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Successful treatment by tolvaptan of the syndrome of inappropriate antidiuretic hormone secretion that may be associated with chemotherapy-induced tumour lysis in a patient with small-cell lung carcinoma

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Abstract

Here, we report the case of a patient with small-cell lung carcinoma (SCLC) who developed the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This syndrome may be associated with chemotherapy-induced tumour lysis. Our patient was successfully treated with tolvaptan. A 70-year-old man was diagnosed with SCLC and was treated with carboplatin and etoposide. Episodes of hyponatremia occurred after every four cycles of chemotherapy that achieved tumour reduction; however, the hyponatremia was improved by temporary administration of tolvaptan. In SIADH associated with chemotherapy-induced tumour lysis, tolvaptan may improve hyponatremia and enable the continued administration of effective chemotherapy.

Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is an important complication in a patient with small-cell lung carcinoma (SCLC) and is usually diagnosed before treatment. Both antitumor agents and tumour lysis can cause SIADH after chemotherapy. Treatment of hyponatremia with SIADH is crucial to continue chemotherapy. Hypertonic saline and fluid restriction can be used to improve hyponatremia, and recently, tolvaptan (a vasopressin-2-receptor antagonist) has been reported to improve SIADH in SCLC patients [1]. However, there have been no reports of SIADH associated with chemotherapy-induced tumour lysis treated with tolvaptan. We describe a case of an SCLC patient with decreases in sodium levels that developed after four cycles of chemotherapy each and that was improved by tolvaptan.

Case Report

A 70-year-old man who had been treated with amlodipine for hypertension was referred to our hospital because of coughing for 2 months. A chest X-ray showed upper lung field infiltration and an abnormally high position of the diaphragm (Fig. 1). Chest computed tomography (CT) revealed a mass lesion in the right upper lobe and pleural fluid. Haematological examination showed normal sodium levels of 142 mEq/L. Serum levels of pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) were 36,700 pg/mL and 306 ng/mL, respectively. Cytopathological examination of the pleural fluid indicated small-cell carcinoma. Staging revealed hepatic metastasis, but magnetic resonance imaging (MRI) of the head showed no metastasis.

Chemotherapy with carboplatin (AUC = 5) and etoposide (100 mg/m^2) was initiated. The patient's serum sodium levels decreased, and 11 days after initiation of

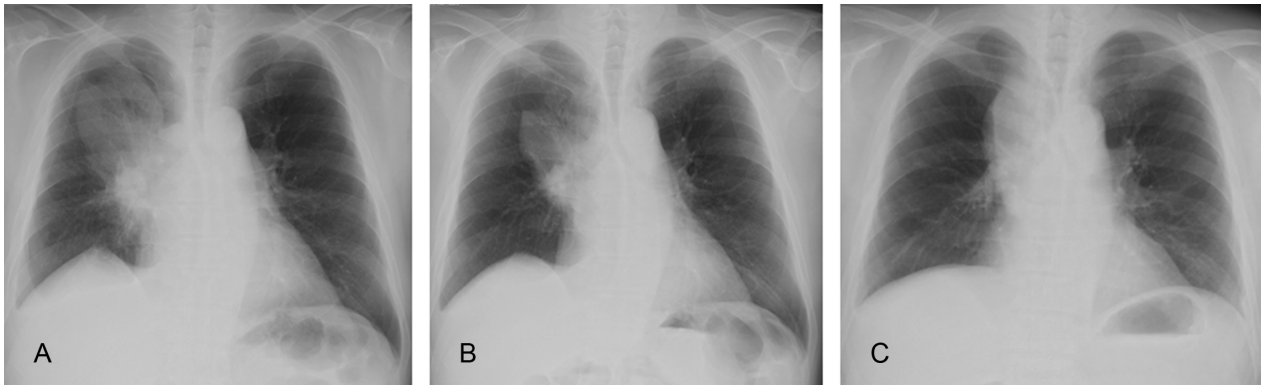

Figure 1. Chest X-ray showed upper lung field infiltration at diagnosis (A). After one cycle of carboplatin and etoposide (B). After four cycles of carboplatin and etoposide (C).

chemotherapy, he developed asymptomatic hyponatremia (114 mEq/L), with a decreased serum osmolarity of 239 mOsm/L (Fig. 2). His thyroid, renal, and adrenal functions were normal. His urine osmolarity was 538 mOsm/L, and his urine sodium was 112 mEq/L. His plasma antidiuretic hormone secretion (ADH) was 6.1 pg/mL, which is unusual for hyponatremia. A diagnosis of SIADH was made based on the accepted diagnostic criteria [2].

Hypertonic saline infusion and fluid restriction did not result in a sufficient improvement of his serum sodium level. Subsequently, those treatments for hyponatremia were discontinued, and the administration of low doses of tolvaptan (7.5 mg/day) was started. His serum sodium level was improved after initiation without an excessive increase (> 12 mEq/L over 24 h).

After 5 days, the tolvaptan was stopped, and his serum sodium level normalized 10 days later. A chest X-ray showed a reduction in tumour size, and the serum level of ProGRP was 6650 pg/mL, indicating that the chemotherapy was effective. We decided to continue carboplatin and etoposide. His second to fourth cycles of chemotherapy induced hyponatremia repetitively, and short-term tolvaptan improved his hyponatremia. He received a total of four cycles of carboplatin and etoposide, and then, tolvaptan was stopped. After a month, CT showed that the hepatic metastasis had increased in size, and the hyponatremia had recurred, suggesting the tumour had the ability to produce ADH. Hypertonic saline infusion and fluid restriction were not sufficient to improve his serum sodium level, but administration of tolvaptan improved his hyponatremia.

