Metabolic emergencies

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Introduction

In oncology, metabolic emergencies can be defined as life- or quality-of-life-threatening conditions related to the homeostasis of ions (e.g. calcium, sodium, potassium) and glucose; adrenal gland dysfunction; and disturbances in acid-base balance (tumour lysis syndrome, lactate acidosis). They may result from the disease itself or be a complication of anti-cancer treatment. In order to limit morbidity and mortality, it is important to prevent metabolic complications and if they occur, to recognise and treat them as soon as possible.

Hypercalcaemia

Hypercalcaemia is defined as a plasma calcium of more than 10.4 mg/dL. It is the most common metabolic emergency in cancer patients with an incidence of 15–20 per 100,000 people and is reported in 10–30% of them during their disease [1]. Hypercalcaemia may be the presenting condition but is more commonly seen in patients after diagnosis and with advanced disease. The most common malignancies associated with hypercalcaemia are breast and lung cancer, multiple myeloma and squamous cell carcinoma of the head and neck [1].

Pathophysiology

Plasma calcium homeostasis is mainly maintained by three hormones: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and calcitonin. These hormones act on the bone, where calcium is stored; the kidney, which secretes calcium; and the small intestine, where calcium absorption takes place. The entire system is controlled through a feedback loop and the individual hormones respond as needed to increase or decrease the serum calcium concentration. Calcium homeostasis may be changed by an excess of PTH, calcitriol, or serum factors that can mimic these hormones, or by a calcium load [2,3].

In cancer, hypercalcaemia is mostly the result of the production of a parathyroid hormone-like protein secreted by the tumour (e.g. breast and lung cancer, multiple myeloma), while minor causes are local bone destruction with the release of cytokines (e.g. multiple myeloma), and tumour production of vitamin D analogues (e.g. Hodgkin's disease).

Clinical presentation and diagnosis

Hypercalcaemia induces non-specific symptoms such as asthenia, anorexia, nausea, constipation, weakness and vague muscle/joint aches, headache, polyuria, and polydipsia. When hypercalcaemia is more pronounced, patients become lethargic and confused or might develop a coma. Symptoms correlate with the degree of the hypercalcaemia and the rapidity of onset [3].

Physical examination may show signs of dehydration and hypovolaemia due to excessive fluid loss and impaired fluid intake.

Diagnosis is made by determination of the serum calcium level. The reference range of serum calcium levels is 8.7–10.4 mg/dL with ±40% protein bound and 50% ionised, which is the physiologic active form and 10% complexed to anions (e.g. citrate) [2,3]. Changes in serum protein concentrations alter the total serum calcium level but do not affect the unbound fraction. The corrected total calcium (mg/dL) can be calculated by the following formula: (measured total calcium mg/dL) +0.8 (4.4 – measured albumin g/dL). The reference range of corrected calcium is 9–10.6 mg/dL [1–3].

The serum creatinine, ions (sodium, potassium, chloride) and alkaline phosphatase should also be determined to exclude renal insufficiency and ion disturbances while an increased alkaline phosphatase indicates bone metastases.

Hypercalcaemia may produce abnormalities on the electrocardiogram (ECG) with QT interval shortening and PR interval prolongation. At very high serum calcium levels, the QRS interval may lengthen, T waves may flatten or invert, and a variable degree of heart block may develop.

Other causes of hypercalcaemia

Other causes of hypercalcaemia are primary hyperparathyroidism (serum PTH [normal range 2–6 mmol/L]), granulomatous diseases (sarcoidosis, tuberculosis), medication (thiazide, calcium carbonate, excess intake of vitamin D or A, intoxication with lithium, theophylline, salicylate, or thyroid hormone), milk-alkali syndrome, endocrinopathies (hyperthyroidism, adrenal gland insufficiency and pheochromocytoma), familial hypocalciuric hypercalcaemia, tertiary hyperparathyroidism (post-renal transplant, initiation of chronic haemodialysis), immobilisation, hypophosphataemia, acquired immunodeficiency syndrome (AIDS), rhabdomyolysis, Paget disease, parenteral nutrition or advanced chronic liver disease [2].

Treatment

Untreated, symptomatic hypercalcaemia is a life-threatening complication that needs immediate intervention. However, when it occurs in patients with advanced untreatable cancer, it may be appropriate to start symptom control measures only.

Treatment is by:
- Discontinuation of calcium sources (e.g. oral calcium supplements) and medications that increase calcium level (e.g. thiazide diuretics, vitamin D).
- Correction of hypovolaemia by intravenous (IV) saline: saline 250–500 mL/h intravenous until euvolaemia is achieved and 100–150 mL/h IV after volume repletion in patients without impaired cardiac function.
- Blocking the osteoclastic bone resorption by bisphosphonates. This is the treatment of choice. Pamidronate (60–90 mg IV during 2–4 h) and zoledronic acid (4 mg IV during 15 min) are commonly used. In randomised studies, zoledronic acid proved to be more potent than pamidronate to control hypercalcaemia [4]. Bisphosphonates should be used cautiously in patients with renal insufficiency. Other bisphosphonates (etidronate 0.5 mg/kg IV over 4 h for 3–7 d, ibandronate 2–6 mg IV bolus, clodronate 900 mg IV over 4 h) are also active but less used [2].
- Use of other medications. There are some other active drugs in the treatment of hypercalcaemia, but with the use of bisphosphonates their indication is limited: subcutaneous or intramuscular calcitonin (4–8 IU/kg SC or IV every 12 h); mithramycin (plicamycin) (25 μg/kg administered over 4–6 h as a single dose), gallium nitrate (100–200 mg/m^2 continuous IV for 5 days), and glucocorticoids (prednisone, 60 mg/d orally; hydrocortisone, 100 mg every 6 h IV).
- Dialysis, which may be appropriate for patients with renal failure or congestive heart failure when aggressive hydration and bisphosphonates cannot be used safely.
- Anti-cancer treatment after correction of hypercalcaemia.

