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A review in the treatment of oncologic emergencies

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Abstract

Aim: Oncologic emergencies are often categorized as a group of metabolic abnormalities associated with the diagnosis of cancer or the initiation of chemotherapy for treatment. These syndromes often arise in the acute setting, demanding an accurate knowledge of the associated condition and current treatment. In this review, we evaluate five oncologic emergencies: tumor lysis syndrome, hypercalcemia, hyponatremia, spinal cord compression, and disseminated intravascular coagulation.

Summary: Oncologic emergencies are often diverse in etiology and are often associated with the initiation of chemotherapy. Tumor lysis syndrome presents as severe electrolyte abnormalities that need to be addressed urgently, sometimes prior to initiation of chemotherapy. Hypercalcemia of malignancy is treated with aggressive rehydration, furosemide, and intravenous bisphosphonates. If a patient with cancer presents with normovolemic hyponatremia, syndrome of inappropriate antidiuretic hormone should be suspected. Malignant spinal cord compression happens when cancer cells grow in, or near to, the spine and press on the spinal cord and nerves. This causes swelling and a reduction in the blood supply to the spinal cord and nerve roots. Disseminated intravascular coagulation is characterized by systemic activation of blood coagulation, which results in generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to multiple organ dysfunction syndrome.

Conclusion: Knowledge of oncology emergencies is critical to the understanding of these emergent syndromes in oncology patients. Each of these disease states requires careful evaluation of the patient's symptoms, monitoring parameters for conditions and supportive care measures and interventions.

Keywords

Tumor lysis syndrome, hypercalcemia, hyponatremia, oncologic emergencies, spinal cord compression, disseminated intravascular coagulation

Introduction

Oncologic emergencies are potentially life-threatening conditions that should be recognized immediately with decisive intervention in order to minimize mortality and morbidity. The signs and symptoms of an oncologic emergency may present at any time from the time before diagnosis to the end-stage of the hematologic or oncologic malignancy.

In order to determine the aggressiveness of treatment for the oncologic emergency, the overall management should incorporate disease prognosis, goals of care and quality of life. Most common oncologic emergencies occur due to metabolic and hormonal abnormalities, treatment of the malignancy and the invasive tumor compressing on vital organs. This article reviews updated management strategies of tumor lysis syndrome, hypercalcemia, hyponatremia, malignant spinal cord compression and disseminated intravascular coagulation.

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a potentially life-threatening emergency commonly seen in patients with hematologic malignancies, bulky tumors, tumors with high proliferative rates, and tumors

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that are highly responsive to therapy. TLS can occur spontaneously, but it arises more often after initiation of chemotherapy and/or radiation therapy. TLS is characterized by metabolic abnormalities resulting from acute destruction of neoplastic cells and release of their intracellular contents into the circulation in quantities that exceed the kidney's ability to eliminate.

The incidence and severity of TLS depends on numerous factors including tumor mass, type of malignancy, type and intensity of anticancer therapy, high proliferation rate of cancer cells, sensitivity of cancer cells to anticancer therapy, increased lactate dehydrogenase levels, and presence of pre-existing conditions such as renal insufficiency, hypotension, dehydration, etc.[1,2] TLS occurs most frequently in patients with high-grade non-Hodgkin lymphomas (NHL), especially with Burkitt's lymphoma, and other hematologic malignancies, such as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). In a retrospective study of 102 patients with high-grade NHL, the incidence of TLS was reported to be 42%, although clinically significant TLS was only 6%.[3,4]

Pathophysiology

When tumor cells lyse in response to therapy, intracellular contents including potassium, phosphorus, proteins and nucleic acids are released into the bloodstream. The release and catabolism of nucleic acids can result in hyperuricemia, specifically purine nucleic acids that are metabolized by xanthine oxidase into uric acid, which is eliminated through the kidneys at a rate of approximately 500 mg/day.[4] In hyperuricemic conditions, crystal formation and deposition increase leading to renal insufficiency or failure.

Hyperkalemia can be a life-threatening consequence of TLS, especially in patients with decreased renal function.[3] Occasionally, hyperkalemia may result from excess iatrogenic potassium administration during induction therapy. Hyperkalemia can lead to cardiac arrhythmias and sudden death.

Hyperphosphatemia results from the massive release of intracellular phosphorus. It has been postulated that malignant cells may contain as much as four times the amount of organic and inorganic phosphorus compared to normal cells.[3] Hyperphosphatemia can result in neuromuscular irritability, dysrhythmia and seizures.

Hypocalcemia may occur secondary to hyperphosphatemia when the calcium-phosphorus product exceeds 70 mg^2/dL.[2–4] Patients may be asymptomatic or symptomatic. In extreme cases, hypocalcemia can result in cardiac arrhythmia, hypotension, tetany, muscular cramps, and seizures.

