CASE REPORT

Tuberculous lymphadenitis and syndrome of inappropriate antidiuresis, improbable partners

Helena Vitorino, Andrea Castanheira, Manuela Zita Veiga, Alberto Mello Silva

Department of Medicina 1,
Centro Hospitalar Lisboa
Occidental, Hospital de Egas
Moniz, Lisbon, Portugal

Correspondence to

Helena Vitorino,
helenavitorino@gmail.com

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SUMMARY

A patient with acute respiratory infection and severe hyponatraemia was admitted to our department. The hyponatraemia study was compatible with syndrome of inappropriate antidiuresis (SIAD) and an association with the respiratory problem was initially assumed. The recurrence of hyponatraemia after resolution of the pulmonary infection led to further investigation and to the diagnosis of tuberculous lymphadenitis. After treatment of this condition, discontinuation of SIAD treatment was possible, making this association presumable. We would like to highlight the importance of considering alternative conditions in the approach to SIAD.

BACKGROUND

Hyponatraemia is a common electrolyte disturbance and is defined as serum sodium concentration under 135 mmol/L. It has the potential of becoming a life-threatening situation resulting from cerebral oedema induced by water movement into the brain and is associated with adverse outcomes in a wide variety of disorders.^{1 2} The clinical symptoms, morbidity and mortality, depend on its severity, duration and speed/rate of onset.³ Syndrome of inappropriate antidiuresis (SIAD) is the most common cause of euvoalaemic hyponatraemia, and is a clinical manifestation of a wide range of disorders. Classic aetiologies include: neoplastic by ectopic production of antidiuretic hormone, notably small-cell lung cancer (but rarely seen in other lung tumours), iatrogenic (particularly psychoactive drugs and chemotherapy), lung disorders (viral, bacterial and tuberculous pneumonia, asthma, acute respiratory insufficiency) and any central nervous system disorder (including stroke, haemorrhage, infection, trauma and psychosis). Rarer causes are sometimes identified.³⁻⁶ Diagnostic criteria include: (1) hyponatraemia <135 mmol/L and decreased plasma osmolality <275 mOsm/kg; (2) inappropriate urine osmolality >100 mOsm/kg; (3) urine sodium concentration >30 mmol/L with normal dietary salt and water intake; (4) clinical euvoalaemia as defined by the absence of signs of hypovolaemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) and hypervolaemia (subcutaneous oedema, ascites); (4) absence of renal, adrenal, thyroid and pituitary insufficiency; (5) no use of diuretics in the preceding week; (6) normal renal function.^{2 3} The treatment of hyponatraemia in SIAD involves three components: (1) treatment of the underlying disease when possible; (2) Initial therapy to raise serum sodium; and (3) prolonged therapy when persistent SIAD is present. A number

of treatment options are available to correct hyponatraemia, with fluid restriction, salt administration and vasopressin receptor antagonists being most important, always paying attention on the rate of correction.^{3 6} Other treatments have been used including demeclocycline, lithium and urea.^{3 7 8}

CASE PRESENTATION

A 75-year-old woman was admitted to our emergency department with symptoms of productive cough and dyspnoea. The patient had been well until 6 days earlier, when productive cough and dyspnoea gradually started developing. She was observed 2 days earlier by her primary care provider, who prescribed her amoxicillin 1000 mg 8/8 h for an empiric diagnosis of respiratory infection. This, however, did not lead to any clinical improvement. She denied orthopnoea, nocturnal paroxysmal dyspnoea, chest pain and urinary or digestive symptoms. She had a history of ischaemic and hypertensive heart disease with New York Heart Association (NYHA) classification II heart failure, permanent atrial fibrillation, hypercholesterolaemia and cerebrovascular disease with an ischaemic cerebral event 3 years earlier, without neurological sequelae. Medication included amlodipine 5 mg, simvastatin 20 mg, propafenone 150 mg, three times a day, acetylsalicylic acid 150 mg, once daily, lisinopril 20 mg/hydrochlorothiazide 12.5 mg and acenocumarol 4 mg according to international normalised ratio (INR). No allergies were known. The patient had a sedentary life and there was no tobacco, alcohol or illicit drugs use. Before retirement, she worked as an office administrator. She denied contact with domestic animals and recent travels to other countries. On examination, the patient was alert, afebrile, with severe dyspnoea (oxygen saturation of 85% and respiratory rate of about 30/min), heart rate of 95 bpm and blood pressure of 123/70 mm Hg, with wheezing and rales in the lower half of the right lung. There was no other relevant sign on physical examination. At this time, the main differential diagnoses considered were an acute pulmonary infection, since she presented with productive cough and dyspnoea of 6 days' duration, and acute decompensated heart failure caused by the infection. However, the patient did not present signs of congestion, such as oedemas, orthopnoea or nocturnal paroxysmal dyspnoea. We considered a pulmonary thromboembolic disease as a less probable diagnosis because the patient was anticoagulated with acenocumarol.