  Diuretics and phosphates should not be used.

Prognosis

While in the past hypercalcaemia was a major cause of cancer mortality, the use of bisphosphonates decreased death due to hypercalcaemia substantially. However, the prognosis of cancer-associated hypercalcaemia is poor with a 1-year survival rate of 10–30% and is mainly dependent on the response of the primary tumour to anti-cancer treatment [2].

Hypocalcaemia

Hypocalcaemia is defined as a serum calcium level less than 8.5 mg/dL. Hypocalcaemia is probably more common than hypercalcaemia. While in the past symptomatic hypocalcaemia was mainly a complication of thyroid surgery with accidental removal of the parathyroids, it has recently also been described due to bisphosphonates use. It is observed in 39% (grade 3–4: 1.2%) of patients treated with zoledronic acid and causes more complications in patients with a pre-existing vitamin D deficiency. It might also be a complication of osteoblastic metastases (e.g. breast cancer, prostate cancer) or tumour lysis syndrome [5].

Pathophysiology

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signalling. Intracellular calcium regulates cyclic adenosine monophosphate (cAMP)-mediated messenger systems and most cellular functions. The intracellular calcium level is controlled by pumps.

Of the total body calcium, 99% is found in bone while 1% is present in extracellular fluids.

Since serum calcium is controlled by PTH (see Hypercalcaemia), surgery to the thyroid with accidental removal of the parathyroid glands may cause hypocalcaemia. Other causes of hypocalcaemia in cancer patients are hypoalbuminaemia (most common cause), hypomagnesaemia due to cisplatin treatment,

hyperphosphataemia, multifactorial enhanced protein binding, medication (e.g. calcitonin, bisphosphonates), PTH deficiency or resistance, and vitamin D deficiency due to decreased oral intake [5].

Clinical presentation and diagnosis

Acute hypocalcaemia may lead to syncope, congestive heart failure and angina pectoris due to its multiple cardiovascular effects. Other symptoms are muscle cramping, shortness of breath secondary to bronchospasm, tetanic contractions, distal extremity numbness and tingling sensations. Chronic hypocalcaemia may lead to cataract, dry skin, coarse hair, brittle nails, psoriasis, chronic itching, and poor dentition [5].

Clinical examination may reveal dry skin and psoriasis, perioral anaesthesia, cataract, papillar oedema, laryngeal stridor, wheezing, dysphagia, stridor, bradycardia, rales, S3 gallop, tetany, focal numbness, and muscle spasms (Chvostek sign, Trousseau sign, main d'acoucheur), irritability, confusion, hallucinations, dementia, extra-pyramidal manifestations and seizures.

Acute hypocalcaemia causes prolongation of the QT interval, which may lead to ventricular dysrhythmias.

Diagnosis is made by determining serum calcium and albumin. Magnesium, phosphate, and other electrolyte levels; BUN and creatinine; liver function tests, coagulation parameters; and the PTH level should also be determined.

Other causes of hypocalcaemia

Hypocalcaemia may also be a complication due to hypomagnesaemia (due to pancreatitis, aminoglycoside treatment, amphotericin B, loop diuretics, alcoholism, and malnutrition) which causes end-organ resistance to PTH; acute pancreatitis (due to chelation of calcium by free fatty acids); rhabdomyolysis with increase of phosphates; from creatine phosphokinase and other anions (e.g. lactate, bicarbonate) leading to chelation of calcium; sepsis or toxic shock syndrome; hepatic or renal insufficiency; dysfunction of the parathyroid gland due to infiltration by sarcoidosis, tuberculosis or haemochromatosis; medication (e.g. phenobarbital and phenytoin enhancing vitamin D catabolism and decreasing calcium absorption in the gut; foscarnet complexing with calcium; fluoride chelating calcium; estrogens inhibiting bone resorption; cimetidine decreasing gastric pH and slowing fat breakdown; and aluminium or alcohol suppressing PTH).

Treatment

Prevention: All patients treated chronically with bisphosphonates should be given prophylactically 500 mg oral calcium and 400 IU vitamin D daily [6].

Treatment: Symptomatic patients with classic clinical findings of acute hypocalcaemia require immediate treatment with IV calcium (100–300 mg calcium in 5–10 min followed by a continuous infusion of calcium at 0.5 mg/kg/h and increased to 2 mg/kg/h) until repletion [5,6].

Most patients with chronic hypocalcaemia are diagnosed by clinical suspicion and laboratory testing. They are treated with oral calcium replacement (1–3 g/d) [5,6].

Prognosis

Severe, symptomatic hypocalcaemia may result in cardiovascular collapse, hypotension unresponsive to fluids and vasopressors, and dysrhythmias. When recognised and with an appropriate treatment hypocalcaemia has a good prognosis and death is rare but has been reported. Cancer has a greater impact on morbidity and mortality than hypocalcaemia itself [6].

