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Oncologic Emergencies

I recall rounding on the oncology ward as a medical student. The prognosis in those days was bad for nearly every patient. Children with acute lymphoblastic leukemia were expected to live less than one year. Adults with acute myeloblastic leukemia, less than three months. What a difference in the past three decades.

With longer survival, however, there are more patients presenting with life-threatening emergencies related to their treatment and tumor. The Baby-Boomers are now entering their 60s and will clearly add to the number of patients with malignancy. In addition, there is more urgency now than 30 years ago to treat these patients, as many survivors will go on to live productive lives.

This article will deal with several of the true emergencies seen in patients with cancer. Cancer patients may present to the emergency department with a variety of clinical complaints. Many of these must be diagnosed and treated urgently and represent an immediate threat to the patient's life or functional capacity. These constitute a variety of metabolic and structural entities that will be addressed in turn.

—Sandra M. Schneider, MD, FACP, Editor

Fever in the Neutropenic Cancer Patient

Fever in the neutropenic patient is a medical emergency. Historically, infections accounted for approximately 75% of the mortality related to cancer chemotherapy. Despite improvements in antibiotics and neutrophil function, infection is still the number one cause of cancer death. Fever is defined as a single temperature of greater than 38.3° C or a sustained temperature of greater than 38° C for more than one hour.[1] Neutropenia is defined as an absolute neutrophil count (ANC) of less than 0.5 X 10^9/L or 500 cells/microliter or less than 1.0 X 10^9/L with an expected decline to less than 0.5 X 10^9/L within 24 hours.[2] Most chemotherapy regimens result in a neutrophil trough 7-10 days after treatment, with an expected rise after 5 more days.[3] Fever in the cancer patient may have non-infectious causes: inflammation, tumor necrosis, transfusions, and medications, to name a few. However, neutropenic febrile patients should be treated for infection. Factors that favor an infectious cause include prolonged duration of neutropenia, the presence of central and peripheral venous catheters, or a rapid decline in ANC.[4,5] (*See Table 1.*)

The risk of infection increases as the ANC diminishes. While neutropenia decreases the patient's ability to fight infection, chemotherapy may increase infection by inducing mucositis throughout the gastrointestinal tract and causing seeding of endogenous flora. The use of rectal temperatures in these patients has been called into question because of the possibility of bacterial seeding and disseminated infection. Surgical procedures and underlying immune defects may contribute to infectious risk. An indwelling nasogastric feeding tube may predispose to sinusitis. Indwelling catheters, venous or urinary, often are the sites of infection.

The history should include the type of chemotherapy and when it was given. Patients often are keenly aware of their blood counts, and this should be documented. Any symptoms associated with the fever may be helpful; however, these often are absent. The physical examination should include examination of the skin

Executive Summary

- A neutropenic patient with fever may show few focal signs of infection but should be cultured and started on broad spectrum antibiotics.
- Spinal cord compression is a medical emergency and should be treated rapidly to prevent further neurologic deterioration. MRI or CT myelogram is the diagnostic study of choice. Initial treatment is dexamethasone.
- Patients with intracranial metastases and increased intracranial pressure should be treated by raising the head of the bed 10 degrees. Hyperventilation carries the risk of decreasing cerebral perfusion pressure. Mannitol is rapidly effective but can lead to rebound edema. Dexamethasone is used to decrease pressure long term.
- Think hypercalcemia in patients who present with acute mental status changes, constipation, polyuria/polydipsia, and anorexia. Initial treatment is saline infusion.
- Hyperviscosity syndrome leads to mental status changes and neurologic symptoms, bleeding, and visual changes.

and mucous membranes for erythema, cellulitis, ulcers, paronychia, and rectal inflammation. It is particularly important to examine the teeth and oral mucosa. All indwelling lines should be examined for swelling or erythema. Funduscopic examination may show evidence for endophthalmitis.

An infectious source is identified in only approximately one-third of febrile neutropenic episodes.[6] Diagnostic studies to be performed include a complete blood count and differential so that an ANC can be calculated. Blood chemistries, including transaminases, amylase, and coagulation studies, should be obtained, as well as urine cultures and two sets of blood cultures. At least one set of cultures should be drawn from an indwelling venous line if one is present. A chest x-ray should be obtained with the caveat that an infiltrate may not be visible if the inflammatory response is minimal. Chest CT is more sensitive for detecting pneumonia if clinically suspected by persistent fever.[7] Lumbar puncture should be considered if there is any suspicion of meningitis or alteration of mental status.

Emergency physicians must be aware of infection patterns within their hospital. While gram-negative infections predominated in the 1970s, more recently gram-positive infections accounted for most infections, perhaps related to an increase in indwelling central venous catheters.[8,9] Fungal infections, especially with Candida species, are common. Immunocompromised patients may be infected with histoplasma, aspergillosis or other species. Candida is especially common in line infections. Aspergillosis may manifest itself with skin ulcers, pneumonia, or sinusitis.[10] Important viral pathogens in the cancer patient include herpes simplex, cytomegalovirus, and Epstein-Barr virus.