Diagnosis

To aid in the diagnosis of TLS, the definition of TLS which comprises both clinical TLS (CTLS) and laboratory TLS (LTLS) was standardized by Cairo and Bishop in 2004. According to Cairo and Bishop, LTLS is present when two or more metabolic values are abnormal or if they change by 25% within 3 days before or 7 days after initiation of therapy (Table 1).[1–5]

CTLS is defined as the presence of LTLS in addition to one or more of the following clinically significant complications: renal insufficiency, cardiac arrhythmias, seizures and sudden death (Table 2). Based on this classification, LTLS is considered as either present or absent, whereas the grade of CTLS is defined by the maximal grading of clinical manifestation.[3,4]

In hyperuricemia, uric acid crystals can obstruct urine flow in renal tubules, leading to acute obstructive uropathy. Clinical manifestations of obstructive uropathy include hematuria, flank pain, hypertension, azotemia, acidosis, edema, oliguria, anuria, lethargy and somnolence.[3]

Hyperkalemia is the most serious manifestation of acute TLS. General clinical symptoms are nausea, vomiting, diarrhea and anorexia. Hyperkalemia may also lead to neuromuscular (muscle weakness, cramps, paresthesias and possible paralysis) and cardiac (peaked T-wave or widening of QRS complex on an electrocardiogram (ECG), asystole, ventricular tachycardia or fibrillation, syncope) abnormalities and possible sudden death.[3,4]

In severe hyperphosphatemia, patients may present with nausea, vomiting, diarrhea, lethargy and seizures.

Severe hypocalcemia may be associated with muscular (muscle cramps and spasms, paresthesias, tetany), cardiovascular (ventricular arrhythmias, heart block, hypotension), and neurological (confusion, delirium, hallucinations and seizures) complications. More devastating rare complications include bradycardia, cardiac failure, coma, and death.[3]

Table 1. Cairo-Bishop definition of laboratory tumor lysis syndrome.[3]

Metabolites	Value	Change from baseline
Uric acid	≥476 μmol/L or 8 mg/dL	25% increase
Potassium	≥6 mEq/L or 6 mg/dL	25% increase
Phosphorus	≥2.1 mmol/L for children, ≥1.45 mmol/L for adults	25% increase
Calcium	≤1.75 mmol/L	25% decrease

Table 2. Cairo-Bishop definition and grading of clinical tumor lysis syndrome.[3]

	Grade					
Complication	0	1	2	3	4	5
Creatinine	$\leq 1.5 \times$ ULN	$>1.5 \times$ ULN	>1.5–$3 \times$ ULN	>3–$6 \times$ ULN	$>6 -$ ULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure	None	Brief partial seizure; no loss of consciousness	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which is prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death

ULN: Upper limit of normal; CHF: congestive heart failure; ADL: activities of daily living.

Management

Prevention and immediate initiation of appropriate treatment are necessary to reduce morbidity and mortality from TLS. The main factor in successful management of acute TLS is to identify patients by risk group and proactively institute aggressive prophylactic strategies to prevent and/or reduce the severity of the clinical manifestations in high risk patients. Ideally, tumor therapy should be delayed until prophylactic measures for TLS are initiated in patients at risk for TLS. Standard supportive care includes monitoring electrolytes before and during cytoreductive regimens as well as during aggressive hydration, which is initiated at least 24 h prior to cytoreductive therapy. Vigorous hydration enhances urine flow, thereby promoting excretion of uric acid and phosphate by improving intravascular volume, renal blood flow, and glomerular filtration. Diuretics, specifically loop diuretics, may be required to maintain this urine output if there is no evidence of acute obstructive uropathy and/or hypovolemia.

Urine alkalinization, by adding sodium bicarbonate to intravenous (IV) fluid to maintain urine pH ≥ 7, has historically been a general recommendation and standard practice for prevention and treatment of TLS, specifically with concomitant use of allopurinol. However, due to lack of clear evidence demonstrating efficacy, the use of sodium bicarbonate for urine alkalinization is no longer recommended.[4]

Hyperuricemia

Hyperuricemia is defined as serum uric acid ≥ 8 mg/dL or 25% increase from baseline, occurring 3 days before or 7 days after initiation of cytotoxic therapy (usually developing 48–72 h after therapy).[2] The standard of care for hyperuricemia is hydration and use of hypouricemic agents, such as allopurinol and/or rasburicase. Aggressive hydration is highly recommended, usually 1–2 times the daily maintenance. Urine output is usually maintained at a rate of 80–100 mL/m^2/h in adults and 2–3 L/m^2/d (or 200 mL/kg/d if ≤ 10 kg) for pediatric patients.

Allopurinol is a xanthine analogue that, when converted *in vivo* to oxypurinol, is a competitive inhibitor of xanthine oxidase, which inhibits the metabolism of xanthine and hypoxanthine to uric acid. Allopurinol should be considered as a prophylactic measure for intermediate-TLS risk patients. For adult patients, it is recommended to start allopurinol 1 to 2 days prior to the start of induction and may be continued for up to 3–7 days, depending on the ongoing risk for TLS. The recommended dosing of allopurinol for prevention of uric acid uropathy is 100 mg/m^2/dose every 8 h (max 800 mg/d) orally or 200–400 mg/m^2/d in 1–3 divided doses IV (max 600 mg/d).[4] Side effects have been reported to occur in 3% of patients receiving allopurinol,[6] which include gastrointestinal irritation, rash, fever, hypersensitivity reactions and xanthine nephrolithiasis. If allergic reactions occur, allopurinol should be discontinued immediately to prevent further

development of Stevens-Johnson syndrome. Allopurinol is excreted renally; therefore, dose adjustment is necessary for patients with renal insufficiency.[7]

There are limitations to allopurinol therapy. First, allopurinol has a slow onset of action of 24–72 h, during which time it places the kidneys at risk for damages. Secondly, allopurinol has no effect in the excretion of uric acid that is already formed. In contrast, urate oxidase, such as rasburicase, works by catabolizing uric acid to a more soluble allantoin, which is 5 to 10 times more soluble than uric acid in the urine.

