

A rare case of sorafenib-induced severe hyponatremia

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Abstract

Background: Sorafenib is an anti-angiogenic tyrosine kinase inhibitor used to treat patients with renal cell cancer and advanced hepatocellular cancer. Common adverse effects of sorafenib are rash, diarrhea, nausea, and abnormal liver function test and hand-foot syndrome.

Case presentation: Here, we present a case of a 90-year-old male who was prescribed sorafenib after being diagnosed with hepatocellular cancer. At 1 week after sorafenib initiation, he was admitted to the emergency room for an evaluation of weakness. The patient had hyponatremia, a common electrolyte abnormality seen in cancer patients. His hyponatremia improved when the sorafenib was stopped, suggesting that this was a rare case of hyponatremia induced by sorafenib.

Conclusion: Although sorafenib is used in the treatment of hepatocellular cancer, it can cause life-threatening complication such as hyponatremia. Early identification of the cause of hyponatremia can prevent serious adverse event.

Keywords

Sorafenib, hyponatremia, hepatocellular cancer, weakness

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Introduction

Sorafenib is a chemotherapeutic drug used to treat hepatocellular cancer, renal cell cancer, differentiated thyroid cancer, angiosarcoma, and gastrointestinal stromal tumors.^{1,2} Of these, sorafenib is most beneficial to patients with hepatocellular cancer without extrahepatic spread, particularly those without pulmonary metastasis.³ Importantly, hepatocellular cancer is the third leading cause of cancer-related deaths, with increasing mortality rates.⁴ The annual incidence of hepatocellular cancer is also increasing steadily, and in 2014 it was 6 per 100,000.⁵

Sorafenib acts by inhibiting tyrosine kinases, including the proangiogenic vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR), and Raf family kinases.⁶ Common adverse effects of sorafenib are rash, diarrhea, and hand-foot syndrome. Other less common adverse effects include elevated blood pressure, leukopenia, nausea, vomiting, abnormal liver function test, hypophosphatemia, and depression.^{7,8} Hemorrhagic and cardiac events have also been reported with sorafenib.⁹ Hyponatremia is also an uncommon adverse effect of sorafenib.

The mechanism of drug-induced hyponatremia includes reset osmostat, sodium water homeostasis, inappropriate secretion of antidiuretic hormone, and renal salt wasting syndrome. In this case report, we describe a rare case of sorafenib-induced hyponatremia, a condition defined by low serum sodium concentrations.

Case presentation

The patient was a 90-year-old male with a past medical history of coronary artery disease, diabetes mellitus, benign prostatic hyperplasia, atrial fibrillation, and hepatocellular cancer

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Table 1. Serial measurements of serum electrolytes.

	One week before starting sorafenib	Day 1 of admission	Day 2	Day 3	Day 5	Day 7	Day 9
Sodium (mmol/L) (135–145)	137	114	119	125	129	135	136
Potassium (mmol/L) (3.7–5.3)	4.6	5	3.7	3.6	4.2	3.8	3.7
Blood urea nitrogen (mg/dL) (9–20)	16	23	16	14	15	15	14
Creatinine (mg/dL) (0.6–1.2)	0.9	0.6	0.5	0.5	0.7	0.6	0.5

Table 2. Laboratory values at the time of admission.

Serum osmolarity (mOsm/kg)	261 (275–305)
Urine osmolarity (mOsm/kg)	240
Urine sodium (mEq/L)	<5 (30–90)
Serum sodium (mEq/L)	114 (135–145)
Thyroid-stimulating hormone	4.1 (0.4–4.6)
Serum cortisol (mg/dL)	16.5 (10–20)
Serum protein (g/dL)	7.2 (6.2–8.2)
Serum uric acid	6.5 (3.5–8.5)

came for the evaluation of weakness. His home medications included aspirin, metoprolol, tamsulosin, glipizide, glucophage, eliquis, and acarbose. He quit smoking 5 years prior to admission and had a 30-pack-year smoking history, occasionally drank alcohol, and did not use any recreational drugs. He denied abdominal pain, nausea, vomiting, or diarrhea. He also reported no recent sickness exposure or travel.