Hyponatraemia

Hyponatraemia is defined as a serum sodium level <130 mEq/L. It occurs in 4% of cancer patients and is most often seen in patients with lung, central nervous system, nasopharynx, duodenum, stomach, pancreas, ureter, prostate or uterus cancer. Clinically significant hyponatraemia in cancer patients is relatively uncommon [3,7].

Pathophysiology

Serum sodium is regulated by thirst, anti-diuretic hormone (ADH), the renin-angiotensin-aldosterone system and the kidney.

- Increases in serum osmolarity above the normal range (280–300 mOsm/kg) stimulate hypothalamic osmoreceptors, which cause an increase in thirst and in circulating levels of ADH. ADH increases free water re-absorption from the urine.
- Aldosterone is synthesised by the adrenal cortex and is regulated primarily by serum potassium. Aldosterone causes absorption of sodium at the distal renal tubule.
- The healthy kidney regulates sodium balance independently of ADH or aldosterone by varying the degree of sodium absorption at the distal tubule.

Hyponatraemia can be classified as:
- Hypovolaemic hyponatraemia, in which total body water (TBW), total body sodium and extracellular fluid (ECF) volume are decreased;
- Euvolaemic hyponatraemia in which TBW is increased while total sodium is normal. The ECF volume is increased minimally to moderately, but there is no oedema; and
- Hypervolaemic hyponatraemia, in which total body sodium and TBW is increased while ECF is markedly increased resulting in oedema.

In cancer patients the most common reason of hyponatraemia is the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). It is caused by the secretion of ectopic vasopressin (AVP) or vasopressin-like peptide. This causes an excess of renal water reabsorption resulting in a dilutional hyponatraemia. Due to the volume expansion, aldosterone secretion is reduced with progressive salt loss in the urine.

SIADH is present in patients with small cell lung carcinoma, pancreatic cancer, lymphomas, mesothelioma, and primary and metastatic brain tumours. It is also a complication of treatment with vinca alkaloids, vinorelbine, alkylating agents (high-dose cyclophosphamide and less commonly low-dose cyclophosphamide, melphalan and chlorambucil) and combination chemotherapy including cisplatin. Also chemotherapy-induced nausea, simulating AVP release and excessive pre-hydration for cisplatin administration cause SIADH.

Hyponatremia is physiologically significant when it causes extracellular hypo-osmolarity and a shift of free water from the vascular to the intracellular space. Although cellular oedema is well tolerated by most tissues, cerebral oedema might be life-threatening.

Clinical presentation and diagnosis

Patients with acute hyponatraemia (developing over 48 h or less) may develop cerebral oedema and morbidity and mortality are due to brainstem herniation and mechanical compression of vital midbrain structures.

Patients with chronic hyponatraemia experience milder degrees of cerebral oedema and might die due to status epilepticus (sodium $\leqslant$110 mEq/L) or cerebral pontine myelinolysis (demyelination syndrome when chronic hyponatraemia is corrected too quickly).

Symptoms due to hyponatraemia relate to the severity and the rapidity of onset. When serum sodium gradually decreases, levels as low as 110 mEq/L may be reached with minimal symptoms while a sudden fall in 24–48 h may lead to severe cerebral oedema, coma, or brainstem herniation.

Symptoms may be anorexia, nausea and vomiting, muscle cramps, concentration difficulties, confusion, lethargy, agitation, headache, seizures, coma, or status epilepticus.

Physical findings are highly variable and dependent on the degree and the duration of hyponatraemia. Most prominent physical signs are neurological disturbances: changes in conscience (agitation to coma), cognitive impairment (e.g. difficulty with short-term recall; loss of orientation to person, place, or time; confusion or depression) and focal or generalised seizures. Signs of brainstem herniation include coma; fixed, unilateral, dilated pupil; decorticate or decerebrate posturing and respiratory arrest.

In addition, patients may exhibit signs of hypovolaemia or hypervolaemia:
- Dry mucous membranes, tachycardia, diminished skin turgor and orthostasis are observed in hypovolaemic hyponatraemia due to excessive loss of body fluids and replacement with inappropriately diluted fluids.
- Pulmonary rales, S3 gallop, peripheral oedema, or ascitis in hypervolaemic hyponatraemia due to excess retention of sodium and free water (e.g. cirrhosis, nephrotic syndrome, congestive heart failure).

The diagnosis of hyponatraemia is made by serum analysis. Pseudohyponatraemia should be excluded and may be caused by incorrect sampling (e.g. venous puncture proximal to an infusion of hypotonic saline or dextrose in water); hyperglycaemia; mannitol; hyperlipidaemia; or hyperproteinaemia.

Urine sodium levels distinguish renal causes of hyponatraemia from non-renal causes and urine osmolarity is helpful for the diagnosis of SIADH (urine osmolarity $\geqslant$100 mOsm/L).

Serum thyroid-stimulating hormone and free thyroxine should be checked if hypothyroidism is suspected. Adrenal function should be assessed, via random serum cortisol levels or an adrenocorticotropic hormone (ACTH) stimulation test, in patients who recently have taken oral steroids or in any patient suspected of having cortisol deficiency.

