CASE REPORT

Hyponatraemia in patients with multiple myeloma

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Accepted 19 November 2015

SUMMARY

Hyponatraemia is the most common electrolyte disturbance encountered in clinical practice. Several causes of hyponatraemia are recognised and in many patients the aetiology may be multifactorial. An important cause is water intoxication and this is often iatrogenic. We present three patients, all of whom suffered from multiple myeloma, who illustrate different aspects of hyponatraemia, its causes and management.

BACKGROUND

Hyponatraemia is the most common electrolyte disturbance, affecting 15–38% of hospital inpatients, and is defined as a plasma sodium concentration of <135 mmol/L.¹ Hyponatraemia is independently associated with in-hospital mortality and also increased risk of falls in elderly patients.^{2–3} Mild hyponatraemia can present with anorexia, nausea, malaise and falls; more severe cases can progress to headache, irritability, confusion, weakness, encephalopathy and seizures.

Multiple myeloma (MM) is a malignant proliferation of plasma cells usually associated with secretion of an immunoglobulin (Ig) or Ig fragment (Bence-Jones protein), seen as a paraprotein on serum or urine electrophoresis. Clinical presentation of MM includes the quintessential 'CRAB' features: hypercalcaemia, Renal failure, Anaemia and Bone lesions.⁴ Patients with a paraproteinaemia are at increased risk of pseudohyponatraemia due to an increased intravascular oncotic pressure. In addition, paraproteins are positively charged and can thereby decrease the sodium level, causing a true hyponatraemia.⁵

We present three patients with MM who developed hyponatraemia. These cases emphasise the multifactorial aetiology of hyponatraemia and the role of the clinician in preventing iatrogenic causes; the learning points are relevant not just to myeloma but to all patients.

CASE PRESENTATION**Case 1**

An 87-year-old woman had suffered from polymyalgia rheumatic for many years. She was diagnosed with MM in 2010, with a Bence-Jones proteinuria. Bone marrow was hypercellular with 30% κ light chain-restricted plasma cells. There was no paraprotein, but normal immunoglobulin levels were reduced and light chains were abnormal with an elevated serum κ light chain of 475 mg/L (<25 mg/L). The patient was treated with cyclophosphamide, prednisolone, thalidomide and bortezomib. She responded well, κ light chains were

reduced to 28 mg/L and treatment was stopped in 2012.

She relapsed in February 2014 with κ light chains >550 mg/L and haemoglobin 110 g/L (115–160 g/L), and was started on bortezomib and dexamethasone. After 3 months of treatment, a hyponatraemia of 128 mmol/L (135–145 mmol/L) was identified while the patient was attending for hospital treatment. She informed the consultant, 'I'm really struggling to drink three litres a day'. She had been advised to do so by a nurse. Two days later she had a fall at home, and was admitted via accident and emergency. On examination, she was confused and disorientated with hypotension (90/50 mm Hg). She had signs in her chest compatible with pneumonia, confirmed on chest X-ray. Investigations showed haemoglobin 107 g/L, serum sodium reduced to 112 mmol/L, random urine sodium 35 mmol/L and urine osmolality 472 mmol/kg (80–1200 mmol/kg). She was treated with fluid restriction, fludrocortisone and antibiotics. She improved rapidly and 5 days later serum sodium had recovered to 138 mmol/L.

Case 2

A 77-year-old woman had an 11-year history of MM. On diagnosis in 2003, she had an IgA paraprotein level of 22 g/L and bone marrow biopsy demonstrated 60% plasma cells. She was treated with a series of chemotherapy regimens including melphalan and prednisolone; CIDEK chemotherapy (CCNU (chloroethyl-cyclohexyl-nitrosourea), idarubicin and dexamethasone) and, following sub-optimal response, bortezomib, which decreased the paraprotein level to a plateau of 5 g/L. In 2006, 3 years after diagnosis, routine biochemistry revealed a hyponatraemia, which has persisted intermittently for 8 years and has been as low as 126 mmol/L on three occasions. The patient was referred for endocrine review and investigated with a random cortisol (normal), paired plasma and urine osmolality (both reduced), random urine sodium (38 mmol/L), thyroid function tests (normal) and fasting lipids (normal). The paraprotein level has remained low, ranging from 3 to 16 g/L, most recently 4 g/L. In 2009, the patient's myeloma relapsed with 80% plasma cells in bone marrow and she was started on CDT (cyclophosphamide, dexamethasone and thalidomide). Her condition stabilised but, in 2011, she relapsed again and was treated with melphalan and prednisolone, followed by bortezomib, dexamethasone, cyclophosphamide and, most recently, lenalidomide and prednisolone. In 2013, the patient revealed she had been assiduously following advice given by a nurse specialist and was drinking 3 L of water a

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To cite: Mirvis E, De-Silva D, Mehta A. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212838

day. She was advised to reduce her daily fluid intake to 1–1.5 L, whereon her sodium improved from 126 to 136 mmol/L. She is currently well.