At 1 month prior to admission, he underwent magnetic resonance imaging (MRI) of his abdomen following complaints of abdominal pain. This revealed a mass in his right inferior hepatic lobe measuring 8 cm. Later, a computed tomography–guided biopsy of the mass demonstrated the scirrhous variant of hepatocellular cancer. As the patient was not considered to be a surgical candidate, he was started on sorafenib for his hepatocellular cancer.

He was admitted to the hospital for an evaluation of weakness 1 week later. A physical examination revealed that the patient was of thin build, not in respiratory distress, afebrile with a temperature of 97°F, a heart rate of 87 beats per minute, a blood pressure of 108/60 mmHg, a respiratory rate of 12 breaths per minute, and an oxygen saturation of 94% on 2 L of oxygen via a nasal cannula. A chest examination indicated that he had bilateral bronchial breath sounds, while a cardiovascular examination confirmed that his heart sounds were normal. His abdomen was soft upon palpation, with hepatomegaly noted, and his neurological examination was unremarkable.

Laboratory analysis performed 1 week prior to starting sorafenib and subsequent values after sorafenib discontinuation are shown in Table 1 and are notable for hyponatremia. Further work-up of hyponatremia, including serum osmolarity, serum uric acid, urine sodium, urine specific gravity (1.021), thyroid-stimulating hormone, serum cortisol, and total protein, is shown in Table 2.

Our initial assessment concluded that sorafenib induced hyponatremia, so the drug was discontinued. After starting the patient on 3% saline, his sodium levels improved slowly. Other common causes of hyponatremia were excluded, supporting our initial assessment that this was a rare case of hyponatremia secondary to sorafenib. Because the patient was a poor candidate for any intervention for his hepatocellular cancer, he was accepted to hospice.

Discussion

In this report, we describe a rare case of a patient with hepatocellular cancer presenting with sorafenib-induced hyponatremia. Hyponatremia is a common electrolyte abnormality seen in cancer patients and is defined by serum sodium levels less than 135 mEq/L.¹⁰ Joint European guidelines classify hyponatremia as mild if serum sodium is 130–134 mmol/L, moderate if serum sodium is between 125 and 129 mmol/L, and profound or severe hyponatremia if serum sodium is less than 125 mmol/L.¹¹

This condition most commonly results from an inability to suppress antidiuretic hormone (ADH). Hyponatremia can be classified as hypotonic, hypertonic, or isotonic, where hypotonic hyponatremia is defined by an excess of water relative to sodium. It can also be hypervolemic, euvolemic, or hypervolemic.¹²

Hyponatremia, though a common electrolyte abnormality in cancer patients, not only has an adverse prognostic factor, but is also a risk factor for poor outcomes.¹³ Hyponatremia in hepatocellular cancer patients with cirrhosis is associated with shorter survival and more complications.¹⁴ Symptoms of hyponatremia are fatigue, lethargy, weakness, headache, dizziness, ataxia, muscle cramps, nausea, vomiting, decrease in cognition, attention deficit, confusion, and non-cardiogenic pulmonary edema. Acute hyponatremia may also lead to seizures, respiratory arrest, and brain herniation.^{15,16}

In cancer patients, the main cause of hyponatremia is excess production of arginine vasopressin by cancerous tissue,¹⁰ but it can be associated with multiple factors, including chemotherapy, pain, narcotic medications, nausea, vomiting induced by chemotherapy, and physical or emotional stress.¹⁷ The proportion of hyponatremia cases specifically related to tumors is almost 14%. In these cases, the most common causes of hyponatremia are volume depletion and inappropriate ADH secretion.

Drugs associated with hyponatremia include diuretics, antidepressants, antiepileptics, oxytocin, and angiotensin-converting enzyme inhibitors.¹⁸ Chemotherapeutic agents that can cause hyponatremia are vincristine, vinblastine, bleomycin, etoposide, cyclophosphamide, cisplatin, and mitomycin.¹⁹ Cisplatin-based chemotherapy may cause hyponatremia secondary to the syndrome of inappropriate ADH secretion and renal salt wasting syndrome. Increased levels of beta-2 microglobulin in urine are seen in renal salt wasting syndrome which differentiates it from the syndrome of inappropriate ADH secretion.²⁰

In patients with chronic liver disease, patients classified as Child–Pugh B had worse survival and efficacy with sorafenib than Child–Pugh A.²¹ A study by Llovet et al.²² showed that treatment with sorafenib prolonged patient median survival and delayed hepatocellular cancer progression by 3 months.