Other causes of hyponatraemia

Other causes of hyponatraemia are pneumonia; active tuberculosis; pulmonary abscess; asthma; central nervous system infections, hypothyroidism; adrenal insufficiency or trauma. It is also associated with medication (acetazolamide, amiloride, amphotericin,

atovaquone, thiazide diuretics, amiodarone, basilixi-mab, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, carbamazepine, carvedilol, celecoxib, clofibrate, desmopressin, donepezil, eplerenone, gabapentin, haloperidol, heparin, indomethacin, ketorolac, loop diuretics, nimodipine, oxcarbazepine, opiates, oxytocin, pimozide, propafenone, proton pump inhibitors, sirolimus, ticlopidine, selective serotonin reuptake inhibitors, sulfonylureas, trazodone, tolbutamide, zalcitabine, and zonisamide); poor dietary intake; large amounts of beer and after use of recreational drugs (e.g. ecstasy) [3,7].

Treatment

Appropriate treatment of hyponatraemia depends upon the type, the severity of symptoms, and the severity of hyponatremia.

Rapid identification and correction of serum sodium is necessary in patients with severe acute hyponatraemia to avert brainstem herniation and death.

- Causes of hyponatraemia (e.g. tumour, non-tumoural causes) should be identified and corrected when possible. If possible, medication causing hyponatraemia should be discontinued. The source of free water must be identified and eliminated.
- Neurological symptoms due to hyponatraemia are an acute life-threatening condition and immediate supportive care should include anticonvulsant therapy to patients with seizures, intubation and initiation of hyperventilation to reduce intracranial pressure in case of signs of brainstem herniation. Hypotonic IV fluids should be avoided because they may exacerbate cerebral oedema.
- Sodium should be corrected:
  - In patients with brainstem herniation and sodium levels below 120 mEq/L, a rapid serum sodium increase by 4–6 mEq/L should be realised during the first 1–2 h with hypertonic (3%) saline. The adult dose required volume is calculated by: (desired change in serum sodium)(TBW)/(Sodium in IV fluid – current serum sodium), in which TBW = body weight $\times 0.6$. Further correction should proceed at an overall rate that is no greater than 0.5 mEq/L/h or 12 mEq/L/day.
  - In patients with chronic hyponatraemia, hyponatraemia is corrected at a rate of less than 0.5 mEq/L/h or 12 mEq/L/day to prevent cerebral pontine myelinolysis.
- Patients with hypovolaemic hyponatraemia may be treated with isotonic saline; serum sodium levels should be monitored frequently to ensure that serum sodium increases no faster than 0.5 mEq/L/h or 12 mEq/L/day.
- Patients with hypervolaemic hyponatraemia should be treated with sodium and water restriction.
- Patients with euvolaemic hyponatraemia should be treated with free water restriction [3,7].

Prognosis

The prognosis of hyponatraemia is dependent on its severity and rapidity of onset. If adequately handled prognosis is determined by the underlying condition.

Hypernatraemia

Hypernatraemia is defined as a serum sodium level >145 mEq/L. In oncology, it may be a consequence of insufficient water intake due to chemotherapy-induced nausea or vomiting or decreased conscience; due to a general poor condition; secondary renal pathology (e.g. renal diabetes insipidus due to vinblastine); or loss of free water by central diabetes insipidus due to suprasellar or intrasellar tumours [8].

Pathophysiology

Hypernatraemia results from a disequilibrium of water homeostasis. Water homeostasis is related to water intake and loss from the kidney, the lungs, the skin and the gastrointestinal tract. Salt homeostasis is regulated by the kidneys that adjust salt urine concentration to match salt intake and loss. Hypernatraemia is the result of a relative free water loss or salt loading.

Hypernatraemia causes cellular dehydration by direct extraction of water by the osmotic force of sodium or by the body's free water deficit. The result is that cells shrink and transport electrolytes across the cell membrane to compensate for the osmotic force. Intracellular organic solutes are generated in an effort to restore cell volume and avoid structural damage.

Clinical presentation and diagnosis

Symptoms of hypernatraemia are non-specific and patients may complain of anorexia, restlessness, nausea, and vomiting, followed by altered mental status, lethargy or irritability, and stupor or coma.

Patients may show muscle twitching, hyperreflexia, ataxia or tremor; non-focal neurological symptoms (e.g. mental status changes, ataxia, seizure), although focal deficits (e.g. hemiparesis) may occur.

Physical examination is non-specific but the patient might show signs of dehydration (mucous membranes, skin turgor, orthostatic vital signs, neck veins).

The differential diagnosis is dependent on the patient's volume status:
- Hypovolaemic hypernatraemia (water deficit > sodium deficit) due to extrarenal losses (e.g. diarrhoea, vomiting, fistulas, significant burns); renal losses (e.g. osmotic diuretics, diuretics, postobstructive diuresis, intrinsic renal disease) or decreased thirst.
- Hypervolaemic hypernatraemia (sodium gain > water gain) due to hypertonic saline; sodium bicarbonate; accidental salt ingestion; mineralo-corticoid excess (Cushing syndrome).
- Euvolaemic hypernatraemia due to extrarenal (increased insensible loss (e.g. hyperventilation)) or renal losses (central or nephrogenic diabetes insipidus).

Diagnosis is made by determining the serum sodium level: levels more than 190 mEq/L indicate long-term salt ingestion; more than 170 mEq/L diabetes insipidus and levels between 150–170 mEq/L dehydration.