Rasburicase is a recombinant urate-oxidase produced by a genetically modified *Saccharomyces cerevisiae* strain. The cDNA coding for rasburicase was cloned from a strain of *Aspergillus flavus*.[8] Rasburicase retained the efficacy of the aspergillus-derived form with a marked reduction in side effects and improved tolerability.[9] In a clinical study, Pui et al. demonstrated a significant reduction of uric acid level within 4 h of rasburicase administration[8] with <2% of patients experiencing side effects which were mainly minor allergic reactions such as headaches, rashes and itching. Serious side effects are rare but include wheezing, edema and anaphylactic reactions. Hydrogen peroxide, a potent oxidizing agent and a by-product of the conversion of uric acid to allantoin can cause hemolytic anemia and/or methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Rasburicase is U.S. Food and Drug Administration (FDA)-approved for use as initial management of hyperuricemia in pediatric and adult patients with leukemia, lymphoma and solid tumor malignancies who are receiving anticancer therapy and expected to result in tumor lysis and subsequent elevation of plasma uric acid. The approved dosing of rasburicase is 0.2 mg/kg infused over 30 min daily, for up to 5 days. Because rasburicase has demonstrated effectiveness in reducing uric acid levels even after a single dose, different dosing options have been explored and evaluated: fixed- and weight-based dosing. Currently, practitioners use one-time rasburicase dosed either as a fixed dose of 3, 6, or 7.5 mg or weight-based dose of either 0.05 or 0.15 mg/kg. It has been shown that both dosing schema clearly demonstrated significant lowering of serum uric acid levels quickly comparatively, therefore, the debate of ideal dosing of rasburicase is still unresolved and still being evaluated.

Hyperkalemia

Hyperkalemia usually occurs 6 to 72 h after initiation of cytotoxic therapy, and can be exacerbated by acute kidney injury (AKI).[10] For asymptomatic patients with potassium level ≥6 mEq/L, the initial treatment is to eliminate all IV and oral potassium supplements and administer sodium polystyrene sulfonate (15–30 g for adults; 1 g/kg with 50% sorbitol for pediatric patients). For patients with severe hyperkalemia (≥7 mEq/L) and/or who are symptomatic, a more intense intervention is necessary, such as IV administration of short-acting insulin (10 U for adult patients, 0.1 U/kg for pediatric patients) with glucose (25–40 g of 50% dextrose for adults; 2 mL/kg of 25% dextrose for pediatrics). Sodium bicarbonate (50 mEq for adult; 1–2 mEq/kg for pediatrics) can be given to induce influx of potassium into cells, and slow infusion of calcium gluconate 10% (1 g for adults; 100–200 mg/kg/dose for pediatrics) with ECG monitoring for bradycardia can be used to treat life-threatening arrhythmias. In some incidences, dialysis has been used to remove excess potassium.

Table 3. Tumor lysis syndrome.[3]

	Risk		
Type of cancer	High	Intermediate	Low
Non-Hodgkin's lymphoma (NHL)	Burkitt's lymphoma, B-cell ALL	DLBCL	Indolent NHL
Acute lymphocytic leukemia (ALL)	WBC ≥ 100,000	WBC 50,000–100,000	WBC ≤ 50,000
Acute myeloid leukemia (AML)	WBC ≥ 50,000, monoblastic	WBC 10,000–50,000	WBC ≤ 10,000
Chronic lymphocytic leukemia (CLL)		WBC 10,000–100,000, treatment with fludarabine	WBC ≤ 10,000
Other hematologic malignancies and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

DLBCL: Diffuse large B-cell lymphoma; WBC: white blood cell.

Hyperphosphatemia

Hyperphosphatemia usually occurs 24–48 h after initiation of cytotoxic therapy. It is usually defined as a phosphorus level >2.1 mmol/L in children and >1.45 mmol/L in adults.[4] For asymptomatic hyperphosphatemia, initial treatment consists of eliminating phosphate from diet and IV solutions, maintaining adequate hydration, and administration of phosphate binders. Calcium carbonate should not be used in patients with elevated calcium levels. In addition, patients with hyperphosphatemia should not receive calcium infusions, except in patients with symptomatic hypocalcemia. For severe hyperphosphatemia, hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration (CVVH) has been used with success. Hemodialysis appears to clear phosphate better than CVVH and peritoneal dialysis.

Hypocalcemia

Because the risk of precipitating metastatic calcification is high, especially in a setting of hyperphosphatemia, treatment is generally not recommended for asymptomatic hypocalcemia. Hypocalcemia usually resolves without any intervention as tumor lysis improves. However, in patients with symptomatic hypocalcemia, slow IV administration of calcium gluconate (50–100 mg/kg or 1–3 g for adults) with ECG monitoring may be given.