Case 3

A 65-year-old woman was diagnosed with MM 13 years ago, in 2002. She was treated with the VBMCP protocol of vincristine, bis-chloroethyl-nitrosourea (BCNU), melphalan, cyclophosphamide and prednisolone followed by autologous stem cell transplant. She achieved plateau phase with 5% plasma cells in her bone marrow and a paraprotein of only 3 g/L. She relapsed in April 2014 and was treated with bortezomib and dexamethasone. A second autologous stem cell transplant was planned and she was admitted to hospital for stem cell collection. She was treated with a stem cell mobilisation protocol of cyclophosphamide 2 g intravenous and granulocyte colony-stimulating factor (G-CSF). She became acutely unwell, had a generalised seizure and was confused. Biochemistry revealed an episode of acute hyponatraemia with serum sodium 118 mmol/L. Plasma osmolality, measured as $2 \times \text{Na} + \text{urea} + \text{glucose}$, was reduced at 245.8 mOsmol/kg (278–305 mOsmol/kg). Urine was concentrated with osmolality of 235 mOsmol/kg (<100 mOsmol/kg) and sodium of 55 mmol/L (<20 mmol/L). The patient was clinically euvolaemic. In this context, although antidiuretic hormone (ADH) level was not measured, the decreased plasma osmolality and raised urine osmolality and sodium are consistent with syndrome of inappropriate ADH (SIADH). The patient's hyponatraemia was slowly corrected with intravenous fluids, she proceeded to receive the stem cell transplant and has now recovered well.

DISCUSSION

Sodium concentration and plasma osmolality are tightly controlled by release of ADH from the posterior pituitary in response to raised plasma osmolality. ADH acts on the distal renal tubules and collecting ducts to increase expression of the membrane protein aquaporin 2, which increases water permeability at these sites, resulting in more concentrated urine and reduced plasma osmolality.⁶

Hyponatraemia has a wide differential diagnosis in sick patients, most commonly iatrogenic fluid overload with hypotonic saline or 5% dextrose.⁷ Blood should not be taken from a drip arm as this can cause a falsely low sodium result. Broadly, hyponatraemia can be classified into three groups, based on a fluid assessment of the patient:⁸

1. Hypovolaemic hyponatraemia—sodium is lost in excess of water. Water can be lost via the kidneys (diuretic excess, renal tubular acidosis) or through extrarenal losses (diarrhoea, vomiting, burns, pancreatitis).
2. Euvolaemic hyponatraemia—causes include hypothyroidism, Addison's disease and SIADH.
3. Hypervolaemic (dilutional) hyponatraemia—this is the commonest cause of hyponatraemia resulting from relative water excess, for example, nephrotic syndrome, cirrhosis, cardiac failure or iatrogenic fluid overload.

Pseudohyponatraemia occurs when sodium appears spuriously low due to high serum triglycerides or proteins (eg, paraproteins). These non-aqueous components constitute 7% of normal plasma volume; the indirect ion selective electrode (ISE), the standard chemistry system in many hospital laboratories, is standardised to measure electrolytes in samples with this normal proportion of non-aqueous components. When triglycerides or proteins are substantially raised, however, they displace plasma water, resulting in a falsely low sodium.⁹

The cases above highlight multiple mechanisms of hyponatraemia in patients with myeloma. The first patient had significantly elevated Ig light chains and the other two had a paraproteinaemia, potentially contributing to pseudohyponatraemia. In addition, myeloma-related renal dysfunction can cause proteinuria, resulting in dilutional hyponatraemia.

Patients with myeloma are often encouraged to maintain daily fluid intake of up to 3 L regardless of their weight.¹⁰ This is excessive in petite patients and can result in overhydration and hyponatraemia, especially when compensatory diuresis is impaired by renal failure. In our second case, chronic hyponatraemia was corrected simply by reducing fluid intake. Advice regarding fluid intake should be tailored to the patient's weight.

Patients with myeloma have impaired cellular and humoral immunity. Infective complications including pneumonia are therefore common and can be associated with SIADH, such as in our first case. SIADH occurs when stimuli, for example, drugs, infection or head injury, override the physiological osmolality control, resulting in excess ADH secretion and impaired dilution of urine. Many lung disorders, including pneumonia, pneumothorax and bronchial asthma, can cause SIADH via an unknown mechanism.¹¹ ADH levels are not routinely measured in hospital laboratories and diagnosis of SIADH relies on the Bartter-Schwartz criteria (1967), which include:

- Hyponatraemia and hypo-osmolality;
- Raised urinary sodium;
- Urine less than maximally dilute;
- Absence of clinical evidence of hypovolaemia;
- Absence of other causes of hyponatraemia;
- Correction of hyponatraemia by fluid restriction.¹²

Drugs can also contribute to hyponatraemia via several mechanisms. Excess diuretic use results in hypovolaemic hyponatraemia. Other drugs, including cyclophosphamide, have very rarely been reported to cause severe hyponatraemia, although the mechanism is unknown. To the best of our knowledge, our third patient's is only the third reported case of cyclophosphamide-induced SIADH in a patient with MM.^{13 14}

Our cases illustrate that there are often exacerbating circumstances—infection and drugs—causing inappropriate ADH. This can be life-threatening. Early recognition and intervention is important, as hyponatraemia is treatable with a good outcome.

Learning points

- Symptoms of hyponatraemia are insidious in onset, requiring a low threshold of clinical suspicion.
- Patients with myeloma are susceptible to hyponatraemia due to the underlying disease as well as end-organ damage, for example, renal dysfunction, and to the drugs to which they are exposed. They are also generally an elderly population with multiple comorbidities, which may contribute.
- Special care should be taken to assess and manage an individual's fluid balance and a holistic approach is required when managing electrolyte imbalances.

Contributors AM devised the concept of the case series and is the guarantor. EM collected the data, and drafted and revised the paper. DD-S drafted the discussion. AM reviewed the manuscript, and all the authors approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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