Urine osmolarity and sodium levels should be determined:
- Hypertonic urine:
  - Extrarenal hypotonic fluid losses (e.g. vomiting, low sodium diarrhoea, sweat, evaporation from burns, low sodium ostomy output).
  - Salt overload
- Isotonic urine:
  - Diuretics, osmotic diuresis (mannitol, glucose, urea)
  - Salt wasting
- Hypotonic urine: diabetes insipidus

A water deprivation test is indicated if diabetes insipidus is suspected: water deprivation induces serum hyperosmolality and hypernatreamia, but urine osmolality does not increase appropriately.

ADH stimulation differentiates between nephrogenic and central diabetes insipidus: with nephrogenic diabetes insipidus urine osmolality does not increase after ADH or desmopressin acetate administration.

Imaging of the head by CT scan or MRI is suggested in all patients with severe hypernatraemia [8].

Treatment

Hypernatraemia should not be corrected at a rate greater than 1 mEq/L/h since cerebral oedema can occur if water replacement does not allow cellular adaptation.
- Hypovolaemic patients with unstable vital signs should be treated with isotonic sodium chloride solutions before correcting free water deficits since hypotonic fluids leave the intravascular space and might cause more pronounced oedema. Once stabilisation has occurred, free water deficits can be replaced orally or intravenously
- Euvolaemic patients are treated with hypotonic fluids, either orally or intravenously (e.g. dextrose 5% in water solution, quarter or half isotonic sodium chloride solution)
- Hypervolaemic patients require removal of excess sodium by a combination of diuretics and dextrose 5% in water infusion. Patients with acute renal failure may require dialysis.

The free water deficit is calculated by: body weight (kg) × TBW × ([serum Na/140] – 1), in which the TBW is 0.6% in young men; 0.5% in young women and elderly men and 0.4% in elderly women.

Prognosis

The mortality rate due to hypernatraemia is high, especially among elderly patients and rates of 42–75% have been reported for acute and 10–60% for chronic hypernatraemia [8].

Morbidity in survivors is high with many patients experiencing permanent neurological deficits.

Acute adrenal crisis

An acute adrenal crisis is a medical emergency due to the sudden lack of adrenal gland hormones. In cancer patients, it may be:
- Primary due to insufficiency of the adrenal gland itself by invasion of metastatic disease with a bleeding complication, or
- Secondary due to exogenous steroids that suppress the hypothalamic-pituitary-adrenal axis.

Prior steroid use with 20 mg daily of prednisone or its equivalent for at least 5 days may lead to an acute adrenal crisis if suddenly discontinued. It may also occur in patients with severe physiologic stress (e.g. sepsis, trauma, burns, surgery), infections (e.g. Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumonia, tuberculosis, fungi or meningococcemia); septic shock, azotemia; anticoagulants, hemorrhagic diathesis; AIDS or drug treatment (topical or inhalation steroids, ketoconazole, phenytoin, rifampin, mitotane) [3,9].

Pathophysiology

The adrenal cortex produces three steroid hormones: glucocorticoids (cortisol), mineralocorticoids (aldosterone, 11-deoxycorticosterone), and androgens (dehydroepiandrosterone).

Cortisol is the most important hormone in acute adrenal crisis:

– It enhances gluconeogenesis and provides substrate through proteolysis, protein synthesis inhibition, fatty acid mobilisation, and enhanced hepatic amino acid uptake.
– It indirectly induces insulin secretion to counterbalance hyperglycaemia but also decreases insulin sensitivity.
– It has a significant anti-inflammatory effect through stabilising lysosomes, reducing leukocytic responses and blocking cytokine production. Phagocytic activity is preserved, but cell-mediated immunity is diminished in cortisol deficiency.
– It facilitates free water clearance.
– It enhances appetite.
– It suppresses adrenocorticotropic hormone (ACTH) synthesis.

In case of adrenal insufficiency, all these aspects are dysregulated.

Clinical presentation and diagnosis

An acute adrenal crisis manifests itself with nausea and vomiting, abdominal or flank pain, hyperthermia or hypothermia, and hypovolaemic shock refractory to fluid and pressor resuscitation.

Other symptoms of adrenal gland insufficiency are weakness, weight loss, anorexia, nausea and vomiting (90%), hyperpigmentation of skin and mucous membranes or postural hypotension (80%).

Laboratory examinations are abnormal in 56% of patients with hyponatraemia, hyperkalaemia, hypercalcaemia, hypoglycaemia and mild metabolic acidosis. Serum cortisol less than 20 μg/dL in severe stress or after ACTH stimulation is indicative of adrenal insufficiency. After an ACTH-stimulation test (Cosyntropin 250 μg IV), an increase of cortisol less than 9 μg/dL (measured 30 and 60 min later) is considered diagnostic of adrenal insufficiency. A low-dose test (Cosyntropin 10 μgIV) may have a better sensitivity [9].

Treatment

– Administration of glucocorticoids in supra-physiological doses is the recommended treatment:
  • Dexamethasone (8 mg IV, followed by 16–24 mg/d as IV injection q 4–6 h or as continuous infusion (CIV)) is the treatment of choice since it does not interfere with serum cortisol assay. It has little mineralocorticoid activity and fluid and electrolyte replacement is essential.
  • Hydrocortisone (50–100 mg IV q 6 h for 7 d, then discontinue or reduce to 50 mg IV q 6 h for four doses; then taper by one half q d until discontinued or until prior maintenance dose) is the treatment to provide mineralocorticoid support.
  • Delaying glucocorticoid replacement therapy while awaiting the results of the ACTH stimulation test is inappropriate and dangerous.
– Aggressive fluid replacement with 5 or 10% intravenous dextrose and saline solutions
– Treatment of hyperkalaemia
– Fludrocortisone (0.1–0.2 mg orally (PO) q d) should be given as maintenance treatment for its mineralocorticoid effect [3,9].

