Metabolic Emergencies in cancer patients

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Should we wake the oncologist at 3 am?
Oncologic emergencies

• Metabolic emergencies:
  – Hypercalcemia
  – SIADH
Hypercalcemia of malignancies

- Most common cancer: breast, lung, multiple myeloma
- 3 major mechanisms:
  - osteolytic metastases with local release of cytokines (including osteoclast activating factors)
  - tumor secretion of parathyroid hormone-related protein (PTHrP)
  - tumor production of calcitriol
Hypercalcemia of malignancies: osteoclast and tumor cells
Molecular interaction between osteoclast and tumor cell
Hypercalcemia of malignancies

• Clinical features:
  – Fatigue, anorexia, nausea, constipation, polyuria, polydipsia
  – Muscle weakness, lethargy, apathy, alteration mental status, seizures, coma
  – Nehroprogenic diabetes insipidus, acute and chronic renal insufficiency
  – Nephrolithiasis
Hypercalcemia : treatment

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Treatment Options</th>
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<tbody>
<tr>
<td>Increase urinary calcium excretion</td>
<td>Isotonic saline with or without a loop diuretic</td>
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<tr>
<td>Diminished bone resorption</td>
<td>Calcitonin, Bisphosphonates, Gallium nitrate, Plicamycin (mithramycin)</td>
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<tr>
<td>Decreased intestinal calcium absorption</td>
<td>Corticosteroids, Oral phosphate</td>
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<tr>
<td>Chelation of ionized calcium</td>
<td>EDTA or intravenous phosphate, Oral phosphate</td>
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<tr>
<td>Dialysis</td>
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Hypercalcemia: treatment

• Saline infusion: 200 to 300 mL/h that is then adjusted to maintain the urine output at 100 to 150 mL/h.

• Careful monitoring of fluid overload: in patients who cannot excrete the administered salt because of renal insufficiency, which can be induced by hypercalcemia, or heart failure. In such patients or those who are fluid overloaded at presentation, a loop diuretic should be given.
Hypercalcemia: treatment

- Bisphosphonate:
  - Clodronate 1500 mg in 500 cc normal saline, 4 hours infusion
  - Zoledronic acid 4 mg in 500 cc normal saline, 15-30 minutes infusion
Hypercalcemia: treatment

- salmon calcitonin (4 IU/kg), with remeasurement of serum calcium in several hours.
- If a hypocalcemic response is noted, then the patient is calcitonin-sensitive and the calcitonin can be repeated every six to 12 hours (4 to 8 IU/kg).
Hypercalcemia: treatment

• glucocorticoids (eg, prednisone in a dose of 20 to 40 mg/day) will usually reduce serum calcium concentrations within two to five days by decreasing calcitriol production by the activated mononuclear cells in the lung and lymph nodes.
Hypercalcemia: treatment

- Chelation of ionized calcium, using sodium EDTA (ethylenediaminetetraacetic acid) or intravenous phosphate, has the advantage of almost immediate onset of action. However, toxicity limits the use of these agents.
Hypercalcemia: treatment

- **DIALYSIS** — Hemodialysis with little or no calcium in the dialysis fluid and peritoneal dialysis (though it is slower) are both effective therapies for hypercalcemia, and are considered treatments of last resort.

- Dialysis may be indicated in patients with severe malignancy-associated hypercalcemia and renal insufficiency or heart failure, in whom hydration cannot be safely administered.
<table>
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<th>Clinical manifestation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Mild, chronic, asymptomatic (Ca 11-12 mg/dL)</td>
<td>Oral hydration high salt diet gluokortikoid oral phosphat</td>
</tr>
<tr>
<td>Severe, symptomatic (Ca &gt; 12 mg/dL)</td>
<td>Isotonic saline bisphosphonate calcitonin</td>
</tr>
<tr>
<td>Severe (Ca 18-10 mg/dL)</td>
<td>hemodyalisis</td>
</tr>
</tbody>
</table>
SIAD

• Malignant diseases:
  – Carcinoma: lung, oropharynx, gastrointestinal tract, genitourinary tract, thymoma
  – Lymphoma
  – Sarcoma: Ewing’s sarcoma

SIAD: diagnosis

• Essential features:
  – Decrease osmolality (<275 mOsm/kg)
  – Urine osmolality >100 mOsm/kg
  – Clinical euvolemia
  – Urinary Na > 40 mmol/l
  – Normal thyroid and adrenal function
  – No recent use of diuretic agents
SIAD: diagnosis