A study performed by Berardi et al. showed an increased risk of hyponatremia in cancer patients who were treated with biological agents. They grouped high-grade hyponatremia into two categories: one group was on inhibitors of angiogenesis like sorafenib, brivanib, and pazopanib and the other group was on anti-epithelial growth factor receptor tyrosine kinase inhibitors like cetuximab or gefitinib. The highest relative risk of high-grade hyponatremia was seen in brivanib (relative risk (RR)=6.5), sorafenib (RR=2.4), and vorinostat (RR=2.1).²³

In a phase II trial by Lalami et al. evaluating the safety of sorafenib in patients with recurrent or metastatic squamous cell cancer of head and neck, grade III and IV toxicities were lymphopenia, hyponatremia, hypophosphatemia, hand-foot syndrome, and fatigue. Among these toxicities, sorafenib-induced hyponatremia was seen in nine patients, accounting for a rate of 39%.²⁴

A prospective study performed by Huo et al. incorporated serum sodium levels into a model for end-stage liver disease (MELD) to enhance its prognostic ability for cirrhosis. In patients with hepatocellular carcinoma, the MELD-Na score is an independent predictor for long- and short-term mortality. In cirrhotic patients, hyponatremia indicates liver decompensation and is associated with an increased risk of mortality. The MELD-Na score was divided into low (score less than 10), intermediate (score between 10 and 20), and high (score more than 20). Patients with a higher MELD-Na score had lower serum sodium levels. When the MELD-Na score was between 10 and 20, there was a 2.1-fold risk of death, and when the score was more than 20, the risk of death was increased 7.5-fold. Although Child–Turcotte–Pugh, MELD, and MELD-Na scores were all significant predictors of 6-month mortality in univariate analysis, only MELD-Na scores were an independent predictor of mortality in multivariate analysis. This study confirms that a MELD-Na score serves as a better prognostic predictor and a more reliable parameter for reflecting the severity of cirrhosis in hepatocellular cancer patients.²⁵

Hyponatremia as a side effect of sorafenib is rare and has been reported in only one other study.²⁶ Other common side effects of sorafenib are renal impairment, hypertension, thromboembolism, thyroid dysfunction, bleeding rash, hand-foot skin reaction, muscle wasting, and encephalopathy.^{27,28} Although hand-foot skin reaction was the most common adverse reaction of sorafenib in phase I and phase II trials done by Naito et al.,²⁹ hyponatremia was seen in 6 out of 21 patients.

The mechanism by which sorafenib causes hyponatremia is not well understood. Possible mechanisms include decreasing papillary solute concentrations and increasing urinary osmolality, which may contribute to excess release of vasopressin. However, further studies are needed to confirm these mechanisms.

The common causes of hyponatremia were excluded in our patient. For example, our patient was not on a diuretic, antidepressant, or pain medication. He did not have heart failure or renal insufficiency, nor was he vomiting or having diarrhea which can cause electrolyte abnormalities. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is less likely because urinary sodium was less than 5 mEq/L. Dehydration was excluded because blood pressure, blood urea nitrogen levels, serum uric acid levels, and skin turgor were normal. Psychogenic polydipsia was excluded because he was not drinking excessive water. Hypothyroidism and Addison's disease were excluded because his thyroid function and cortisol levels were within a normal range. In our case, after excluding all of the above common causes of hyponatremia, sorafenib was discontinued, and there was a steady improvement in sodium levels.

Conclusion

Hyponatremia, an electrolyte abnormality commonly seen in cancer patients, can have serious neurological consequences. Quickly identifying the cause of hyponatremia can improve patient outcomes. In this case report, we describe a patient who had severe hyponatremia due to sorafenib and, upon discontinuation, his sodium levels improved.

Author contributions

M.K. and K.M. searched the literature and wrote the manuscript. M.K. conceived and edited the manuscript, supervised the patient treatment, and critically revised and edited the manuscript. F.T. was involved in patient care along with M.K. and K.M. All authors have made significant contributions to the manuscript and reviewed it before submission. All authors have confirmed that the manuscript is not under consideration for review at any other journal. All authors have read and approved the final manuscript.

Declaration of conflicting interests

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Ethical approval

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Informed consent

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