Hypercalcemia of malignancy

Hypercalcemia is a metabolic emergency which occurs in 20–30% of cancer patients at some time throughout the course of their disease.[11] It most commonly occurs in advanced malignancies, and is usually observed in patients with a previously established cancer diagnosis. Breast cancer, lung cancer, and multiple myeloma are the most common malignancies associated with hypercalcemia of malignancy.[12] Hypercalcemia often indicates a poor prognosis with regard to the course of malignancy, especially when associated with an elevation of parathyroid hormone-related protein (PTHrP) levels.[13]

Pathophysiology

In patients without cancer, hypercalcemia often occurs due to severe hypovolemia resulting from fluid loss or decreased fluid intake; such patients should be evaluated for malignancy. Hypercalcemia of malignancy occurs due to a number of physiologic processes, the most common of which is the excess production of PTHrP by the tumor.[14] Due to structural similarities between the two compounds, PTHrP can mimic the actions of parathyroid hormone (PTH), and thus its overproduction leads to hypercalcemia due to increased bone resorption and calcium reabsorption in the distal tubule. Osteolysis is another common cause of hypercalcemia of malignancy, induced as a result of cytokine production by malignant cells.[15] The cytokines, which include tumor necrosis factor and a number of interleukins, stimulate the differentiation of osteoclasts, resulting in bone destruction and hypercalcemia. The overproduction of vitamin D analogues such as calcitriol is another mechanism, most commonly seen in hematologic malignancies, which leads to hypercalcemia through increased production of serum calcium.[16]

Diagnosis

Hypercalcemia often presents with a number of nonspecific symptoms including confusion, lethargy, nausea, constipation, polyuria, and polydipsia, although it can also present as an asymptomatic laboratory abnormality.[17] The presence of symptoms is often associated with a more severe degree and rapid onset of hypercalcemia. The diagnosis of hypercalcemia requires the measurement of ionized serum calcium, or the correction of total serum calcium for the serum albumin level. Corrected calcium is calculated by the formula: corrected calcium = total calcium + [0.8 × (4.0−albumin)]. Other pertinent laboratory values include serum creatinine, alkaline phosphatase, PTH, PTHrP, and other electrolytes. The levels of serum chloride and PTH are usually low in hypercalcemia of malignancy, although normal or increased levels do not rule out malignancy as the cause. Serum PTHrP levels, while not essential for diagnosis, can be useful in determining the mechanism of hypercalcemia.[18] In addition, there is evidence that PTHrP levels >12 pmol/L correlate with a less reliable response to bisphosphonate therapy and a greater risk of recurrence of hypercalcemia within two weeks of the initial episode.[19]

Management

As severe hypercalcemia (corrected calcium >14 mg/dL) and moderate hypercalcemia (corrected calcium 12–14 mg/dL) are usually accompanied by hypovolemia, the initial treatment is IV hydration with normal saline (Table 4). Fluids should be administered aggressively, up to 500–1000 mL in the first hour and continued at 150–250 mL/h until intravascular volume is repleted and urine output is achieved. Hydration should be administered with care in patients with a history of CHF, and loop diuretics should be avoided until the patient is euvolemic, in order to avoid further diminishing the renal excretion of calcium. The initial assessment should also ensure that sources of calcium

Table 4. Treatment options for hypercalcemia of malignancy.

Medication	Dose	Drug class	Time of onset	Comments/concerns
Hydration with normal saline	500–1,000 mL in first hour, then 150–250 mL/h until euvolemic	N/A	Rapid	Administer with care in patients with history of congestive heart failure
Zoledronic acid	4 mg IV over 15–30 min	Bisphosphonate	48–72 h	Use with caution in renal impairment; no dosage adjustment recommended for hypercalcemia
Pamidronate	60–90 mg IV over 2–6 h	Bisphosphonate	48–72 h	Use with caution in renal impairment; increase duration of administration in renal insufficiency
Calcitonin	4–8 IU/kg SC or IV every 8–12 h	N/A	30–60 min	Should not be given longer than 72 h; can cause flushing and tachyphylaxis
Denosumab	120 mg SC on days 1, 8, 15, and 29, then every 4 weeks thereafter	RANKL inhibitor	72–96 h	Should be given in setting of refractory hypercalcemia at least seven days after bisphosphonate
Furosemide	20–40 mg IV every 24 h	Loop diuretic	15–30 min	Should be avoided until euvolemic, unless in the setting of heart and renal failure
Prednisone/ Hydrocortisone	Prednisone 60 mg PO daily; hydrocortisone 100 mg IV q6h	Glucocorticoids	1–2 h	Chronic use should be avoided due to side effects and immunosuppression

intake, as well as medications that can increase the calcium level, such as vitamin D and thiazide diuretics, are eliminated.

In addition to hydration, IV bisphosphonates (pamidronate and zoledronic acid), which interfere with osteoclast activity and stimulate osteoclast apoptosis, represent the mainstay of treatment for hypercalcemia of malignancy. There is evidence that zoledronic acid may be superior to pamidronate in the treatment of moderate to severe hypercalcemia of malignancy, but the clinical significance of this difference is controversial.[20] Both pamidronate and zoledronic acid are cleared renally and should be used cautiously in patients with renal dysfunction. Dose reductions for renal insufficiency have not been established for the treatment of hypercalcemia, although dosing recommendations do exist for their other FDA-approved indication (prevention of skeletal-related events from bone metastases). If pamidronate or zoledronic acid are given in the setting of renal dysfunction, prolonged infusion should be considered. The onset of action for the IV bisphosphonates is 24–72 h. For persistent or refractory hypercalcemia, repeat doses of bisphosphonates should not be given fewer than 7 days after the previous administration.[21,22]

