tumour lysis syndrome [created by Paul Young 16/11/07]

general

- Tumour lysis syndrome is an oncologic emergency that is characterized by severe metabolic derangements.
- It typically occurs in patients with lymphoproliferative malignancies who are exposed to chemotherapy, radiation, or corticosteroids, but can occur spontaneously in the absence of treatment.

aetiology

-Tumour lysis syndrome is most commonly observed following chemotherapy for high-grade lymphoproliferative malignancies such as acute lymphocytic leukemia and Burkitt lymphoma. It has also been reported in many different types of solid tumors, including lung and breast carcinoma

- Various chemotherapeutic agents have been implicated, including cisplatin, etoposide, fludarabine, intrathecal methotrexate, and paclitaxel. In addition, rituximab, ionizing radiation, interferon, and endocrine therapies such as corticosteroids and tamoxifen have been implicated. These agents increase renal risk because of their increased antitumor activity, rather than a direct toxicity of the renal tubules.

- Risk factors include:
(i) large tumor burdens,
(ii) lactate dehydrogenase levels above 1500 IU,
(iii) extensive bone marrow involvement, and
(iv) high tumor sensitivity to chemotherapeutic agents.

metabolic consequences

Electrolyte	Pathophysiology	Clinical Consequence	Treatment Options
Potassium	Rapid expulsion of intracellular K^+ into the circulation due to cell lysis.	Adverse skeletal and cardiac manifestations (e.g., ventricular arrhythmia, weakness, paresthesias)	Insulin/glucose, sodium bicarbonate, inhaled beta-agonist, K-binding resins, dialysis, calcium gluconate
Phosphate	Release of intracellular $PO4^-$ due to cell lysis. May be compounded by renal dysfunction.	Muscle cramps, tetany, arrhythmias, seizures	Dialysis, phosphate binders
Calcium	Precipitation of the calcium phosphate complex due to the rapid increase in the phosphorous concentration.	Muscle cramps, tetany, arrhythmias, seizures, renal failure (acute nephrocalcinosis)	Calcium gluconate (treatment should be reserved for those with neuromuscular irritability)
Uric acid	Cell lysis leads to increased levels of purine nucleic acids into the circulation that are metabolized to uric acid.	Renal failure (uric acid nephropathy)	Hydration, dialysis, xanthine oxidase inhibitors, alkalization of urine, urate oxidase

hyperkalaemia

- Hyperkalemia may appear from 6 to 72 hours after the initiation of chemotherapy and is the most serious manifestation of tumor lysis syndrome. Potassium is generally concentrated intracellularly. Cell lysis results in the liberation of large amounts of intracellular potassium into extracellular fluid.
- Chronic kidney disease, acute renal failure, or concurrent acidosis may exacerbate hyperkalemia as the excretory capacity of the kidney can be overwhelmed by transcellular shifts due to potassium release from l ysing cells as well as acidosis.
- Symptoms of hyperkalemia include weakness, paresthesias, muscle cramps, nausea, vomiting, diarrhea, and anorexia.
- Severe hyperkalemia (>7.0 mmol/L or change in K>2.0 mmol/L.) can adversely affect skeletal and cardiac muscle function. Electrocardiographic changes include widening of the QRS complex and peaked T waves. Hyperkalemia must be corrected rapidly before potentially fatal ventricular arrhythmias occur.

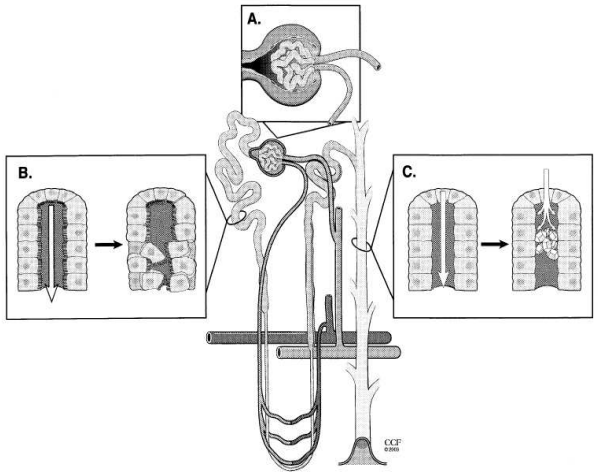
hyperphosphataemia & hypocalcaemia

- Hyperphosphatemia develops from 24 to 48 hours following initiation of chemotherapy.
- Release of intracellular phosphate can exceed the renal threshold for phosphate excretion, leading to hyperphosphatemia.
- Malignant hematologic cells may contain up to four times more intracellular phosphate compared with normal mature lymphoid cells. Additionally, acute destruction of tumor cells during chemotherapy prevents the rapid reuse of phosphate for newly synthesized tumor cells.
- Precipitation of calcium phosphate occurs when the solubility product of calcium and phosphate is exceeded, possibly leading to hypocalcemia. Muscle cramps, tetany, cardiac arrhythmia, and seizures can result. Acute nephrocalcinosis, or precipitation of calcium phosphate in the renal tubules with an inflammatory response, may lead to acute renal failure. Calcium and phosphate abnormalities should be identified and treated early.

