Syndrome of inappropriate antidiuretic hormone secretion associated with bortezomib

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We observed severe hyponatremia in a patient who was treated with bortezomib for multiple myeloma. The patient was diagnosed with the syndrome of inappropriate secretion of antidiuretic hormone due to bortezomib.
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Introduction

Hyponatremia is frequently observed in hematologic patients and may lead to severe cerebral symptoms. Differential diagnosis of hyponatremia is broad. In subjects with no clinical signs for volume depletion or hyperhydration, it includes the syndrome of inappropriate antidiuretic hormone secretion (SIADH) which is characterised by reduced plasma osmolality with inadequately high urine osmolality. Major etiologies for an SIADH include drugs and malignancies.

Case Report

Since august 2012, a 64-year old black male patient was treated for his multiple myeloma. At that time, the patient had already suffered for several years from severe renal insufficiency due to nephroangiosclerosis and granulomatous interstitial nephropathy due to allopurinol. He was treated with hemodialysis between 2006 and 2008 and with renal allograft in 2008. He also suffered from hypertension, diabetes mellitus type 2 and hyperlipemia. For more than two years, the patient received continuous treatment with methylprednisolone 4 mg/d, mycophenolate mofetil, tacrolimus, gliquidon, losartan, nebivolol, association altizide and spironolactone, allopurinol, acetylsalicylic acid, moxonidine, and simvastatin. In 2007, a multiple myeloma IgG Kappa was diagnosed; a wait-and-watch policy was adopted. In 2012, a rapid increase of the M protein was observed with hypercalcemia and degradation of renal function. Since august 2012, the patient was treated with bortezomib in combination with dexamethasone: bortezomib 1.3 mg/m^2 SC and dexamethasone 40 mg PO at day 1,4,8,11 every three weeks. A partial response was observed after two cycles, i.e. the amount of M protein decreased by more than 50%. An amelioration of the patient's renal insufficiency and hypercalcemia was also observed. At this time, the patient had developed a polyneuropathy grade 1 and therefore the dose of bortezomib was reduced to 1 mg/m^2. Ten days after the last injection of the fourth cycle, he was hospitalised for dizziness. He was normohydrated with no oedema and his blood pressure was 130-80 mmHg, vigilance was normal and neurologic examination revealed no focal deficit. Laboratory evaluation showed severe hyponatremia (sodium: 116 mmol/L) with plasma osmolality of 238 mOsm/l (N: 275-300), eGFR from MDRD formula calculated at 83 ml/min/1.73m^2 with creatinine of 11.4 mg/L, urea of 0.44 g/L, uric acid of 32 mg/L, protein of 61 g/L, glycaemia of 1.22g/L, haemoglobin of 9.5g/L and haematocrit of 30%. The urinary osmolality was 500 mOsm/kg, the urinary sodium concentration was not measured. The diagnosis of SIADH was suspected and the patient was treated with IV administration of sodium chloride during 24 hours, diuretic interruption and then with fluid restric-

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Key messages for clinical practice

1. When neurologic disturbances or confusion are observed in a patient treated with bortezomib, sodium levels should be determined in order to eliminate the possible diagnosis of SIADH.
2. SIADH is a potential side-effect of bortezomib.

tion at home. Electrolytes improved within five days (serum sodium at day 4: 127 mmol/l) allowing him to be discharged from the hospital. At day eleven, serum sodium was 122 mmol/L, plasma osmolality 250 mOsm/Kg, natriuria and urinary osmolality 120 mmol/L and 527 mOsm/Kg respectively. Electrolytes normalised completely at day twenty: serum sodium was 133 mmol/L, plasma osmolality was 276 mOsm/kg and urinary osmolality was 231 mOsm/kg. One month later, the patient started on association altizide and spironolactone therapy because of onset of hypertension, without recurrence of hyponatremia. This evolution confirmed the diagnosis of SIADH and bortezomib was likely to be the cause of it. The treatment with bortezomib was stopped after four cycles because of this complication and owing to a worsening of the polyneuropathy (grade 3). Six months later, the patient is still in partial response with a 75% decrease of the M protein with normal creatinine and calcium levels, therapy was no longer necessary.

Discussion

The most common tumour associated with SIADH is small-cell lung carcinoma and several chemotherapeutic drugs could also induce SIADH: platinum compounds, some alkylating agents and vinca alkaloids. Our case reports a SIADH following myeloma therapy with bortezomib. Multiple myeloma has been associated with SIADH in only three cases.[1,2] In our case a tumour-related cause is very unlikely because hyponatremia was not observed at the time of diagnosis of multiple myeloma, but after treatment with bortezomib. Although the patient was also given a combination of the diuretic agents' altizide and spironolactone for more than two years, this is very unlikely to be the cause of the hyponatremia because no significant side effects were observed upon their use and after their reintroduction. Side effects of bortezomib mainly include polyneuropathy, thrombopenia, gastrointestinal symptoms and herpes-zoster reactivation, nevertheless electrolytic disturbance has been reported in 1-10% of these patients.[3] Like vinca alkaloids, bortezomib exhibits peripheral neurotoxicity that involves the autonomic nervous system and may be accompanied with SIADH, these neurotoxic effects are dependent on cumulative doses and on the frequency of administration. In the past, the association of bortezomib with SIADH has only been reported once; in this patient, hyponatremia occurred after the eighth injection.[4]

In conclusion, when neurologic disturbances or confusion are observed in a patient treated with bortezomib, sodium levels should be determined in order to eliminate the possible diagnosis of SIADH.

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