Pseudohyponatraemia in a patient with human immunodeficiency virus infection and plasma cell disorder

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SUMMARY

A 59-year-old man was admitted and treated for smear positive pulmonary tuberculosis. His co-morbidities were human immunodeficiency virus infection, schizophrenia and right otitis externa. He was initially thought to have persistent severe hyponatraemia, which was resistant to various therapeutic measures, including intravenous normal saline infusion, fluid restriction and even hypertonic saline correction. To complicate matters further, his blood electrolytes samples frequently showed technical errors in the analysers and could not be reported due to hyperviscosity state of the specimen. The presence of pseudohyponatraemia was subsequently confirmed based on normal measured serum osmolality, as well as normonatraemia seen on his venous blood gas analysis results. Investigations of pseudohyponatraemia led to discovery of a plasma cell dyscrasia, the possible diagnosis of which included Waldenström macroglobulinemia or IgM multiple myeloma. The patient eventually refused bone marrow aspiration and trephine biopsy for further evaluation. A high index of suspicion is required to differentiate pseudohyponatraemia from true hyponatraemia, to avoid misdiagnosis and mismanagement. When such circumstance is suspected, particularly in the setting of hyperproteinaemia or hyperlipidaemia, an analyser which utilises direct ion-selective electrodes, such as a blood gas machine, often reports normal sodium concentration and thus confirms pseudohyponatraemia.

INTRODUCTION

Hyponatraemia is a common electrolyte abnormality encountered in daily clinical practice, the presence of which at hospital admission has been associated with greater all-cause mortality and longer hospital stay.[1] Nonetheless, it is important to distinguish pseudohyponatraemia from true hyponatraemia as overzealous correction of the former can lead to adverse outcomes.

Pseudohyponatraemia is a laboratory artefact whereby sodium concentration of a given volume of serum is reduced when measured by indirect ion-selective electrodes (ISE) due to involvement of a preanalytical dilution step. This condition typically happens in the setting of marked hyperlipidaemia (hypertriglyceridaemia or hypercholesterolaemia) as well as hyperproteinaemia (paraproteinaemia, hypergammaglobulinaemia or intravenous immunoglobulin administration).[2]

We report a patient who initially manifested apparent resistant hyponatraemia, but was later found to have pseudohyponatraemia secondary to hyperproteinaemia due to a plasma cell disorder, two weeks after hospitalisation.

CASE PRESENTATION

A 59-year-old homeless man, who was a chronic smoker and had a history of intravenous heroin use more than three decades ago, presented to emergency department with a one-week history of intermittent fever, associated with cough productive of yellowish sputum mixed with blood streaks. He also experienced weight loss over the past two weeks but was unable to quantify it. Auscultation of the lungs revealed coarse crepitations over the left mid zone. His chest radiograph showed reticulonodular shadowing at the right upper zone as well as left upper and mid zones. He was admitted with a provisional diagnosis of community-acquired pneumonia, highly suspicious of pulmonary tuberculosis. Two days after admission, his sputum direct smear was tested positive for acid fast bacilli, for which he was treated with three tablets daily of a four-drug fixed-dose combination of antituberculosis therapy and pyridoxine 10 mg daily. Besides pulmonary tuberculosis, he was also diagnosed to have human immunodeficiency virus (HIV) infection, schizophrenia, and right otitis externa, all of which were managed by respective teams.

His initial laboratory investigations are shown in Table I. Plain computed tomography (CT) of brain was normal. Lumbar puncture was not performed due to patient's and family's refusal. In view of the finding of severe hyponatraemia (< 100 mmol/L) and hypokalaemia (1.8 mmol/L), he received 1.5 to 2.5 litres of intravenous normal saline with potassium supplementation every day during his first three days of hospitalisation. Workup of hyponatraemia showed normal measured serum osmolality, urine osmolality, urine sodium, serum cortisol and thyroid function. As the sodium levels did not seem to normalise with hydration, he was placed on fluid restriction due to a concern of possible syndrome of inappropriate antidiuretic hormone secretion (SIADH). Rapid sodium correction with hypertonic saline was also performed on one occasion. However, subsequent monitoring of his sodium levels turned out to be difficult due to either undetectable sodium levels (measured by indirect ISE) or repeated rejection of blood electrolytes samples by the chemical pathology laboratory (Table II). Further clarification from the laboratory revealed that his

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Table I: Initial blood investigations during admission

Investigations	Reference range	Values
Hb (g/L)	130 - 170	49
WBC (10^9/L)	4.0 - 10.0	5.8
Platelet (10^9/L)	150 - 410	479
Sodium (mmol/L)	136 - 145	<100
Potassium (mmol/L)	3.5 - 5.1	1.8
Chloride (mmol/L)	98 - 107	<50
Urea (mmol/L)	3.0 - 9.2	6.3
Creatinine (µmol/L)	64 - 104	81
Total Protein (g/L)	64 - 83	94
Albumin (g/L)	34 - 48	21
Globulin (g/L)	-	73
Total Bilirubin (µmol/L)	3.4 - 20.5	6.2
ALT (U/L)	0 - 55	7
AST (U/L)		43
ALP (U/L)	40 - 150	110
Corrected calcium (mmol/L)	2.10 - 2.55	2.78
Phosphate (mmol/L)	0.74 - 1.52	0.92
Magnesium (mmol/L)	0.66 - 1.07	0.83
CK (U/L)		<11
LDH (U/L)		965
CRP (mg/L)	< 5	179.5
ESR (mm/hr)	0.00 - 14.00	2
Morning cortisol (nmol/L)	-	369.2
TSH (mIU/L)	0.35 - 4.94	0.527
free T4 (pmol/L)	9.01 - 19.05	9.41
Triglycerides (mmol/L)	< 1.7	0.4
Total cholesterol (mmol/L)	< 5.2	1.5
HDL-Cholesterol (mmol/L)	> 1.0	0.5
LDL-Cholesterol (mmol/L)	-	0.9
HIV-	Positive	
HBsAg	-	Non-reactive
Hepatitis C antibody	-	Reactive
RPR	-	Non-reactive

Hb haemoglobin, WBC white blood cell, ALT alanine transaminase, AST aspartate aminotransferase, ALP alkaline phosphatase, CK creatine kinase, LDH lactate dehydrogenase, CRP C-reactive protein, ESR erythrocyte sedimentation rate, TSH thyroid-stimulating hormone, T4 thyroxine, HIV human immunodeficiency virus, HBsAg hepatitis B surface antigen, RPR rapid plasma regain

blood samples were too "viscous" to be analysed. The patient was otherwise alert and well-orientated despite being delusional with auditory hallucination.

Meanwhile, several venous blood gas analyses during this admission demonstrated mostly normal sodium levels (measured by direct ISE), ranging between 133 mmol/L and 145 mmol/L (Table II). The presence of normal sodium concentration, analysed using a blood gas analyser which measures sodium in serum water phase, as well as a normal serum osmolality confirmed that the low sodium levels reported by the laboratory were in fact pseudohyponatraemia, the possible cause of which in this patient was hyperproteinaemia (Table I). Further assessment for causes of hyperproteinaemia was carried out. The patient was subsequently discharged to a shelter home after sputum smear conversion and continued directly observed therapy (DOT) of antituberculosis treatment at chest clinic. He also received antiretroviral (ARV) therapy from the infectious diseases team and risperidone 1 mg every night by the psychiatry team.

One month after discharge, he was reviewed in haematology clinic. His peripheral blood film showed rouleaux formation. Free light chain kappa/lambda ratio was normal (1.336, normal range: 0.310 – 1.560) but serum immunoglobulin M (IgM) and beta-2 microglobulin were both elevated (32 g/L, normal range: 0.22 – 2.40, and 7.34 mg/L, normal range: 1.09 – 2.53, respectively). Additionally, serum protein electrophoresis and immunofixation showed oligoclonal bands with prominent IgM kappa paraproteinemia of 44.3 g/L near beta zone. The working haematological diagnosis was Waldenström macroglobulinemia or IgM multiple myeloma. Despite counselling on the risk of disease progression and potential complications of hyperviscosity, the patient refused bone marrow aspiration and trephine biopsy for further evaluation.

DISCUSSION

We report a case of pseudohyponatraemia secondary to markedly elevated IgM in the setting of a plasma cell dyscrasia. Our patient was found to have hyponatraemia during his admission for smear positive pulmonary tuberculosis and HIV infection. Common aetiologies which could underlie such presentation include dehydration, adrenal insufficiency, thyroid insufficiency or SIADH.[3] All these conditions exhibit low measured serum osmolality,

Table II: Serial serum sodium concentration monitoring during admission and the corresponding fluid management

Investigations	20.11.22	21.11.22	22.11.22	24.11.22	25.11.22	26.11.22	27.11.22	1.12.22	3.12.22	4.12.22	5.12.22	7.12.22	8.12.22	10.12.22	11.12.22
Laboratory sodium (mmol/L)	129	127	120	Rejected	<100	124	<100	119	Rejected	Rejected	-	Rejected	<100	-	<100
VBG sodium (mmol/L)								133	134	144	145	133		143	139
Serum osmolality (mOsm/kg)	300					291		300							
Urine osmolality (mOsm/kg)	631					529		352							
Urine sodium (mmol/L)	80					120		109							
Fluid management	1.5-2.5 L 0.9% NS/day		ROF 800 cc/day		3% saline correction	1.5-2 L 0.9% NS/day						1 L 0.9% NS/day		Liberal oral fluid intake	

VBG venous blood gas, NS normal saline, ROF restriction of fluid

which is not the case in our patient whereby the measured serum osmolality was normal. Besides, neither intravenous fluid therapy nor fluid restriction normalised his sodium levels. Furthermore, normal serum cortisol and thyroid function excluded adrenal and thyroid insufficiencies. The huge discrepancy between laboratory-measured sodium levels (indirect ISE method) and those measured by the blood gas machine (direct ISE method) subsequently alerted the treating team to the possibility of pseudohyponatraemia.

Water constitutes approximately 93% of a normal individual's serum. Sodium is only found in the serum water phase. In patients who have marked hyperlipidaemia or hyperproteinaemia, serum water fraction reduces significantly. Consequently, the sodium concentration per litre of serum (not serum water) becomes artifactually low. Among the two ISE methods (direct ISE and indirect ISE) used for measurement of serum electrolytes, indirect ISE is prone to give rise to pseudohyponatraemia in the setting of marked hyperlipidaemia or hyperproteinaemia because it involves a preanalytical dilution step. In our case, our laboratory used an indirect ISE method to measure serum sodium, thus resulted in spuriously low sodium concentrations. Meanwhile, the sodium concentration in the serum water phase is unaffected by changes in water percentage. Therefore, blood gas machine analysers, which uses a direct ISE method and does not have a predilution step, directly measures sodium concentration in the serum water phase and reported mostly normal sodium levels in our patient.[2]

Differentiating pseudohyponatraemia from true hyponatraemia is imperative to avoid unnecessary treatment with intravenous isotonic or hypertonic saline which may lead to iatrogenic hypernatraemia. When hyponatraemia occurs in the presence of hyperproteinaemia or hyperlipidaemia, suspicion of pseudohyponatraemia should arise. A repeat sodium concentration measurement by an analyser which utilises direct ISE method, for instance a point-of-care device or a blood gas analyser, should be performed. Of note, direct ISE method is also available in chemistry analysers. However, due to the higher cost, most laboratories measure electrolytes using indirect ISE method. If the repeat sodium concentration, measured by direct ISE method, is normal, then pseudohyponatraemia is confirmed. On the other hand, if a blood gas analyser is unavailable, pseudohyponatraemia can also be confirmed by a normal serum osmolality together with a high concentration of proteins or lipids. This is because true hyponatraemia, such as that seen in adrenal insufficiency or SIADH, is associated with low serum osmolality.[2]

Cases of pseudohyponatraemia have been described in patients with HIV infection and are attributed to hypergammaglobulinaemia.[4] Our patient has concomitant HIV infection and a plasma cell disorder (Waldenström macroglobulinemia or IgM multiple myeloma). HIV-infected individuals are known to have higher risks for plasma cell disorders, ranging from polyclonal hypergammaglobulinaemia, monoclonal gammopathy to multiple myeloma. Antigen stimulation and immunodeficiency are two possible mechanisms which contribute to this observation. Treatment of plasma cell disorders in HIV-infected patients is similar to that in general population.[5] In our case, since Waldenström macroglobulinemia and IgM multiple myeloma are two distinct entities with different prognoses and treatment plans, a bone marrow aspiration and trephine biopsy is essential in confirming the diagnosis and thereby guiding further management. However, it was not performed due to our patient's refusal.

CONCLUSION

Pseudohyponatraemia should be suspected when hyponatraemia occurs alongside normal measured serum osmolality, particularly in the setting of hyperproteinaemia and hyperlipidaemia. Recognition of this laboratory abnormality prevents misdiagnosis and thence inappropriate patient management.

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DECLARATIONS

Written consent from the patient's carer has been obtained prior to the publication of this case report. Both authors declare no conflict of interest.

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