Review Article

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Oncological Emergencies in Critical Care

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Abstract

Cancer patients are at risk for several life threatening emergencies, including metabolic, cardiologic, neurologic, and infectious events. These oncologic emergencies can occur at any time during the course of a malignancy, from the presenting symptom to end-stage disease and may require an admission into the intensive care unit (ICU) at any time. Knowledge of such 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. Many of these high risk situations can be prevented and managed effectively if promptly recognized and timely treated. This review addresses the more commonly encountered emergencies and possible management in cancer patients.

Key words: Hypercalcemia; SIADH; Superior Vena Cava; Leukostasis; Tumor Lysis; Intracranial Pressure.

Cancer is the one of the leading cause of death in the India with over 600 000–700 000 deaths annually. Despite improvements in survival and decreased prevalence of certain malignancies the overall prevalence of cancer is expected to rise. Individuals with malignancy may present with a cancer-related emergency; for many, this will be their initial manifestation of cancer. Efficient diagnosis and proper management of life-threatening complications may facilitate either definitive treatment of the underlying malignancy or palliation.

Cancer and its treatment may lead to a range of potentially life-threatening conditions that require urgent action to correct them. This article includes the following major oncological emergencies:

- Hypercalcaemia.
- Neutropenia.
- Acute tumour lysis syndrome.
- Leukostasis.
- Syndrome of inappropriate antidiuretic hormone
- Raised intracranial pressure.
- Spinal cord compression.
- Superior vena cava obstruction.

Other oncological emergencies include hypoglycemia, pericardial effusion and cardiac tamponade, seizures, hyperviscosity syndrome, leukostasis and airway obstruction [1]. Adverse effects of chemotherapy may also require urgent intervention, like extravasation and anaphylactic reactions [2].

Hypercalcaemia

This is the most common serious metabolic disorder associated with malignancy, affecting up to one third of cancer patients at some point in their disease course [1]. Malignancies most commonly associated include lung cancer, breast cancer, renal cancer, multiple myeloma and adult T-cell lymphoma. Its symptoms may mimic the features of terminal malignancy. Hypercalcaemia is a poor prognostic indicator in malignant disease and may indicate uncontrolled tumour progression and metastasis. The 30-day mortality rate of cancer patients admitted to hospital with hypercalcaemia is almost 50% [2].

The symptoms of hypercalcaemia are nonspecific; delayed recognition can worsen morbidity and mortality [2]. Presenting features include nausea and vomiting, anorexia, thirst and polydipsia, polyuria, lethargy, bone pain, abdominal pain, constipation, confusion and weakness. Renal tract stones may occur. The degree of hypercalcemia can be classified by total serum calcium level as mild (10.5–11.9 mg/dL), moderate (12.0–13.9 mg/dL), or severe (≥14.0 mg/dL).

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Clinical effects of hypercalcemia are related more to the rate of rise in serum calcium and the underlying volume depletion resulting from osmotic diuresis than the absolute serum calcium value [2]. Electrocardiographic findings in clinically significant hypercalcemia include prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, and brady-dysrhythmias leading to cardiac arrest when serum calcium exceeds 15 mg/dL.

Investigation

Ionised calcium is the most reliable laboratory test. If total calcium is used, it is important to calculate the corrected calcium level to allow for hypoal buminaemia [2]. Other investigations should include alkaline phosphatase, renal function and electrolytes, X-rays (may show lytic or sclerotic lesions of the bone) and a bone scan (to identify any metastases).

Management

There may be a palliative benefit from improving the symptoms of hypercalcaemia, even in patients with advanced malignancies. Urgent intervention is required to treat symptomatic hypercalcaemia. Management includes intensive rehydration and intravenous bisphosphonates. Normal saline infusion is recommended at 200–500 mL/hr and adjusted for a urine output of 100–150 mL/hr, absent any contraindications. However, fluids only modestly decrease serum calcium levels, and ≤ 30% of patients achieve normocalcemia with fluids alone [3]. Loop diuretics to inhibit calcium reabsorption in the ascending loop of Henle [4,5] risk worsening electrolyte abnormalities and volume loss, and should only be used in volume overload. Hemodialysis is generally indicated for congestive heart failure, severe kidney injury (glomerular filtration rate ≤ 10–20 mL/min), clinically significant neurological findings, or calcium concentration ≥18 mg/dL.