As pamidronate and zoledronic acid may take up to several days to take effect, subcutaneous (SC) or intramuscular calcitonin can be used in conjunction with aggressive hydration to acutely lower serum calcium levels. Nasal administration of calcitonin is not effective for this indication.[23,24] Calcitonin should not be continued for longer than 72 h, as longer durations of administration increase the risk of tachyphylaxis and rebound hypercalcemia. Dialysis may be appropriate for the treatment of patients with renal failure or CHF, when aggressive hydration and administration of bisphosphonates are unsafe or not feasible.[25] In the setting of persistent hypercalcemia after failure of bisphosphonate therapy, corticosteroids may be added, but adverse effects limit their chronic use.[26]

In order to reduce the risk of recurrent hypercalcemia, the use of medications with risk of increasing calcium levels should be avoided. Because hypercalcemia of malignancy is caused by the tumor, treatment of the underlying disease with chemotherapy and/or radiation is paramount to the consistent control of hypercalcemia.

While the advent of the bisphosphonates has greatly enhanced the treatment of malignant hypercalcemia, the introduction of denosumab presents another therapeutic option. Denosumab is a human IgG2 monoclonal antibody that binds human receptor activator of nuclear factor kappa-B ligand (RANKL), which inhibits osteoclast activity and prevents bone resorption. Like the bisphosphonates above, denosumab is FDA-approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors at a dose of 120 mg SC every 28 days.[27] In three phase III trials which led to its FDA approval for the prevention of skeletal-related events, the most common adverse event observed was hypocalcemia with an incidence of 9.6% versus 5.0% for zoledronic acid.[28,29] A recent

phase II clinical trial was published which investigated the use of denosumab for the treatment of bisphosphonate-refractory hypercalcemia. The trial, in which patients had a corrected serum calcium of greater than 12.5 mg/dL at least seven days and less than or equal to 30 days after treatment with bisphosphonates, showed that denosumab lowered corrected serum calcium to less than or equal to 11.5 mg/dL within 10 days in 64% of patients.[30] In December 2014, the FDA approved the use of denosumab for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Hyponatremia

Hyponatremia is a common electrolyte disorder in hospitalized patients that can lead to serious neurological complications.[31] It is defined as a sodium level <135 mmol/L[32] and categorized as either mild, moderate or severe hyponatremia. For cancer patients on chemotherapy, the definition may be based on the standard grading scale for adverse events with the Common Toxicity Criteria for Adverse Events (CTCAE) which states Grades 1–2 (mild/moderate) for sodium values between 131 and 134 mmol/L, Grade 3 (severe) for 121–130 mmol/L, Grade 4 (life-threatening) for ≤120 mmol/L, and Grade 5 for death.[33]

The incidence of hyponatremia varies from 3.7% to 47% in hospitalized cancer patients.[34–36] Hyponatremia has been associated with medications, increasing age (>30 years), cancers and other medical conditions.[37] Hyponatremia is caused by pituitary or adrenal dysfunction, paraneoplastic production of ADH, chemotherapy-induced, and the use of aggressive hydration that is required for therapy.[38] Hyponatremia caused by medications may be due to their effects on antidiuretic hormone (ADH; or vasopressin) and disruption in water and sodium balance (Table 5).[39–41] Cancers that are commonly associated with hyponatremia, especially syndrome of inappropriate antidiuretic hormone (SIADH) secretion, are solid tumors (of the lung, breast, head, and neck),[38] and other malignancies such as gastrointestinal, genitourinary, endocrine, sarcomas and lymphomas.[34,38,41]

Table 5. Drug-induced hyponatremia.[40,45]

Type of hyponatremia	Mechanism of hyponatremia	Drug
Hypovolemic	Affect sodium and water homeostasis	Diuretics, Thiazides, amiloride, indapamide, loop diuretics
Euvolemic	Increased release or enhance ADH	Chemotherapeutics Alkylating agents Melphalan Cyclophosphamide Ifosfamide Vinca alkaloids Vincristine Vinblastine Platinum compounds Cisplatin Carboplatin Immunomodulating agents Interferon Interleukin-2 Pentostatin Methotrexate Nonsteroidal anti-inflammatory drugs Opiates

Pathophysiology

Hyponatremia is a disruption in water and sodium balance[31] which is regulated by thirst and ADH. ADH is released from the posterior pituitary and causes increased permeability for the reabsorption of water at the renal collecting tubules. The body will maintain a normal plasma osmolality between 280 and 295 mOsm/kg.[42] When the plasma osmolality is high with low blood volume, the thirst response is activated and increased secretion of ADH occurs. In low plasma osmolality, the thirst response and ADH are not stimulated.

Diagnosis

Most patients with hyponatremia are usually asymptomatic. Depending on the severity and acuity of hyponatremia, common clinical symptoms include neurological changes such as cerebral edema that can lead to lethargy, disorientation, seizures, coma, and respiratory arrest.[43] Mild symptoms, especially in patients with chronic hyponatremia, include increased risk for falls, dizziness, attention deficits, gait disturbance, headache, and nausea.[39,44] Hyponatremia is classified as hypovolemic, euvolemic and hypervolemic based on extracellular fluid (ECF) volume status.[31] In order to determine the type of hyponatremia, the ECF volume status, plasma osmolality and urine sodium excretion should be obtained (Table 6).

