Hyponatraemia in oncology patients- what physicians should know?

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Case vignette

A 65-year-old patient with hyponatraemia is referred to a physician from the oncology unit. She has a history of endometrial carcinoma which has recently been treated with adjuvant chemotherapy (cisplatin). Currently she is being managed for a right sided pneumonia. Patient is drowsy and dehydrated. She is in a 1500 ml negative fluid balance with a urine output of over 3L per day. Her blood pressure is 105/90 mmHg while pulse rate is 110 bpm. Her serum electrolytes are as follows:

Serum sodium – 122 mEq/L
Serum Potassium - 3.8 mEq/L

What is the likely cause for the hyponatraemia in this patient?
How do you evaluate this patient?

Overview

Hyponatraemia is a common occurrence in patients with malignancies. Although aetiopathogenesis is most often similar to that in non-cancer patients, it can occur as a result of the cancer itself or its treatment. Hyponatraemia has also shown to be a potential negative prognostic factor associated with both solid and haematological malignancies. Patients may present with symptoms or may be detected on laboratory testing before, during or after treatment. Treatment has to be decided based upon multiple factors including aetiology, symptom severity and timing of onset. Under the circumstances where cancer incidence is rising globally, general physicians frequently encounter and are involved in multidisciplinary team management of such patients. Further, there are no published guidelines on management of hyponatraemia in oncological patients. Therefore, it is a timely need that physicians are updated and are well conversant with aetiology, diagnostic approach, and principles of management of these complicated patients.

Causes of hyponatraemia

Although the aetiology is broad in hyponatraemia, one must bear in mind the following important causes in oncological patients.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hyponatraemia in cancer patients is most frequently caused by SIADH. In this context, ectopic antidiuretic hormone secretion by tumour cells is a recognised cause. While SIADH is most commonly described in patients with small cell lung cancer (SCLC), it is also reported in other multiple solid and haematological malignancies. SIADH may also be caused by multiple anticancer or palliative drugs either through increased hypotalamic vasopressin production or potentiating its' action.

Refer to table 1.

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**Table 1 - Anticancer agents and palliative medicines causing Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)**

<table>
<thead>
<tr>
<th>Anticancer agents</th>
<th>Palliative care medicines</th>
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</thead>
<tbody>
<tr>
<td>Vinca alkaloids (vincristine, vinblastine)</td>
<td>Analgesics (opioid analgesics, non-steroidal anti-inflammatory drugs)</td>
</tr>
<tr>
<td>Platinum compounds (cisplatin, carboplatin)</td>
<td>Other supportive care medicines (antidepressants, antipsychotics, antiepileptics)</td>
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<tr>
<td>Alkylating agents (cyclophosphamide, ifosfamide, melphalan)</td>
<td><strong>Cisplatin may also cause hyponatraemia by damaging renal tubules and interfering with sodium reabsorption</strong></td>
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**Renal Salt wasting syndrome**

Renal salt wasting syndrome is characterised by polyuria, hyponatraemia and extracellular fluid depletion and often mistaken for SIADH due to their basic clinical and laboratory similarities. It occurs due to a tubular defect in sodium transport and some anticancer agents, particularly platinum compounds can cause direct nephrotoxicity with renal tubular damage leading to interference with sodium reabsorption.(9)

**Cerebral salt wasting syndrome**

Cerebral salt wasting causes hyponatraemia in the setting of central nervous system (CNS) diseases and can occur due to brain metastases, CNS surgery head trauma, or CNS infections in oncology patients.(10) The exact mechanism of salt wasting with brain disease is still unclear. Postulated mechanisms are the release of brain natriuretic peptide (BNP) or injury to the sympathetic nervous system interfering with sodium reabsorption.

The diagnostic approach is basically similar to that of a non-cancer patient, but the physician must be familiar with the aetiologies and clinical context specific to the individual patient.

The following three step approach (flow chart 1) provides a focused assessment of hyponatraemia in oncological patients.(11)

**Diagnostic approach**

**Step 1**

First step is to measure serum osmolality. A serum osmolality >280 mOsm/kg is suggestive of isotonic or hypertonic hyponatraemia where there are osmotically active particles in the plasma (like in hyperglycaemia, hypertriglyceridaemia) and if serum osmolality is <280 mOsm/kg, it is a hypotonic hyponatraemia where further evaluation is necessary to establish a diagnosis.

**Step 2**

Next, urine osmolality should be measured to assess if the renal dilution system is intact in the face of hyponatraemia. Normal kidneys will maximally dilute urine (<100 mOsm/L) in the presence of hyponatraemia. If urine osmolality is <100 mOsm/kg it indicates an appropriate renal dilution which occurs in the case of compulsive water intake. If urine sodium is >100 mOsm/kg there is an inappropriate renal dilution which should be evaluated further.

**Step 3**

The final step is to determine the extracellular volume status. This can be done through clinical assessment combined with investigations. Presence of postural hypotension, tachycardia, dry mucous membranes, and poor skin turgor will indicate hypovolaemia which could be due to either renal (urine sodium > 20mEq/L) or extra renal (urine sodium < 10 mEq/L) sodium loss. Renal salt wasting syndromes and diuretics are causes for renal sodium loss. Presence of concomitant hypokalaemia is observed with thiazide and loop diuretics. Extra renal sodium loss can occur with vomiting/diarrhoea.

