CASE REPORT

SIADH and partial hypopituitarism in a patient with intravascular large B-cell lymphoma: a rare cause of a common presentation

Simeen Akhtar,¹ Edmund Cheesman,² Edward B Jude³

¹Department of Endocrine, Southport and Ormskirk Hospitals NHS Trust, Southport, UK

²Department of Pathology, Tameside Hospital NHS Foundation Trust, Ashton under Lyne, UK

³Department of Diabetes and Endocrinology, Tameside Hospital NHS Foundation Trust, Ashton under Lyne, UK

Correspondence to

Dr Edward B Jude, edward.jude@tgh.nhs.uk

SUMMARY

Hyponatraemia is a very common electrolyte abnormality with varied presenting features depending on the underlying cause. The authors report the case of a 75-year-old, previously fit, gentleman who presented with weight loss, lethargy and blackouts. He required four admissions to the hospital over an 8-month period. Investigations revealed persistent hyponatraemia consistent with a diagnosis of syndrome of inappropriate antidiuretic hormone secretion, macrocytic anaemia and partial hypopituitarism. Unfortunately, all other investigations that were performed failed to identify the underlying cause and a diagnosis of intravascular large B-cell lymphoma was only confirmed following postmortem studies. The authors recommend that endocrinologists should be involved at the outset in the management of patients with persistent hyponatraemia and that intravascular large B-cell lymphoma should be considered in the differential diagnosis of hyponatraemia.

BACKGROUND

Hyponatraemia is the most frequently encountered electrolyte abnormality in hospitalised patients. Incorrect diagnosis and management have an adverse effect on the outcome, and often, no cause can be identified despite extensive investigations. Intravascular large B-cell lymphoma, a rare form of non-Hodgkin's lymphoma, usually presents with extranodal involvement, and the absence of lymphadenopathy and tumour formation makes the diagnosis difficult. Many patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) are labelled as idiopathic, and uncommon causes should be considered in the differential diagnosis. We report a case of persistent hyponatraemia secondary to SIADH and partial hypopituitarism in whom a diagnosis of intravascular large B-cell lymphoma was made only after postmortem studies.

CASE PRESENTATION

A 75-year-old man presented with a 1-year history of rapid weight loss of 14 kg and increasing tiredness. He had been previously fit and well, played golf and looked after his grandchildren. He had several episodes of black-outs, when he was noted to be clammy, incontinent and, on one occasion, hypoxic. There was no witnessed seizure activity and recovery was spontaneous and quick. He was

admitted to hospital on four occasions over a period of 8 months.

At the time of his first admission to hospital in December 2009, he was noted to have a macrocytic anaemia (Haemoglobin 12.3 gm/dl, mean corpuscular volume 104 fl), secondary hypothyroidism (FT4 5.8 pmol/l, thyroid stimulating hormone 1.68 IU/l) and persistent low sodium (113–120 mmol/l). Further investigations for anaemia, including an oesophagogastroscopy, revealed angiodysplasia of the stomach. A bone marrow biopsy was considered by the haematologist but not performed as his haemoglobin had remained stable during the course of his admission. Serum and urine osmolality were 258 and 393 mosmol/kg, respectively, and urine sodium was 40 mmol/l, consistent with a diagnosis of SIADH. Short synacthen test was performed and the baseline serum cortisol level was 178 nmol/l rising to 618 nmol/l 30 min postsynacthen. CT scan of the brain was normal. He was fluid-restricted and started on demeclocycline which he was unable to tolerate. He was subsequently started on fludrocortisone and discharged after 4 weeks in hospital, with sodium of 123 mmol/l.

He required another admission in March 2010 when he was noted to be hypoxic at the time of his blackout. Sodium levels were normal on this occasion (136 mmol/l). Haemoglobin was 10.3 g/dl. d-Dimer was elevated and a subsequent ventilation perfusion scan suggested a low probability of pulmonary embolism. Clinically, it was felt that pulmonary embolism was unlikely, and he was discharged.