Hypovolemic hyponatremia is defined as a decrease in both total body water volume and sodium; however, the decrease in sodium exceeds the water volume.[42] Patients with hypovolemic hyponatremia will usually present with volume depletion. Most common causes in cancer patients include medications such as thiazide diuretics used for hypertension, and increased renal

Table 6. Classification and diagnosis of hyponatremia.[45]

	Hypovolemic	Euvolemic	Hypervolemic
Serum sodium		<135 mmol/L	
Serum osmolality		<280 mOsm/kg	
Urine osmolality		>100 mOsm/kg	
Total body water	Total body water ↓ Total body sodium ↓↓	Total body water ↑ Total body sodium ↔	Total body water ↑↑ Total body sodium ↑
Urine sodium	Renal sodium loss >20 mmol/L Extrarenal sodium loss ≤20 mmol/L	>20 mmol/L	Renal failure >20 mmol/L HF; cirrhosis ≤20 mmol/L
Supportive labs	Uric acid normal or elevated BUN elevated	Uric acid normal or low BUN normal or low	BNP elevated
Signs	Dehydration, weight loss, dry mucous membranes	No dehydration or edema	Edema, ascites, weight gain

BNP: brain natriuretic peptide; BUN: blood urea nitrogen; HF: heart failure.

elimination of sodium in cerebral salt wasting (CSW) which has a similar presentation as SIADH; in this situation, the ECF volume status should be kept in mind to ensure appropriate treatment.

Euvolemic hyponatremia is defined as an increase in total body water while sodium is near normal. It is most commonly diagnosed in hospitalized patients, specifically SIADH[42] which is due to increased ADH despite low plasma osmolality, causing water retention and continued urine sodium elimination.

Hypervolemic hyponatremia is defined as an increase in both the total body water volume and sodium; however, the increase in the water volume exceeds sodium.[42] This impairment of water elimination is due to inappropriately elevated amounts of ADH. Patients with hypervolemic hyponatremia will present with volume overload or edema.

Management

Treatment may be based on patients with clinical acuity of symptoms and severity.[45] Offending medications that may cause hyponatremia should be avoided and discontinued in all patients (Table 5). In addition, treating the underlying malignancy and medical conditions may improve hyponatremia. The optimal amount of sodium correction is not consistent; however, it is recommended to be <8–10 mmol/L within 24 h and 18 mmol/L in 48 h to minimize the risk for osmotic demyelination.[41,42,46]

In hypovolemic hyponatremia, the main treatment is to optimize fluid replacement with isotonic saline in order to reverse volume depletion (Table 7). In order to improve sodium concentrations, sodium chloride tablets may be administered. Fludrocortisone has also been shown to improve volume status in combination with sodium replacement for patients with CSW and SAH at risk of vasospasms.[46–49]

For euvolemic and hypervolemic hyponatremia, treatment can be modified based on severity and symptoms. For patients with asymptomatic or mild hyponatremia, first-line option is fluid restriction between 500 and 1000 mL/day.[38,41] In addition, fluid restriction may be based on targeting 500 mL/day less than the average urine output.[42] If patients continue to be hyponatremic despite fluid restriction, medications may be used.

Medications such as demeclocycline and urea have been used in the past; however, they are not commonly used due to variable efficacy and toxicities. Demeclocycline continues to be an option for the treatment of hyponatremia. It induces reversible nephrogenic diabetes insipidus by inhibiting the effects of ADH in the renal tubules.[42,50,51] Its effect may not be seen for three to four days and may cause nephrotoxicity at higher doses. Urea is an osmotic diuretic, which increases the free water and decreases sodium elimination.[42] It has fallen out of favor due adverse effects such as azotemia and liver dysfunction, with limited availability. Urea is recommended to be administered with orange juice due to its poor taste.[41,45]

Newer medications that are U.S. FDA-approved for the treatment of euvolemic and hypervolemic hyponatremia are conivaptan and tolvaptan (Table 7). Conivaptan is a non-selective inhibitor of vasopressin receptors.[52] It targets V_{1A} receptors causing vasoconstriction and increased blood pressure, and V_2 receptors

Table 7. Treatment of hyponatremia.[38,42,45,55]

Management	Dose	Duration	Comments
Hypovolemic – mild to moderate hyponatremia			
0.9% Normal saline (154 mmol Na/L)	Rate based on severity and volume repletion needed	Resolution of hyponatremia	First-line
Sodium chloride tablets (1 gm = 17 mmol Na/L)	Dose based on mEq needed 1–3 gm orally every 6–12 h	Resolution of hyponatremia	Calculation: mEq NaCl needed = 0.6 × weight (Kg) × (desired Na – Actual Na)
Fludrocortisone	0.1 mg orally three times daily	Days	May be beneficial for CSW and SAH at risk for vasospasms Side effects: hypokalemia, fluid overload, hypertension
Euvolemic and hypervolemic – mild to moderate hyponatremia			
Fluid restriction	Restrict fluids to <500–1000 mL/day; or target 500 mL/day less than the average urine output	Days until hyponatremia resolves	First-line
Demeclocycline	600–1200 mg/day orally in divided doses	Days; effects may not be seen for 3–4 days	Second-line Does not require concomitant fluid restriction Side effects: GI intolerance, nephrotoxicity (higher doses), liver dysfunction
Urea	15–30 gm/day orally in divided doses	Days until hyponatremia resolves	Second-line Dissolve in orange juice for taste Side effects: azotemia, liver dysfunction
Conivaptan	Infuse 20 mg bolus over 30 min followed by 20 mg continuously over 24 h for up to 4 days	Days until hyponatremia resolves; Max: 4 days after the loading dose	Third-line Dose adjustment required for mild hepatic dysfunction Drug interactions with CYP3A4 inhibitors and inducers Side effects: infusion site reactions, headache, hypotension, nausea, constipation
Tolvaptan	15 mg orally once daily; dose may be increased up to 60 mg daily	Days until hyponatremia resolves; Max: 30 days due to increased risk for liver injury	Third-line Drug interactions with CYP3A4 inhibitors and inducers No dose adjustments for renal (not studied in CrCl <10 mL/min) or hepatic dysfunction Side effects: dry mouth, polyuria, constipation, hyperglycemia
Severe hyponatremia			
3% Sodium (513 mmol Na/L)	Infuse 1–2 mL/kg/h until resolution of symptoms then 0.5 mL/kg/h	Hours until resolution of clinical symptoms	Total correction should be <10 mmol/L within 24 h Monitor sodium every 2–4 h the first 24 h