Treatment should be initiated with antimicrobial therapy as soon as possible after appropriate cultures have been obtained. The optimal regimen should be bactericidal, relatively nontoxic, and address a broad range of likely gram-positive and gram-negative pathogens. (*See Table 2.*) Vancomycin should be added if there is a high suspicion for gram-positive infection, as from *Staphylococcus epidermidis* from an indwelling line. Suggested initial antibiotic therapy for patients with neutropenic fever includes:

- monotherapy with meropenem or ceftazidime;
- monotherapy with imipenem or cefepime;
- piperocillin-tazobactam;
- addition of vancomycin for patients with hypotension, suspected line sepsis or mucositis, with linezolid as an alternative for patients intolerant to vancomycin;
- addition of an aminoglycoside for better gram-negative coverage in critically ill patients [1,11,12]

Although not of direct relevance to emergency practice, anti-fungal therapy with amphotericin B, voriconazole, or capsofungin may be given to patients with persistent fever after 4 days of antibiotic therapy. The most common fungal infections in febrile neutropenic patients are candiasis and aspergillosis, and autopsy studies of neutropenic patients with prolonged fever indicate that 40-69% of patients had evidence of an invasive fungal infection.[13] Colony-stimulating factors may reduce the duration of neutropenia but have not been demonstrated to reduce mortality acutely and are not within the scope of emergency practice. Patients who are hypotensive, hypothermic, or have an altered mental status have poorer prognosis.

Malignant Spinal Cord Compression

Approximately 2.5% of patients with cancer have malignant spinal cord compression (MSCC) as a complication.[14] The risk is greatest in the last 5 years of life. Epidural spinal cord compression occurs when cancer within the epidural space compresses either the cauda equinae or the spinal cord itself. Breast, prostate, and lung cancers account for most of the cases, although lymphomas, sarcomas, multiple myeloma, and renal cell carcinoma are not unusual.[15] The thoracic spine is the most common site of metastases that cause spinal cord compression.[16] MCSS may be the initial

Table 1: Factors in Consideration of the Cancer Patient with Suspected Sepsis

- In-dwelling catheters
- Disruption of mucous membranes or skin
- Cancer not in remission
- Prolonged steroid use, other immunosuppression

Table 2: Suggested Antibiotic Regimens for Antimicrobial Therapy of the Febrile Neutropenic Cancer Patient

- Monotherapy with cefepime or ceftazidime or a carbapenem (meropenem or imipenem/cilastatin) or piperacillin-tazobactam
- Addition of an aminoglycoside if better gram-negative coverage needed
- Addition of vancomycin or linezolid if additional gram-positive coverage needed (hypotension, mucositis, indwelling catheter site infection, colonization with MRSA)
- Any antipseudomonal penicillin (ticarcillin/clavulanate, piperacillin-tazobactam) with or without an aminoglycoside

presentation of tumor in a patient with no prior diagnosis of malignancy in approximately 20% of cases.[17]

In general, epidural masses occur as the result of extension of metastasis from the spine. Vertebral body tumors arise from the hematogenous spread of tumor cells. Approximately 60% of cases occur in the thoracic spine, 30% in the lumbosacral spine, and 10% in the cervical spine.[15] Tumors may grow through the intravertebral foramen, sparing the vertebral bone itself, making bony destruction on x-ray an unreliable finding. Venous plexus obstruction can cause cord edema, while arterial occlusion by tumor can cause an acute infarction. As tumor grows in the epidural space, it encircles the thecal sac, causing vasogenic edema.

Intramedullary spinal cord metastasis is less common than epidural cord compression. Solid tumors that may cause this include lung and breast cancer as well as lymphoma. It is difficult to differentiate between intramedullary involvement and epidural involvement. The long-term prognosis for patients with intramedullary tumors is poor. Regardless of location, the goal is to establish the diagnosis prior to the development of spinal cord damage.

The great majority of patients with MSCC have back pain and a pre-existing diagnosis of malignancy. Pain may be severe and is worse in the recumbent position. Presenting symptoms may include radicular pain, gait disturbance, motor weakness, or loss of bowel or bladder function. The pain may precede any other symptoms of malignancy by 1-2 months. Although the pain may be radicular, as in disc disease, the pain from malignancy is constant and progressive. Abrupt worsening of pain may signify a pathologic compression fracture.

On examination, midline bony tenderness may be present. The patient may have a sensory loss distal to the lesion. Ataxic gait may be present. Hyperereflexia below the level of the compression may be seen. Motor weakness at the time of diagnosis is seen in the great majority of cases, and typically is symmetric.[18] A lateral epidural lesion may preferentially affect a nerve root and show a peripheral motor radiculopathy. As with lumbar disc disease, the pain may increase with straight leg raise or with maneuvers that increase intrathoracic pressure, such as the Valsalva maneuver.

Other disorders with similar presentation include disc herniation, epidural abscess, bleeding, and other infections, such as tuberculosis. The differential diagnosis includes meningiomas and neurofibromas, which may present in a fashion similar to MSCC and also may require urgent intervention.

The primary determinant of the patient's outcome is his or her neurologic status at presentation. Since neurologic deficits may not improve with treatment, it is paramount to diagnose this entity as early as possible before neurologic dysfunction develops. Tragically, however, the majority of patients with newly diagnosed MSCC are not ambulatory at diagnosis.[19,20]

The imaging modality of choice is magnetic resonance imaging (MRI). Although some abnormal findings on plain radiographs have been reported in up to 80% of patients with symptomatic spinal metastases,[21] CT or MRI gives much more useful information. X-rays in a cancer patient who is experiencing back pain may show vertebral body collapse and pedicle erosion in MSCC, but MRI or CT myelography demonstrates the required anatomy much more reliably. Plain films of the spine are useful only if they are abnormal; there is a high false-negative rate because not all tumor invades the epidural space via the bone. Furthermore, 30-50% of bone must be destroyed before it will be visible on plain film. However, in a cancer patient with back pain, vertebral body collapse or pedicle erosion predicts a high chance of MSCC when a more definitive test is performed.[22]

Radionuclide bone scanning is sensitive for detecting bone metastases but does not show thecal sac compression and therefore is not a useful modality for diagnosing MSCC.