If the patient is in a fluid overloaded state (with...
Oedema, ascites), in the presence of urine sodium urine sodium > 20 mEq/L, renal failure is the likely cause for hyponatraemia and when urine sodium is < 10 mEq/L, heart failure or liver failure is likely.

Patients without volume depletion or overload are considered euvolemic. In the presence of urine sodium > 20 mEq/L, the most likely cause for hyponatraemia is SIADH. However, thyroid and adrenal insufficiency must be ruled out before confirming SIADH and where there is clinical suspicion of such, thyroid stimulating hormone (TSH) and 9 AM cortisol can be performed for initial evaluation.

Blood urea nitrogen (BUN) and serum uric acid can aid determination of the volume status. High BUN and serum uric acid indicates hypovolaemia. Therefore, clinical assessment combined with osmolality studies (serum and urine osmolality, serum and urine sodium), renal functions and in selected cases TSH and 9 AM cortisol levels are sufficient to unravel the underlying cause for hyponatraemia in these patients.

The main diagnostic challenge is differentiating salt wasting syndromes from SIADH because both are characterised by low plasma osmolality, high urine sodium concentration and high urine osmolality. The cardinal feature differentiating these two entities are the volume status of the patient where in the case of salt wasting syndromes, the patients are polyuric and dehydrated with elevated blood urea and serum uric acid levels. Although there is emerging evidence that fractional excretion of urate (FEurate) provides a better differentiation of these two entities, it is not practical to measure, especially in low resource settings. However, this differentiation is mandatory in selecting the correct approach for management.

**Management**

There are no published guidelines on management of hyponatraemia in oncological patients. The following management approach and options are derived based on available current literature. The treatment should be guided by considering following patient factors:

1. Presence of symptoms
2. Severity of symptoms
3. Extracellular volume status

While symptomatic patients require prompt attention to prevent complications, the serum sodium levels should be raised at a controlled rate at <12 mEq/L in 24 hours and <18 mEq/L in 48 hours to prevent osmotic demyelination syndrome. The available treatment options are hypertonic or isotonic saline, fluid restriction, oral salt replacement and pharmacological agents which can be used based on the principles outlined.
Management of SIADH (euvolemic) and hypervolaemic patients

The correction of symptomatic hyponatraemia in euvolemic (acute/chronic) or hypervolaemic patients is achieved by administering hypertonic (3%) saline via continuous infusion or bolus with aim of rapid increase in serum sodium by 4-6 mmol/L.

- 100 mL bolus infused over 10 minutes – May repeat 3 times as needed
- 150 mL over 20 minutes – May repeat twice or until target increase is achieved

Treatment with hypertonic saline should be stopped once symptoms resolve and either when a safe or maximum serum sodium concentration is reached. Asymptomatic SIADH (euvolemic) or hypervolaemic patients are managed with initial fluid restriction to achieve a negative water balance. This may take several days to cause a significant rise in sodium levels. However, for patients on chemotherapy requiring adequate hydration with fluids, the same approach for symptomatic patients can be followed in order to correct sodium levels while continuing anticancer treatment.

Management of salt wasting syndromes

In salt wasting syndromes, patients’ volume status and sodium should be restored with isotonic (0.9%) saline and fluid replacement should be guided by the volume status and sodium concentration of the patient. However, in symptomatic patients, hypertonic (3%) saline and/or oral salt replacement (1-2 g per day up to three times a day) should be considered. Free water intake must be restricted.

Pharmacological agents

Since compliance to fluid restriction is often suboptimal pharmacological interventions may be required. Many of the older medications like lithium and demeclocycline are limited by toxicity, poor efficacy and tolerability. Vasopressin V2 receptor antagonists (e.g.: tolvaptan) which are used in medical patients to manage euvolemic and hypervolaemic hyponatraemia can successfully be used in cancer patients with the added benefit of being able to continue chemotherapy with platinum-based regimens without worsening hyponatraemia. Tolvaptan can be used in euvolemic and hypervolaemic patients but contraindicated in hypovolaemic patients and also during pregnancy and breastfeeding. Further, it is not useful when urgent correction is needed. Starting dose is 15m g once daily which can be increased to 30 mg once daily with a maximum daily dose of 60 mg. Treatment is preferably started while the patient is in the hospital allowing for therapeutic response monitoring and controlled correction.

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With the underlying pneumonia and treatment with cisplatin, the main differential diagnosis is SIADH and renal salt wasting. Presence of polyuria and dehydration favours cisplatin induced renal salt wasting which was the ultimate diagnosis of the patient. She was successfully managed with initial hypertonic saline followed by fluid and salt replacement.

Conclusion

Aetiopathogenesis of hyponatraemia is somewhat different and is a negative prognostic indicator in oncological patients. Differentiating SIADH from salt wasting syndromes and other hypovolaemic states is crucial for selecting appropriate treatment schedules. General physicians are increasingly involved in medical management of these patients owing to rising cancer incidence and multidisciplinary approach of management. Therefore, physicians should be empowered with the necessary knowledge to assess and manage these patients in order to optimise patient care.

References


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