He was admitted again in May 2010 as there were concerns about the continued rapid deterioration in his health. He was getting increasingly confused and sodium was once again noted to be persistently low. He underwent CT scans of chest, abdomen and pelvis and an MRI of the pituitary which did not show any abnormality. His haemoglobin had decreased, ranging from 7.7 to 9.2 g/dl and repeat endoscopy showed once again multiple angiodysplasia. Myeloma screen was negative. At this point, he was referred for an endocrinology opinion and endocrine tests were performed. Short synacthen test was repeated and the baseline serum cortisol was 322 nmol/l with the 30 min postsynacthen level rising to 777 nmol/l. Further tests revealed partial hypopituitarism with low testosterone (0.6 ng/dl) and gonadotrophins; glucagon-stimulation test showed a reduced growth hormone response, but normal cortisol response (peak plasma cortisol level postglucagon—652 nmol/l).

To cite: Akhtar S, Cheesman E, Jude EB. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007147

He was started on testosterone and continued to take levothyroxine and fludrocortisone as before. His sodium improved but never normalised. He was discharged in August 2010 to a rehabilitation unit after almost 3 months in hospital.

OUTCOME AND FOLLOW-UP

Unfortunately, he continued to deteriorate and died 2 weeks later. A postmortem was carried out, and histology of the lungs, kidneys, adrenal glands and pituitary gland (figure 1) demonstrated large atypical lymphoid cells within small blood vessels, with a minor extravascular component. Immunohistochemistry showed these cells to be positive for CD20 (figure 2) and CD79a, markers of B-lymphocyte lineage. No solid lymphomatous component was identified. Overall, the histological features were consistent with intravascular large B-cell lymphoma.

DISCUSSION

Hyponatraemia in hospitalised patients is associated with increased morbidity, length of stay and mortality.¹ Clinical presentation is varied, depending on the underlying cause, and early referral to endocrinology team is advised as incorrect diagnosis and management errors result in adverse outcomes.²

Hyponatraemia secondary to SIADH is associated with malignancy but only a few reports show association of SIADH with lymphomas. Intravascular large B-cell lymphoma (also referred to as angiotropic large B-cell lymphoma) is rare, and diagnosis is often delayed owing to variable clinical presentations, with little or no evidence of tumour formation.³ Patients are usually elderly, of both sexes, with the median age being reported as 67 years.⁴ Patients can present with general fatigue, gastrointestinal symptoms, neurological symptoms, dyspnoea, oedema, urinary tract infection and skin eruptions. It can involve any organ including the central nervous system (CNS), pituitary, thyroid gland, adrenal glands, skin, bone marrow, liver, spleen and, rarely, even the eye. Various mechanisms have been proposed for the development of SIADH including excess anti-diuretic hormone secretion from lymphoma cells, involvement of CNS and endocrine glands or chemotherapy.

It is important to consider the possibility of rare causes of SIADH, including malignancy, when evaluating patients with vague symptoms and hyponatraemia secondary to SIADH, especially when investigations fail to identify any tumours. Pekic *et al*⁵ have reported a case of intravascular large B-cell lymphoma complicated with hypopituitarism, treated with immunochemotherapy which resulted in remission and gradual and late reversal of hypopituitarism. In our patient, deficiencies of thyroid stimulating hormone, testosterone and growth hormone

Figure 2 CD20 immunostaining of pituitary gland showing atypical B lymphocytes.

resulted from the involvement of the pituitary gland. Unfortunately, a bone marrow biopsy was not performed, which may or may not have suggested the diagnosis. A role for repeated bone marrow biopsies has also been suggested.⁶ Other organs, including the kidneys, liver and lungs are also potential targets for biopsies. In this case, investigations that could have been carried out and suggested the diagnosis of intravascular large B-cell lymphoma antemortem include measurement of serum lactate dehydrogenase, serum interleukin 6 and a skin biopsy. Random skin biopsy, even in the absence of skin lesions, can yield positive results, as sufficient samples can be obtained with little invasion.⁷ Positron emission tomography/CT has also been reported to show the characteristic pattern of fluorodeoxyglucose uptake in the lungs, kidneys and bones.⁸