hyperuricaemia

- Hyperuricemia develops from 48 to 72 hours following initiation of treatment.
- Tumor cell lysis releases purine nucleic acids, which are metabolized into uric acid. Malignant cells carry a large burden of nucleic acid products due to their high cellular activity and turnover. The high turnover rate of neoplastic cells leads to ongoing DNA catabolism. The breakdown of purine nucleotides yields high amounts of hypoxanthine. Xanthine oxidase catalyzes the conversion of hypoxanthine into uric acid.
- After spontaneous or cytotoxic therapy-induced lysis, large amounts of uric acid are produced, leading to rapid increases in plasma and renal tubular concentrations.

mechanisms of ARF



A - a reduction in GFR mediated by volume depletion and cytokine mediated alterations in renal perfusion
B - ischaemic ATN with disruption of active transport, sloughing of cells into the lumen and obstruction
C - precipitation of uric acid crystals in tubules

prevention & treatment

General:
- The principles of management should address three critical areas: hydration, metabolic abnormalities, and supportive treatment of renal failure.

Hydration
- Hydration should begin 2 days prior to, and continue 2 to 3 days after, chemotherapy.
- Volume expansion with isotonic saline reduces serum concentrations of uric acid, phosphate, and potassium. Excluding patients who are at risk of volume overload, aggressive fluid administration has been recommended in all patients presumed to be at risk of the syndrome. As a result of increased renal blood flow, glomerular filtration rate, and urine volume, the concentration of solutes in renal tubules is decreased, making precipitation less likely.

Hyperkalemia
- The major goals of the treatment of acute hyperkalemia are cardiac membrane stabilization, intracellular shift of potassium, and reduction of total potassium load.
(i) Membrane stabilization is achieved with 10% calcium gluconate to prevent life-threatening cardiac arrhythmias. Its duration of action, however, is short lived, and treatment may need to be repeated.
(ii) Insulin promotes the intracellular shift of potassium, and is administered with dextrose to prevent hypoglycemia. Inhaled beta2-agonists may also produce an intracellular shift of potassium.
(iii) Isotonic sodium bicarbonate can be used to reduce metabolic acidosis and also to shift potassium intracellularly. However, sodium bicarbonate should be administeredjudiciously in patients with acute renal failure since it can lead to inappropriate volume expansion.
(iv) Net potassium excretion can be achieved by several methods. Diuretics facilitate the renal excretion of potassium. Potassium- binding resins, such as sodium polystyrene sulfate, exchange sodium for potassium cations in the gastrointestinal tract. Since resins typically require a longer time to effect removal, faster methods of lowering potassium such as dialysis may be required, especially in the setting of acute renal failure.

Hyperuricemia
- The cornerstone of prevention and treatment of hyperuricemia includes both inhibiting the formation of uric acid as well as increasing its renal clearance
(i) Urinary alkalinization increases the solubility of uric acid. At a physiologic pH, more than 98% of uric acid exists in the plasma as its ionized salt, urate; in an acidic urinary filtrate environment, uric acid will precipitate in the renal tubule
- The goals of urinary alkalinization should be to raise the urine pH to >7.0.
- Since calcium and phosphate can precipitate at an alkaline pH and worsen renal failure, sodium bicarbonate should be administered judiciously and discontinued when serum uric acid normalizes.
(ii) In some cases, increasing urinary flow rates alone may be as effective as urinary alkalinization for decreasing the risk of uric acid nephropathy associated with tumor lysis syndrome.
(iii) Xanthine oxidase catalyzes the formation of both hypoxanthine and xanthine. Allopurinol is a structural analog of hypoxanthine and a competitive inhibitor of xanthine oxidase . The dose of oral allopurinol for tumor lysis syndrome ranges up to 800 mg/d.
(iv) Urate oxidase catalyzes the oxidation of uric acid to allantoin, which is five times more soluble than uric acid. Recombinant urate oxidase, (rasburicase) is both efficacious and well tolerated

Hypocalcemia
- Asymptomatic hypocalcemia should not be treated due to the risk of exacerbating calcium phosphate precipitation. Intravenous calcium gluconate is indicated for symptomatic hypocalcemia. Hypocalcemia usually resolves with treatment of the concomitant hyperphosphatemia.

renal replacement therapy:
- Dialysis is indicated when the resolution of tumor lysis- induced acute renal failure is unlikely, or whenever life threatening electrolyte disorders or volume overload occurs.
- Dialytic support is used primarily to correct the metabolic abnormalities seen in tumor lysis syndrome and potentially limit further renal injury.
- Experience with continuous therapies in the treatment of tumor lysis syndrome is generally favorable, although it is not known if they are much more effective than intermittent therapy.
- Continuous renal replacement therapy has been utilized as a prophylactic adjunct to the treatment of patients at high risk of tumor lysis syndrome in select cases, with some encouraging results.