

Acquired Gitelman Syndrome Secondary to Bendamustine Use

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INTRODUCTION

Gitelman syndrome is an autosomal recessive disorder caused by inactivating mutations in the thiazide-sensitive sodium-chloride cotransporter (NCCT) that is expressed on the luminal surface of renal distal convoluted tubule cells.¹ First described in 1966,² Gitelman Syndrome is characterized by hypokalemic metabolic alkalosis, hypocalciuria, and low-normal blood pressure.³ It classically presents in late childhood or adulthood. Predominant symptoms include muscle cramps and weakness, tetany, salt craving, polydipsia, and fatigue.⁴

Acquired Gitelman-like syndromes also have been described. In Sjogren's syndrome, anti-NCCT autoantibodies are postulated to inhibit or disrupt NCCT function and thereby precipitate the classical syndromic findings. Likewise, a Gitelman-like syndrome has been described in patients treated with the DNA alkylating agent, cisplatin.⁵ Although the mechanism of cisplatin nephrotoxicity is not well characterized, morphologic studies in humans with cisplatin nephropathy demonstrate focal tubular necrosis predominantly in the distal convoluted tubule and the collecting ducts.⁶ These findings raise the possibility that cisplatin-induced damage to the distal convoluted tubule, and perhaps to the SLC12A3 gene (coding for NCCT) itself, may underlie the pathophysiologic process.

Herein we describe a case of suspected bendamustine-induced Gitelman-like syndrome in a patient undergoing treatment for follicular lymphoma with bendamustine and rituximab.

CASE PRESENTATION

A 51-year-old man presented with the chief complaint of severe bilateral leg cramping and weakness. Review of systems was positive for recent poor dietary intake. He denied polyuria, vomiting, diarrhea, weight loss, laxative use, diuretic use, licorice ingestion, or changes in home medications. His medical history was notable for essential

hypertension treated with combination amlodipine-benzepiril; active stage IV follicular lymphoma for which he was undergoing treatment with bendamustine and rituximab; and hypokalemia, which was diagnosed after completing his first cycle of bendamustine-rituximab and had been taking oral potassium chloride. At the time of presentation he had completed six cycles of bendamustine-rituximab therapy, with bendamustine last administered six weeks prior to presentation.

On physical examination, he appeared chronically ill but was in no acute distress. His vital signs were as follows: temperature 97°F, heart rate 80 beats/min, blood pressure 99/58 mmHg, respiratory rate 20 breaths/min, and O₂ saturation 100% on room air. Rest of physical exam was normal.

Laboratory studies showed serum sodium 140 meq/L, potassium 1.6 meq/L (normal 3.5 to 5 meq/L), chloride 97 meq/L, HCO₃⁻ 36 meq/L (normal 22 to 32 meq/L), BUN 10 mg/dL, creatinine 0.88 mg/dL, calcium 8.9 mg/dL, magnesium 1.6 meq/L (normal 1.5 to 2 meq/L) and phosphorus 1.6 mg/dL (normal 2.5 to 4.5 mg/dL). In addition, creatinine kinase was 2685 IU/L (normal 22 to 198 IU/L), and venous blood gas showed pH 7.43 and pCO₂ 59. The patient's electrocardiograms demonstrated sinus rhythm with a corrected QT interval of 457 ms and non-specific repolarization abnormalities. Subsequent work-up revealed urine creatinine 89 mg/dL, urine potassium 28 mEq/L, urine sodium 74 mEq/L, urine calcium 0.1 mg/dL, and urine chloride 93 mEq/L, which corresponded to a urine potassium-to-creatinine ratio of 31 mEq/g, a transtubular potassium gradient of 9.25, and a urine calcium-to-creatinine ratio of 0.001. 24-hour urine confirmed potassium wasting with a potassium excretion of 107 mEq. A diuretic screen was negative. Serum renin activity was elevated at 5.32 ng/ml/h. Serum aldosterone was <1 ng/dL. Other studies were notable for TSH 3.1 uIU/mL, corticosterone <20 ng/dL, and 11-deoxycortisol <20 ng/dL. Renal ultrasound demonstrated normal appearing kidneys with normal Doppler waveforms and flow velocities. The patient was treated with oral and intravenous potassium and as well as with spironolactone 50 mg by mouth daily. Potassium values returned to the normal range and his leg cramps and weakness improved. The patient's home amlodipine-benzepiril was discontinued.

One month after hospital discharge the patient was found to be hyperkalemic to 5.4 mEq/L (normal 3.5 to 5 meq/L);

potassium chloride and spironolactone were discontinued. To date, the patient has continued on rituximab maintenance therapy and remains in remission. He has received no further bendamustine therapy. Serum potassium and bicarbonate have been monitored routinely and remain in the normal ranges since discontinuation of spironolactone and supplemental potassium. He has remained normotensive for over 1 year since hospital discharge.

DISCUSSION

We described a case of hypokalemic metabolic alkalosis, hypocalciuria, hyperreninemia, and normotension in a patient undergoing treatment for follicular lymphoma with combined bendamustine and rituximab therapy. This constellation of metabolic abnormalities is similar to those seen in classical Gitelman syndrome. To our knowledge, this represents the first case of a bendamustine-induced Gitelman-like syndrome.