Identification of a precipitating cause and administration of empiric antibiotics is indicated. Reversal of coagulopathy should be attempted with fresh frozen plasma. Pressors (e.g. dopamine, norepinephrine) may be necessary to treat hypotension.

Management of known or suspected primary or secondary adrenocortical insufficiency during stress includes:

• Acute illness: Hydrocortisone 100 mg IV every 6–8 h for four doses, taper if patient stabilises
• Peri-operative steroid therapy is summarised in Table 1.

Table 1
Perioperative steroid therapy for primary or secondary adrenocortical insufficiency

Timing	Hydrocortisone	Fludrocortisone
Routine daily	20 mg PO at 8 am 10 mg PO at 4 pm	0.1 mg PO at 8 am
Day of operation	10 mg/h CIV	
Postoperative day 1	5–7.5 mg/h CIV	
Postoperative day 2	2.5–5 mg/h CIV	
Postoperative day 3	2.5–5 mg/h CIV or 40 mg PO at 8 am 20 mg PO at 4 pm	0.1 mg PO at 8 am
Postoperative day 4	40 mg PO at 8 am 20 mg PO at 4 pm	0.1 mg PO at 8 am
Postoperative day 5	40 mg PO at 8 am 20 mg PO at 4 pm	0.1 mg PO at 8 am
Postoperative day 6	20 mg PO at 8 am 20 mg PO at 4 pm	0.1 mg PO at 8 am
Postoperative day 7	20 mg PO at 8 am 10 mg PO at 4 pm	0.1 mg PO at 8 am

Prognosis

The survival of patients with acute adrenal crisis is dependent on prompt recognition and treatment. With adequate treatment the survival rate is 85%. However, because the true incidence of adrenal crisis is unknown, the mortality rate is unknown [3,9].

Hypoglycaemia

Hypoglycemia is defined as a serum glucose level of <40 mg/dL. In oncology, it is most commonly observed in patients with insulin-producing islet cell tumours that occur alone or as part of multiple endocrine neoplasia but may also be present in tumours that produce compounds with low molecular weight and non-suppressible insulin-like activity (e.g. insulin-like growth factor (IGF)-1, IGF-2, somatomedin A and somatomedin C). Furthermore, bulky solid tumours (e.g. soft tissue sarcoma) or acute leukaemia with large amounts of leukocytes may cause hypoglycaemia due to glucose consumption.

It may also be a complication of anti-cancer drug treatment (e.g. methotrexate or 6-mercaptopurine) [3, 10].

Clinical presentation and diagnosis

Symptoms may occur at glucose levels higher than 40 mg/dL depending on the rapidity of onset. Symptoms are worst in the early morning. They include weakness, dizziness, diaphoresis, and nausea and may progress to diffuse neurological deficits, seizure, coma and death.

C-peptide should be measured and is elevated in insulinoma; normal or low with exogenous insulin and elevated with oral sulfonylureas. Also liver function, serum insulin, cortisol and thyroid levels should be determined.

Other causes of hypoglycaemia

The most common cause of hypoglycaemia is medication (e.g. insulin, oral hypoglycaemic drugs, coumarin, salicylates, p-aminobenzoic acid, propoxyphene, haloperidol, stanozolol, ethanol, hypoglycin, carbamate insecticide, disopyramide, isoniazid, methanol, pentamidine, sulfonamide, tricyclic antidepressants, organophosphates, propranolol plus ethanol, didanosine, chlorpromazine, quinine, sulfa drugs, fluoxetine, sertraline, fenfluramine, trimethoprim, thiazide diuretics, thioglycolate, tremetol, ritodrine, disodium ethylenediaminetetraacetic acid (EDTA), clofibrate, angiotensin converting enzyme (ACE) inhibitors, and lithium.), but is might be seen in severe infections, septic shock, hepatic or pituitary failure.

Treatment

Mild hypoglycaemia may be managed by:
- Increasing frequency of food intake
- Administration of IV infusions of dextrose solutions.

Symptomatic hypoglycaemia may require:
- Glucose IV infusions: administration 50 mL of 50% dextrose IV bolus followed by 10% glucose IV infusion in water by central venous line to avoid vein sclerosis.
- Corticosteroids
- Glucagon (1 mg/dose IV) produces a glucose increase in patients with insulinoma. However, because its insulin-releasing effect, it may also stimulate the insulinoma to release its insulin and subsequently cause hypoglycaemia. It acts on liver glycogen converting it to glucose.
- Diazoxide (3–8 mg/kg/d PO divided q 8 h) produces an increase in blood glucose within 1 h by inhibition of insulin release from the tumour.
- Specific anti-cancer treatment.

Prognosis

The prognosis depends on the primary tumour. Most often this symptom is an end-stage symptom with a bad prognosis. Delay in treatment can result in severe complications as coma, cardiac dysrhythmia, permanent neurological deficits or in death [3,10].

Tumour lysis syndrome

Tumour lysis syndrome (TLS) is characterised by several metabolic life-threatening disturbances. It is defined as a metabolic triad of hyperuricaemia, hyperkalaemia, and hyperphosphataemia. Renal failure and symptomatic hypocalcaemia are secondary complications associated with TLS. It is observed in patients treated for haematological malignancies such as acute lymphoid leukaemia (ALL), acute myeloid leukaemia (AML), high-grade lymphoma (e.g. Burkitt lymphoma), or after initial treatment for bulky solid tumours. It may also occur spontaneously.