MRI produces anatomically accurate images of the spinal cord and intramedullary pathology. Unlike CT myelography, MRI can image the entire thecal sac even if a subarachnoid block is present and can be performed in patients with coagulopathy or thrombocytopenia.

If MRI is unavailable or contraindicated, CT myelography should be used. Myelography entails a lumbar or cervical puncture. MRI and CT myelography are roughly equivalent in terms of sensitivity and specificity.[23]

CT myelography can delineate extradural compression of the thecal

sac. This technology may be more widely available than MRI at some institutions. It has the disadvantage of being invasive and uncomfortable, but it can image the entire spinal axis in a single study and may be employed in patients with mechanical valves, pacemakers, or shrapnel in whom MRI is not possible. It also affords the opportunity for cerebrospinal fluid (CSF) analysis, essential for the diagnosis of leptomeningeal metastases. On rare occasions, patients with complete subarachnoid block can deteriorate neurologically when CSF pressure has been reduced by the lumbar puncture.

For patients with recent onset of symptoms or rapid progression of symptoms from MSCC, urgent treatment is warranted. Pain should be addressed, as should management of the primary tumor. However, specific therapy for MSCC is paramount. Treatment entails glucocorticoid administration as soon as the diagnosis is made. Dexamethasone is given as an initial dose of 10-16 mg followed by 4 mg every 4 hours. A dose as high as 100 mg of dexamethasone has been proposed.[24] The beneficial actions of steroids in MSCC may be related to treatment of vasogenic edema. The initial treatment of these patients should be coordinated with an oncologist or neurosurgeon.

Radiation therapy historically has been a mainstay of treatment,[25] but radical tumor resection followed by radiation may give a better functional outcome.[26] In patients with spine instability or rapidly progressive symptoms, surgery may be preferred. Surgery may be appropriate to control pain, limit the progression of neurologic deficits, and allow stabilization of the spine. A tissue diagnosis may be obtained as well. Long-term prognosis may depend on the type of malignancy causing the cord compression and how quickly the syndrome is recognized and therapy initiated. In one report, there was a median delay to treatment of 2 months in patients with back pain and known malignancy, and a median of 14 days from onset of symptoms until signs of spinal cord compression.[19]

Brain Metastasis and Elevated Intracranial Pressure

Intracranial metastases occur in as many as 25% of patients dying of cancer.[27] While any number of malignancies are capable of metastasizing to the brain, the most common tumors are lung, breast, and melanomas. Brain metastases arise from hematogenous spread of the tumor and are found mostly in the supratentorial region at the junction of white and gray matter.[28]

Most patients with brain metastases have already been diagnosed with cancer. However, brain metastases may be the initial manifestation of disease. In some cases, the primary tumor is never found.[29]

The clinical features of brain masses result from direct destruction or compression of brain tissue either by the metastases or from tumor-associated brain edema. Compromise of vasculature or of cerebrospinal fluid flow may cause additional brain injury from elevated intracranial pressure (ICP). Symptoms may be focal or generalized depending upon location of the lesions.

Headache occurs in approximately 50% of patients.[30] Brain tumors cause headache due to alteration in ICP or via traction on pain-sensitive areas within the brain. These include venous sinuses and the dura matter. The headache associated with brain metastases and increased ICP typically is retro-orbital and associated with nausea and vomiting. The headache may be worse in the morning, but this is not a reliable finding. Seizure of new onset may be a presenting complaint. The patient may complain of blurred or double vision or visual field defects. If the ICP continues to worsen, alterations in mental status may develop.

With localized tissue compression and destruction, focal neurologic deficits are common, including motor or sensory deficits, cerebellar symptoms, or personality changes. These often are subtle and slow in onset. If there is hemorrhage into the tumor and an acute change in the ICP, life-threatening symptoms may develop rapidly, necessitating acute intervention. Herniation may be seen and can be central, uncal, or tonsillar and manifested by alteration in respiratory pattern, papillary size, or level of consciousness.

The diagnosis can be made with contrast CT or MRI, although MRI is more sensitive, especially for lesions in the posterior fossa.[28,31] When available and renal function permits, an MRI with gadolinium contrast is preferred. In the patient with a known primary cancer capable of producing brain metastases, tissue diagnosis usually is not necessary. For those patients with no known primary cancer, a focused evaluation for a primary tumor is initiated. Evaluation, therefore, might include chest radiograph or CT, abdominal CT, complete examination of the skin and breasts, and rectal and testicular examination as appropriate. If no primary tumor is identified, the patient then may require a brain biopsy.

Acute changes in mental status, new focal abnormalities, and acute seizures result from vasogenic cerebral edema. Urgent intervention to prevent cerebral herniation may be needed with 4-16 mg or more of dexamathasone. The airway should be addressed with intubation if necessary. Elevation of head to 10 degrees is helpful in lowering intracranial pressure. Hyperventilation to a pCO_2 of 25-30 mm Hg is only a temporizing measure to lower ICP and is used with caution. There is concern that hyperventilation, while it decreases intracranial pressure, also decreases blood flow to watershed areas, decreases cerebral perfusion pressure, and decreases systemic mean arterial blood pressure by decreasing diastolic filling of the heart. The effect is not long lasting (10-20 hours), as the pH of the cerebrospinal fluid equilibrates.[32] For elevated ICP, mannitol 1 gram/kg intravenously repeated in 4-6 hours or furosemide 40-120 mg intravenously has been employed. Mannitol is rapidly acting with an effect in 1-5 minutes, peaking in 20-60 minutes. The effect lasts 1.5-6 hours. However, there is a rebound effect if other measures to decrease

Table 3: Emergency Management of Hypercalcemia in Malignancy

Therapy	Dosage
Saline	250-500 mL/h IV, assessing hydration until normovolemic and 100-150 mL/h IV thereafter to maintain urine output at 100-150 mL/hr
Furosemide	20-40 mg IV for fluid overload or after patient rehydrated
Bisphosphonates	
Pamidronate	60-90 mg IV over 2-4 h or
Zoledronic acid	4 mg IV over at least 15 min
Calcitonin	4-8 IU/kg SC or IV every 12 h
Glucocorticoids	Prednisone, 60 mg/d orally; Hydrocortisone, 100 mg every 6 h IV, may be useful in Hodgkin's disease and some lymphomas

pressure (such as steroids or surgery) are not initiated.

Seizures may be managed with a benzodiazepine such as lorazepam, or phenytoin/fosphenytoin.

For less significant problems related to tumor edema, the patient may be given lower doses of dexamethasone to improve symptoms but limit side effects. Additional measures such as pain control and exact diagnosis should be addressed. Approximately 70-80% of patients with brain metastasis will improve, at least temporarily, with dexamethasone.[33]

More definitive treatment of the underlying malignancy should be discussed with oncology, radiation therapy, or neurosurgery. While radiation has been the mainstay of therapy for brain metastases, stereotactic radiosurgery has emerged as an option for selected patients with metastatic disease to the brain.[34]

The decisions about how aggressively to diagnose and treat these patients rests with a team of providers, which includes the family and patient's wishes, the status of the primary cancer, the performance status of the patient, and the number of brain metastases. Since solid tumor metastasis to brain portends an ominous course, treatment may be strictly palliative.

Hypercalcemia

Hypercalcemia is a frequently occurring event in patients with advanced malignancy, having been reported in 10-30% of patients with cancer at some time during their disease.[35,36] Hypercalcemia of malignancy may be due to several factors: elaboration of a parathyroid-hormone-related protein, local bone destruction, and tumor-producing vitamin D-like substances.[36]

The severity of symptoms may not correlate with serum calcium levels. The rate of increase in serum calcium concentration as well as the degree of hypercalcemia often determine symptoms and urgency of therapy.[37] Patients with chronic hypercalcemia may be minimally symptomatic with levels of 15 mg/dL, while patients with acute hypercalcemia may present with coma with levels as low as 12 mg/dL. Acute hypercalcemia presents with CNS effects ranging from personality changes such as lethargy, paranoia, confusion, depression, or somnolence to coma. Chronic hypercalcemia may present with constipation, polyuria, polydipsia, anorexia, nausea, memory loss, or a shortened QT interval of the electrocardiogram.

The most common malignancies associated with hypercalcemia include multiple myeloma, lung cancer, and breast cancer.[25,35] These patients may have other fluid/electrolyte abnormalities, such as hypokalemia or dehydration. Serum phosphorus, albumin, and alkaline phosphatase should be measured as well. In patients with hypoalbuminemia, total serum calcium concentration may be normal when serum ionized calcium is elevated. The measured serum calcium should be added to 0.8 (4.0-albumin) to correct for hypoalbuminemia.[25] A serum calcium level above 14 mg/dL generally constitutes a medical emergency requiring treatment even if the patient appears minimally symptomatic.

Therapy usually is initiated with isotonic saline intravenously (> 200 mL/hr if tolerated). (*See Table 3.*) This restores blood volume and increases urinary calcium excretion. The aim is to maintain urine output at 100-150 mL/hour. If the patient is fluid overloaded initially, a loop diuretic that inhibits passive reabsorption of sodium, such as furosemide, can be given. Patients should be monitored for hypomagnesemia, hypokalemia, and hypovolemia if a loop diuretic is given. Medications that increase serum calcium should be avoided, including thiazide diuretics.

Bisphosphonates inhibit calcium release by interfering with osteoclast-mediated bone resorption.[38] Their maximum effect occurs in 2-4 days, and they usually are given with saline as above and, possibly, calcitonin.[36,39] Pamidronate 60-90 mg intravenously over several hours or zoledronic acid 4 mg IV over at least 15 minutes are recommended.[36] Other oral bisphosphonates are not used emergently. Etidronate is available IV but is less effective than the other parenteral agents. Side effects of all bisphosphonates include impaired renal function, hypophosphatemia, and osteonecrosis of the jaw.[40]

Calcitonin increases renal calcium excretion and decreases bone reabsorption. In intramuscular or subcutaneous

Table 4: The Clinical Presentation of Hyperviscocity Syndrome

- **Visual disturbances:** Blurring, diplopia, vision loss, retinal vein occlusion, retinal hemorrhage
- **Bleeding:** Epistaxis, gingival bleeding, hematuria, vaginal bleeding, rectal bleeding
- **Neurologic:** Mental status changes, headache, ataxia, vertigo, seizures, tinnitus, deafness
- **Other:** Dyspnea, congestive heart failure

Table 5: Laboratory Abnormalities in SIADH

- Low sodium
- Elevated urinary sodium (>20-40 mEq/L)
- Inappropriately elevated urine osmolality

doses of 4 IU/kg, calcitonin works rapidly to lower serum calcium by 1-2 mg/dL within 4-6 hours.[41] Gallium nitrate was found to lower calcium incidentally in patients undergoing gallium imaging but does not appear to have a role in the emergency setting. Glucocorticoids, such as hydrocortisone 100 mg IV every 6 hours, may be useful if the hypercalcemia is related to elevated levels of vitamin D, as in Hodgkin's disease and some lymphomas. Treatment of the underlying malignancy ultimately controls the hypercalcemia. As a treatment of last resort, hemodialysis or peritoneal dialysis are effective therapies for hypercalcemia.[42,43]

Hyperviscosity Syndrome

Hyperviscosity syndrome (HVS) commonly is seen in certain cancers and polycythemia vera, but also may complicate certain benign entities such as collagen vascular disease. Elevated serum proteins elaborated by some cancers or elevated levels of leukocytes or erythrocytes may increase the viscosity of patients' blood, with sludging and decreased perfusion at the microvascular level. The systems most at risk from vascular sludging are the visual, cardiopulmonary, and central nervous systems, respectively.

The most common causes of hyperviscosity syndrome include the dysproteinemias, IgG and IgA myelomas, IgM Waldenstrom's macroglobulinemia, and certain leukemias. Hyperviscosity symptoms were present in 31% of patients with Waldenstrom's macroglobinemia in one report.[44] The risk of developing this syndrome in patients with leukemias increases in those patients with granulocyte counts above 100,000 and lymphocyte counts greater than 750,000.

Classically, HVS presents with the triad of bleeding, visual disturbances, and neurologic symptoms. (*See Table 4.*) Neurologic symptoms include vision loss or blurring, headache, vertigo, diplopia, ataxia, nystagmus, and deafness. Seizures may be jacksonian or generalized. More marked viscosity may progress to confusion, dementia, stroke, or loss of consciousness.[45] Hemorrhagic diathesis may be manifested by epistaxis or gingival bleeding, hematuria, or rectal or vaginal bleeding. The physical examination may show pallor due to anemia, lymphadenopathy or hepatosplenomegaly from the underlying malignancy.[46] Papilledema, retinal hemorrhages or exudates, or retinal detachment may be noted. Manifestations apart from the typical triad include cardiac complications such as angina, myocardial infarction, and heart failure.

The diagnosis of HVS is largely clinical, based upon the presence of typical symptoms in a patient at risk. Coagulation, CBC, and renal profiles should be obtained, as well as serum and urine protein electrophoresis. Rouleaux formation may be noted on a peripheral smear. In patients with diseases that put them at risk of HVS, a serum viscosity level may be obtained. This is measured in units of centipoises (CP), with a normal level less than 1.8 CP and most patients becoming symptomatic at levels greater than 6 CP. This number reflects the serum viscosity relative to water.

Management of HVS begins with recognition. Initial treatment includes careful hydration and diuresis. For the patient with extreme elevation of the white blood cell count, leukopheresis should be considered. If a dysproteinemia is the cause, plasmapheresis is indicated. If neither of these interventions is available immediately at an institution, phlebotomy should be performed with initial aliquots of 100-200 cc. The patient then should be transferred expeditiously to a center capable of plasmapheresis and leukopheresis.

Syndrome of Inappropriate Antidiuretic Hormone

In patients with cancer, the syndrome of inappropriate antidiuretic hormone (SIADH) is a paraneoplastic syndrome resulting from the secretion of arginine vasopressin (also known as antidiuretic hormone). The increased production of ADH results in a characteristic constellation of chemical abnormalities including hypo-osmolality, hyponatremia, and an inappropriately elevated urine osmolality, generally above 100 mosmol/kg. (*See Table 5.*) Urine sodium usually is above 40 meq/liter. Potassium levels typically are unaffected, and acid-base balance should be normal unless there are confounding factors.[47,48]

SIADH may result from stroke, hemorrhage, infection, or other central nervous system disorders that can enhance ADH release. The secretion of vasopressin causes increased water reabsorption in the collecting ducts of the kidneys and an increased loss of sodium in the urine. In patients with cancer, the increase in ADH levels usually is the result of increased secretion by certain tumors. Ectopic production

of ADH by a tumor is most often due to small cell carcinoma of the lung; SIADH may occur in up to 10% of cases. However, other cancers of the head and neck, pancreas and duodenum may be responsible.[49,50] Some drugs can enhance ADH release or effect, notably the chemotherapy drugs vincristine and cyclophosphamide.[51]

The clinical findings of SIADH are due primarily to hyponatremia. In some cases, the patient will be asymptomatic. Patients may complain of fatigue, emesis, myalgias, and poor appetite. As the sodium level falls, patients may develop altered mental status, seizures, psychosis, lethargy, or coma.

Recent chemotherapeutic agents should be reviewed, along with a search for central nervous system disease or pulmonary disease, especially pneumonia, asthma, atelectasis, or pneumothorax.[52]

The hallmark for diagnosis of SIADH is hyponatremia with hypoosmolality, elevated fractional excretion of sodium (> 40 mEq/L), and normal volume status. As noted above, there should be an inappropriately elevated urine osmolality (> 100 mosmol/kg). There should not be other reasons for normovolemic hyponatremia, such as: diuretic therapy, pre-existing renal disease, adrenal insufficiency, or hypothyroidism.

