 7.5 to 8.0 mEq/L, the ECG shows flattened P waves and widened QRS complexes. With potassium levels greater than 8.0 mEq/L, the ECG may show a sine-wave pattern, ventricular fibrillation, or heart block.[2,6] Hyperkalemia is treated with multiple agents to reduce serum potassium levels. β-Adrenergic agonists, glucose, and insulin drive potassium into the cells, while sodium-potassium exchange resin facilitates gastrointestinal excretion of potassium. Calcium administration should be avoided unless there is QRS widening, as supplemental calcium may cause

metastatic precipitation of calcium phosphate. Patients with a serum potassium level greater than 6.0 mEq/L may require hemodialysis.

Malignant cells may contain up to four times the normal intracellular concentration of phosphorus. As levels increase, phosphate combines with calcium and precipitates in soft tissue and renal tubules, which leads to hypocalcemia and renal failure. Serum phosphate levels can be decreased with phosphate binders, which have a limited effect, or by the administration of glucose and insulin. Hemodialysis is effective in correcting all abnormalities of TLS, although a large phosphate burden (>10 mg/dL) may require repeat dialysis at 12- to 24-hour intervals.[2]

Catabolism of DNA and RNA produces uric acid, which may precipitate in the renal tubules. Rapid IV hydration is the single most important initial intervention. Allopurinol can also be given to reduce the conversion of nucleic acid by-products. As allopurinol has no effect on preexisting uric acid, it often takes 48 to 72 hours for levels to fall. Most authors also agree that there is a theoretical benefit of enhancing renal excretion via urine alkalinization. This can be accomplished by adding 2 ampules of sodium bicarbonate to 1 L D5W IV infusion or by administration of acetazolamide, with a urine pH level of 7.1 to 7.5 as the goal of treatment. Overalkalinization of urine should be avoided, as this increases the likelihood of calcium phosphate precipitation in the renal tubules, which can lead to acute renal failure. Patients with a serum uric acid level greater than 10 mg/dL may require hemodialysis.[5]

Hypercalcemia
Hypercalcemia is defined as a serum calcium level greater than 10.5 mEq/L or an ionized calcium level greater than 2.7 mEq/L. It is one of the most common metabolic complications of malignancy, occurring in 20% to 30% of patients at some time during the course of their disease and more commonly in patients with advanced disease.[6,7] The presence of hypercalcemia associated with cancer is associated with a poor prognosis, as this metabolic disorder may result in numerous life-threatening complications, including severe dehydration, bradycardia, seizures, pancreatitis, and coma. Up to 50% of patients die within 30 days of detection of elevated calcium levels.[3]

Clinical signs occur with serum calcium levels greater than 12 mEq/L. A common mnemonic for the causes of hypercalcemia is PAM P. SCHMIDT: Parathyroid hormone, Addison disease, Multiple myeloma, Paget disease, Sarcoidosis, Cancer, Hyperthyroidism, Milk-alkali syndrome, Immobilization, excess vitamin D, and Thiazide diuretics. Symptoms can occur in almost any organ system and depend on the level of plasma calcium, the rate of rise of serum calcium and the condition of the patient. "Stones [renal calculi], bones [bone destruction secondary to malignancy], abdominal groans, and psychiatric overtones" is a rhyming device that may help clinicians remember common symptoms of hypercalcemia.

Renal involvement includes formation of calculi as well as polydipsia and polyuria due to interference with ADH action at the distal nephron, causing a diabetes insipidus–like syndrome. The resulting dehydration further exacerbates the existing hypercalcemia.

Normal calcium regulation occurs through the interaction of parathyroid hormone (PTH), calcitonin, and $1,25(OH)_2$ vitamin D. In malignancy, the derangement of this regulation leads to increased bone resorption and occasionally to decreased renal excretion of calcium. Hypercalcemia of malignancy is most commonly caused by production of a PTH-related peptide that is structurally similar to PTH. The PTH-related peptide binds to PTH receptors, thereby mobilizing calcium from bones and increasing renal reabsorption of calcium.[6,7] Some malignancies, such as multiple myeloma, secrete factors that stimulate osteoclasts to resorb bone.[7]

Hypercalcemia of malignancy typically presents with nonspecific signs and symptoms. The possibility of calcium abnormalities must be considered in any cancer patient with mental status changes or lethargy. In general, calcium levels do not correlate with symptoms, since the acuity of the rise is more important.[3] Gastrointestinal symptoms such as anorexia, nausea, vomiting, and constipation are common; these symptoms occur early in the disease course and may be erroneously attributed to underlying disease or therapy.