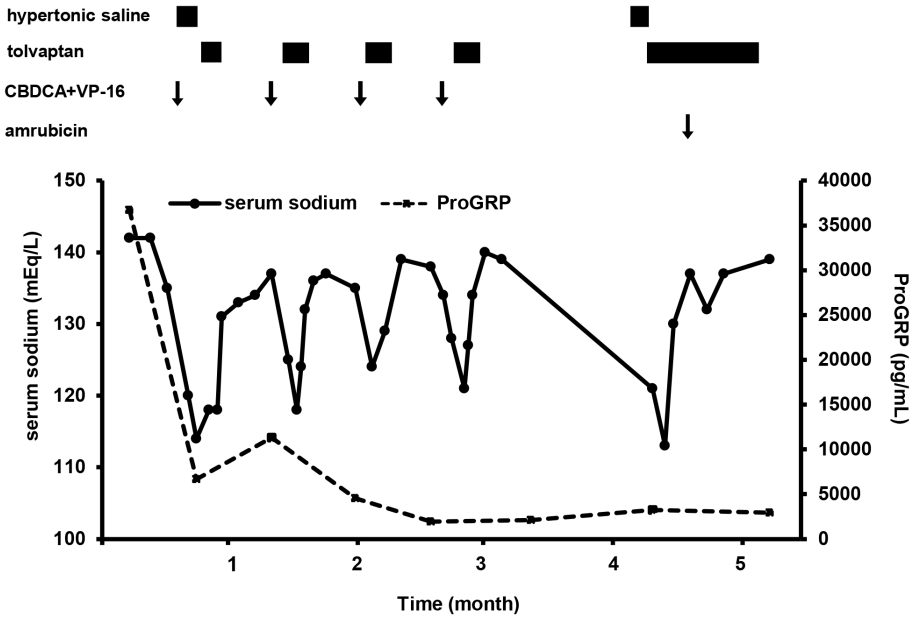

Figure 2. Clinical course of the patient. In the upper part of the diagram, each drug used for the treatment of SIADH and small-cell lung carcinoma is shown. In the lower part, transitional serum levels of sodium and pro-gastrin-releasing peptide (ProGRP) are demonstrated.

He was administered amrubicin (35 mg/m^2) as second-line chemotherapy, and hyponatremia did not occur during the continuation of tolvaptan treatment.

Discussion

We have described a case of SIADH that was treated by tolvaptan following effective chemotherapy, which may be associated with chemotherapy-induced tumour lysis. In such cases, tolvaptan may alleviate hyponatremia and enable the continuation of effective chemotherapy.

SIADH has been reported in approximately 10% of patients with SCLC [3]. Hyponatremia is usually detected on presentation as paraneoplastic SIADH, caused by the release of ADH/ADH-like substances from the tumour. Hyponatremia can improve with tumour regression by effective chemotherapy. Even though SIADH resolves with chemotherapy, hyponatremia often recurs at the time of tumour relapse [4]. In this case, SIADH occurred after effective chemotherapy, although hyponatremia did not occur before the first course of chemotherapy. It is rare for hyponatremia to occur after chemotherapy compared to before chemotherapy. We presumed that the cause of SIADH was an administered drug (carboplatin or etoposide) or chemotherapy-induced tumour lysis. However, it is difficult to differentiate the cause because both are expected to occur after effective chemotherapy, and both improve after the treatment course. One month after the fourth cycle of chemotherapy, SIADH recurred with tumour progression, suggesting that the growing tumour, which had been reduced by chemotherapy, could produce ADH. Subsequent recurrence and concurrent SIADH without chemotherapy indicated that an anticancer drug was not implicated at the time of tumour relapse. The clinical course lent support to the hypothesis that the previous episode of SIADH was not due to an anticancer drug. Therefore, we diagnosed the patient with SIADH that was induced by tumour lysis.

Tolvaptan is sufficient to stabilize sodium levels in SIADH associated with chemotherapy-induced tumour lysis. Retrospective data showed that hyponatremia and the lack of correction of sodium can lead to a poor outcome in SCLC patients [5]. Correction and stabilization of the sodium levels are required before continuing chemotherapy treatment [1]. In general terms, hypertonic saline and fluid restriction are first administered to correct hyponatremia in SIADH. Pharmacology therapy such as tolvaptan has been effective in SIADH when those therapies are insufficient. In SCLC patients with SIADH, tolvaptan has been reported to achieve correction of the sodium level and commencement of chemotherapy [1].

In the present case, hypertonic saline and fluid restriction did not correct the sodium level sufficiently, whereas tolvaptan did. It has been reported that fluid restriction [6] and fludrocortisone [7] are effective to treat SIADH associated with chemotherapy-induced tumour lysis. However, to the best of our knowledge, there have been no previous reports of cases with SIADH associated with chemotherapy-induced tumour lysis treated with tolvaptan. In the present case, despite severe hyponatremia for which control by hypertonic saline and fluid restriction was inadequate, we decided to continue chemotherapy and completed four cycles with tolvaptan treatment.

In SIADH associated with chemotherapy-induced tumour lysis, tolvaptan may increase the possibility of continuing effective chemotherapy.

Disclosure Statement

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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