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Ancillary tests revealed a normal haemogram with a haemoglobin level of 12.4 g/dL, a white cell count of 6300/ μ L, with 66.4% neutrophils, 23.9% lymphocytes, 7.3% monocytes and 2.1% eosinophils and a platelet count of 220 000/ μ L. Creatinine level was 0.30 mg/dL, serum urea 19 mg/dL; sodium level was 116 mmol/L, potassium 3.7 mmol/L and chloride 78 mmol/L. Erythrocyte sedimentation rate was 31 mm/h and C reactive protein 3.15 mg/dL (reference range <0.5 mg/dL). The INR was 2.5.

The patient also presented with hypoxaemia (60 mm Hg in blood arterial gas at rest and no supplementary oxygen). Chest radiography disclosed an interstitial pattern in the lower right lobe and ECG showed atrial fibrillation with a ventricular rate of 93/min. She was admitted to the internal medicine ward with the diagnosis of lower pulmonary infection and hyponatraemia. She was initiated on empiric treatment with amoxicillin/clavulanic acid after obtaining sputum specimens for culture examination.

OUTCOME AND FOLLOW-UP

During the hospital stay, hydrochlorothiazide was stopped and the hyponatraemia was investigated. We excluded non-hypotonic hyponatraemia as the serum osmolality was less than 275 mOsm/kg. Within the group of hypotonic hyponatraemia, three types can be considered, depending on the extracellular fluid volume: hypotonic hyponatraemias with decreased, normal or increased extracellular fluid volume. In the presence of hypotonic hyponatraemia, extremely dilute urine would be physiologically expected. However, in the case of nonsuppressed vasopressin activity, urine osmolality usually exceeds serum osmolality, which was the case in our patient. As the urine osmolality was over 100 mOsm/kg, we excluded excess water intake, such as primary polydipsia and low solute intake, as causes of the hyponatraemia. Urine sodium concentration under 30 mmol/L suggests causes associated with low effective arterial blood volume such as heart failure, liver cirrhosis and nephrotic syndrome (extracellular fluid expanded), diarrhoea, vomiting and third spacing (extracellular fluid reduced).¹ Our patient had a urine sodium concentration over 30 mmol/L. The next step was to exclude diuretics and kidney disease. The investigation of hyponatraemia in our patient was made after suspension of diuretics. There was no history of renal disease and the evaluation of her renal function markers was normal. She had normal extracellular fluid volume, so we considered and discarded causes of hyponatraemia from decreased extracellular fluid volume, such as renal salt wasting, cerebral salt wasting and primary adrenal insufficiency and focused on causes with normal extracellular fluid. At this time our main differential diagnoses were SIAD, secondary adrenal insufficiency and hypothyroidism. Our investigation of hyponatraemia was consistent with SIAD: our patient met all the essential diagnostic criteria, which included serum osmolality 243 mOsm/kg, urine osmolality 477 mOsm/kg, urine sodium concentration 48 mmol/L, with clinical euvoemia, and absence of adrenal, thyroid, pituitary (normal levels of adrenocorticotrophic hormone, cortisol, thyroid stimulating hormone and thyroid hormones) and renal insufficiency. The patient also met some of the supplemental criteria for SIAD such as a serum uric acid of 3.5 mg/dL (<4 mg/dL), serum urea of 19 mg/dL (<21.6 mg/dL) and fractional sodium excretion of 0.73% (>0.5%). The diagnosis of SIAD was admitted in the context of respiratory infection. Because of severe hyponatraemia (116 mmol/L) despite water restriction, the patient was started on sodium reposition with sodium chloride 1.3%, which presented a good initial response. Nevertheless, recurrence after discontinuation occurred (minimum 112 mmol/L),

with confusion and deep somnolence. Treatment with urea 30 g/day was initiated. It was well tolerated and presented an excellent response (Na 134 to 137 mmol/L).