Management of calcium metabolism includes eliminating medications (e.g., thiazides) that increase intestinal absorption of calcium and glucocorti-costeroids (Prednisone, 40–100 mg PO; or hydrocortisone, 200–400 mg IV daily for 3–5 days) to decrease extra-renal calcitriol production in lymphoma or myeloma increase renal excretion and inhibit osteoclastic resorption. The bisphosphonates, pamidronate and zoledronate, are first line therapy for MAH. These pyrophosphate analogues bind to hydroxyapatite and inhibit bone crystal dissolution and osteoclastic resorption.

Calcium levels decrease 2–4 days after administration, reach their nadir between 4 and 7 days, and usually normalize for 1–4wks, affording time to treat the underlying malignancy [4].

Neutropenic Fever

Febrile neutropenia contributes to 50% of deaths associated with leukaemia, lymphomas and solid tumours [1]. Neutropenia is most often seen as an effect of cytotoxic therapy. Infection is responsible for at least half of the cases of neutropenic fever. The neutrophil count usually reaches a lowest level 5 to 10 days after the last dose of chemotherapy.

- Gram-positive cocci are now responsible for the majority of culture-positive cases of neutropenic fever, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Enterococcus faecalis* and *Enterococcus faecium*. Corynebacterium is the most likely gram-positive bacillus.
- Gram-negative bacilli include *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*.
- Candida is the most common fungal infection, but aspergillosis and other systemic mycoses can cause more serious infections.
- Often no causative organism is found and the patient improves as the neutrophil count increases.

The vulnerability to infection substantially rises at a neutrophil count less than 1×10^9/L, but the risk continues to increase as the neutrophil count falls.

Management

- The patient should have an infection screen, including blood cultures, urine cultures, swabs of any indwelling catheters, venflons and central lines, CXR, sputum cultures, cultures from any open wounds and stool cultures.
- Empirical antibiotic therapy should be started immediately based on local guidelines, with modification based on the results of microbiological investigations. The addition of antifungal coverage should be considered in high-risk patients who remain febrile after 4 to 7 days of broad-spectrum antibiotics with no identified causative organism.
- Growth colony stimulating factor can be given if the patient is haemodynamically unstable or if the neutropenia is slow to improve. It has been shown to be more effective in refractory gram-

negative and fungal infections than in gram-positive infections.

Acute Tumour Lysis Syndrome

Tumour lysis syndrome is caused by the abrupt release of large quantities of cellular components into the blood following the rapid lysis of malignant cells. It occurs most often in patients with haematologic malignancies, eg acute lymphoblastic leukaemia (ALL) or Burkitt's lymphoma. Treatment-provoked tumour lysis syndrome can occur following chemotherapy, radiotherapy, surgery or ablation procedures [2]. In some cases, tumour lysis syndrome can lead to acute kidney injury and death [6]. Patients particularly at risk have treatment-sensitive tumours, renal impairment or volume depletion. High pre-treatment urate, lactate and lactate dehydrogenase (LDH) are also risk factors. Onset is usually within 1-5 days of starting therapy (but can be delayed by days or weeks in patients with a solid tumour) and symptoms/biochemical features include weakness, paralytic ileus, cardiac arrhythmias, seizures, acute kidney injury, sudden death, hyperuricaemia, hyperkalaemia, hyperphosphatemia and hypocalcaemia.

Investigation

Full metabolic and biochemical profile to detect the above abnormalities. Monitoring of serum lactate, urate and LDH may predict the imminent onset of the syndrome.

Management

The key to the management of tumour lysis syndrome includes awareness of its causes, identification of high-risk patients, implementation of appropriate prophylactic measures, vigilant monitoring of electrolyte levels in patients undergoing chemotherapy, and initiation of more active treatment measures when necessary.

- Those at risk should have preventative management by receiving intravenous hydration with normal saline 3-6L/24 hours, with sodium bicarbonate.
- Acetazolamide is used to alkalinise the urine and prophylactic allopurinol/Febuxostat is given.
- Dialysis may be needed in severe cases.