Neurologic symptoms are common in patients with elevated calcium levels and can include cognitive and behavioral changes, altered mental status, and neuromuscular disturbance. Psychiatric symptoms may resemble those of schizophrenia or mania.

Significant hypercalcemia is a true metabolic emergency. ED management includes continuous IV administration of normal saline at a rate based on severity of hypercalcemia, degree of dehydration, and the patient's ability to tolerate volume expansion. This should cause a modest decrease in the plasma calcium. Clinical improvement occurs within 24 to 48 hours, but IV fluids alone rarely normalize the plasma calcium level. Administration of diuretics was previously recommended, but there is little evidence to support this approach.[8] If supportive efforts do not result in clinical improvement, calcitonin 4 to 8 U/kg SC or IM every 6 to 12 hours may be initiated. This usually lowers plasma calcium within 2 to 4 hours. It may cause a hypersensitivity response, and tachyphylaxis may develop up to 3 days after administration of calcitonin.[6,7] Glucocorticoids may blunt the tachyphylaxis and may be helpful in the short term in and of themselves, especially with sensitive tumors such as lymphoma and myeloma.[6,7,9] Bisphosphonates are potent inhibitors of bone resorption and produce a sustained decrease in calcium for approximately 2 to 4 weeks beginning 12 to 48 hours after administration. Bisphosphonate is given slowly to prevent precipitation of bisphosphonate-calcium complexes in the kidney and subsequent renal failure. Gallium nitrate, mithramycin, and plicamycin are rarely used due to their toxicity.[6,7] Hemodialysis is indicated for patients with profound mental status changes, renal failure, or inability to tolerate a saline load.[1,6,7,10]

HEMATOLOGIC EMERGENCIES
Hyperviscosity Syndrome
Hyperviscosity syndrome describes a group of pathologic conditions resulting from impaired blood flow due to abnormal blood characteristics that lead to sludging, stasis, impaired microcirculation, and tissue hypoperfusion. The flow properties of blood are dependent on its fluid and cellular contents. Abnormally elevated plasma paraprotein levels are commonly seen with Waldenström macroglobulinemia. Erythrocytosis (hematocrit level >60%) from overproduction of red cells by the bone marrow or from paraneoplastic syndromes (renal cell carcinoma and hepatomas) often results in clinically significant hyperviscosity, as does leukocytosis (with a white blood cell count >100,000 cells/μL or a leukocrit level >10%) from acute and chronic leukemias.[5] Dehydration exacerbates the effects of all hyperviscosity syndromes.

If hematocrit levels exceed 60%, fatigue, abdominal pain, blurred vision, headache, or altered mental status may occur. Thrombosis with resultant stroke symptoms or signs of mesenteric ischemia is also possible.[5] Specific physical findings are rare. Funduscopic exam may reveal retinal hemorrhages, exudates, and the classic "sausage-link" vessels. The diagnosis depends on a high index of suspicion coupled with laboratory findings. Peripheral blood smear may reveal rouleaux formations (red cells stacked like coins). Serum viscosity may be more than four to five times greater than normal. Protein electrophoresis is diagnostic. Initial therapy for the symptomatic patient consists of 2-unit phlebotomy and intravascular volume repletion with 2 to 3 units of crystalloid.[5] Early consultation with a hematologist is required. Emergent plasmapheresis or leukophoresis is indicated for definitive therapy.

Neutropenia and Infection

Patients who have cancer have a 30% higher risk for death from sepsis, which accounts for approximately 10% of all cancer deaths.[11] Neutropenia is a common feature. Neutropenia is defined as an absolute neutrophil count below 500 cells/mL and is the most frequent predisposing factor to infection, especially bacteremia, in cancer patients. Febrile neutropenia is an absolute medical emergency. The mortality rate in neutropenic patients with bacteremic infection who go untreated is about 50%.[6] The most common presenting symptom is fever, which is defined as recurrent body temperatures exceeding 38.0°C or a single reading higher than 38.3°C.