Regarding the lower pulmonary infection, the sputum culture examination obtained in the emergency department identified *Haemophilus influenza* sensitive to clarithromycin. Treatment with amoxicillin/clavulanic acid was suspended and clarithromycin was initiated directed to the *Haemophilus influenza*. The respiratory symptoms initially improved; however, by the seventh day of treatment with clarithromycin, the patient initiated a productive purulent cough and presented with a radiological infiltrate at the right lower lobe. There was also an increase in inflammatory markers (C reactive protein of 17.2 mg/dL). A diagnosis of nosocomial pneumonia was assumed. New sputum specimens were obtained for culture examination and empiric treatment with piperacilin/tazobactam 4.5 g every 6 h was initiated, with frank improvement. The sputum culture examination did not identify any pathogenic agent. Direct smear examination of sputum by Ziehl-Neelsen staining technique and cultural examination of *Mycobacterium tuberculosis* from sputum samples were both negative. There was complete resolution of respiratory symptoms after treatment with piperacilin/tazobactam. Throughout her treatment, the patient never presented signs of congestion.

Despite the improvement of the respiratory condition, there was no improvement of the hyponatraemia, which led to the investigation of alternative causes.

During a more thorough examination, evidence of an anterior cervical adenopathy, about 2.5 cms in diameter, painless, non-adherent and rubbery in consistency, was found. As differential diagnosis we considered infections, neoplastic disorders and non-infectious inflammatory disorders. Reactive viral lymphadenopathy is the most common cause of cervical lymphadenopathy, especially in children. Upper respiratory infections caused by adenovirus, rhinovirus or enterovirus can be associated with cervical lymphadenopathies. Localised lymphadenopathies can also be due to some systemic infections, such as infectious mononucleosis caused by Epstein-Barr virus (EBV), cytomegalovirus (CMV) and HIV. Bacterial infections can also be associated with localised or generalised lymphadenopathies, such as streptococcal pharyngitis and skin infections, as well as tularaemia, brucellosis and cat-scratch disease. The patient did not have any epidemiological context or clinical manifestations suggestive of these last infections. Serological tests for HIV, syphilis, hepatitis B and hepatitis C virus were negative. Serological tests for EBV and CMV were IgM negative and IgG positive. It was also important to exclude mycobacterial infections. Non-infectious inflammatory disorders are less common than the other aetiologies of lymphadenopathy, and include sarcoidosis, systemic lupus erythematosis, Castleman disease, Kawasaki disease and Kikuchi's disease. Antinuclear antibodies anti-neutrophil cytoplasmatic antibodies and antiglomerular basement membrane antibody were negative. Complement C3 and C4, immunoglobulins A, G, E and M were normal. Regarding neoplastic disorders, it was important to exclude metastatic head and neck cancer, as well as a lymphoproliferative disease. The patient was observed by an otolaryngologist who found no alterations on clinical examination. Electrophoresis of plasma proteins was without alterations.

A cervical/thoracic/abdominal and pelvic CT was performed and confirmed the presence of a jugular-digastric adenopathy of 10×8 mm. There was no other relevant alteration. An excisional biopsy was performed, revealing a non-necrotising granulomatous lymphadenopathy. Flow cytometric immunophenotyping

showed no alterations. A tuberculin skin test was performed and an induration of >25 mm with central necrosis appeared. The mycobacterial cultural examination of the cervical ganglia revealed *Mycobacterium tuberculosis complex* at day 22, which was susceptible to all first line antituberculosis treatment. Direct and cultural examinations for mycobacteria of bronchoalveolar lavage were negative. The patient was started on isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1500 mg/day and etambutol 800 mg/day. She was also given piridoxin 150 mg and allopurinol 100 mg/day. This treatment led to hepatotoxicity with elevation of serum aminotransferase (maximum aspartate aminotransferase of 1064 U/L (reference range 17–59 U/L) and alanine aminotransferase of 386 U/L (reference range 21–52 U/L)) and hyperbilirubinaemia (maximum 2.10 mg/dL). All four drugs were stopped and then reinitiated according to Portuguese Society of Pulmonology recommendations, when hepatic function was recovered.⁹ There was no other side effect reported and the treatment was completed in 9 months. The patient became asymptomatic.