This case highlights the difficulties in diagnosing intravascular large B-cell lymphoma antemortem and the extremely poor prognosis in most patients owing to delay in diagnosis. With advances in treatment of SIADH in terms of the availability of vasopressin receptor antagonists (tolvaptan), the use of the agent will help normalise sodium levels rapidly, though the recommendation is not to increase plasma sodium by more than 12 mmol/l in the first 24 h.^{9 10} Hyponatraemic patients not responding to fluid restriction could be given tolvaptan especially if patient remains symptomatic and/or the plasma sodium remains below 125 mmol/l.¹¹ The treatment of intravascular large B-cell lymphoma in the postrituximab era has shown some promise and, therefore, it is imperative that this diagnosis is considered and not missed in patients with an otherwise unexplained hyponatraemia, SIADH and endocrine hormone deficiencies as the outcome may be different if diagnosed antemortem.¹²

Figure 1 Pituitary gland showing large atypical lymphocytes within blood vessels.

Learning points

- ▶ Hyponatraemia is common and presents with varied clinical features depending on the underlying cause.
- ▶ Underlying cause of hyponatraemia should be actively sought and endocrinologists should be involved in the management of hyponatraemia.
- ▶ Intravascular large B-cell lymphoma is difficult to diagnose as there is little or no tumour formation.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Waikar SS, Mount DB, Curham GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009;122:857–65.
- 2 Huda MS, Boyd A, Skagen K, *et al.* Investigation and management of severe hyponatraemia in a hospital setting. *Postgrad Med J* 2006;82:216–19.
- 3 Nakashima MO, Roy DB, Nagamine M, *et al.* Intravascular large B-cell lymphoma: a mimicker of many maladies and a difficult and often delayed diagnosis. *J Clin Oncol* 2011;29:e138–40.
- 4 Shimada K, Kinoshita T, Nao E, *et al.* Presentation and management of intravascular large B-cell lymphoma. *Lancet Oncol* 2009;10: 895–902.
- 5 Pekic S, Milicevic S, Colovic N, *et al.* Intravascular large B-cell lymphoma as a cause of hypopituitarism: gradual and late reversal of hypopituitarism after long-term remission of lymphoma with immunochemotherapy. *Endocrine* 2008;34:11–16.
- 6 Narimatsu H, Morishita Y, Saito S, *et al.* Usefulness of bone marrow aspiration for definite diagnosis of Asian variant of intravascular lymphoma: four autopsied cases. *Leuk Lymphoma* 2004;45:1611–16.
- 7 Namekawa M, Nakano I. Diagnosis of intravascular lymphoma: usefulness of random skin biopsies. *Brain Nerve* 2011;63:451–8.
- 8 Miura Y, Tsudo M. Fluorodeoxyglucose-PET/CT for diagnosis of intravascular large B-cell lymphoma. *Mayo Clin Proc* 2010;85:e56–7.
- 9 Sterns R, Nigwekar S, Hix J. The treatment of hyponatraemia. *Semin Nephrol* 2009;29:282–99.
- 10 Hannaway RK, Cowie F, Jude E. Unusual case of hyponatraemia. *BMJ Case Rep* 2012 Aug 1. doi:pii: bcr0320126143.
- 11 Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion. *Endocrinol Nutr* 2010;57(Suppl 2):30–40.
- 12 Masaki Y, Dong L, Nakajima A, *et al.* Intravascular large B-cell lymphoma: proposed of the strategy for early diagnosis and treatment of patients with rapid deteriorating condition. *Int J Hematol* 2009;89:600–10.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow