Oncologic Emergencies: Pathophysiology, Presentation, Diagnosis, and Treatment

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Abstract

Oncologic emergencies can occur at any time during the course of a malignancy, from the presenting symptom to end-stage disease. Although some of these conditions are related to cancer therapy, they are by no means confined to the period of initial diagnosis and active treatment. In the setting of recurrent malignancy, these events can occur years after the surveillance of a cancer patient has been appropriately transferred from a medical oncologist to a primary care provider. As such, awareness of a patient's cancer history and its possible complications forms an important part of any clinician's knowledge base. Prompt identification of and intervention in these emergencies can prolong survival and improve quality of life, even in the setting of terminal illness. This article reviews hypercalcemia, hyponatremia, hypoglycemia, tumor lysis syndrome, cardiac tamponade, superior vena cava syndrome, neutropenic fever, spinal cord compression, increased intracranial pressure, seizures, hyperviscosity syndrome, leukostasis, and airway obstruction in patients with malignancies. Chemotherapeutic emergencies are also addressed. **CA Cancer J Clin 2011;61:287-314. ©2011 American Cancer Society.**

Introduction

In this review, we discuss the pathophysiology, presentation, diagnosis, and treatment of commonly encountered emergencies in hematology and oncology. We have chosen to categorize emergencies as metabolic, cardiovascular, infectious, neurologic, hematologic, or respiratory to highlight their lack of disease specificity and to facilitate their recognition during system-by-system assessment of the patient. These conditions require prompt recognition and treatment. For providers administering chemotherapy, we also address the problems of extravasation and anaphylactic reactions.

Metabolic Emergencies

Hypercalcemia

Pathophysiology

Hypercalcemia will be experienced by up to one-third of cancer patients at some point in their disease course.[1] Among patients hospitalized for hypercalcemia, malignancy is the most common cause, although primary hyperparathyroidism is much more prevalent in the general population.[2] Breast, lung, and renal cell carcinomas; multiple myeloma; and adult T-cell leukemia/lymphoma are the prevailing causes of hypercalcemia.[1,3] A variety of mechanisms can explain elevated calcium in cancer patients: systemic release of parathyroid hormone-related peptide (PTHrP) by the tumor, which does not require the presence of bone metastases; local paracrine stimulation of osteoclasts by metastases to bone, leading to osteolytic effects; and systemic secretion of vitamin D analogues by the tumor, which also does not require the presence of bone metastases.[4]

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Up to 80% of malignant hypercalcemia is caused by PTHrP released by the tumor into the systemic circulation.[4] Given its homology to parathyroid hormone (PTH), PTHrP can mimic the action of PTH on the bones and kidneys but, unlike PTH, PTHrP does not influence intestinal absorption of calcium.[5] The effects of PTHrP represent a true paraneoplastic syndrome (ie, systemic signs and symptoms caused by a tumor, but not confined to the area in direct proximity to the tumor), with circulating PTHrP causing bone resorption and renal retention of calcium. Squamous cell carcinomas from the aerodigestive and genitourinary tracts commonly cause this type of "humoral" hypercalcemia but this can also be seen in breast, kidney, cervical, endometrial, and ovarian cancer.

Bone metastases may cause a local paracrine effect by producing several factors that stimulate osteoclasts, leading to bone resorption with resultant hypercalcemia and bone destruction.[6] This is most commonly seen in metastatic breast cancer and multiple myeloma. Prostate cancer, despite the frequency with which it metastasizes to bone, only rarely causes hypercalcemia, underscoring that it is not just osseous involvement but the specific tumor-bone interaction that determines calcium liberation from bone. New agents, such as those that alter the receptor activator of nuclear factor κB ligand (RANKL) (denosumab) or inhibit osteoclastogenesis (osteoprotegerin), can be used to modify the tumor microenvironment to control hypercalcemia and bone resorption.

Very rarely, a tumor will manufacture PTH itself.[7]

Tumor production of vitamin D analogues is a less common etiology of malignant hypercalcemia, with non-Hodgkin lymphoma and Hodgkin lymphoma each capable of producing elevated calcitriol levels.[8]

Presentation

The symptoms of hypercalcemia are nonspecific, and delayed recognition of this metabolic derangement can worsen morbidity and mortality.[9] The mnemonic "bones, stones, moans, and groans" is used to emphasize skeletal pain, nephrolithiasis, abdominal discomfort, and altered mentation as presenting symptoms. Bone pain is usually related to discrete metastases rather than diffuse liberation of calcium. Even in the setting of profound hypercalciuria, not all patients will form kidney stones, which may be due to differences in the urine mineral concentration needed to precipitate calculi.[10] Abdominal pain can arise from dysregulated intestinal motility, pancreatitis, or severe constipation. Changes in sensorium can occur along a spectrum from lethargy to coma. In addition, hypercalcemia shortens the QT interval and can produce arrhythmias.

Diagnosis

Ionized calcium is the most reliable laboratory test with which to detect hypercalcemia and is considered to be elevated when above 1.29 mmol/L.[11] If measuring total calcium, it is important to correct for hypoalbuminemia, using the following formula: corrected calcium in mg/dL = measured total calcium in mg/dL + 0.8(4 − measured albumin in g/dL).[12] There is no absolute level of calcium at which patients will become symptomatic, and the rate of increase is likely more significant than the magnitude of elevation; relatively high levels may be well tolerated if the rate of increase has been gradual.[13]

Measuring PTHrP has not been proven to affect outcome and should not guide initial management. PTHrP-driven hypercalcemia should be suspected on the basis of the underlying tumor type, especially when bony metastases are not evident. However, patients presenting with PTHrP levels above 12 pmol/L may be less responsive to bisphosphonates and more prone to develop recurrent hypercalcemia.[14] Serum chloride is a more readily available test, and hypochloremia less than 100 mEq/L supports a diagnosis of humoral hypercalcemia.[15] PTH levels can be checked to investigate the possibility of primary hyperparathyroidism; however, PTH levels are often low in patients with humoral hypercalcemia due to suppression of endogenous PTH release by PTHrP-mediated negative feedback.

Treatment

The 30-day mortality rate of cancer patients hospitalized with hypercalcemia has been shown to approach 50%.[16] Even in patients with advanced malignancies in whom efforts to lower calcium do not demonstrably prolong life, there can be a palliative benefit to improving the symptoms of hypercalcemia.[16] Urgent intervention is needed to normalize symptomatic hypercalcemia (Table 1).

TABLE 1. Treatment of Hypercalcemia

MEDICATION	USUAL DOSE	POINTS TO REMEMBER
Normal saline	Rapid infusion 300-500 cc/h until euvolemic	Use caution in patients with heart failure
Furosemide	20-40 mg iv every 12-24 h	Only after adequate hydration
Pamidronate	60-90 mg iv	Adjust infusion time to creatinine clearance
Zoledronic acid	4 mg iv	Consider alternative treatment in patients with renal failure
Calcitonin	4-8 IU/kg sq or iv every 12 h	Tachyphylaxis occurs quickly
Steroids	Hydrocortisone, 100 mg iv every 6 h or prednisone, 60 mg orally daily	Role usually limited to lymphomas; anticipate hyperglycemia
Mithramycin and gallium		Of historical interest only
Denosumab	Under investigation	Currently approved only for the prevention of skeletal-related events from bone metastases

iv indicates intravenous; sq, subcutaneous.

Hydration is the cornerstone of initial management because almost all patients with clinically meaningful hypercalcemia have intravascular volume depletion. Correction of volume depletion will help to restore a brisk urine output. If the patient has intact left ventricular systolic function, normal saline can be safely infused at rates up to 500 cc/hour until hypovolemia has resolved. At that time, loop diuretics, such as 40 mg of furosemide intravenously (iv) every 12 to 24 hours, can be initiated to promote calciuresis. Thiazide diuretics should be avoided as they increase calcium reclamation from the urine. Exogenous sources of calcium and vitamin D should be curtailed. Intravenous phosphates should be avoided due to the potential for calciphylaxis when the calcium-phosphorus product exceeds 70 mg/dL. Oral phosphates have, in the past, been utilized to correct hypercalcemia by binding calcium in the gut, but this method is rarely used currently.

Bisphosphonates block bone resorption by osteoclasts but, even when given iv, do not lower calcium rapidly enough to replace aggressive hydration as the first step in management. Calcium usually declines within 48 to 96 hours of infusion and nadirs at 1 week.[4] Bisphosphonates may rarely cause osteonecrosis of the mandible in patients with poor dentition. More common adverse effects include acute bone pain, ocular inflammation,[17] electrolyte abnormalities such as hypophosphatemia or "overshoot" hypocalcemia,[18] and possibly atrial dysrhythmias.[19] Zoledronic acid at a dose of 4 mg can be infused more quickly than 60 to 90 mg of pamidronate (15 minutes vs 2 hours), but zoledronic acid is relatively contraindicated in patients with severe renal insufficiency (glomerular filtration rate < 30 mL/minute or serum creatinine > 3.0 mg/dL) due to the risk of acute tubular necrosis. Pamidronate can be more safely administered as a longer infusion (4-6 hours) but still carries the risk of nephrotoxicity through focal segmental glomerulosclerosis.[20] Hemodialysis may be a faster and less hazardous method of correcting hypercalcemia in patients with diminished kidney function.[21] Dialysis also allows calcium attenuation in the setting of congestive heart failure or other conditions that preclude the administration of high volumes of iv fluids.[22]

Calcitonin administration lowers the calcium more quickly than bisphosphonates, often producing normocalcemia within 12 to 24 hours, but it rapidly loses efficacy through tachyphylaxis.[23] It should not be used as a single agent due to rebound hypercalcemia. Calcitonin can be administered by the intramuscular (im) or subcutaneous routes at a dose of 4 to 8 IU/kg every 12 hours, but intranasal administration is not effective for treating hypercalcemia. Salmon-derived calcitonin carries a risk of hypersensitivity reaction but anaphylaxis is sufficiently rare that a test dose is no longer routinely recommended.[24]

Glucocorticoids, such as 60 mg of prednisone orally daily or 100 mg of hydrocortisone iv every 6 hours, can be helpful in mediating the release of cytokines and prostaglandins that stimulate osteoclasts. In addition to their direct lympholytic effect, steroids inhibit calcitriol production by macrophages

and appreciably lower the calcium level within 3 to 5 days of administration.[8] The duration of use should be limited to minimize glucocorticoid toxicities.

Gallium and mithramycin are increasingly becoming of historical interest. Gallium has to be given as a continuous 5-day infusion[25] and does offer a higher response rate than bisphosphonates for humoral hypercalcemia but at the expense of greater nephrotoxicity.[26] Mithramycin (also known as plicamycin) inhibits osteoclast RNA synthesis and lowers calcium during infusion[27] while being given as a single dose over 4 to 6 hours, but carries significantly more side effects than the bisphosphonates, including hematologic and hepatic derangements.[28]

Receptor activator of nuclear factor κB (RANK), found on the surface of osteoclast precursors, and its ligand (RANKL), which is secreted by lymphocytes and found on the surface of osteoblasts and bone marrow stromal cells, stimulate osteoclast precursors to complete their differentiation and begin bone resorption, liberating calcium.[3] PTH and 1,25-dihydroxyvitamin D_3 drive osteoclast formation by increasing RANKL expression on osteoblasts and bone marrow stroma.[29] Denosumab is a fully humanized monoclonal antibody with high affinity and specificity for RANKL that is approved for use in the management of postmenopausal osteoporosis[30] as well as in the prevention of skeletal events from bone metastases,[31] and has potential application in hypercalcemia of malignancy.[32] Osteoprotegerin, a decoy receptor of RANKL and an inhibitor of osteoclast maturation, has been demonstrated to correct hypercalcemia more quickly and durably than bisphosphonates.[33]

Hyponatremia

Physiology

The assessment of hyponatremia in cancer patients, as in all patients, requires a critical determination of volume status. Fluid in the body is divided among compartments: the circulatory volume (plasma), the interstitial space outside the vasculature, and the cells. Osmotic gradients drive fluid between compartments, with movement toward higher concentrations. The sodium concentration is the largest contributor to plasma osmolarity and reflects how much water is present in the blood relative to the cells, in which the majority of the body's water is stored.[34] Laboratory measurement of the sodium concentration thus reveals the distribution of water among the body's fluid compartments, and hyponatremia means that intravascular water is present in excess relative to sodium, either through water retention and/or sodium loss.

Presentation

The amount of sodium in the body, not the plasma sodium concentration, determines the volume of fluid outside the cells, and this volume can be readily measured by physical examination. If the total body sodium is high, then the extracellular fluid volume is large and the patient will appear edematous. If the total body sodium is low, then the extracellular space (including the circulatory volume) will contract and the patient will progressively develop tachycardia and hypotension. A low plasma sodium concentration can thereby be associated with clinical hypervolemia, hypovolemia, or euvolemia, depending upon total sodium content. The physician must correctly evaluate the hyponatremic patient's volume to understand both their sodium and water balance and then select the appropriate treatment.[35]

Euvolemic hyponatremic patients with cancer have normal extracellular fluid volume, reflecting appropriate total sodium content, but excessive water in the intravascular space, most commonly mediated through the syndrome of inappropriate antidiuretic hormone (SIADH). Antidiuretic hormone promotes free water uptake in the distal tubules by binding to the vasopressin 2 (V_2) receptor. Compounding the problem is continued free water intake because the thirst mechanism is not sufficiently inhibited.[36]

SIADH should be suspected based upon the location of primary and metastatic tumors because SIADH is more commonly encountered in diseases originating in or involving the lungs, pleura, thymus, and brain. Between 10% to 45% of patients with small cell lung cancer will show evidence of SIADH.[37] Iatrogenic causes of hyponatremia include cisplatin,[38] cyclophosphamide,[39] ifosfamide,[40] the vinca alkaloids,[41,42] and imatinib.[43] Each of these drugs can cause SIADH, but all can also produce hyponatremia through a variety of other mechanisms (eg, platinum-induced salt-wasting nephropathy), and therefore careful evaluation is required to determine the underlying etiology of hyponatremia in patients receiving these medications.

Drugs with high emetogenic potential can stimulate ADH release through nausea, an appropriate physiologic response that may be confused with SIADH.

Diagnosis

Hyponatremia can be classified as mild (131-135 mmol/L), moderate (126-130 mmol/L), or severe (<125 mmol/L). Serum glucose should be measured to ensure that hyperglycemia is not creating a spurious finding of hyponatremia. The serum sodium can be adjusted for elevated glucose through the following formula: corrected sodium in mmol/L = measured serum sodium in mmol/L + .016 (measured glucose in mg/dL, − 100).

SIADH is diagnosed when, after exclusion of adrenal insufficiency and hypothyroidism,[44] the effective osmolality (calculated by subtracting [blood urea nitrogen (BUN)/2.8] from the measured osmolality) is less than 275 milliosmoles (mOsm)/kg of water, and the urine osmolality exceeds 100 mOsm/kg of water.[45] Urine sodium greater than 40 mmol/L in the absence of excessive dietary sodium intake, hypouricemia less than 4 mg/dL,[46] and BUN less than 10 mg/dL all support the diagnosis of SIADH.[47]

Treatment of Hyponatremia

Treatment of hyponatremia in malignancy is dependent upon the underlying cause. Low serum sodium concentrations, especially those below 125 mmol/L, can create the life-threatening consequence of cerebral edema. However, it is primarily the rate at which the hyponatremia develops that determines the patient's symptomatology. A patient with chronic hyponatremia that is "severe" by laboratory criteria may actually tolerate their electrolyte disturbance better than a patient whose "moderate" hyponatremia develops acutely within 48 hours.[37] The most concerning symptoms of hyponatremia are neurologic, including lethargy, delirium, seizures, and coma, all of which merit urgent treatment.

Hypovolemic hyponatremic patients have lost sodium and management involves infusing sodium-containing fluids. Severe hyponatremia with neurologic symptomatology can merit very careful use of hypertonic (3%) saline. Otherwise, normal (0.9%) saline is an appropriate infusate. The serum sodium should not be corrected at a rate greater than 0.5 mEq/L/hour to avoid central pontine myelinolysis, a condition in which rapid, osmotically driven shrinkage of brainstem cells can result in quadriparesis, pseudobulbar palsy, "locked-in" syndrome, coma, and death.[18] The sodium correction per L of infusate can be estimated by the following formula: change in serum sodium (Na) in mEq/L = [(infusate Na − serum Na)/(total L of body water + 1)] (reference values: infusate Na = 513 mEq in 3% saline, infusate Na = 154 mEq in 0.9% saline, total L of body water = weight in kg × 0.6).[48]

Asymptomatic, euvolemic hyponatremic patients with cancer are treated by removing the offending stimulus for their ADH secretion, such as controlling nausea, lessening pain, and treating the underlying malignancy. Restriction of free water intake to 500 to 1000 mL/day will increase plasma osmolality and normalize the sodium level in many patients with SIADH. Demeclocycline, a tetracycline antibiotic with the side effect of inducing nephrogenic diabetes insipidus, can be used at a dosage of 600 to 1200 mg/day,[36] but patients need to be monitored for profound polyuria and can actually develop hypernatremia if their restriction to free water is continued. The vaptans bind competitively to the V_2 receptors in the collecting duct where ADH exerts its effect on the kidney. Intravenous conivaptan[49] (20 mg infused over 30 minutes, followed by 20 mg infused over 24 hours) and oral tolvaptan[50] (starting at a dose of 15 mg daily) have been shown in clinical trials to achieve rapid correction of hyponatremia through almost pure aquaresis. The rate of vaptan-induced sodium correction needs to be closely monitored to ensure it is not excessive.[51]

Hypoglycemia

Pathophysiology

Hypoglycemia can arise in the patient with cancer through several etiologies. Some tumors are capable of ectopic production of substances that affect glucose metabolism. Insulin is made in excess by insulinomas and nesidioblastosis.[52] Mesenchymal tumors like sarcoma, including gastrointestinal stromal tumor[53] and solitary fibrous tumor,[54] can produce insulin-like growth factors (IGFs) such as IGF-2, which increases glucose utilization by tissues and blunts the secretion of growth hormone.[55] Levels of a related protein, IGF-1, have been reported to be elevated in rare cases of lung cancer.[56,57] Rapidly proliferating neoplasms can consume glucose prodigiously. Overexpression of the mitochondrial

enzyme hexokinase II allows some cancer cells to maintain glycolysis even in the presence of oxygen.[58] In fact, this disproportionate uptake through the Warburg effect is exploited in ^{18}-fluorodeoxyglucose positron emission tomography imaging to visualize tumors against a background of normal tissue. Given the anabolic and biosynthetic demands of dividing cells, tumors with high mitotic rates may consume glucose with sufficient briskness as to induce hypoglycemia; this is most often seen in aggressive lymphomas (eg, Burkitt lymphoma) but has also been described in small cell lung cancer. The swift proliferation may be associated with increased lactic acid,[59] even in the absence of hypoxemia. Tumors can infiltrate organs that play crucial roles in normal glucose metabolism,[60] such as hepatocellular carcinoma replacing the liver parenchyma or pheochromocytoma overtaking the adrenal gland.[61] It is rare for metastases to the adrenal gland to precipitate hypoadrenalism.[62]

Presentation

Signs and symptoms of hypoglycemia arise both from neuroglycopenia and adrenergic counterregulation.[63] Neurologic manifestations range from confusion and blurred vision to seizures and coma. The catecholamine response to hypoglycemia can result in diaphoresis, palpitations, and dilation of the pupils.

Diagnosis

The Whipple triad, initially developed to determine eligibility for pancreatic surgery in patients with insulinoma, includes measured hypoglycemia, symptoms attributable to hypoglycemia, and reversal of symptoms when normoglycemia is restored. In the absence of insulin secretagogues, an otherwise healthy adult can usually maintain a glucose level above 50 mg/dL throughout a 72-hour fast.[64,65] High insulin and C-peptide levels implicate islet cell tumors whereas an elevated IGF-2 to IGF-1 ratio suggests a mesenchymal tumor.[66]

Treatment

The treatment of cancer-related hypoglycemia can include surgical removal of the underlying tumor, or chemotherapy and radiation for unresectable tumors. Interim management may include the administration of glucagon at a dose of 1 mg iv/im, dextrose infusion, diazoxide (3 mg/kg/day initially),[67] and cessation of nonselective beta-blockers that blunt adrenergic response to low blood sugar.[68] Exogenous glucocorticoids and regimented frequent carbohydrate intake have also been proposed as interventions.[69]

Tumor Lysis Syndrome

Pathophysiology

Tumor lysis occurs when cancer cells release their contents into the bloodstream, either spontaneously or following antineoplastic therapy,[70,71] leading to an influx of electrolytes and nucleic acids into the circulation. The sudden development of hyperkalemia, hyperuricemia, and hyperphosphatemia can have life-threatening end-organ effects on the myocardium, kidneys, and central nervous system (CNS). Recent animal models further suggest a detrimental effect on the microvasculature by emboli formed from the nuclear and cytoplasmic debris of lysed tumor cells.[72] Hypocalcemia, a consequence of hyperphosphatemia, is included in the constellation of metabolic disturbances known as tumor lysis syndrome (TLS).

Presentation

Patients are variably symptomatic from the metabolic derangements of TLS. Clinical TLS is diagnosed when one or more of 3 conditions arise: acute renal failure (defined as a rise in creatinine to 1.5 times or more the upper limit of normal that is not attributable to medications), arrhythmias (including sudden cardiac death), and seizures. Acute renal failure can manifest as a decrease in urine output, uremia-related altered sensorium, or crystalline obstructive uropathy. Arthralgias can arise from gout flare.

TLS is more common in the rapidly proliferative hematologic malignancies such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and Burkitt lymphoma, but has been documented in solid tumors, notably small cell lung cancer,[73] germ cell tumors,[74] inflammatory breast cancer,[75] and melanoma.[76] Liver metastases may increase TLS risk.[71]

Treatment-provoked TLS can occur following chemotherapy, treatment with single-agent corticosteroids in patients with sensitive tumors,[77,78] radiation,[79] surgery, or ablation procedures.[71] The onset of TLS can be delayed by days to weeks in a patient with a solid malignancy.[71]

TABLE 2. Laboratory Definition of Tumor Lysis Syndrome Using the Cairo-Bishop Classification

LABORATORY TUMOR LYSIS SYNDROME
Uric acid $\geq$ 8 mg/dL ($\geq$ 476 μmol/L) or 25% increase from baseline
Potassium $\geq$ 6 mEq/L ($\geq$ 6 mmol/L) or 25% increase from baseline
Phosphorus $\geq$ 6.5 mg/dL ($\geq$ 2.1 mmol/L) or 25% increase from baseline
Calcium $\leq$ 7 mg/dL ($\leq$ 1.75 mmol/L) or 25% decrease from baseline
CLINICAL TUMOR LYSIS SYNDROME
Creatinine $\geq$ 1.5 times the upper limit of normal
Cardiac arrhythmia or sudden death
Seizure

NOTE. Two or more laboratory changes must be observed within 3 days before or 7 days after cytotoxic therapy.

Adapted from Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3–11, with permission from Blackwell Publishing Group. © 2004. All rights reserved.

Diagnosis

Laboratory TLS was initially defined as any 2 of the following occurring within 4 days of starting treatment: a 25% increase in the baseline values of uric acid, potassium, phosphorous, and BUN and/or a 25% decrease in calcium.[80] This definition of TLS was then updated to omit BUN and to recognize a 25% increase in uric acid, potassium, or phosphorous and/or a 25% decrease in calcium within 3 days before and 7 days after the initiation of treatment (Table 2).[81] Absolute values of uric acid of 8 mg/dL or greater, potassium of 6 mEq/L or greater, phosphorus of 6.5 mg/dL or greater, or calcium of 7 mg/dL or less are also considered significant in adults.[81] Because of the need to establish a temporal relationship to treatment, the same criteria do not apply to spontaneous TLS. In spontaneous TLS, hyperphosphatemia is less likely, possibly due to reuptake of phosphorus by the rapidly dividing tumor.[82]

Treatment

Prophylaxis is appropriate in high-risk patients, including those with bulky tumors, rapidly proliferating disease, and expectations of immediately effective cytotoxic treatment. Patients with renal insufficiency, volume depletion, or hyperuricemia are at increased risk. Complex algorithms can be used to estimate the disease-specific risk of TLS.[83] A high urine output and alkalinization of the urine minimize the risk of urate crystal precipitation within the genitourinary tract, but sodium bicarbonate or acetazolamide may increase calcium-phosphate crystallization.[71]

Allopurinol inhibits xanthine oxidase, thus decreasing uric acid production, and can be given preventively starting up to 48 hours before treatment at doses of 100 mg/m^2 every 8 hours (maximum daily dose: 800 mg). Allopurinol's interference with purine metabolism requires dose reductions of 6-mercaptopurine and azathioprine. Allopurinol does not alter uric acid that has already formed and is not recommended as prophylaxis for patients with pretreatment uricemia of 7.5 mg/dL or greater. In such patients, rasburicase can be given at dosages of 0.15 to 0.2 mg/kg/day for up to 5 or 7 days.[84] Rasburicase is recombinant urate oxidase, an enzyme not naturally found in humans, that converts uric acid into water-soluble allantoin. Unlike allopurinol, it does not cause accumulation of xanthine and hypoxanthine, which demonstrate poor water solubility and can worsen renal function.[13] Rasburicase is contraindicated in pregnancy and in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Due to its expense, it should be used judiciously in the appropriate patient populations and does not replace the need for adequate hydration.

The electrolyte complications of TLS are not directly remedied by allopurinol or rasburicase (Table 3). Hyperkalemia can be treated with loop diuretics. Immediate reduction in serum potassium through intracellular shifting can be achieved by the injection of 10 U of regular insulin, followed immediately by 50 mL of 50% dextrose and then an hour-long infusion of 50 to 75 mL of 10% dextrose to prevent hypoglycemia.[85] Inhaled beta-agonists, such as 20 mg of nebulized albuterol, can quickly and durably lower potassium.[86] Cation exchange resins like sodium polystyrene sulfonate are not routinely recommended because they take several days to lower potassium and carry the risk of gastrointestinal (GI) necrosis, especially when coupled with sorbitol.[87] A 1000-mg infusion of calcium gluconate can stabilize myocyte membranes and reverse electrocardiographic changes such as first-degree atrioventricular block and a widened QRS.[88] Hyperphosphatemia is managed by a phosphorous-restricted diet or by short-term use of oral phosphate binders like aluminum hydroxide (300 mg with meals), aluminum carbonate (30 mL every 6 hours), or calcium acetate (two 667-mg capsules with each meal, which should be avoided in patients with hypercalcemia).[88] Dialysis may ultimately be

TABLE 3. Treatment of Metabolic Derangements in TLS

PROBLEM	INTERVENTION	DOSAGES	COMMENTS
Renal insufficiency and hypovolemia	Intravenous fluids	Normal saline, 3 L/m^2 daily	Use with caution if decreased systolic function
	Dialysis		For fluid-unresponsive oliguric renal failure or patients with CHF
Hyperuricemia	Allopurinol	100 mg/m^2 per dose orally every 8 h (maximum daily dose: 800 mg)	Drug-drug interactions with 6-MP and azathioprine; only effective for prophylaxis
	Rasburicase	0.15-0.2 mg/kg/d iv	Contraindicated in pregnancy and G6PD deficiency; costly
Hyperphosphatemia	Minimize phosphate intake	Minimal consumption of dairy and bread products	
	Phosphate binders (aluminum hydroxide or aluminum carbonate)	30 mL orally every 6 h	
	Dialysis		If no response to oral therapy
Hyperkalemia	Insulin (regular)	10 U iv	
	Dextrose	50 mL of 50% dextrose iv push, then infuse 50-75 mL of 10% dextrose over 1 h	
	Albuterol	20 mg nebulized	
	Dialysis		If no response to other therapy
	Calcium gluconate	1000 mg iv	If hyperkalemic EKG changes are noted
Hypocalcemia	Calcium gluconate	1000 mg iv (no faster than 200 mg/min)	Use with caution in severe hyperphosphatemia

6-MP indicates 6-mercaptopurine; CHF, congestive heart failure; EKG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; iv, intravenously; TLS, tumor lysis syndrome.

necessary to treat any refractory, life-threatening electrolyte derangements, especially in the context of volume overload and renal insufficiency.

Cardiovascular Emergencies

Pericardial Effusion and Cardiac Tamponade

Pathophysiology

The pericardial sac is distensible up to a volume of 2 L, if stretching occurs over a slow time period.[89] Rising intrapericardial pressure affects all 4 cardiac chambers, but the right ventricular wall is much thinner and more susceptible to extrinsic compression. Diastolic pressures throughout the chambers begin to equalize and adversely affect cardiac output by compromising filling.[90] At this point, tamponade physiology emerges.

Malignant pericardial effusions develop through direct or metastatic involvement of the pericardial sac. Direct extension is most common in those tumors with sites of origin adjacent to the heart: lung cancer, breast cancer, and mediastinal lymphoma.[91] Metastases to the epicardium are seen in noncontiguous breast and lung cancer, as well as in melanoma.[92] Primary neoplasms of the pericardium are exceedingly rare, but include mesothelioma.[93] Cancer treatment, especially thoracic irradiation, can cause transudative effusions. Immunosuppression can also allow suppurative infections to develop in the pericardial space.

Presentation

Pericardial effusions can be asymptomatic, although their presence portends a poor prognosis, especially if larger than 350 mL.[94] Pericarditis symptoms may precede the emergence of tamponade. Tamponade classically presents with the Beck triad: hypotension, elevated jugular venous pressure, and a muffled precordium. However, only a minority of patients actually demonstrate all 3 signs.[95] Most patients complain of dyspnea and chest discomfort, which may begin abruptly. Tamponade physiology can arise from volumes of as little as 100 mL if they accumulate rapidly. Even if the effusion forms over a longer period of time, the "last drop" phenomenon describes the critical point of physiologic collapse at which intrapericardial pressure finally overcomes the compensatory

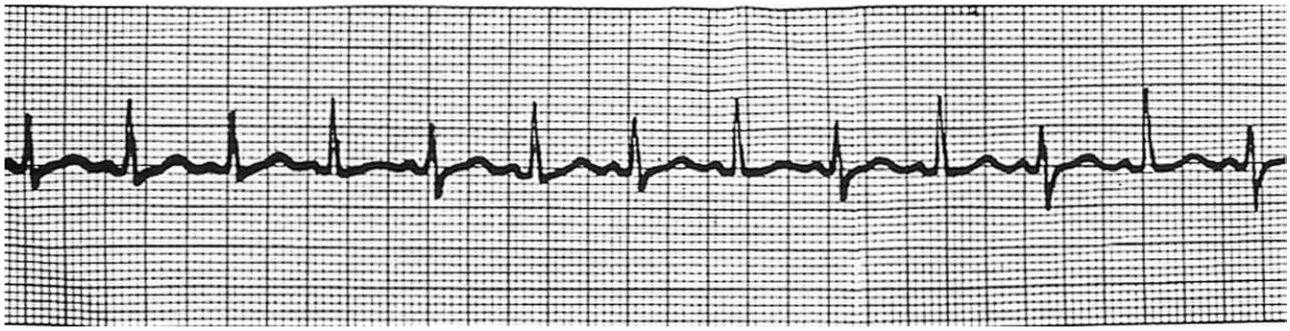

FIGURE 1. Electrical Alternans in the Setting of Pericardial Effusion.

mechanisms of the heart and causes cardiac output to drop precipitously.[96] In this manner, a chronic effusion can cause hyperacute symptomatology.

Diagnosis

The diagnostic utility of the physical examination should not be discounted but should be coupled with appropriate studies. Tachycardia is nearly universal, and pulsus paradoxus is an ominous finding,[97] with a value greater than 10 mm Hg having been arbitrarily defined as abnormal.

Chest x-rays may show cardiomegaly and the classic "water bottle" cardiac silhouette. Electrocardiography can show low voltage and electrical alternans (Fig. 1) from the shifting axis of the heart as it moves like a pendulum within the fluid-filled sac. Echocardiography is the definitive test, demonstrating right ventricular collapse during early diastole.

Treatment

Sonographically guided pericardiocentesis has decreased complication rates 4-fold over blind subxiphoid pericardiocentesis, which should be reserved for patients in extremis.[98,99] A catheter can be placed into the sac to drain residual or reaccumulating fluid. Adenocarcinoma-provoked pericardial effusions are more likely to recur and these patients may be more appropriate for a pericardial window or pericardiectomy, whereas virtually all other histologies can be managed with pericardiocentesis and insertion of a drainage catheter.[100]

Patients often report immediate symptomatic improvement from pericardiocentesis but still require close monitoring. Decompression can produce paradoxical hemodynamic instability requiring admission to the intensive care unit and pressor support. The risk of such decompensation increases with hematologic malignancies and also rises in direct proportion to pericardial fluid volume.[101]

Instillation of chemotherapy into the pericardial space has been explored as a means of lowering recurrence rates of malignant pericardial effusions.[102] However, one study found that systemic control of the underlying neoplasm was the only significant factor influencing survival.[103] Before undertaking elective invasive pericardial procedures, their risks should be carefully weighed alongside expectations for overall treatment efficacy and life expectancy.[103]

Superior Vena Cava Syndrome

Pathophysiology

The thin-walled superior vena cava (SVC) returns all blood from the cranial, neck, and upper extremity vasculature to the right side of the heart. Primary or metastatic tumors can cause compression. Nononcologic etiologies include syphilitic aortic aneurysms (vanishingly rare since the advent of penicillin), fibrosing mediastinitis (classically associated with histoplasmosis), substernal hypertrophy of the thyroid, granulomatous disease (such as tuberculosis and sarcoidosis), and thrombosis, particularly that due to an underlying hypercoagulable state or endothelial damage from an indwelling vascular device.

Presentation

The extent of SVC obstruction and acuity of development dictate the patient's presentation. Blockage is better tolerated when there has been time for collateral veins to develop in adjacent venous systems like the azygos and internal mammary, a process that usually takes weeks. The veins on the patient's chest wall may be visibly distended (Fig. 2). Edema in the arms, facial plethora (not necessarily unilateral), chemosis, and periorbital edema may also occur. Stridor is an alarming sign that edema is narrowing the luminal diameter of the pharynx and larynx. Hoarseness and dysphagia can result from edema around

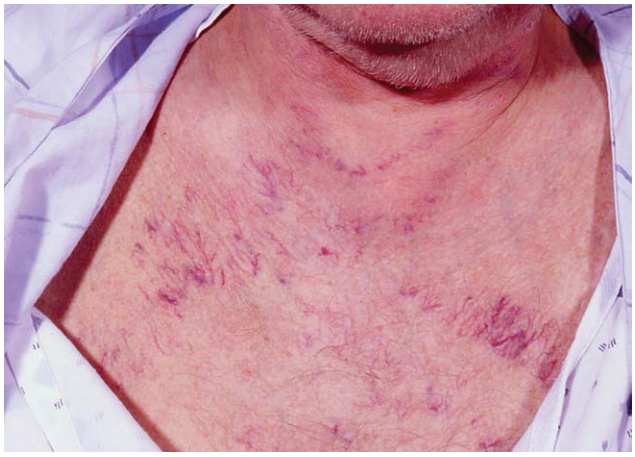

FIGURE 2. Dilated Chest Wall Veins in Superior Vena Cava Syndrome.

the aerodigestive tracts. Presyncope or syncope is more common early on, when cardiac output declines without compensation. Headaches stem from distention of cerebral vessels against the dura, but confusion may indicate cerebral edema. All of these symptoms may be more noticeable when the patient is supine.

Cancers classically associated with SVC syndrome include lung cancer (particularly right-sided), breast cancer, primary mediastinal lymphoma, lymphoblastic lymphoma, thymoma, and germ cell tumors (either primary or metastatic to the mediastinum).

Diagnosis

Radiographic imaging is crucial to diagnosis and treatment planning, especially if radiation and endovascular stents are potential interventions. While the gold standard for localizing obstruction remains selective venography, multidetector computed tomography (CT) or magnetic resonance imaging (MRI) are usually preferable for their noninvasiveness, easier availability, and decreased contrast load.[104]

Treatment

SVC syndrome requires prompt recognition and treatment, but the clinical course typically permits completion of appropriate diagnostic studies before definitive therapy begins.[105] In a review of 1986 patients with this presentation, there was only one well-documented case in which death was directly attributable to SVC obstruction.[106] Thus, when SVC syndrome heralds malignancy, the practitioner usually still has time to perform biopsies or other diagnostic procedures without endangering the patient, although therapy should not be delayed unnecessarily.[106] Patients who have neurologic symptoms or airway compromise merit immediate treatment; endovascular stenting can provide prompt palliation that should not interfere with further diagnostic maneuvers and generally relieves symptoms more quickly than chemoradiation.[104] Decreased diagnostic yield with prebiopsy use of steroids is not well documented, even in cases of hematologic malignancy, but the overall efficacy of steroids is questionable. Randomized trials weighing management options in malignancy-related SVC syndrome have been understandably difficult,[107] but determining the histology of the responsible malignancy can often guide therapy. Chemotherapy may be the only necessary treatment in patients presenting in nonemergent fashion with small cell lung cancer, lymphoma, or germ cell tumors. Changes in the SVC lumen following mediastinal radiation may be disproportionately small relative to the magnitude of symptom improvement, and some of the benefit previously attributed to radiation may actually result from the additional time during therapy for collateral veins to form. Cases of catheter-related thrombosis have been successfully treated with instillation of thrombolytics into the device,[108] but fibrinolytic therapy should be administered carefully in cases in which brain metastases have been diagnosed or not excluded.

Infectious Emergencies

Neutropenic Fever

Pathophysiology

A patient's absolute neutrophil count (ANC) can decline through a cancer's direct interference with hematopoiesis, as in leukemia or metastatic replacement of the bone marrow, but neutropenia is most commonly seen as an effect of cytotoxic therapy. For the majority of outpatient chemotherapy regimens, the nadir in ANC occurs 5 to 10 days after the last dose. Inpatient regimens, especially those used to treat hematologic malignancies, tend to produce a neutropenia of greater depth and duration, both of which amplify risk.[109] Other risk factors include the rapidity of the ANC decline; exposure to prior chemotherapy or current immunosuppression; pretreatment elevations in alkaline phosphatase, bilirubin, or aspartate aminotransferase levels; reduced glomerular filtration rate; and cardiovascular comorbidities. The classes of chemotherapy with the

highest risk of inducing neutropenia are the anthracyclines, taxanes, topoisomerase inhibitors, platinums, gemcitabine, vinorelbine, and certain alkylators like cyclophosphamide and ifosfamide.[110]

A minority of cases of febrile neutropenia will have an offending infectious agent identified. Of those that do have a documented infectious source, a variety of organisms can be responsible. Gram-positive cocci, which are now responsible for the majority of culture-positive cases of neutropenic fever, include *Staphylococcus aureus*, *Staphylococcus epidermidis* (especially in patients with indwelling devices), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, the *Streptococci viridans*, and *Enterococcus faecalis* and *faecium*. *Corynebacterium* is the most likely gram-positive bacillus. Gram-negative bacilli include *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*.[111] *Candida* is the most common fungal infection,[112] but *Aspergillus* and *Zygomycetes* are more feared for their angioinvasive predilection.

Presentation

Infection is responsible for at least half of the cases of neutropenic fever.[113] Fever is a single oral temperature of 38.3°C (101°F) or higher, or temperatures of 38.0°C (100.4°F) or higher measured 1 hour apart.[113] A patient's reduced ability to mount an inflammatory response can limit localizing signs and symptoms, and therefore fever may be the only abnormal finding at presentation. Skin and soft tissue infections may not be associated with erythema or induration, and abscesses will not accumulate in the absence of pus-generating neutrophils. Pulmonary infections may not result in audible or radiographically visible infiltrates.

Diagnosis

When the ANC is less than 500/mm^3, or the ANC is less than 1000/mm^3 with a predicted decline to less than 500/mm^3 within 48 hours, the patient is considered neutropenic. The vulnerability to infection substantially rises at an ANC less than 1000/mm^3,[114] but the risk continues to increase as the ANC falls. At least one-fifth of all patients with an ANC less than 100/mm^3 are bacteremic.[113]

A careful, thorough physical examination is crucial. Particular attention should be given to any focal areas of pain or disruption of mucosal barriers, especially the gums, pharynx, perineum, and anus, avoiding digital rectal examination. Examination should also include funduscopy, palpation of the maxillary and frontal sinuses, and inspection of vascular access sites.

At a minimum, 2 sets of blood cultures should be drawn in each patient. If an intravascular device is present, at least one set of blood cultures should be obtained through that route, and ideally through each lumen of a multiple-port catheter. The collection times of peripherally and device-drawn cultures ought to be carefully recorded; when catheter-obtained blood cultures have a time to positivity that is at least 120 minutes earlier than that of peripheral cultures, it strongly suggests that the catheter is the source of infection.[115] Urinalysis and urine culture should also be obtained, but the lack of neutrophils may preclude pyuria. Chest x-rays can be ordered to evaluate respiratory symptoms.

Treatment

Prior to the era of empiric antibiotics, 50% to 75% of chemotherapy-related mortality was due to infections.[116] Empiric therapy is justified by the acuity with which the neutropenic patient can develop fever and progress to sepsis. Antimicrobial coverage can then be narrowed as more microbiologic data become available. While the minority of blood cultures obtained at presentation will yield identifiable organisms, it is still vital to adapt management to positive culture and susceptibility results; failure to change therapy appropriately in response to this information doubles the patient's mortality risk.[117]

Empiric antibiotic therapy can be administered in the inpatient or outpatient setting depending upon the patient's initial risk assessment (Fig. 3). The Infectious Disease Society of America has recently updated its febrile neutropenia guidelines to define high-risk patients as those in whom neutropenia is anticipated to last longer than a week with an ANC of 100/mm^3 or less, and/or worrisome aspects of presentation, including hypotension, acute abdominal pain, neurologic changes, or suspicion of pneumonia. Such patients require hospitalization for close monitoring and iv antibiotics. Monotherapy is acceptable only with a sufficiently broad-spectrum agent such as the fourth-generation cephalosporin cefepime, a carbapenem, or piperacillin-tazobactam, all of which offer antipseudonomal activity. Vancomycin can be added for skin and soft tissue infections, pneumonia, or suspicion of an infected device, but it should not be used as monotherapy.[118]

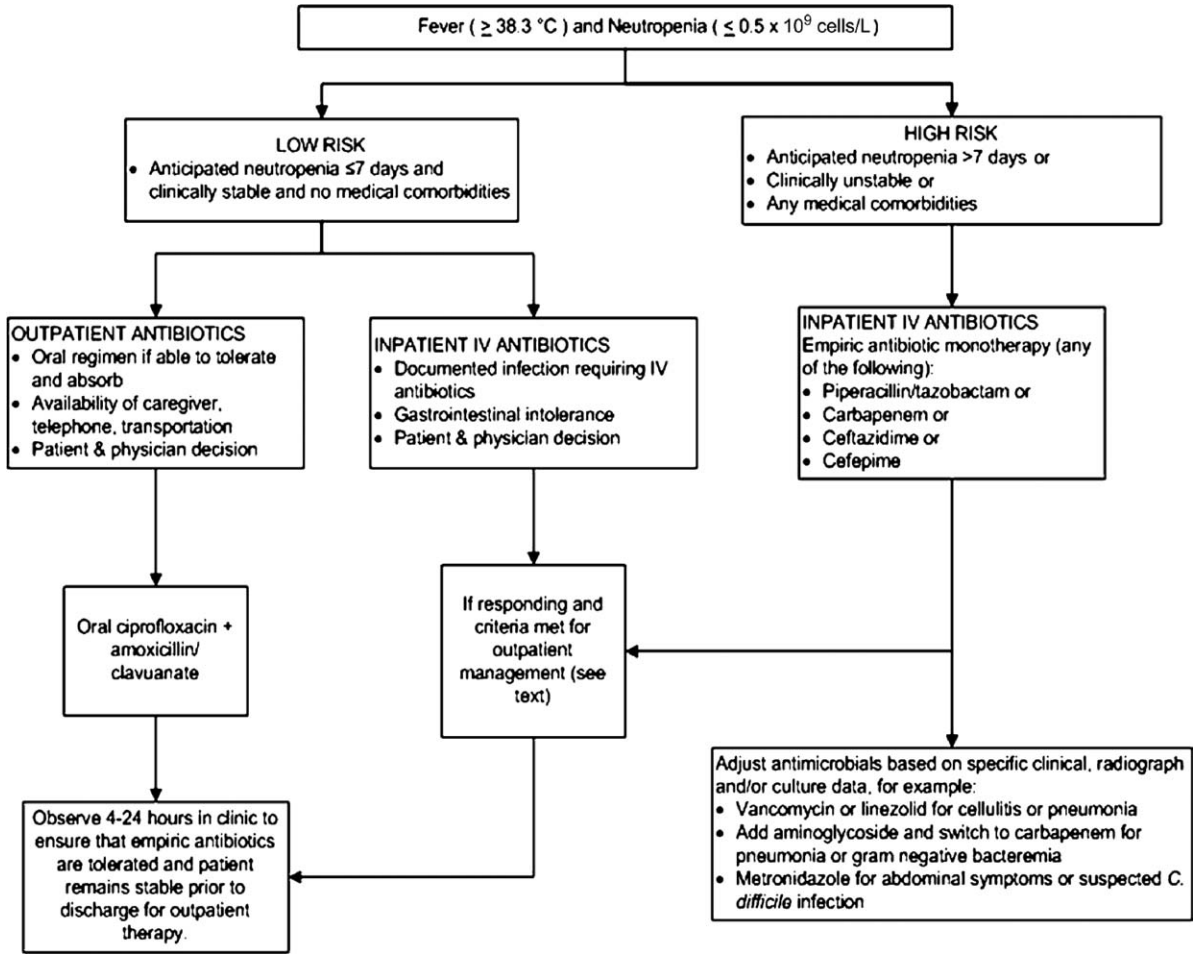

FIGURE 3. Initial Management of Febrile Neutropenia. IV indicates intravenous. Reprinted with permission from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:427–431, by permission of Oxford University Press on behalf of the Infectious Diseases Society of America. © 2011.

In low-risk patients without significant comorbidities whose neutropenia is expected to last less than a week and who have not been receiving quinolone prophylaxis, oral empiric therapy with ciprofloxacin and amoxicillin-clavulanate (both at a dose of 500 mg every 8 hours) is appropriate, but patients still require daily outpatient monitoring to ensure compliance and clinical improvement. If fever persists at 48 hours, the patient should be hospitalized.[118]

Antibiotic therapy should be continued at least until the ANC improves to above 500/mm^s. The addition of antifungal coverage should be considered in high-risk patients who remain febrile after 4 to 7 days of broad-spectrum antibiotics with no identified causative organism.[118] Diagnosis of an iv catheter-related infection does not necessarily require removal of the catheter if the culprit organism is a coagulase-negative *Staphylococcus*, but retention of the device does incur a higher risk of recurrent infection.[119] For catheter infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria, device removal followed by at least 14 days of antimicrobial therapy is recommended.[118]

The most recent American Society of Clinical Oncology guidelines on the applications of myeloid colony-stimulating factors (CSFs) do not routinely recommend their use in the active treatment of patients with febrile neutropenia.[120] However, the prophylactic use of CSFs has benefit in patients with an anticipated risk of febrile neutropenia that equals or exceeds 20%.[120] CSFs should then be employed during subsequent cycles of any regimen in which febrile neutropenia has previously occurred.[121]

Due to the accompanying risk of respiratory decompensation, especially in patients being treated for pneumonia, granulocyte infusions should be considered only in cases of prolonged neutropenia when bone marrow recovery is expected. They have been more demonstrably effective in refractory gram-negative and fungal infections than in gram-positive infections.[122]

Neurologic Emergencies

Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) was first described in 1925 by Spiller and remains a common oncologic emergency that requires prompt treatment to relieve pain and preserve neurological function.[123,124] Although all tumor types have the potential to cause MSCC, breast, prostate, and lung cancer each account for approximately 15% to 20% of the cases, with non-Hodgkin lymphoma, renal cell carcinoma, and myeloma each causing 5% to 10% of cases.[109,125] Although most cases of MSCC occur in patients with a known diagnosis of malignancy, 5% to 25% of MSCC cases occur as the initial presentation of malignancy.[126,127]

Pathophysiology

MSCC is defined as the compressive indentation, displacement, or encasement of the thecal sac that surrounds the spinal cord or cauda equina by cancer.[128] Compression can occur by posterior extension of a vertebral body mass, by anterior extension of a mass arising from the dorsal elements, or by growth of a mass invading the vertebral foramen.[128] The majority of the cases occur when metastatic tumor reaches the vertebral bodies via hematogenous spread, with secondary erosion into the epidural space. Approximately 15% of the cases occur when a paravertebral lesion spreads into the spinal canal through an intervertebral foramen and directly compresses the spinal cord. This is more commonly seen in neuroblastomas and lymphomas.[129] Metastases to vertebral bone can lead to weakening of the bone and vertebral collapse with displacement of bone fragments into the epidural space as well. In rare cases, metastases occur directly to the spinal cord and meninges.[129-131]

The most common location for MSCC is in the thoracic spine (60%) followed by the lumbosacral region (30%) and, lastly, the cervical spine (10%).[125,130] It is also important to recognize that metastatic lesions are seen at multiple levels of the spinal cord in almost half of all patients.

Presentation

Early detection is critical because the single most important prognostic factor for regaining ambulation after treatment of MSCC is pretreatment neurologic status.[132-135] The clinical presentation of MSCC can vary significantly depending on severity, location, and duration of the compression. The most common initial symptom is back pain, which occurs in approximately 90% of the cases.[128] Because back pain is a common symptom and has multiple causes, clinicians must always keep MSCC in their differential diagnosis. It is also important to remember that MSCC can be the initial presentation of malignancy. In a retrospective series of 337 patients with MSCC at the Mayo Clinic, compression was the first sign of malignancy in 20% of the cases, with lung cancer, multiple myeloma, and non-Hodgkin lymphoma accounting for approximately 75% of these initial presentations manifested by spinal epidural metastases.[127]

The back pain associated with MSCC may gradually worsen over time and usually precedes neurologic symptoms by weeks to months. Referred pain is common and varies according to the location of the offending lesion. Cervical compression can present as subscapular pain, thoracic compression as lumbosacral or hip pain, and lumbosacral compression as thoracic pain.[136]

Once symptoms other than pain are present, the progression can be quite rapid. These symptoms include motor weakness, sensory impairment, and autonomic dysfunction. Cauda equina syndrome may present as urinary retention and overflow incontinence (90% sensitivity and 95% specificity). Other symptoms include decreased sensation over the buttocks, posterior superior thighs, and perineal region.[125,136]

Physical examination findings depend on the location of the lesion(s) as well as the degree and duration of impingement. Most patients have tenderness to percussion over the affected spinal region. The Valsalva maneuver may worsen their back pain. Hyperreflexia, spasticity, and loss of sensation (position, temperature, pinprick, and vibratory) can occur early. Deep tendon reflexes may then become hypoactive or absent. Late signs include weakness, Babinski sign, and decreased anal sphincter tone.

Diagnosis

Because there is no clinical model to rule out MSCC in cancer patients with back pain, all reports of new-onset back pain should prompt an immediate assessment. For those patients with only back pain and a normal neurologic examination, imaging of the spinal axis should be completed within the next 48 to

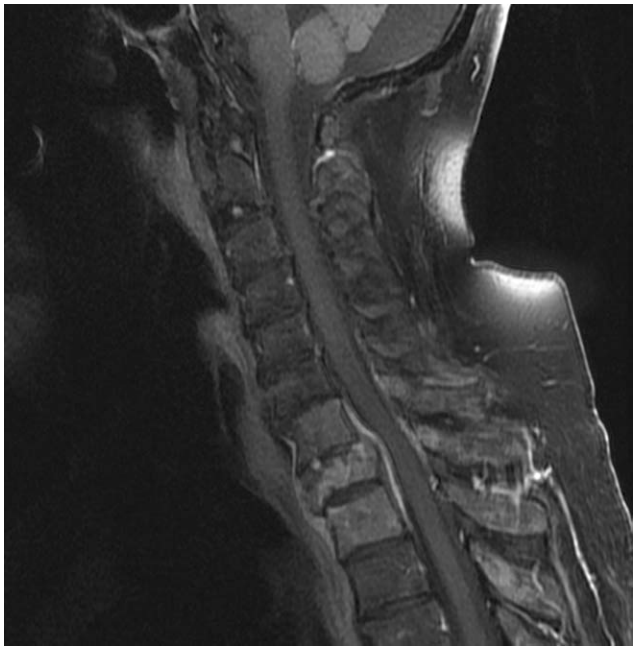

FIGURE 4. Magnetic Resonance Imaging of Spinal Cord Compression.

72 hours. Those with neurologic deficits need emergent evaluation before nerve damage becomes permanent.[130]

The gold standard for the diagnosis of MSCC is MRI, with a sensitivity of 93%, a specificity of 97%, and an overall accuracy of 95% (Fig. 4).[130,137,138] Plain films will not detect paraspinous masses that have entered the intervertebral foramen if there is no bone erosion, and they have a false-negative rate of 10% to 17%. Therefore, plain films should not be used to rule out impingement upon the spinal cord.[126,130] Because one-third of patients with MSCC present with multiple epidural lesions, imaging should include the entire thecal sac.[139] In a series of 337 patients with MSCC at the Mayo Clinic, 30% of the patients presented with multiple lesions. If MRI is contraindicated or not available, CT myelography can be used.[109,131]

Treatment

Management of patients with MSCC includes glucocorticoids, surgery, and external beam radiation therapy (EBRT).[13,127,128] In the case of patients with chemosensitive tumors, systemic therapy can also be used.

Corticosteroids are an integral component of the initial therapy, although the ideal dose is still debated. There have been 3 main clinical trials[140-142] that have addressed the optimal initial dose of glucocorticoids, and meta-analysis of these studies provided insufficient evidence as to the appropriate dose. Higher doses (96 mg vs 16 mg iv as the initial dose) were not associated with better outcomes, but were found to be associated with a higher incidence of adverse events including ulcers, psychosis, and infection.[140,142] There is no current consensus on the best dose, but dexamethasone is typically given as a 10-mg to 16-mg iv bolus followed by 4 mg to 6 mg every 4 hours, with a taper during or immediately after completion of radiation.[109,125,130] In patients with severe neurologic deficits in whom the severity of the deficits outweighs the possible side effects of high-dose therapy, many clinicians chose to use 96 mg of iv dexamethasone followed by 24 mg administered 4 times daily for 3 days, then tapered over 10 days.[130]

Definitive treatment depends largely on spinal column stability, degree of compression, and radiosensitivity of the tumor. If spinal instability is present, surgical decompression should be considered.[13,128] The Spine Oncology Study Group, which uses 6 components of spinal instability to produce a final Spine Instability Neoplastic Score, has established a novel classification system for spinal instability. Patients with a score of 7 or higher are considered at risk of spinal instability and warrant surgical consultation. The 6 components evaluated in this scoring system include global spinal location of the tumor, pain, bone lesion quality (lytic/blastic/mixed), spinal alignment, vertebral body collapse, and posterior involvement of the spinal elements.[143] Other considerations, such as disease burden and overall prognosis, should also be taken into consideration.

Radiation therapy plays a critical role in the treatment of MSCC, including in patients who have undergone surgical decompression. In 2005, Patchell et al reported the first phase 3 randomized clinical trial comparing decompressive surgery and radiation with radiation alone.[144] Patients were given 100 mg of dexamethasone followed by 24 mg every 6 hours and then were either treated with radiation therapy alone (30 gray [Gy] in 10 fractions) or surgery (generally within 24 hours) followed by the same course of radiation administered within 2 weeks of surgery. The study was discontinued after enrollment of 100 of the 200 planned patients because predetermined stopping criteria were met. The percentage of ambulatory patients was significantly higher in the group treated with surgery plus radiation (84% vs 57%), as was their duration of ambulation (median, 122 days

TABLE 4. Criteria of Patchell et al[143]

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Age ≥ 18 y	• Multiple discrete lesions
• Biopsy proven cancer[a]	• Radiosensitive tumors
• General medical status acceptable for surgery	• Compression of only the cauda equina or spinal roots
• Minimum of 1 neurologic symptom/sign	• Preexisting neurologic problems not related to MSCC
• No paraplegia for > 48 h	• Prior radiotherapy that would exclude patient from receiving study dose
• MSCC restricted to 1 area[b]	
• MRI evidence of MSCC[c]	
• Expected survival > 3 mo	

MRI indicates magnetic resonance imaging; MSCC, malignant spinal cord compression.

[a]Not of central nervous system and/or spinal origin.

[b]Can include several contiguous spinal or vertebral segments.

[c]Defined as displacement of the spinal cord by an epidural mass.

vs 13 days) and median survival (126 days vs 100 days).[144] It is difficult to extrapolate these data to all MSCC patients, due to the strict inclusion criteria used in the study. However, in patients who fulfill the criteria as outlined by Patchell et al (Table 4), decompressive surgery for maximal tumor resection and stabilization followed by radiation therapy should be considered.[131,144]

Although there is no consensus with regard to radiation dosing schedules, the therapy port usually extends 1 or 2 vertebral bodies above and below the site of compression, and therapy is often given at a dose of 30 Gy in 10 fractions. Radiation given at a dose greater than 30 Gy has not been shown to improve outcomes, but treatment regimens can range in duration, thus changing the dose per fraction.[13,125,145,146] For patients with a poor prognosis and significant pain, a brief course of EBRT (1 or 2 fractions of 8 Gy) can palliate without the extended treatment course.[147] In lesions involving relatively radioresistant tumors such as renal cell carcinoma and melanoma, stereotactic body radiation therapy in a single fraction is utilized for effective pain relief and local control.[148-150]

Increased Intracranial Pressure

Elevated intracranial pressure (ICP) secondary to malignancy in the brain can cause devastating neurologic injury. Successful management requires prompt recognition and therapy. The vast majority of all intracranial neoplasms are metastatic, with lung cancer (20%), breast cancer (5%), melanoma (7%), renal cancer (10%), and colorectal cancer (1%) being the most common tumors of origin.[151-156] Untreated patients have a median survival of approximately 4 weeks.[13] Prognosis is dependent on Karnofsky performance status, the presence of systemic disease, and the primary tumor.[157]

Pathophysiology

The majority of metastases travel to the brain via hematogenous spread. Tumor microemboli tend to lodge in the distal arteries and small capillaries of the "watershed" areas and the gray-white matter junctions. The distribution of metastases also follows the relative blood flow volume of the brain, with most occurring in the cerebrum, then the cerebellum, followed by the brainstem.[153]

Increased ICP is due to both the mass effect of the tumor as well as cerebral edema caused by neoplastic disruption of the blood-brain barrier, which is caused in part by local production of vascular endothelial growth factor (VEGF).[158,159]

Presentation

The clinical presentation of brain metastases will vary depending on the location, size, and rate of growth of the tumor. In a series of 111 patients with brain metastases, the most common presentation was headache, seen in 48% of patients and most often described as tension (in 77%).[160] In contrast to benign tension headaches, however, these headaches tended to worsen with bending over or with Valsalva maneuvers, and in many cases were also accompanied by nausea or emesis. The "classic" tumor-associated headache pattern, consisting of an early morning headache that improves during the day, occurred in only 36% of the cases.[160] Seizures range from 10% to 20% in incidence and are almost exclusively caused by supratentorial lesions. Strokes occur if the tumor embolizes, bleeds, or compresses an artery. Melanoma, choriocarcinoma, thyroid cancer, and renal cell carcinoma are more likely to cause hemorrhagic strokes.[161] Focal neurologic dysfunction is dependent on the location of the lesion. Clinicians must consider brain metastases in patients with cancer who report new or changing headaches, focal neurologic changes, or cognitive changes. A physical examination should be performed to evaluate for

focal neurologic deficits and papilledema. The triad of signs referred to as the Cushing response (hypertension with wide pulse pressure, bradycardia, and an irregular respiratory rate) is a late effect and indicates impending herniation.

Diagnosis

Once an intracranial malignancy is suspected, contrast-enhanced MRI is the preferred method of diagnosis. Contrast-enhanced MRI is more sensitive than either nonenhanced MRI or CT scanning in differentiating metastases from other CNS lesions.[162,163] Noncontrast CT scan is the preferred scanning technique, however, in an acute situation when hemorrhage or hydrocephalus is suspected.[109,157,164]

Treatment

Glucocorticoids are the initial treatment of choice and can reduce peritumoral edema and local brain compression within hours by repairing the leaky capillary permeability.[165,166] There is no consensus concerning dose, but dexamethasone is the standard agent because of its relative lack of mineralocorticoid activity and because it is associated with a lower risk of infection and cognitive impairment compared with other glucocorticoids.[167,168] The mechanism of action is not fully understood but has been shown to downregulate VEGF, upregulate angiopoeitin-1, and increase clearance of peritumoral edema by facilitating the transport of fluid into the ventricular system.[169] In general, the dose consists of a 10-mg to 24-mg iv bolus followed by 4 mg every 6 hours or 8 mg twice daily.[109,157] In severe cases, mannitol and hyperventilation are used. Mannitol can be administered as an iv bolus or as a continuous infusion to decrease cerebral edema. Intubation and controlled hyperventilation lead to a rapid decrease in cerebral edema. The effects of both mannitol and hyperventilation are transient and not definitive therapy. These should be reserved for critical cases in patients with rapidly declining clinical states.[170]

More definitive treatment modalities include whole-brain radiation therapy (WBRT), surgery, or stereotactic radiosurgery. WBRT generally improves the median survival by 3 to 6 months compared with 1 to 2 months with supportive care alone and is used most commonly in patients with multiple brain lesions or tumors that are too large for surgery or stereotactic radiosurgery.[157,170] Surgical debulking can also be performed depending on tumor location and is the most rapid way to alleviate ICP. Chemotherapy can be used in highly chemosensitive disease such as germ cell tumors, lymphoma, or small cell carcinomas, or in cases in which radiation therapy is not an option.

Seizures

Seizures are the presenting symptom of intracranial metastases in 10% to 20% of patients with intracranial involvement. Seizures may or may not be associated with ICP. Status epilepticus requires emergent treatment, usually with lorazepam, phenytoin, valproic acid, or fosphenytoin.[13,109,157] Patients with brain metastases who have not had a seizure do not benefit from the prophylactic administration of antiseizure medication. A meta-analysis of 5 randomized trials using phenobarbital, phenytoin, or valproic acid as prophylactic anticonvulsants concluded that there was no evidence to support their use, regardless of tumor type.[171] A subsequent systemic Cochrane review also concluded that there was no significant difference between placebo and treatment with phenobarbital, phenytoin, or valproic acid in preventing a first seizure.[172] These drugs also have significant side effects such as bone marrow suppression, as well as interactions with chemotherapeutic and targeted agents, many of which are metabolized via the same cytochrome P450 system induced by antiepileptic medications.[157]

Hematologic Emergencies

Hyperviscosity Syndrome

Hyperviscosity syndrome (HVS) refers to the clinical sequelae caused by increased blood viscosity. Increased serum viscosity (SV) is a result of excess proteins, usually immunoglobulins (Igs), most commonly arising from Waldenström macroglobulinemia (WM) (85%) and multiple myeloma (MM). Increased blood viscosity can result from elevated cellular components seen in hyperproliferative states such as leukemia and myeloproliferative diseases such as polycythemia vera (PV). When hyperviscosity results from elevated white blood cells, it is referred to as hyperleukocytosis or, if symptomatic, leukostasis.[173,174]

Similarly, polycythemia can cause elevated blood viscosity due to increased red blood cell mass. PV can cause vascular symptoms and complications secondary

to thrombocytosis with platelet hyperaggregability, leukocytosis, and/or high hematocrit, causing elevated blood viscosity. A decrease in cerebral blood flow and a high incidence of thrombotic complications are seen in these patients. Periodic phlebotomies can be used to reduce the risk of microvascular occlusion, as can cytoreductive agents.[175]

The focus of the remainder of this section will be on HVS secondary to proteins or leukocytosis. Since the clinical picture can differ between leukostasis and increased SV due to elevated protein levels, these pathologies require distinct treatments, and are discussed separately.

Pathophysiology

In normal healthy subjects, hematocrit is the main determinant of blood viscosity, with fibrinogen being the main determinant of plasma viscosity due to a combination of its large size, asymmetric shape, charge, and concentration, even though albumin is the most abundant protein in the blood. In paraproteinemias, such as WM and MM, excessive amounts of circulating Igs are produced. IgM is the largest Ig (molecular weight, 1,000,000) and is the most likely paraprotein to cause hyperviscosity, but HVS has also been documented in cases of MM or kappa light chain disease.[13,174]

As the concentration of Igs increases, they form aggregates and bind water via their carbohydrate content, which causes a rise in oncotic pressure and increases the resistance to blood flow. Igs are positively charged and therefore decrease the repellant forces between the negatively charged red blood cells. When present in excess, these proteins electrostatically bind to the red blood cells, causing rouleaux formation as well as decreasing the red blood cell malleability. Eventually, this leads to impaired transit of blood cells, microvascular congestion, decreased tissue perfusion, and subsequent tissue damage.[13,173,176]

Interestingly, there is no concise relationship between SV and clinical symptoms. The normal relative SV is approximately 1.4 to 1.8 centipoise (cP). In general, patients will not become symptomatic with an SV of less than 3 cP.[177] In patients with WM, approximately one-third with an SV greater than 4 cP will not have symptoms. Most symptomatic patients present with paraprotein levels between 5 and 8 g/L, with levels above 8 g/L almost always producing symptoms.[109,173,178]

Presentation

The "classic triad" of HVS includes neurologic abnormalities, visual changes, and bleeding, although all 3 need not be present to make the diagnosis.[173] Hyperviscosity causes impaired microcirculation in the brain that manifests itself in the form of headache, altered mental status, nystagmus, vertigo, ataxia, paresthesias, seizures, or even coma.[174] Ophthalmologic examination can detect hyperviscosity, revealing dilated, engorged veins that resemble "sausage links," a finding known as fundus paraproteinaemicus.[13] If untreated, this will progress to complete retinal vein occlusion and flame-shaped hemorrhages. These can be detected early on in the periphery of the retina at lower SV, which then progress to central retinal hemorrhages and vascular dilatation as the viscosity increases.[179,180] Mucosal bleeding and purpura are also common clinical manifestations of HVS, with proteins coating the platelets and hindering their function.[173] Other clinical consequences of HVS include congestive heart failure, ischemic acute tubular necrosis, and pulmonary edema, with multiorgan system failure and death occurring if treatment is not promptly initiated.[109,173,178]

Diagnosis

There is no single definitive test for HVS because it is a clinical diagnosis. A detailed history and physical examination are important. Laboratory studies including an electrolyte panel, SV, peripheral blood smear, coagulation panel, and quantitative Ig levels should be obtained.[178] The peripheral blood smear will likely show rouleaux formation. Pseudohyponatremia, hyperkalemia, and hyperphosphatemia are also often seen.[174] Any patient with an SV greater than 4 cP should be evaluated for HVS.

Treatment

Plasmapheresis is the fastest, most effective method to reduce plasma viscosity.[13,178] It is especially rapid in IgM-related cases since IgM is largely found in the intravascular space. IgA- or IgG-derived syndromes may require a greater volume and a longer treatment schedule. Lowering of serum values will be followed by extravascular to intravascular redistribution. Plasmapheresis should be performed on a daily basis until the symptoms resolve and the plasma viscosity level is near normal. In an emergency setting in which plasmapheresis is not readily available, phlebotomy has been used to reduce acute symptoms.

All these actions, however, are temporizing measures. Unless the underlying dysproteinemia is addressed, the serum concentration will rise again. Red cell transfusions should be avoided unless critically necessary, as this can increase SV, thus worsening HVS.[13]

Leukostasis

Leukostasis is a hematologic emergency that is associated with respiratory failure, intracranial hemorrhage, and early death.[174,181] If it is not recognized and treated promptly, the mortality rate can be as high as 40%.[181] Risk for leukostasis increases with a white blood cell count (WBC) greater than 100,000/mm^3. The incidence ranges from 5% to 13% in patients with AML and 10% to 30% in adult patients with ALL.[181] Other risk factors include younger age (with presentation in infants being most common); ALL with 11q23 rearrangement or the Philadelphia chromosome; and AML subtypes M3, M4, and M5. Hyperleukocytosis portends a poor prognosis, with a higher risk of early mortality, especially in patients with ALL. The WBC count is the most important prognostic factor in ALL, and patients who present with a WBC greater than 50,000/m^3 have a particularly poor prognosis; very few children with hyperleukocytosis become long-term survivors.[174,181,182]

Pathophysiology

The pathophysiology of leukostasis is not completely understood. There is believed to be a component of "sludging" by the leukemic blasts in the microvasculature secondary to increased whole blood viscosity. On average, the leukemic myeloblasts have a mean cell volume that is almost twice that of the leukemic lymphoblasts and therefore the manifestations are more common in patients with AML than those with ALL. There is also differential expression of adhesion molecules on the lymphoblast and myeloblast cells that has been implicated in the higher incidence of leukostasis noted in patients with AML versus patients with ALL.[174,183] Evidence also suggests that there are leukemic blast/endothelial cell interactions that lead to vascular wall disruption as well as complement-induced granulocyte aggregation.[174]

In general, whole blood viscosity is not dramatically increased in leukostasis because the rise in the WBC is often counterbalanced by a decrease in the erythrocyte count.[174,184] This is important to recognize because packed red blood cell transfusions in patients with asymptomatic hyperleukocytosis can rapidly lead to leukostasis.[13,185]

Presentation

Leukostasis can involve any organ system, but the initial symptoms most commonly are related to the respiratory system and the CNS.[174] Pulmonary symptoms can range from exertional dyspnea to severe respiratory distress, with diffuse interstitial or alveolar infiltrates often present on chest x-ray, although these are not required for the diagnosis. Arterial blood gases should be interpreted with caution, especially if the sample is not immediately placed on ice, because pseudohypoxia with artifactually low arterial oxygen tension may be seen secondary to the rapid consumption of plasma oxygen from the abundant leukocytes.[174,181] Neurologic manifestations span the spectrum from mild confusion to somnolence. Patients commonly report headache, dizziness, tinnitus, blurred vision, or visual field defects. Physical examination can reveal papilledema, retinal vein bulging, and retinal hemorrhage. Intracranial hemorrhage can present with focal neurologic deficits. Other symptoms include myocardial infarction, limb ischemia, renal vein thrombosis, and disseminated intravascular coagulation. Fever is almost always seen and can be greater than 39°C. Although infection is found in only a few cases, it does need to be ruled out because this syndrome can mimic sepsis. Thrombocytopenia is also usually present and underestimated because WBC fragments can be counted as platelets in some automated cell counters.[109,174,181] Disseminated intravascular coagulation is often seen in association with this syndrome, most commonly in the M3 subtype of AML, although it can occur in all types of leukemia.[181]

Diagnosis

The diagnosis of leukostasis is made by the combination of patient symptoms and the WBC.

Treatment

Rapid cytoreduction is the initial treatment in these patients. Ideally, this is achieved by induction chemotherapy, which can dramatically reduce the WBC within 24 hours. These patients are at very high risk for TLS and require close monitoring of electrolytes, with prophylaxis by allopurinol or rasburicase depending on renal function and fluid resuscitation.[13,174,181] The use of leukapheresis is a widely accepted initial treatment and was commonly

believed to reduce early mortality; however, it lacks randomized controlled trials and retrospective studies have not shown a survival benefit.[174,186] Leukapheresis is usually initiated when the blast count is greater than 100,000/m^3 or regardless of blast count in the presence of symptoms. In patients with ALL, leukapheresis is usually not done unless symptoms develop or the WBC is greater than 200,000/m^3.[187] Cytoreduction can also be achieved by hydroxyurea, but is usually reserved for patients with asymptomatic hyperleukocytosis who are unable to receive immediate induction chemotherapy.[188] Hydroxyurea can be given at doses of 1 to 2 g every 6 hours and can reduce the WBC by 50% to 80% within 24 to 48 hours.[174,189] Induction chemotherapy should be initiated immediately or as soon as possible because leukapheresis and hydroxyurea are only temporizing measures.[174,181] Leukapheresis is generally not used in patients with acute promyelocytic leukemia because it may worsen the intrinsic coagulopathy associated with this subtype of leukemia. These patients are also at high risk of thrombosis with the placement of the large-bore central venous catheter that needs to be inserted for the procedure.[181] Conversely, careful monitoring of the platelet count is required because these patients can present with thrombocytopenia and disseminated intravascular coagulation. Subsequent leukapheresis can worsen the thrombocytopenia as a small portion of platelets are removed during the procedure.[174]

The role of cranial radiation is still debated, but is currently used less frequently, especially in adults. Single-fraction radiation to the cranium for severe neurologic symptoms due to cerebral leukostasis, or to the lungs for pulmonary leukostasis causing hypoxia, has been used as a temporizing measure in select patients, more commonly in the pediatric population, although there are no controlled studies confirming benefit.[109,181,186]

Respiratory Emergencies

Malignant Airway Obstruction

Airway obstruction can be caused by virtually any malignancy, but the most common culprits include tumors of the tongue, oropharynx, thyroid, trachea, bronchi, and lungs. Mediastinal tumors such as lymphomas and germ cell tumors can also cause airway obstruction, more commonly in the pediatric population.[13] Primary bronchogenic carcinomas are the most common cause of malignant airway obstructions, and up to 30% of patients with primary lung tumors will develop airway obstruction. Airway obstruction does not appear to adversely affect overall survival, with a median survival of 8.2 months versus 8.4 months when comparing patients with airway obstruction with those without.[190] Prompt recognition and treatment can lead to a markedly improved quality of life, with up to 95% of patients reporting a decrease in dyspnea and a significant increase in quality of life after treatment.[191]

Pathophysiology

Airway obstruction may result from external compression of the trachea or bronchi by the tumor, or by an involved lymph node. The obstruction can also occur by infiltration of the tumor within the oropharynx, trachea, and bronchi, causing severe narrowing.[192]

Presentation

The clinical manifestations of malignant airway obstruction depend on the severity and location of the obstruction. The symptoms are nonspecific and can be mistaken for more common conditions including chronic obstructive pulmonary disease exacerbations, asthma, or bronchitis. The most common presentation of malignant airway obstruction is dyspnea. The symptoms usually worsen at night and while lying supine. Patients will often have a productive cough and wheezing, and may also present with stridor, especially if the obstruction is located in the trachea or carina. In these cases, the symptoms may be quite minimal until the airway is critically narrow, but then appear rapidly and pose a life-threatening situation.[192] "Tracheal stenosis syndrome" refers to a constellation of symptoms consisting of dyspnea, cough, wheezing, and stridor, and is seen in approximately 85% of patients with primary tracheal tumors.[192,193] Hemoptysis is reported in up to 45% of patients with obstructing neoplasms.[194]

Diagnosis

Airway obstruction needs to be considered in the differential diagnosis of patients with a history of malignancy who are presenting with new respiratory symptoms. Crackles or fremitus, along with poor expansion of the lung, may be found on physical examination.[194] Chest x-rays should be rapidly

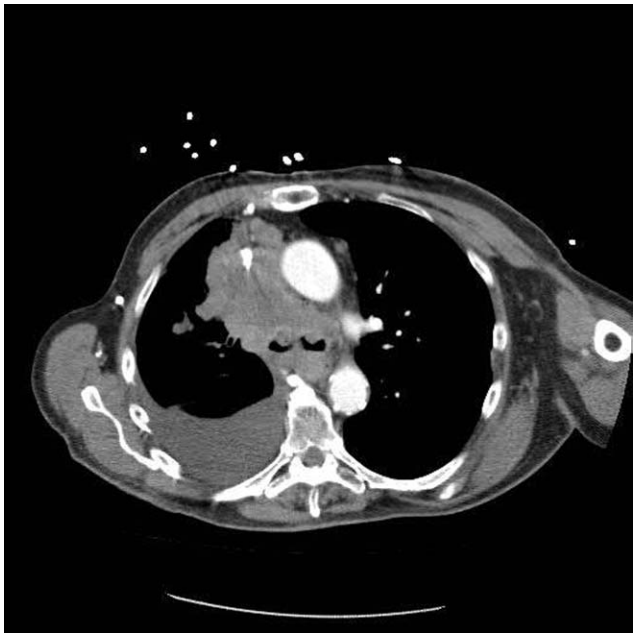

FIGURE 5. Bilateral Mainstem Bronchial Obstruction Shown on Axial Computed Tomography.

obtained to determine the presence of a tumor or indirect evidence of obstruction such as tracheal deviation or airway narrowing, although CT scanning is preferred (Figs. 5 and 6). Pulse oximetry will aid in determining the degree of hypoxemia. In nonemergent settings, flow-volume loops can be obtained and the resultant pattern can help identify whether the obstructing lesion is fixed, extrathoracic, or intrathoracic.[192] However, these loops add little to the diagnosis and are not recommended in urgent/emergent situations. Bronchoscopy allows for direct visualization of the obstruction, as well as provides a method for obtaining tissue for diagnosis and immediate treatment.[13,192,194] This must be done in a controlled setting because bronchoscopy can further increase the obstruction and the accompanying anesthesia may also decrease the gas exchange.

Treatment

The mainstay of treatment is stenting via bronchoscopy because it aids in diagnosis and treatment. Rigid bronchoscopy is preferred in patients with significant airway obstruction as flexible bronchoscopy can potentiate the airway obstruction, and it allows for placement of metallic self-expanding stents that are particularly useful for cases of extrinsic airway compression or for the control of bleeding. Stents are the treatment of choice in patients with acute airway obstruction due to extrinsic tumor compression[195] or in patients with tracheoesophageal fistulas.[196] Although this does not prolong survival, 95% of patients do report relief of symptoms after stent placement.[191] Neodymium yttrium (Nd:YAG) or carbon dioxide (CO_2) lasers can be used to open the airway as well.[13,197] In a retrospective review by Han et al of 110 cases, laser therapy decreased dyspnea (76% response rate) and controlled hemoptysis (94% response rate), with no procedure-related mortality.[198] Similar to bronchoplasty, the effects tend to be transient and some other form of more definitive tumor control should follow, such as radiation or chemotherapy.[13,194,199-201] Postobstructive pneumonia portends a poor prognosis.[192]

Chemotherapeutic Emergencies

Extravasation of Chemotherapy

Pathophysiology

Extravasation, defined as the unintended leakage of the chemotherapy drug into the extravascular space, is a dreaded complication of chemotherapy administration (Figs. 7-9). Vesicants are chemotherapy agents that have the ability to induce tissue necrosis, resulting in functional impairment and disfigurement. There are more than 1 million daily infusions of chemotherapy administered worldwide, and the frequency of extravasation in adults is estimated to be between 0.1% to 6% of peripheral iv infusions and somewhat less in implanted venous access port infusions.[202] Vesicants include the anthracyclines, vinca alkaloids, and mitomycin C. Irritants such as the

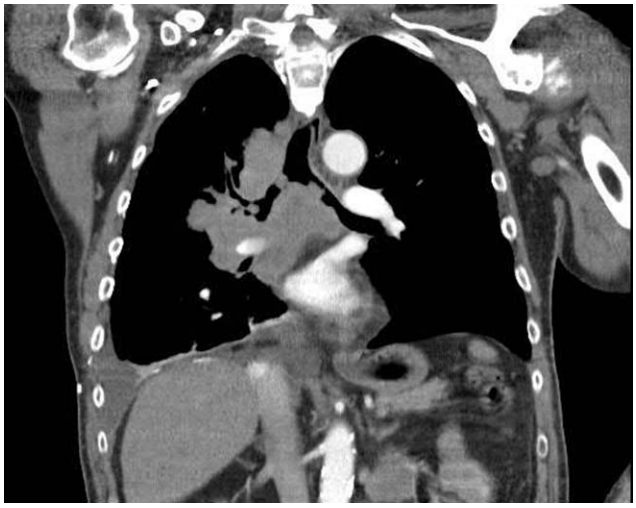

FIGURE 6. Bilateral Mainstem Bronchial Obstruction Shown on Coronal Computed Tomography.

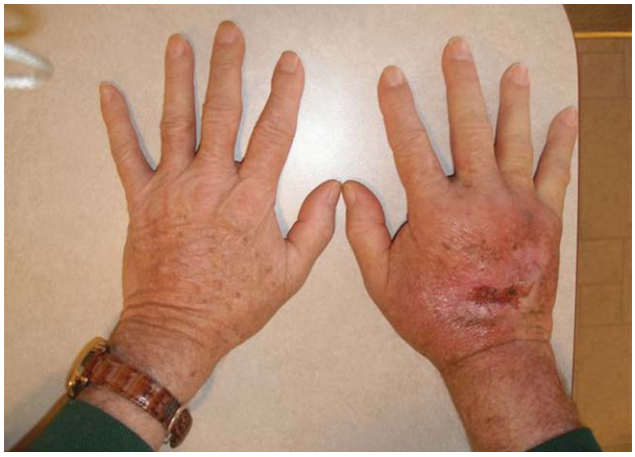

FIGURE 7. Anthracycline Extravasation From a Peripheral Intravenous Administration in the Right Hand Occurred on November 18, 2009. A photograph of the extravasation site was taken on December 28, 2009 (photograph courtesy and reprinted with kind permission of Herbert and Elaine Peterson).

platinum compounds, taxanes, and topoisomerase I inhibitors cause an inflammatory reaction but not tissue necrosis. This classification is not absolute because the severity of tissue injury is dependent on drug concentration and volume. For example, platinums or taxanes can behave like vesicants and induce ulcerations at high concentrations or at large volumes.[203] Nonaggressive agents are drugs that rarely cause any reaction when extravasation occurs.

Presentation

Extravasations vary in their clinical presentation and severity. Symptoms may occur immediately after the incident or develop in subsequent days or weeks. In most cases, initial symptoms include pain, blistering, induration, and discoloration. Ulceration may not appear for several days and may continue to worsen for months, as the drug diffuses into the adjacent tissue. In severe cases, necrosis of the skin and the underlying tissues may develop, leading to infection, scars, treatment delay, functional deficits, amputation, and, rarely, death.[202,204-206] In the case of irritant extravasation, symptoms include erythema, swelling, and tenderness. Phlebitis, hyperpigmentation, and sclerosis can subsequently develop along the vein. These symptoms usually resolve within weeks and long-term sequelae are extremely rare. Patients with small, deep veins or those with damaged veins secondary to multiple venipunctures are at higher risk, as are patients with neurologic deficits because of an inability to follow instructions or secondary to an impaired ability to detect changes in sensation. Obesity and movement during chemotherapy administration also increase the risk of extravasation.[202,206]

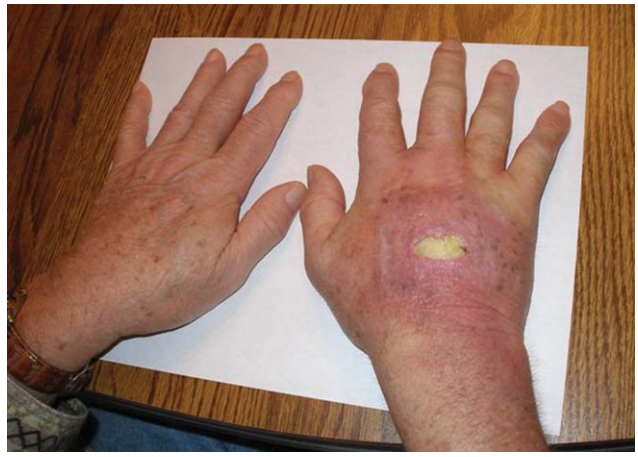

FIGURE 8. Photograph of the Extravasation Site Shown in Figure 7 Taken on February 22, 2010 (photograph courtesy and reprinted with kind permission of Herbert and Elaine Peterson).

Diagnosis

Extravasation is usually diagnosed by local symptoms of pain, erythema, and swelling, or by leakage of fluid around the iv site, but a change in the rate of infusion or absence of blood return from the vascular access may be the initial sign. Once suspected, even if asymptomatic, the infusion needs to be discontinued and treatment initiated immediately.[202,205,206]

Treatment

The best approach to an extravasation injury is prevention. Once extravasation is suspected, treatment should be initiated as quickly as possible. The Oncology Nursing Society and the European Oncology Nursing Society have published comprehensive

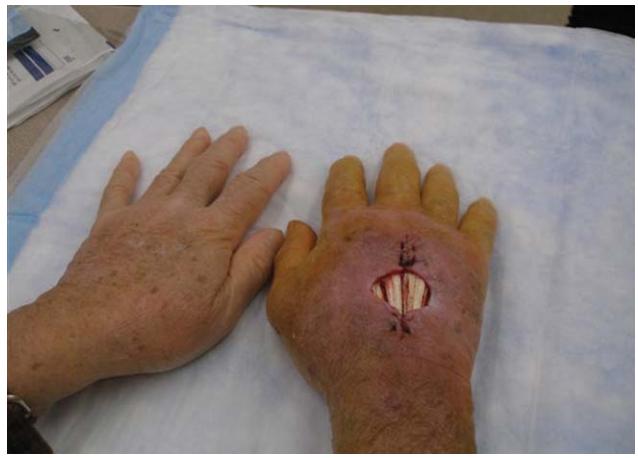

FIGURE 9. Photograph of the Extravasation Site Shown in Figure 7 Taken on March 7, 2010 (photograph courtesy and reprinted with kind permission of Herbert and Elaine Peterson).

TABLE 5. Examples of Common Vesicants and Irritants

VESICANT	COMMONLY USED TREATMENTS
Anthracyclines Daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin C	Dexrazoxane, topical DMSO, topical cooling
Vinca alkaloids Vincristine, vinblastine, vinorelbine	Topical warming, subcutaneous hyaluronidase
Mitomycin C	Topical cooling, topical DMSO
IRRITANTS	**COMMONLY USED TREATMENTS**
Taxanes[a] Docetaxel, paclitaxel	Topical cooling, subcutaneous hyaluronidase
Platinums[a] Carboplatin, cisplatin	Topical cooling, subcutaneous hyaluronidase
Epipodphyllotoxins Etoposide, teniposide	Topical warming
Topoisomerase I inhibitors Irinotecan, topotecan	Topical cooling

DMSO indicates dimethyl sulfoxide.

[a]May have vesicant properties at high concentrations and volumes, but more often act as irritants.

management guidelines.[207,208] The infusion should be discontinued, and the affected limb elevated. The access device should not be removed, but rather should be used to attempt to aspirate fluid from the extravasated area. The next step of treatment is dependent on the specific drug (Table 5), and in many cases remains controversial. Application of ice to the affected area is recommended for extravasation of vesicants and irritant drugs, except the vinca alkaloids and epipodophyllotoxins. The cooling causes vasoconstriction and reduces the extent of local injury and can also reduce pain.[206] Cold is contraindicated for vinca alkaloids and epipodophyllotoxins, as this worsens the ulcerations in animal models,[206,209] and heat is recommended to increase perfusion, theoretically enhancing drug removal.[202,209]

Nonsurgical treatment modalities have been investigated in vesicant extravasation, mainly in animal studies or in studies without a control arm. Although agents such as topical or injected dimethyl sulfoxide (DMSO), hyaluronidase, and corticosteroids are used, only dexrazoxane has been approved by the US Food and Drug Administration for the treatment of extravasation resulting from anthracycline therapy. The mechanism by which dexrazoxane diminishes tissue damage is unknown.[204] Approval was based on 2 prospective, open-label, single-arm, multicenter trials published together by Mouridsen et al.[210] Fifty-seven patients had biopsy-confirmed anthracycline extravasation. The most common agents were epirubicin (56%) and doxorubicin (41%). Most patients developed acute swelling (83%), redness (78%), and pain (43%). Thirteen patients developed late sequelae such as pain, fibrosis, atrophy, and local sensory disturbance. All cases were graded as mild, except in one patient who required surgery despite receiving dexrazoxane within 6 hours of the event. Dexrazoxane is administered iv as a 1- to 2-hour infusion through a separate venous access within 6 hours of extravasation, and then again at 24 hours and 48 hours.[203]

Anaphylactic Reactions to Chemotherapy

Essentially any chemotherapeutic agent has the potential to cause an infusion reaction, which can range significantly in severity. These are often called hypersensitivity reactions; however, because some do not have a hypersensitivity component, they are more properly termed infusion reactions. Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death.[211] It is rare with most conventional cytotoxic agents, although it is well established with platinum drugs and the taxanes. Other agents known to commonly cause infusion reactions include cyclophosphamide, ixabepilone, bleomycin, L-asparaginase, and monoclonal antibodies such as rituximab.

Presentation

Anaphylactic reactions caused by chemotherapeutic agents present with the same variety of signs and symptoms as do anaphylactic reactions secondary to other etiologies. In general, the majority of patients who develop anaphylaxis will present with cutaneous manifestations such as urticaria and angioedema (up to 90% of cases) and respiratory symptoms such as wheezing and dyspnea (up to 70% of cases), with GI and cardiovascular symptoms occurring in up to 35% of cases.[211-213] Platinum agents (cisplatin, carboplatin, and oxaliplatin) tend to cause the classic IgE-mediated hypersensitivity reaction. These reactions can vary significantly in severity and overall, any reaction is rare. All platinum agents can cause

infusion reactions, with some being as severe as anaphylaxis, particularly after repeated cycles. Carboplatin hypersensitivity is seen in up to 2% of patients receiving carboplatin, and is as high as 16% in the gynecologic oncology population, because these patients typically receive repeated exposure to platinum agents.[214,215]

Taxanes have been known to cause anaphylaxis as well. Acute reactions to paclitaxel and docetaxel tend to present shortly after the infusion is initiated, and nearly 95% of the cases develop within the first 2 cycles of therapy.[216,217] However, due to the timing of these reactions, the release of histamine and the associated cytokines does not appear to always be immune-mediated.[217] There is also evidence that anaphylaxis can occur from the drug vehicle rather than the agent itself. Paclitaxel is formulated with Cremophor (BASF SE, Ludwigshafen, Germany), a polyethoxylated castor oil that is also used to deliver other drugs such as ixabepilone, diazepam, and vitamin K.[218] Paclitaxel should be avoided in patients who have had a severe reaction to one of these drugs, although Abraxane (micro albumin-bound paclitaxel particles; Celgene, Summit, NJ) can be considered.[219]

Agents such as docetaxel and iv etoposide are also formulated with vehicles that can cause infusion reactions, some of which are severe. These agents are formulated with polysorbate 80 and can cause symptoms that include chest discomfort, bronchospasm, and angioedema.[220]

Diagnosis

In 2005 and 2006, diagnostic criteria were published by a multidisciplinary group of experts to aid clinicians in recognizing the full spectrum of signs and symptoms of anaphylaxis.[211,212] Anaphylaxis should be highly suspected if any one of the 3 following criteria is present. The first criterion defines an acute illness that develops over minutes to hours of the offending exposure and should involve changes in the skin and/or mucosal tissue, as well as evidence of respiratory compromise (such as stridor or dyspnea) or hypotension. The second criterion requires that 2 or more of the following signs and/or symptoms develop rapidly after exposure to a likely allergen. These symptoms are: 1) involvement of skin/mucosal tissue (such as hives or angioedema); 2) respiratory compromise; 3) reduced blood pressure or associated symptoms (such as syncope); and/or 4) persistent GI symptoms (such as abdominal pain, diarrhea, or emesis). The third criterion requires reduced blood pressure after exposure to a known allergen of that patient.

Treatment

Infusion reactions can vary significantly in severity. In mild cases, without any features of anaphylaxis, the infusion should be temporarily discontinued until proper evaluation of the patient has occurred. Diphenhydramine at a dose of 50 mg iv can help relieve mild symptoms. The infusion can be restarted at a slow rate with close monitoring. In cases of anaphylaxis, the infusion should be discontinued immediately, with subsequent treatment identical to the management of other causes of anaphylaxis. Close assessment of the airway, breathing, and circulation should occur. Epinephrine (0.3-0.5 mg im; 1:1000) should be given immediately and can be repeated every 3 to 5 minutes as necessary. Patients should also be given oxygen and iv fluids as well. Antihistamines and glucocorticoids also can be administered. Epinephrine infusions, vasopressors, and glucagon may need to be used if the patient is refractory to the initial therapies.

In instances in which there has been an infusion reaction but not anaphylaxis, premedications can been used to allow the patient to continue therapy with the offending agent; however, such techniques are beyond the scope of this review. Desensitization has been used in cases in which the antineoplastic agent is necessarily being used with curative intent, even when patients have had an anaphylactic response. If, however, the skin test remains positive after desensitization, a rechallenge is not recommended.[216]

Conclusions

Oncologic emergencies can threaten the well-being of almost any patient with a malignancy. Because these conditions span the chronologic spectrum of a disease's natural history, from initial presentation to late recurrence to end-stage disease, all clinicians should be familiar with the manner in which these conditions emerge, as well as understand the methods for their prompt assessment and treatment. This review is not intended to address these techniques in an entirely

comprehensive fashion, but may provide a framework for the physician to process these alarming events from physiology to intervention, permitting room for exciting new advancements in radiology and pharmacology that should continue to improve the care of the cancer patient in their hour of greatest need. ■

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