Treatment of SIADH depends upon the severity of symptoms and the acuity of onset of the hyponatremia. Mild degrees of hyponatremia may not necessitate any immediate treatment. Mild hyponatremia in an asymptomatic patient can be treated as an outpatient with fluid restriction. Symptomatic patients with significant hyponatremia may need to be hospitalized. In more severe cases unresponsive to fluid restriction, therapy with demeclocycline may induce a reversible nephrogenic diabetes insipidus that counteracts the influence of the excess vasopressin. If the SIADH is due to chemotherapeutic agents, the patient's therapeutic regimen will need to be altered.

In those patients with more severe degrees of hyponatremia or those with significant central nervous system symptoms related to their hyponatremia, normal saline can be initiated. For those with seizures and altered mental status, 3% hypertonic saline (300-500 cc at a time over 3-4 hours) may be administered, followed by furosemide to control intravascular volume.[53] It is desirable to control the rate of correction of serum sodium to no more than 0.5-1 mEq/L/hour to prevent central nervous system disorders such as central pontine myelinolysis. These patients will require admission to intensive care.

Table 6: Laboratory Abnormalities in Tumor Lysis Syndrome

- Elevated uric acid level
- Elevated BUN, creatinine
- Elevated phosphorus
- Decreased calcium
- Elevated potassium
- Elevated lactate dehydrogenase (LDH)

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency caused by a massive destruction of cancer cells, with ensuing release of nucleic acids, potassium, and phosphate into the circulation. Hyperuricemia is a result of the breakdown of purine nucleic acids to hypoxanthine and xanthine, and then to uric acid via the enzyme xanthine oxidase. The precipitation of uric acid into the renal tubules can lead to renal failure. TLS most commonly occurs in cancer types with a high proliferative rate, large tumor burden, or those particularly sensitive to cytotoxic therapy. These include acute lymphoblastic leukemia and Burkitt's or other non-Hodgkin's lymphomas, but other tumor types have been implicated.

Specific laboratory abnormalities were proposed in 2004 to define TLS.[54] These include an elevated uric acid > 8 mg/dL, a serum potassium of > 6.0 mmol/L or 25% increase from baseline, an elevated serum phosphate > 6.5 mg/dL in children or > 4.5 mg/dL in adults, and/or a depressed serum calcium < 7 mg/dL or a 25% decrease from baseline. (*See Table 6.*) Serum lactate dehydrogenase (LDH) typically is elevated.[55]

Clinically, TLS presents with increased serum creatinine, cardiac dysrhythmia or sudden death, or a seizure. Other manifestations of TLS include nausea, vomiting, diarrhea, lethargy, anorexia, tetany, cramps, or syncope. Urinalysis may show urate crystals. An electrocardiogram should be performed in patients with serious electrolyte abnormalities.

Historically, the xanthine oxidase inhibitor allopurinol has been employed to lower the peak uric acid level and to prevent uric acid nephropathy.[56] Allopurinol acts by decreasing uric acid formation. If there is pre-existing hyperuricemia, the agent rasburicase is preferred. Allopurinol treatment leads to the accumulation of hypoxanthine and xanthine. Since xanthine is less soluble than uric acid, it may precipitate in the renal tubules. Urinary alkalinization increases the solubility of uric acid, but not of xanthine, and its use has fallen out of favor as therapy for TLS because of the potential to form xanthine crystals resulting in obstruction of renal tubules.[54]

Treatment includes aggressive hydration at approximately 3-6 liters per day of IV fluid to keep urine output at 100-200 mL per hour. Potassium should be withheld from hydration fluids initially due to the risk of hyperkalemia, as should calcium due to the risk of calcium phosphate precipitation. Urinary alkalinization has the potential disadvantage of promoting calcium phosphate deposition in the kidney and elsewhere.[57]

The usual allopurinol dose in adults is 10 mg/kg/day in 3 divided doses, initiated 24-48 hours before chemotherapy and continued for up

Table 7: Causes for Superior Vena Cava Syndrome

- **Malignancy:** Non-small cell lung cancer, small cell lung cancer, non-Hodgkin's lymphoma
- **Other tumors:** thymoma, mediastinal germ cell tumors, mesothelioma
- **Non-malignant:** fibrosing mediastinitis/prior fungal infection, tuberculosis, post-radiation fibrosis, thrombosis from indwelling intravascular devices

Table 8: Symptoms of Superior Vena Cava Obstruction

- Dyspnea
- Fatigue
- Facial flushing and edema, upper extremity edema
- Headache
- Dilated veins of upper extremities, neck, and chest
- Altered mental status, coma
- Chest pain
- Syncope
- Cough
- Dysphagia

to one week.[57] The alternative to allopurinol, rasburicase, a recombinant urate oxidase, catalyzes the degradation of uric acid and rapidly lowers serum uric acid levels. It is effective in preventing and treating hyperuricemia and in treating TLS.[58] It may be given at a dose of 0.15 to 0.2 mg/kg in 50 mL of isotonic saline infused over 30 minutes once daily for 5-7 days but is only approved for pediatric patients. Serum levels of calcium, phosphate, uric acid, potassium, creatinine, and LDH should be monitored.

Hyperphosphatemia can be treated with aluminum hydroxide, a phosphate binder, and with restriction of phosphate intake. Dialysis may be necessary to treat persistent hyperphosphatemia, hypocalcemia, or low urine output. The best management is prevention via intravenous hydration and with hypouricemic agents.[57]

Neoplastic Cardiac Tamponade

Pericardial effusions are seen in patients with advanced cancer and may be asymptomatic. Effusions can result from metastases or from direct invasion of the cancer. An accumulation of fluid in the pericardial sac and an accompanying rise in intrapericardial pressure prevents ventricular filling and results in circulatory compromise. Tachycardia is seen and the kidneys retain sodium and water as a result of decrease in renal blood flow. Tamponade may result in sudden deterioration or death. Most patients with a malignant pericardial effusion die within one year of diagnosis.[59] The most common primary cancers causing tamponade include breast, lung, melanomas, leukemias, and lymphomas.[60] Tamponade may seen with post-radiation fibrosis or constrictive pericarditis. This is a difficult diagnosis to make.

Presenting signs and symptoms include dyspnea, anxiety, hypotension, or chest pain. The patient may have a cough, nausea/vomiting, or hiccups. Right upper quadrant pain or epigastric pain result from visceral congestion. The patient may appear pale or diaphoretic, confused, or unresponsive. The patient may have rapid, labored breathing or distended jugular veins. Neck fullness and facial erythema mimic superior vena cava syndrome. The classic Kussmaul signs of quiet heart sounds, tachycardia, pulsus paradoxus, and enlarged cardiac silhouette may be present. Ascites, hepatomegaly, and peripheral edema are indicative of elevated venous pressure. Pulsus alternans may be present.[25]

Most cases of autopsy-proven malignant pericardial disease historically have not been diagnosed premortem. Other diagnoses that should be considered include congestive heart failure and pulmonary embolism. The ECG may demonstrate low voltage, sinus tachycardia, or non-specific ST-T abnormalities. Electrical alternans may be present, which represents a variation in QRS size due to a pendular swinging of the heart within the pericardial fluid. Chest x-ray findings include possibly an enlarged cardiac silhouette, with a typical "water bottle" appearance.

Echocardiography is the simplest and most sensitive test to diagnose pericardial effusion, although thoracic CT is widely employed in hemodynamically stable patients. MRI is utilized less frequently but may show structural abnormalities such as intracardiac tumors or tumors that invade the pericardium.[61]

Treatment for life-threatening pericardial tamponade starts with removal of fluid via pericardiocentesis. As much fluid should be removed as possible, with insertion of an indwelling catheter to prevent reaccumulation of fluid over the ensuing 24 hours. Intravenous hydration may improve perfusion pending more definitive treatment such as pericardial window or pericardiectomy. Radiation therapy and intrapericardial chemotherapy have been used for palliation.[62]

Malignancy-Related Superior Vena Cava Syndrome

Superior vena cava syndrome (SVC) results from any condition that causes obstruction of blood flow through the superior vena cava, impairing blood return to the right side of the heart. SVC obstruction leads to dilatation of venous collateral circulation, especially from the azygous venous system. However, this takes weeks to develop.[63] Malignancy

accounts for over 90% of cases of SVC obstruction, with the great majority of these being lung cancer. (*See Table 7.*) The tumor or an enlarged lymph node may be the cause of external compression.[64] Lymphoma, breast cancer, and germ cell tumors are more unusual causes. There are other causes of SVC that are non-malignant, such as thrombosis of the vena cava in patients with an in-dwelling central venous catheter.

Presenting symptoms include facial and neck edema, typically worse on arising in the morning and worse on lying down, bending forward, coughing, or sneezing. The patient most frequently has dyspnea or extreme fatigue. Headache, visual disturbances, flushing, and confusion may be present. (*See Table 8.*) Symptoms may be of sudden onset, as with hemorrhage into a tumor, or gradual.[65] Physical examination may demonstrate facial redness and swelling, with peri-orbital edema. Dilated veins in the arms and upper thorax may be visible.

Diagnosis is made by contrast-enhanced chest CT, which should be performed urgently. The CT scan may differentiate between extrinsic compression and intravascular thrombosis. Venography may be necessary if stenting is considered as therapy. A biopsy can confirm histologic diagnosis.[3]

Management begins with placing the patient in a upright sitting position and administering oxygen. Corticosteroid treatment is initiated with a typical dose of dexamethasone 4 mg four times daily. Steroids are particularly effective in certain lymphomas but may also decrease peritumor edema of other types of malignancy. Insertion of an intravascular stent provides relief within 24-48 hours typically. Radiation provides palliative therapy for the tumor itself but may interfere with the ability to interpret a biopsy.[66]

Conclusion

Cancer remains the second leading cause of death in the United States. With an aging population, it is inevitable that the number of patients with acute illness and disability from malignancy will increase. The accurate diagnosis and treatment of oncology emergencies potentially can forestall disability and enhance quality of life.