CrCl: creatinine clearance; GI: gastrointestinal; Na: sodium; NaCl: sodium chloride
SAH: subarachnoid hemorrhage; CSW: cerebral salt wasting.

in the renal collecting ducts to promote free water elimination. Tolvaptan selectively inhibits ADH from binding to the V_2 receptors in the collecting ducts in order to promote free water elimination.[53] Tolvaptan has been shown to improve hypervolemic hyponatremia in patients with heart failure, and may have improved edema and provided dyspnea relief.[54] Initiation and re-initiation should be in a hospital with close monitoring of patient's sodium and fluid status. Both agents have different formulations; conivaptan is a solution for IV infusion while tolvaptan is an oral tablet. Both agents are not used for severe hyponatremia due to an increased risk for overcorrection within the first 24 h. When patients are taking vasopressin receptor antagonists, they should not be on fluid restrictions for the first 24 h due to the risk for hypovolemia. Patients should continue to ingest fluids based on thirst during the first 24 h. Conivaptan is a strong CYP3A4 inhibitor and substrate while tolvaptan is a CYP3A4 substrate. Medications that are CYP3A4 inhibitors and inducers should be avoided or used with caution. Tolvaptan is limited to 30 days due to the risk for serious liver injury with prolonged use and is not recommended for patients with underlying liver disease.

In severe cases wherein sodium is <120 mmol/L or in patients with neurologic changes, 3% saline may be administered.[38,41,45,55] Rapid correction of sodium should be avoided due to the risk for osmotic demyelination, especially in patients with chronic hyponatremia. Risk for osmotic demyelination is higher with rapid correction of sodium >12 mmol within 24 h. For emergent correction of hyponatremia, the hypertonic saline should be infused at a rate of 0.5–2 mmol/L/h until symptoms resolve; however, total correction should be <10 mmol/L within 24 h. Sodium should be monitored frequently, every 2–4 h, during the first 24 h of correction. Once hyponatremia and symptoms are resolved, the hypertonic saline may be discontinued.

Treatment for hyponatremia may be complicated when patient's own diuresis improves or has overcorrection of sodium. In patients who have been overcorrected and experience worsening neurologic symptoms due to osmotic demyelination, hypotonic saline or dextrose 5% with or without DDAVP may be administered. DDAVP is a vasopressin analogue that binds to the V2 receptor in the renal collecting tubules to increase water resorption and can be administered SC or IV at a dose ranging from 1 to 4 mcg (usually 1 to 2 mcg) every 6 to 8 h until sodium correction normalizes.[41,56]

Malignant spinal cord compression

Malignant spinal cord compression (MSCC) is an oncologic emergency that can cause pain and potential paralysis.[57,58] MSCC affects 5% of terminal cancer patients in the last 2 years of their lives with a less than 6 months median survival from diagnosis.[59] Approximately 20% of patients present with MSCC as their initial finding.[60] Lung, breast, and prostate cancer each account for 15–20% of all MSCC. Multiple myeloma, NHL, and renal cell carcinoma account for 5–10% each.[61]

Pathophysiology

MSCC occurs when tumor compresses the thecal sac by invading the epidural space. Destruction of cortical bone by tumor can compound this compression by vertebral-body collapse and retropulsion of bony fragments into the epidural space.[61] Sixty percent of cases occur in the thoracic spine, 30% in the lumbosacral spine, and 10% in the cervical spine. The degree of compression and its location impact the symptoms the patient may experience.[62]

Diagnosis

Signs and symptoms of MSCC include pain (83–95%), motor defects (60–85%), sensory deficits (40–90%), bowel and bladder dysfunction, and ataxia.[61] Back pain is typically the first symptom and precedes the other symptoms by up to 2 months.[59,63,64] Initially, the pain is localized and may become more radicular due to the potential involvement of other areas in the spine.[59,61,63,64] Pain intensity increases over several weeks and may be aggravated by lying down.

Weakness is the most apparent and problematic manifestation of MSCC. Approximately two-thirds of patients are nonambulatory when diagnosed. Sensory deficits are less common with most patients usually unaware of these symptoms. Spinal sensory levels are usually one to five segments below the anatomic level of cord compression. Bowel and bladder dysfunction tend to occur late and typically match the degree of weakness.[61,63,65]

The diagnosis of MSCC is confirmed by radiologic findings preferably through magnetic resonance imaging. Computed tomography can be used initially and is beneficial in the planning of treatment, such as for radiotherapy.[58,59,66] Imaging should include the entire thecal sac since multiple sites of disease affect treatment planning and prognosis.[58,59,66] The novel classification system for spinal instability in neoplastic disease as reported by Fisher et al. is a useful resource in determining scores on the clinical and radiologic findings of MSCC.