Pathophysiology

TLS is caused by massive release of intracellular contents after tumour cell death:
- The catabolism of nucleic acids to hypoxanthine and xanthine by xanthine oxidase results in hyperuricaemia. The high concentration of uric acid

can lead to crystallisation within the renal tubules, resulting in obstruction of tubular flow and acute renal failure. Renal failure is further exacerbated by hypovolaemia.
– The release of intracellular potassium, present in the cytoplasm of tumour cells at concentrations substantially higher than in the extracellular space together with a decreased renal function leads to hyperkalaemia.
– Increasing levels of phosphorus due to immediate cellular release result in secondary hypocalcaemia due to the down-regulation of calcium by the hyperphosphataemia [1,3,11].

Clinical presentation and diagnosis

The symptoms and signs of TLS are usually non-specific. Due to renal failure, patients may manifest symptoms of uraemia or volume overload. Seizures and arrhythmias can occur.

Laboratory studies usually show elevated uric acid, phosphorus, potassium, and lactate dehydrogenase (LDH) levels and a low calcium level.

An ECG should be performed in all patients with electrolyte abnormalities to detect serious arrhythmias and conduction abnormalities.

Treatment

Prevention: TLS should be anticipated and prevented in patients with tumours with a high proliferative rate; high baseline uric acid; bulky disease (e.g. white blood cell count $>50\times10^9$/L) or chemo-sensitive disease:
– Administration of allopurinol (300–600 mg/d) for 2 to 3 days before planned treatment. This xanthine oxidase inhibitor reduces the conversion of nucleic acid metabolites to uric acid and prevents urate nephropathy and renal failure. Dose reduction is necessary in renal insufficiency and if given concomitantly with mercaptopurine, 6-thioguanine or azathioprine.
– Adequate hydration. Intravenous hydration in high-risk patients should start 24–48 h before initiation of cancer therapy and continue for 48–72 h after completion of treatment. If the cardiovascular status allows, continuous infusion of 4–5 L saline 0.9%/d yielding urine volumes of at least 3 L/d should be given.
– Recombinant urate oxidase (rasburicase (0.15–0.2 mg/kg/d IV infused over 30 min for 5 d)) can be used when the uric acid levels cannot be lowered sufficiently by standard approaches. Rasburicase catalyses the conversion of poorly soluble uric acid to soluble allantoin. This effectively decreases plasma and urinary uric acid levels. It does not increase the excretion of xanthine and other purine metabolites and does not increase tubule crystallization. It is contraindicated in pregnancy and glucose-6-phosphate dehydrogenase deficiency, in which it accelerates catabolism of xanthine and hypoxanthine, inducing an accumulation of excess hydrogen peroxide causing haemolytic anaemia and met-hemoglobinaemia.
– Urinary alkalinisation with intravenous isotonic sodium bicarbonate solutions remains controversial. Hypothetically it promotes alkaline diuresis and might minimise intratubular precipitation of uric acid when urinary pH is above 7.0. However, it may worsen hypocalcaemia by shifting ionised calcium to its non-ionised form and increase the likelihood of calcium phosphate precipitation in renal tubules.
– Diuretics should be used with caution.

Patients with an acute tumour lysis syndrome before anticancer therapy should start immediately with treatment, and anticancer therapy should be postponed until all parameters are corrected, if possible.

Patients at high risk and those with evidence of tumour lysis syndrome should have at least 3-daily laboratory monitoring of blood urea nitrogen, creatinine, uric acid, potassium, calcium, phosphate, and LDH. Monitoring should continue for the first 48–72 h after the start of chemotherapy.

Treatment: Patients with established TLS need to be hospitalised and monitored. Treatment is by:
– Administration of intravenous fluids. They should be given to maintain a urine output of 100 mL/m^2/h or greater. An infusion rate of 3 L/m^2/day is appropriate if cardiovascular status allows.
– Administration of allopurinol (600–900 mg/d up to a maximum of 500 mg/m^2/d) orally or IV. Dose reduction is necessary in patients with renal insufficiency.
– Administration of recombinant urate oxidase rasburicase (see prevention).
– Aggressive treatment of hyperkalaemia:
  • Restriction of potassium intake and discontinuation of potassium sparing medication.
  • Sodium polystyrene sulfonate (Kayexalate®) 15–30 g every 6 h orally (can be used rectally) in combination with sorbitol.
  • Insulin (regular) 10 units IV in dextrose (50%) 50–100 mL IV.
  • Calcium gluconate (10%) 10–20 mL (100–200 mg) IV.

- Sodium bicarbonate 45 mEq IV (1 ampule of 7.5% NaHCO3) in case of acidosis; can be repeated after 30 min.
- Albuterol inhalations (2.5 mg).
- Dialysis is indicated in severe hyperkalaemia not responsive to other measures; renal failure; volume overload

– Treatment of hyperphosphataemia. This can be by restricting phosphate intake, phosphate binders such as aluminium hydroxide or glucose in combination with insulin. It may lead to hypocalcaemia, which usually resolves after phosphate levels are corrected.
– Correction of hypocalcaemia should only be done if there is evidence of neuromuscular irritability (e.g. Chvostek or Trousseau sign).
– Dialysis. This is indicated in patients with oliguric renal failure, congestive heart failure, or severe hyperkalaemia or patients who do not respond to medical therapy [1,3,11].