Metabolic Abnormalities in Acute Tumor Lysis Syndrome [7,8,9]

Metabolic Abnormality	Value or change from Baseline	Clinical Implications	Management
Hyper-Kalemia	6.0 mmol/L or 6 mEq/dL Or 25% increase	Muscle cramps Paresthesias Dysrhythmias VF, & Cardiac arrest	• Polystyrene sulfonate 1 gm/kg • Insulin 0.1 unit/kg with dextrose 25% @2 mL/kg • Sodium bicarbonate 1–2 mEq/kg IV push • Calcium gluconate 100–200 mg/kg slow IVinfusion
Hyper-Phospahemia	2.1 mmol/L for Children or 1.45 mmol/L for adults or 25% increase	Nausea Vomiting Diarrhea Lethargy Seizures Acute kidney injury	• Volume loading • Removal of • phosphate from IV fluids • Oral phosphate binders • Hemodialysis
Hypo-Calcemia	1.75 mmol/L or 25% decrease	Muscle cramps Tetany Hypotension Dysrythmia	• Calcium gluconate 50- 100 mg/kg slow I/V • infusion with ECG monitoring. • Give only if symptomatic.
Hyper-Urecemia	476 mmol/L or 8 mg/dL or, 25% increase	Acute Kidney Injury	• Volume loading • Rasburicase (recombinant urate oxidase) • Allopurinol(oral/IV) or Febuxostat

Leukostasis

Leukostasis [1] is associated with a very high white cell count, respiratory failure, intracranial haemorrhage (but it can affect any organ system) and early death. Without prompt treatment the mortality rate can be up to 40%. Leukostasis occurs in 5-13% of patients with acute myeloid leukaemia (AML) and 10-30% in adult patients with acute lymphoblastic leukaemia (ALL). The risk is greater for younger patients, and infants are most often affected. A white cell count greater than 50,000/m^3 indicates a particularly poor prognosis.

There is usually a high fever and examination may show papilloedema, retinal vein bulging, retinal haemorrhage and focal neurological deficits. Myocardial infarction, limb ischaemia, renal vein thrombosis and disseminated intravascular coagulation may occur. Thrombocytopenia is usually present.

Management

- Rapid cytoreduction is the initial treatment, ideally with induction chemotherapy, which can dramatically reduce the white cell count within 24 hours.
- There is a very high risk of tumour lysis syndrome and so close monitoring of electrolytes and prophylaxis with allopurinol or rasburicase are required.
- Leukophoresis is usually started when the blast count is greater than 100,000/m3 or in the presence of symptoms.
- Cytoreduction can also be achieved by hydroxyurea, but is usually reserved for patients with asymptomatic hyperleukocytosis who are unable to receive immediate induction chemotherapy.

Syndrome of Inappropriate Antidiuretic Hormone

When a patient with cancer presents with normovolemic hyponatremia, SIADH should be suspected [1,10]. A bronchogenic carcinoma often is the ectopic source of antidiuretic hormone production, although certain chemotherapy agents can cause SIADH. Patients may present with anorexia nervosa, nausea, myalgia, headaches, and severe neurologic symptoms (e.g., seizures, coma). Laboratory testing may reveal hyponatremia (i.e., serum sodium level less than 135 mEq per L [135 mmol per L]), decreased serum osmolarity (less than 280 mOsm per L [280 mmol per L]), and concentrated urine (100 mOsm per L or more).

It is Often Asymptomatic but may Cause:

- Depression and lethargy.
- Irritability and other behavioural changes.
- Muscle cramps.
- Seizures.
- Depressed consciousness leading to coma.
- Neurological signs (such as impaired deep tendon reflexes and pseudobulbar palsy).

Management

Therapy involves treating the tumor producing the antidiuretic hormone or atrial natriuretic factor along with fluid management, usually fluid restriction or induced diuresis. Appropriate combination chemotherapy should be initiated, and brain metastases, if present, should be treated with radiotherapy.

- Fluid intake should be limited to less than 1,000 mL/d and less than 500 mL/d if the patient responds poorly.
- Refractory cases of hyponatremia or patients who can be treated as outpatients can be managed with 600 to 1,200 mg/d of demeclocycline (Declomycin) in divided doses [18].
- Patients who are symptomatic with coma or seizures can be treated with 3% hypertonic saline by *slow* infusion at a rate sufficient to increase the serum sodium level by 0.5 to 1.0 mEq/L/h.
- Rapid correction (greater than 2 mEq/L/h) may be associated with central pontine myelinolysis.
- Normal saline with IV furosemide may also be effective .

Raised Intracranial Pressure

Cranial metastases affect around a quarter of patients who die from cancer [10]. Lung, breast and melanoma are the tumours that most commonly metastasise to the brain. The clinical picture varies with site of metastases and the rate of rise of intracranial pressure. Small metastases may bleed and cause acute symptoms. Common symptoms and signs include:

- Headache.
- Nausea and vomiting.
- Behavioural changes.
- Seizures.
- Focal neurological deficit.