Bone marrow transplants and chemotherapy decimate the immune system and cause neutropenia that can lead to overwhelming infection and in turn could hasten the death of a cancer patient. Muted signs of infection due to an impaired inflammatory response and granulocytopenia may delay diagnosis. Patients may present with only minor symptoms and clinical signs but rapidly deteriorate and die from overwhelming sepsis. Common signs of infection, such as purulence or fluctuance, may not develop. Fever, nausea/vomiting, erythema, or pain may be the only clinical findings. An exhaustive physical exam must be undertaken. Funduscopic examination may show evidence of disseminated infection or papilledema. Signs of pneumonia may be auscultatory only, as granulocytopenia may inhibit the development of an infiltrate on chest radiography. Attention to the skin is imperative, in particular the perirectal area of acute leukemia patients. The rectum and/or perineum should be inspected and palpated for pain and fluctuance indicative of developing deeper space infections such as perirectal abscess and Fournier's gangrene. Digital rectal examination is relatively contraindicated in neutropenic patients and should be withheld until after initial antibiotic administration. Clotted catheters represent a high-risk source of infection due to bacterial colonization, and central venous catheters may be associated with the development of endocarditis.

Initial ED management should focus on the ABCs of resuscitation. If signs of sepsis are evident, early goal-directed therapy should be initiated without delay. Lab tests should include complete blood count, basic metabolic panel, blood and urine cultures, and urinalysis. Chest radiography should also be performed. In patients with productive cough, diarrhea, or wound drainage, Gram stain and culture should be performed on sputum, stool, and wound drainage to evaluate for occult infection. Lumbar puncture is not routinely performed, as the incidence of meningitis is not increased with neutropenia.

Common infectious agents may be viral (cytomegalovirus, herpes simplex virus, varicella zoster), bacterial, or fungal (*Candida*, *Aspergillus*). Bacteremia is most commonly due to aerobic gram-positive cocci (coagulase-negative staphylococci, viridans streptococci, or *Staphylococcus aureus*) or aerobic gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa*). Initial empiric antimicrobial therapy should be broad spectrum to cover the range of potential bacterial pathogens. An aminoglycoside plus an extended-spectrum penicillin and third-generation cephalosporin with or without vancomycin remains the standard regimen in patients without penicillin allergy.[12] Vancomycin should be added if there is severe mucositis, catheter infection, quinolone prophylaxis, or hypotension. Secondary fungal infections are common in those who have received courses of broad-spectrum antibiotics.[12]

RENAL AND UROLOGIC SYNDROMES

Urologic emergencies in cancer patients occur frequently. The most common presentations are bladder hemorrhage, obstruction, and infection.[13] Bladder hemorrhage may be the initial presenting sign

Table. Antidotes and Therapies for Extravasated Cytotoxic Drugs

Drug	Antidote/Therapy	Instructions
Anthracyclines	Dimethyl sulfoxide	• Apply topically, let dry, repeat
	Ice packs	• Apply for 15-20 min, repeat at 6- to 8-h intervals for 1-2 days
Mitomycin	Dimethyl sulfoxide	• Apply topically, let dry, repeat
	Ice packs	• Apply for 15-20 min, repeat at 6- to 8-h intervals for 1-2 days
Mechlorethamine	Sodium thiosulfate	• Mix 1.2 mL 25% sodium thiosulfate + 8.4 mL sterile water for injection • Use existing IV line to inject 2 mL antidote per 1 mg extravasated drug • Remove IV needle, give SC injections around extravasation site
Cisplatin	Sodium thiosulfate	• Mix 1.2 mL 25% sodium thiosulfate + 8.4 mL sterile water for injection • Use existing IV line to inject 2 mL antidote per 100 mg infiltrated cisplatin • Remove IV needle, give SC injections around site
Vinca alkaloids	Hyaluronidase	• Reconstitute with normal saline • Use existing IV line to inject 150-900 U into extravasation site
	Warm packs	• Elevate arm • Apply warm pack for 15-20 min, repeat at least every 6 h for 1-2 days
Paclitaxel	Hyaluronidase	• Reconstitute with normal saline • Use existing IV line to inject 150-900 U into extravasation site
	Ice packs	• Apply for 15-20 min, repeat at 6- to 8-h intervals for 1-2 days

Adapted from Brandoff and Abrahm[15]; Ener et al.[16]

of malignancy, or it may be secondary to tumor invasion, chemotherapy, radiation therapy, or infection. This can progress to a life-threatening emergency with clot retention, obstruction, or hemodynamic instability. Initial ED treatment involves insertion of a multiple-hole bladder catheter with continuous saline lavage. Occasionally, endoscopic clot evacuation is needed. Options to control bleeding include intravesicular agents (alum, prostaglandins, phenol, and silver nitrate), iced saline lavage, and oral or IV aminocaproic acid.