Bendamustine is a nitrogen mustard compound with a mechlorethamine moiety that engenders DNA alkylating properties.⁷ It has a volume of distribution of approximately 20–25 L,⁷ with disproportionately high levels of the drug found in the liver and kidney according to a mouse model.⁸ Cellular uptake of bendamustine is mediated – at least in part – by organic anion transporter proteins 1 and 3 (OAT1 and OAT3), which are expressed on lymphoma cells⁹ and in renal proximal tubule cells.¹⁰ Non-enzymatic hydrolysis is the predominant metabolic mechanism and results in metabolites with little or no cytotoxic activity.¹¹ Phase I metabolism by CYP1A2 also occurs and yields metabolites with cytotoxic activities that are less than or equal to that of the parent compound.¹² Neither inhibitors nor inducers of CYP1A2 appear to affect the bendamustine concentration-time profile.⁷ Elimination occurs largely via the urine, though only a small fraction of drug is excreted in its native form.¹¹ The effective half-life of bendamustine is approximately 40 minutes.⁷

Although bendamustine is not considered to be nephrotoxic per se, hypokalemia was reported in 5% of patients with rituximab-refractory indolent and transformed non-Hodgkin lymphoma being treated with bendamustine monotherapy.⁶ The exact mechanism is unknown. The dose of bendamustine used in these patients was 120 mg/m² on days 1 and 2 of 21-day cycle, with dose reduction to 90 mg/m² if severe toxicities were identified, defined as having either life-threatening adverse events or severe non-life-threatening events that warrant hospitalization. Due in part to the above findings, bendamustine carries a manufacturer's recommendation for routine monitoring of serum potassium levels due to an established risk of hypokalemia.¹³ Our patient developed hypokalemia after receiving bendamustine at 90 mg/m² on days 1 and 2 of a 28-day cycle (total cumulative dose of 180 mg/m²). He then developed a hypokalemic metabolic

alkalosis with hypocalciuria after six (6) cycles of bendamustine-rituximab, equating to a cumulative bendamustine dose of 1080 mg/m², which is the standard dose for the treatment of follicular lymphoma.

The precise mechanism by which bendamustine induced a Gitelman-like syndrome in our patient is not known. He developed a constellation of metabolic derangements consistent with a Gitelman-like syndrome after completing six cycles of bendamustine-rituximab therapy, which equated to a cumulative bendamustine dose of 1080 mg/m² (90 mg/m² on days 1 and 2 of a 28-day cycle for six (6) cycles). These metabolic derangements completely resolved after two months of potassium replacement and spironolactone therapy. Altogether this speaks to a subacute and reversible process as the cause. Therefore, we hypothesize the reversible inhibition of the NCCT by bendamustine or one of its metabolites as a possible underlying pathophysiologic mechanism. Another possibility is a bendamustine-dependent autoimmune process targeting the NCCT specifically or distal convoluted tubule cells in general. In support of this theory, bendamustine has been implicated in a drug-dependent autoimmune process (hemolytic anemia) in a patient with follicular lymphoma.¹⁴ Additionally, and as aforementioned, an autoimmune-type process is thought to have caused an acquired Gitelman Syndrome in a patient with Sjogren's Syndrome.¹⁵

Finally, it is important to comment on the magnesium and aldosterone levels in our patient, specifically that his magnesium level was within our institution's normal range (1.6 mg/L or 0.8 mmol/L) and his aldosterone level was low (<1 ng/mL). Classically, Gitelman syndrome is characterized by hypomagnesemia and elevated aldosterone levels. The pathophysiology of hypomagnesemia in Gitelman syndrome remains to be fully elucidated, but may be related to altered expression of the TRPM6 magnesium transport channel or distal convoluted tubule cell death.¹⁶ Either abnormality would result in renal magnesium wasting. However, this theory has been disputed by Lin et al,¹⁷ who examined two families with proven Gitelman syndrome. They found that affected men had severe hypokalemia with paralysis, but also had normal serum magnesium. As a result, although the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference includes both hypomagnesemia (<0.7 mmol/L) and inappropriate renal magnesium wasting (fractional excretion of magnesium >4%) as biochemical diagnostic criteria for Gitelman Syndrome,¹⁸ KDIGO also acknowledges that hypomagnesemia may be absent in patients with Gitelman Syndrome.¹⁸ Thus, the absence of hypomagnesemia in our patient does not exclude drug-induced Gitelman-like Syndrome as a diagnosis. As for aldosterone, hypovolemia is thought to cause activation of the renin-angiotensin-aldosterone system.¹⁸ Interestingly, the KDIGO Conference does not include elevated aldosterone levels in its proposed diagnostic criteria,¹⁸ but elevated renin levels and activity are included. Our patient did have

elevated renin activity, consistent with our diagnosis. In sum, neither the normal magnesium nor the low aldosterone rules out a diagnosis of drug-induced Gitelman-like syndrome in our patient. In fact, the low aldosterone level may simply reflect the expected downstream effect of benazepril, which he had been taking prior to admission. Furthermore, hypokalemia inhibits aldosterone production, small changes in plasma potassium have a greater effect on aldosterone than on renin secretion.¹⁹ Therefore, his severe persistent hypokalemia would explain the suppressed aldosterone production.

CONCLUSION

In conclusion, our case provides evident that bendamustine is capable of inducing a reversible Gitelman-like syndrome. For this reason, if hypokalemia is detected on routine monitoring, then prescribers should consider evaluating for other metabolic derangements such as those common to Gitelman syndrome given that specific and effective therapies are available.

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