- Falling level of consciousness.
- Papilloedema.
- Unilateral ptosis or third and sixth cranial nerve palsies.
- Bradycardia (late sign).

Investigation

CT or MRI scanning should be conducted urgently to delineate the lesion, if the result is likely to affect the patient's management.

Management

- If the patient has lost consciousness and requires ventilation, then high respiratory rate should be used to lower pCO_2 which helps reduce intracranial pressure.
- Mannitol may be given as a diuretic along with dexamethasone to reduce symptoms and the likelihood of cerebral herniation.
- Further management may involve cranial irradiation, surgery ± radiation or 'gamma knife' radiosurgery, depending on the site, type and number of metastases.

Malignant Spinal Cord Compression

This condition must be diagnosed and treated quickly to prevent permanent neurological disability. It may occur because of extradural spread from a vertebral body metastasis, direct metastases or from a vertebral crush fracture. Cancers that most often metastasise to bone and cause spinal cord compression are cancers of the breast, kidney, thyroid, prostate and lung). Due to anatomic locations, breast and lung cancer most commonly metastasize to the thoracic spine, whereas abdominal malignanciestypically metastasize to the lumbosacral vertebrae. Spread of pelvic cancers (e.g., prostate) is enabled by valveless venous communication with the lumbar spine.

Back pain, the first symptom in 95% of those with MSCC [11], precedes other symptoms by up to 2 months and offers the opportunity to intervene before incurring long-term morbidity. Approximately half of MSCC patients have bowel or bladder dysfunction [12] and postvoid residual aids diagnosis of cauda equina syndrome. About 75% have focal weakness, which, if untreated, progresses to ataxia and paralysis. Spinal cord imaging (MRI, Gold Standard) is necessary to identify the site of obstruction and plan treatment.

Management

- Treatment goals include maintenance of neurological function, control of local tumor growth, spine stabilization, and pain control.
- Corticosteroids mitigate vasogenic edema resulting from compression-induced ischemia. High-dose dexamethasone (96 mg IV bolus, then 24 mg by mouth every 6 hrs for 33 days, then 10-day taper) had significantly increased preservation of ambulation at 3 months after radiation [13], but it can have serious side effects.
- High-dose steroids are recommended for patients with an abnormal neurological exam and moderate-dose steroids (10 mg IV bolus, then 4 mg qid with 2-wk taper) for all others [14].
- Radiotherapy of radiosensitive tumors is fundamental in MSCC. Nearly half of survivors are ambulatory at 1 yr following radiation.
- The older surgical technique of nonselective posterior laminectomy relieves pressure within the vertebral foramen but does not address the lesion, which is typically in the vertebral body.

Superior Vena Cava Obstruction

This may be due to compression of the superior vena cava, caused by primary or secondary tumours. Lung cancer (~85% of cases), lymphoma and metastatic tumours are the most common causes. Although the signs and symptoms of SVCS vary, the most common finding is facial edema). The frequency of findings differ between malignant and benign etiologies, with dyspnea at rest, cough, chest and shoulder pain, and hoarseness more frequent in the former [15,16].

Management

Therapy is directed at the underlying cause. This is normally chemotherapy for lymphoma/small-cell lung cancer, with early response and resolution of superior vena cava obstruction within weeks being the usual outcome. Radiotherapy is usually used for non-chemosensitive tumours or patients who do not respond to chemotherapy.

Elevation of the head of the bed and supplemental oxygen are standard. Although commonly prescribed, glucocorticosteroids are of unclear benefit except in the cases of lymphoma or thymoma where indicated for the underlying malignancy [17]. Thrombosis-related SVC obstruction is treated with anticoagulation, intravascular device removal, and balloon dilatation or stenting if

significant fibrosis remains.

Median survival of patients with cancer-induced SVCS is roughly 6 months after presentation, but many patients have survived over 2 yrs with appropiate treatment and care [17].

Conclusions

As the number of cancer patients grows, the prevalence of malignancy related life threatening complications will increase. Often the stage of malignancy carries a poor prognosis. Yet diagnosis and management of oncologic emergencies can usually improve the duration or quality of patients' lives.

Further Reading & References

- Palliative and Supportive Care, Bandolier
- Macmillan Cancer Support

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