Ureteral obstruction can occur due to direct tumor invasion or compression, retroperitoneal lymph node enlargement, or direct metastases. Surgery, chemotherapy, or radiation therapy can cause retroperitoneal fibrosis with compression. Acute unilateral obstruction presents with symptoms identical to those of ureterolithiasis, while chronic unilateral obstruction is usually asymptomatic and often found incidentally as hydronephrosis on CT. Urologic consultation for relief of obstruction is required.

Lower urinary tract obstruction can be caused by mechanical or neurophysiologic factors. The common treatment regimen of antiemetics, pain medications, and hydration may precipitate urinary retention in male patients with preexisting prostatism. ED treatment is insertion of a bladder catheter. A catheter with a coudé tip may be needed if passage of standard catheters cannot be accomplished.

DERMATOLOGIC/IMMUNOLOGIC EMERGENCIES

Chemotherapy Drug Extravasation and Hypersensitivity Reactions

Drug extravasation and hypersensitivity reactions are the two most common emergencies related to chemotherapy.[14] Not surprisingly, extravasation of most chemotherapeutic agents causes local tissue injury. If extravasation occurs through a peripheral line, the infusion should be stopped and an attempt should be made to aspirate through the line. If an antidote for the particular agent exists (Table),[15,16] it should be administered through the original line while avoiding pressure to the affected area to prevent further dispersion of the offending agent. Other more conservative measures include rest and elevation of the affected part. There are no indications for cortico-steroids or the use of bicarbonate to alter local pH. Hyaluronidase injected locally has been shown to enhance absorption of some drugs. Topical dimethyl sulfoxide has also been proposed as an antidote.[14] It functions as a potent free-radical scavenger, and it also aids in the removal of the drug from soft tissue. Hypersensitivity reactions are treated in the usual manner with epinephrine, H_1 and H_2 blockers, IV fluids, nebulized albuterol, and steroids as needed.[17]

GASTROINTESTINAL EMERGENCIES

Nausea and Vomiting

Nausea and vomiting are common among patients undergoing chemotherapy. Incidence varies by type of chemotherapy. Nausea and vomiting are due to the action of chemotherapeutic agents on the area postrema (vomiting center) located in the medulla. Initial ED evaluation should consider other causes of nausea and vomiting, including increased intracranial pressure, bowel obstruction, infection, and cardiopulmonary disease. ED management includes rehydration with IV crystalloids, correction of electrolyte abnormalities, and administration of antiemetics. Commonly used agents include dopamine receptor antagonists (metoclopramide, promethazine), benzodiazepines, histamine antagonists (diphenhydramine),

and dexamethasone. However, the drugs of choice for treating chemotherapy-induced nausea and vomiting are the serotonin antagonists (ondansetron, dolasetron, granisetron).[10]

PAIN

Pain is extremely common and debilitating in cancer patients. Overall, 75% of patients with cancer experience pain severe enough to require treatment with opioids during their illness.[18] Pain is, of course, subjective and can be influenced by the patient's life experiences, cultural and spiritual beliefs, and physical state. The types of pain experienced by cancer patients can be categorized as somatic (metastatic disease to bone), visceral (neoplastic cell injury to internal organs), and neuropathic (neoplastic cell infiltration or compression of central or peripheral nerves). Several cancer pain syndromes have been identified, including radiation- and chemotherapy-induced mucositis affecting the mouth and lower gastrointestinal tract, vinca alkaloid–induced polyneuropathy, and radiation-induced neuropathy, plexopathy, and myelopathy.

The pain associated with cancer requires aggressive treatment and avoidance of "oligoanalgesia," or the underuse of analgesics. Undertreatment of cancer-related pain, often due to the concern of addiction, is common. The concern of causing addiction in the patient with significant cancer-related pain should be disregarded. First-line therapy should be IV opioids, which allow for a more rapid onset of action and the ability to titrate to effect. Nonopioid analgesics like NSAIDs, acetaminophen, or tramadol may act as adjuvants to narcotic therapies, allowing lower narcotic dosages, and should be concomitantly administered if there are no contraindications. Corticosteroids also can be used as opioid adjuvants, usually in patients in the terminal phases of cancer, although drug, dose, route, and schedule are not standardized.

CONCLUSION

Cancer and its treatments have far-reaching effects on quality and quantity of life. In this age of advancements in cancer therapy, longer disease survival rates, and greater life expectancies in general, it is increasingly common for patients with cancer-related emergencies to present to the ED. Such emergencies can lead to devastating complications, including long-term morbidity and death. Prompt recognition of the emergency, combined with an accurate diagnosis and timely, appropriate treatment, increases the likelihood of a good outcome in these patients. □

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