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Physician CME Questions

71. Fever in a neutropenic patient is defined as:
    A. a single temperature of 38° C
    B. a sustained temperature of > 37° C for over one hour

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

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CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

C. a single temperature of > 38.3° C
D. a temperature of more than 37.5° C in a patient taking steroids
E. both A and D

72. The majority of superior vena cava syndrome is caused by which malignancy?
A. non-Hodgkin's lymphoma
B. breast cancer
C. mesothelioma
D. thymoma
E. lung cancer

73. The most common symptom of superior vena cava syndrome is:
A. chest pain
B. dyspnea
C. headache on standing
D. confusion
E. pedal edema

74. All of the following are likely to metastasize to bone or cause spinal cord compression *except*:
A. kidney
B. multiple myeloma
C. prostate
D. hepatocellular carcinoma
E. breast

75. Which treatment is *not* indicated in hypercalcemia of malignancy?
A. thiazide diuretics
B. furosemide
C. bisphosphonates
D. calcitonin
E. saline hydration

76. Which of the physical findings below suggests pericardial tamponade?
A. bradycardia
B. hypertension
C. widened pulse pressure
D. jugular venous distention and hypotension
E. pulsus paradoxus of 4 mm mercury

77. Which chemical abnormality occurs in tumor lysis syndrome?
A. elevated calcium level
B. low phosphorus level
C. low BUN and creatinine
D. hypokalemia
E. elevated uric acid level

78. Which of the following may be present in patients with epidural spinal cord compression?
A. ataxia
B. bowel or bladder dysfunction
C. midline bony tenderness
D. sensory loss
E. all of the above

79. Which constitutes the classical triad seen in hyperviscosity syndrome?
A. bleeding, visual disturbances, neurologic symptoms
B. chest pain, distant heart sounds, dyspnea
C. fever, elevated white blood count, depressed level of consciousness
D. distended neck veins, hypotension, fever
E. headache, diplopia, vomiting

80. Which chemical abnormality is *least* consistent with the syndrome of inappropriate antidiuretic hormone?
A. hyponatremia
B. decreased renal excretion of sodium
C. elevated renal excretion of sodium
D. normal blood volume
E. inappropriately elevated urine osmolality

CME Answer Key

71. C; 72. E; 73. B; 74. D; 75. A; 76. D; 77. E; 78. E; 79. A; 80. B

In Future Issues

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Oncologic Emergencies

Emergency Management of Hypercalcemia in Malignancy

Therapy	Dosage
Saline	250-500 mL/h IV, assessing hydration until normovolemic and 100-150 mL/h IV thereafter to maintain urine output at 100-150 mL/hr
Furosemide	20-40 mg IV for fluid overload or after patient rehydrated
Bisphosphonates	
Pamidronate	60-90 mg IV over 2-4 h or
Zoledronic acid	4 mg IV over at least 15 min
Calcitonin	4-8 IU/kg SC or IV every 12 h
Glucocorticoids	Prednisone, 60 mg/d orally; Hydrocortisone, 100 mg every 6 h IV, may be useful in Hodgkin's disease and some lymphomas

Suggested Antibiotic Regimens for Antimicrobial Therapy of the Febrile Neutropenic Cancer Patient

- Monotherapy with cefepime or ceftazidime or a carbapenem (meropenem or imipenem/cilastatin) or piperacillin-tazobactam
- Addition of an aminoglycoside if better gram-negative coverage needed
- Addition of vancomycin or linezolid if additional gram-positive coverage needed (hypotension, mucositis, indwelling catheter site infection, colonization with MRSA)
- Any antipseudomonal penicillin (ticarcillin/clavulanate, piperacillin-tazobactam) with or without an aminoglycoside

The Clinical Presentation of Hyperviscocity Syndrome

- **Visual disturbances:** Blurring, diplopia, vision loss, retinal vein occlusion, retinal hemorrhage
- **Bleeding:** Epistaxis, gingival bleeding, hematuria, vaginal bleeding, rectal bleeding
- **Neurologic:** Mental status changes, headache, ataxia, vertigo, seizures, tinnitus, deafness
- **Other:** Dyspnea, congestive heart failure

Causes for Superior Vena Cava Syndrome

- **Malignancy:** Non-small cell lung cancer, small cell lung cancer, non-Hodgkin's lymphoma
- **Other tumors:** thymoma, mediastinal germ cell tumors, mesothelioma
- **Non-malignant:** fibrosing mediastinitis/prior fungal infection, tuberculosis, post-radiation fibrosis, thrombosis from indwelling intravascular devices

Symptoms of Superior Vena Cava Obstruction

- Dyspnea
- Fatigue
- Facial flushing and edema, upper extremity edema
- Headache
- Dilated veins of upper extremities, neck, and chest
- Altered mental status, coma
- Chest pain
- Syncope
- Cough
- Dysphagia

Laboratory Abnormalities in SIADH

- Low sodium
- Elevated urinary sodium (>20-40 mEq/L)
- Inappropriately elevated urine osmolality

Laboratory Abnormalities in Tumor Lysis Syndrome

- Elevated uric acid level
- Elevated BUN, creatinine
- Elevated phosphorus
- Decreased calcium
- Elevated potassium
- Elevated lactate dehydrogenase (LDH)

Factors in Consideration of the Cancer Patient with Suspected Sepsis

- In-dwelling catheters
- Disruption of mucous membranes or skin
- Cancer not in remission
- Prolonged steroid use, other immunosuppression

Supplement to *Emergency Medicine Reports*, March 30, 2009: "Oncologic Emergencies." *Author:* **Jonathan Glauser, MD**, Institute Chairman, Emergency Services Institute, Cleveland Clinic, Cleveland, OH.

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4. Apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed.	○	○	○	○	○	○
5. Understand the differential diagnosis of the entity discussed.	○	○	○	○	○	○
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71. A B C D E 72. A B C D E 73. A B C D E 74. A B C D E 75. A B C D E 76. A B C D E 77. A B C D E
78. A B C D E 79. A B C D E 80. A B C D E