During antituberculosis treatment, two attempts to taper therapy with urea were made. The first attempt was made after 6 months of treatment but was unsuccessful. After 8 months of treatment, the tapering of urea was possible and at the 10th month it was successfully suspended.

DISCUSSION

Hyponatraemia is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It occurs in up to 30% of hospitalised patients.¹ True hyponatraemia is associated with hyposmolality. Non-hypotonic hyponatraemia does not cause brain oedema and patients should be evaluated for the presence of hyperglycaemia and correct the measured sodium concentration for the serum glucose level if the latter is increased. Pseudohyponatraemia is a laboratory artefact that occurs when an abnormally high concentration of lipids or proteins in the blood interferes with accurate measurement.¹ Several classification systems have been used for the aetiology of hyponatraemia with low serum osmolality, the most common being according to volume status.¹⁰ In euvoalaemic patients, SIAD is a prevalent disorder.² Other causes that are important to exclude are renal failure, use of thiazide diuretics, hypothyroidism and hypocortisolism. SIAD was first described by Schwartz *et al*¹¹ in 1957. The wide range of associated disorders makes the diagnosis a challenging one. The reported patient was initially considered to have SIAD secondary to respiratory tract infection. When hyponatraemia did not improve after resolution of acute infection, it was important to consider alternative diagnoses. A thorough examination made the diagnosis of tuberculous lymphadenitis possible. There are reports of SIAD associated with pulmonary, central nervous system and miliary *Mycobacterium tuberculosis* infection.^{12–14} We did not find any published association between tuberculous lymphadenitis and SIAD, but the resolution of hyponatraemia after treatment of that disorder makes this association presumable.

We decided to treat the patient with urea. During the last few years, it has been used as an option for treatment of refractory hyponatraemia associated with SIAD in our department. Demeclocycline is not available in Portugal. Lithium has important side effects such as increased thirst, nausea, diarrhoea and arrhythmias.⁷ Tolvaptan (a vasopressin receptor antagonist) is available in Portugal but not in our department, and its long-term effects are not yet elucidated.² Decaux *et al*¹⁵ showed good results in the treatment of SIAD with urea, without important side-effects (limited to gastrointestinal discomfort).

Urea can be given orally, in powder or capsules and its flavour can be disguised with sugar or orange juice. Daily dose is determined by plasma sodium and can reach 60 g/day. No water restriction is needed.¹⁶ Urea acts by inducing osmotic water elimination and promoting passive sodium reabsorption in the ascending limb of the loop of Henle with progressive increase in plasma sodium and tonicity.¹⁶ Curiously, in animal models, urea seems to have neuroprotective effects during rapid correction of hyponatraemia.^{17–18} Pierrakos *et al*¹⁶ reported the use of urea for treatment of acute SIAD occurring after acute brain injury in an intensive care unit (ICU). Their results showed that urea was an effective and safe treatment for hyponatraemia in patients who develop SIAD, and persistent hyponatraemia after subarachnoid haemorrhage. Decaux *et al*¹⁹ also reported the treatment of euvoalaemic hyponatraemia with urea in the ICU. SIAD is the most common cause of hyponatraemia in the ICU. Urea was effective in treatment of hyponatraemia, and without side effects. Soupert *et al*²⁰ compared the efficacy, tolerability and safety of two oral vaptans with those of oral urea in patients with SIAD in a prospective, long-term study. They concluded that urea has an efficacy similar to that of vaptans for treatment of chronic SIAD. Tolerance was generally good for both agents.

This case emphasises the importance to consider alternative and rare causes in a patient presenting with SIAD when common aetiologies are excluded.

Learning points

- ▶ Syndrome of inappropriate antidiuresis (SIAD) is a common cause of hyponatraemia in hospitalised patients and when severe, may become a life-threatening condition.
- ▶ Our patient had a condition (tuberculous lymphadenitis) not previously identified as a cause of SIAD, but the temporal association between the two conditions makes it presumable.
- ▶ It is important to look for non-classic causes of SIAD when common aetiologies are excluded, because their treatment is essential in effective management of hyponatraemia.

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