Prognosis

The prognosis of TLS depends on early recognition and treatment. In case of early intervention, most complications are reversible. Although renal dysfunction might require dialysis, it is usually reversible with prompt supportive measures.

Lactic acidosis

Lactic acidosis is a metabolic acidosis, in which plasma lactate concentration is significantly higher than normal (1 mEq/L) [12]. It may be seen in patients with leukaemia, lymphoma, or lung cancer.

Pathophysiology

Lactate is a product of anaerobic glucose metabolism and is generated from pyruvate by lactate dehydrogenase. Pyruvate is normally aerobically metabolised to CO2 and H_2O in the mitochondrion by gluconeogenesis. Additionally, pyruvate is in a state of equilibrium with lactate that, under certain conditions, can shift toward the overproduction of lactate.

Lactic acidosis results from an increase in blood lactate levels when lactate production exceeds consumption and the body buffer systems become overburdened. This occurs when tissue oxygenation is inadequate to meet metabolic requirements as a result of either hypoperfusion or hypoxia.

Lactate is cleared from blood, primarily by the liver, kidney, and skeletal muscles.

There are two types of lactate acidosis:
– Type A lactic acidosis with decreased tissue adenosine triphosphate (ATP) due to poor tissue perfusion or oxygenation
– Type B lactic acidosis without poor tissue perfusion or oxygenation although occult tissue hypoperfusion may be present.
  - Type B1 occurs in association with systemic disease such as renal and hepatic failure, diabetes and cancer
  - Type B2 is caused by several classes of drugs (antiretroviral nucleoside analogues (zidovudine, didanosine, lamivudine), beta-adrenergic agents (epinephrine, ritodrine, terbutaline), biguanides (phenformin, metformin), cyanogenic compounds (aliphatic nitriles, nitroprusside), 5-fluorouracil, halothane, iron, isoniazid, propofol, sugars and sugar alcohols (fructose, sorbitol, and xylitol), sulfasalazine, salicylates and valproic acid) and toxins (cocaine, cyanide, strychnine diethyl ether, ethanol, ethylene glycol, methanol, propylene glycol)
  - Type B3 is due to inborn errors of metabolism.

Lactic acid exists in two forms:
– L-lactate is the most commonly measured level as it is the only form produced in human metabolism. Its excess represents increased anaerobic metabolism due to tissue hypoperfusion.
– D-lactate is a by-product of bacterial metabolism and may accumulate in patients with short-gut syndrome or in those with a history of gastric bypass or small bowel resection.

Clinical presentation and diagnosis

Patients with lactate acidosis are critically ill and are at risk for developing multiple organ failure.

They may show dyspnoea with an increased minute ventilation to compensate with respiratory alkalosis, decreased diaphragm contractility; decreased catecholamine responsiveness of the heart with a decreased fibrillation threshold and a decreased contractility at $pH < 7.1$ or increased heart rate and contractility at $pH > 7.2$; increased cerebral blood flow, decreased cerebral metabolism, altered mental status; decreased renal and hepatic perfusion and increased metabolic rate with increased protein catabolism.

There is an increased anion gap calculated as: sodium – [CO_2 + chloride] and arterial blood gas analysis shows acidosis ($pH < 7.4$) with a base deficit. Serum lactate might be determined in arterial and venous blood samples. The normal serum lactate

level is approximately 1 mmol/L with a range up to 2 mmol/L. Values above 4–5 mmol/L are indicative of lactic acidosis.

Other causes of lactate acidosis

Cardiopulmonary failure, sepsis, trauma, thiamine deficiency, side effects of drugs and toxins, and various acquired and congenital diseases can also lead to lactic acidosis.

Treatment

Initial treatment is that of basic resuscitation:
- Airway assessment and stabilisation and supplemental oxygen.
- Intravenous fluid repletion with normal saline in case of tachycardia, hypotension, or other signs of poor tissue perfusion.
- Identification of the primary illness and specific therapy.
- The use of buffering agents is only indicated in the setting of severe acidosis: Sodium bicarbonate in a starting dose of 1/3–1/2 of the calculated extracellular bicarbonate deficit: HCO3 deficit (mEq) = 0.5 × (wt in kg) × (desired HCO_3 − measured HCO_3).
- Thiamine deficiency may be associated with cardiovascular compromise and lactic acidosis. Thiamine repletion (50–100 mg IV followed by 50 mg/d orally for 1–2 weeks) is potentially life saving.

Prognosis

Lactate levels correlate with the presence of tissue hypoperfusion and elevated levels have been shown to be correlated with increased mortality during shock. The mortality rate of patients with a serum lactate level greater than 2 mmol/L persisting after 24 h with an associated acidaemia approaches 70% [1,3,11,12].

Conclusion

Metabolic emergencies in cancer are life-threatening conditions that should be recognised to limit their negative impact on quality-of-life and survival. Most of them are treatable when diagnosed in time. However, one should always be aware that the prognosis of a cancer patient mainly depends on his primary disease, the co-morbid conditions and frailty of the patient. Before starting a treatment one should consider these issues and discuss with the patient and his family about treatment possibilities, treatment outcome and further prospects in relation to quality-of-life and survival.

Conflict of interest statement

No conflict of interest.

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