- **Supplemental features:**
  - Plasma uric acid $< 4$ mg/dl
  - BUN $< 10$ mg/dl
  - Fractional Na excretion $> 1\%$, fractional urea excretion $> 55\%$
  - Failure to correct hyponatremia after 0.9% saline infusion
  - Abnormal result on test of water load ($< 80\%$ excretion of 20 ml water/kg body weight over a period of 4 hours), or inadequate urinary dilution ($< 100$ mOsm/kg water)
  - Elevated plasma AVP levels, despite the present of hypotonicity and clinical euvolemia
SIAD

- Hyponatremia:
  - Mild: Na < 135 mmol/l
  - Moderate: Na < 130 mmol/l
  - Severe: Na < 125 mmol/l
Algorithm for the treatment of hyponatremia associated with SIAD

Severe: Na < 125 mmol/L

Acute (<48h) / coma, seizures
- 3% saline at 1-2 ml/kg/hr, furosemide 20 mg IV, increase Na 2 mmol/l/h, check Na every 2 h

Diagnostic evaluation, 0.9% saline with furosemide 20 mg, increase Na 0.5-2 mmol/l/h, stop when Na rises by 8-10 mmol/l within 48h, Conivaptan, check Na every 4 h

Rule out or address correctable factors

Asymptomatic

Diagnostic evaluation

Moderate symptom

Severe: Na < 125 mmol/L
Algorithm for the treatment of hyponatremia associated with SIAD

Chronic hyponatremia

Restrict fluid intake
dietary intake of salt and protein
demeclocycline 300-600 mg twice daily, or urea 15-60 g daily
Vasopresin receptor antagonis

<table>
<thead>
<tr>
<th>Na urine + K urine</th>
<th>Fluid intake</th>
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<tbody>
<tr>
<td>Na plasma</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>&lt; 500 ml/d</td>
</tr>
<tr>
<td>1</td>
<td>500-700 ml/d</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>&lt; 1 liter/d</td>
</tr>
</tbody>
</table>
Symptomatic hyponatremia

Impending herniation
- 3% NaCl 100cc bolus, 10 min
- repeat bolus once or twice until symptom improve
- aim for a 1-4 mmol/l increase in Na level
- begin infusion as for hyponatremic encephalopathy

Hyponatremic encephalopathy
- 3% NaCl via infusion pump 50-100 ml/h)
- Check Na level every 2 hours
- Stop 3% NaCl infusion when either: the patient is symptom free or there is an acute rise in serum Na of 10 mmol in first 5 h
- Total correction in first 48 h: do not exceed 15-20 mmol, avoid correction to normonatremic or hypernatremic levels

Formula used to estimate the effect of 1 liter of any infusate on serum Na

- Change in serum Na (mmol/L) =

\[
\frac{\text{Infusate Na concentration} - \text{serum Na concentration}}{\text{Total body water} + 1}
\]
Hyponatremia: example

- Case: 58-year-old man with SCLC presented with confusion and lethargy and was diagnosed with SIADH
- His weight 60 kg, Na 108
- Total body water: 0.6 x 60 kg = 36 liters
- 1 liter NaCl 3% → ? Increase Na
Hyponatremia: example

Change serum Na:

\[
\text{Infusate Na concentration} - \text{serum Na concentration} \over \text{Total body water} +1
\]

\[
\frac{513 - 108}{36 + 1} = 10.9 \text{ mmol/L}
\]
Hyponatremia: example

• Initial goal: increase Na 5 mmol/L over first 12h
• 1L NaCl 3% increase Na 10.9 mmol/L
• To increase 5 mmol/l: 5/10.9 = 0.46 L
• 0.46 L over 12 hours = 38 ml per hour
Take home messages

• Cancer patients can come to ED with oncologic emergencies
• Metabolic oncologic emergencies:
  – Hypercalcemia
  – Hyponatremia (SIADH)
Take home messages

• Hypercalcemia:
  – Increase ca excretion with NaCl 0.9 %
  – inhibit bone resorbtion with bisphosphonate, calcitonin
  – Inhibit calcium absorbtion with corticosteroid
  – Dialysis
Take home messages

• Hyponatremia (SIADH):
  – Acute, symptomatic: NaCl 3% to increase natrium 8-12 mmol/L in first 24 h
  – Seizure and coma: NaCl 3% to correct Na 1-2 mmol/liter/h
  – Mild symptom: Na correction 0.5 mmol/liter/jam, with NaCl 0.9%.
Should we wake the oncologist at 3 am?