Management

The goals of treatment for patients with MSCC include pain control, minimizing complications, and preserving

Table 8. Malignant spinal cord compression: indications for surgery.

Any patient with MSCC who can undergo surgical decompression and fixation
Direct compression in the setting of intraspinal bony fragments, which unlikely to respond to radiation
An unstable spine where direct fixation and stabilization is the only way to preserve ambulation
Impending sphincteric dysfunction that prompts rapid decompression
No response to radiotherapy
Radiation dose to spinal cord already at tolerance from previous radiotherapy
Unknown primary tumor
Paraplegia <48 h

or improving neurologic function.[59,61,67] Pretreatment neurological status is by far the most important predictor of function after treatment.[59,61,65–67]

Corticosteroids (dexamethasone 16–100 mg per day) are typically prescribed upon presentation of MSCC.[61,67] Corticosteroids have been shown to reduce edema, inhibit inflammatory responses, and delay the onset of neurological deficit.[68] Corticosteroids may be avoided if pain is the only symptom[69]and other forms of treatment should be considered.

Surgery is the only treatment that leads to immediate relief of MSCC. Table 8 lists the indications for surgery.[59,61] Patients may undergo laminectomy, removal of the posterior neural arch of the vertebra or anterior decompression allowing total removal of the pathological vertebral body and the tumor mass. Vertebroplasty and kyphoplasty followed by radiation therapy (RT) are alternatives to surgery for patients with unstable MSCC who are not candidates for surgery.[61,67,70]

RT is another option for patients with MSCC. It is the initial treatment of choice, following steroids, especially for patients who are not candidates for surgery and have a radiosensitive tumor (i.e. breast, prostate, or ovarian cancer; small cell lung cancer; myeloma; lymphoma). RT is well tolerated, but may cause bone marrow suppression and gastrointestinal toxicity if large areas of the spine are irradiated patients. There is no definitive dose or schedule with RT which allows for a more patient-specific treatment approach. Stereotactic body radiotherapy is an alternative for patients with a radio-insensitive disease. RT is effective with approximately 70% of patients having an improvement in pain.[59,61,67,71,72]

Chemotherapy or hormonal therapy is another option for treating MSCC.[73,74] Limitations include a slow onset and may only be effective in patients with chemotherapy-sensitive disease. Chemotherapy may be administered to patients following RT and/or hormonal therapy to reduce additional metastatic disease.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is caused by an extensive stimulation of the coagulation cascade wherein many small vessels in the body become blocked by the production of fibrin resulting in thrombosis. Complications can result from the bleeding because of the deficiency of coagulation products.

The incidence and severity in cancer patients vary depending on malignancy type. It is estimated that 10–15% of patients with solid tumors (mainly metastatic disease) and 15% of acute leukemia patients have some degree of DIC.[75] The exception is acute promyelocytic leukemia (APL), where severe bleeding resulting from DIC should be ruled out in all patients. If left untreated, APL can result in severe hemorrhage in up to 40% and fatal bleeding events have been described to occur in 5% of patients.[76]

Pathophysiology

The cause of DIC depends on the disease state. In many solid tumors, it is believed that an increased exposure to tissue factor may precipitate DIC. Many solid tumors have increased tissue factor on the tumor surface that may result in a chronic DIC state.[77] In APL, there is a release of annexin II, tissue factor, and cancer procoagulant that combined with fibrinolysis, increase the risk of clotting and bleeding.[78]

Diagnosis

Diagnosis relies on multiple laboratory parameters that indicate thrombin production and fibrinolysis. For acute DIC, the platelet count may be reduced (<100,000/μl) along with decreased fibrinogen, increased prothrombin time (PT) and activated partial thromboplastin time (aPTT). Chronic DIC may not be as pronounced because of compensation. The platelet count may only show a slight decrease along with normal fibrinogen, PT, and aPTT. In cases of APL, these laboratory parameters should be monitored more aggressively (multiple times per day) as the patient is worked up.

Management

The ultimate goal of treatment for DIC related to malignancy is to treat the malignancy itself. Acute DIC, especially related to APL, needs to be treated as a medical emergency. Platelet count should be kept

above 20–30,000/μl and fibrinogen should be kept above 150 mg/dL through transfusion of cryoprecipitate.[79] Some reports recommend a goal of platelet count >50,000 μL.[80] It is recommended to start differentiation therapy with tretinoin (ATRA) as soon as an APL diagnosis is suspected. The period of coagulopathy is lower when patients are treated with ATRA plus chemotherapy compared to chemotherapy alone. Patients need aggressive monitoring of treatment as the risk of death from bleeding may be 10–20%. While heparin therapy has been studied in APL, most of these data pre-date ATRA therapy.[81] Chronic DIC may not require aggressive treatment and the goal should be the treatment of the underlying malignancy.

Conclusion

Oncologic emergencies are often diverse in etiology and often arise in the acute setting. Evaluation of these separate disease state requires critical evaluation of the patient and disease state. Knowledge of these emergent syndromes and their appropriate managements are critical in achieving pre-defined goals of care and improving quality of life for patients.

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