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Case Report

An Unusual Cause of Hypokalemia to Consider

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Abstract

Apparent mineralocorticoid excess syndrome is a rare disorder that can be acquired through inhibition of the enzyme 11 β-hydroxysteroid dehydrogenase type 2 by various substances such as bile acids. We report the case of a 61-year-old woman presenting with painless jaundice. Computed tomography demonstrated a pulmonary as well as a pancreatic tumor, with multiple metastases and dilated bile ducts. Laboratory findings showed persistent hypokalemia despite aggressive enteral and parenteral supplementation, as well as hypertension, metabolic alkalosis, and elevated cholestasis enzymes. Urinary potassium excretion was inappropriately high. Plasma aldosterone concentration was 0.97 ng/dL (26.91 pmol/L) (reference range, 2.21-25.30 ng/dL [61.31-701.82 pmol/L]) and direct renin concentration was 3.9 mIU/L (2.1 ng/L) (reference range, 4.4-46.1 mIU/L [2.53-27.42 ng/L]). Endogenous hypercortisolism was ruled out. After the placement of a metal biliary stent via endoscopic retrograde cholangiopancreatography and the subsequent decrease in cholestasis enzyme levels, potassium levels, hypertension, and metabolic alkalosis gradually normalized. The case was ultimately diagnosed as apparent mineralocorticoid excess syndrome resulting from 11 β-hydroxysteroid dehydrogenase type 2 inhibition caused by elevated bile acids secondary to malignant obstruction of the biliary tract.

Key Words: hypokalemia, pseudohyperaldosteronism, HSD11B2, bile acids, glycyrrhetinic acid-like factors, apparent mineralocorticoid excess syndrome

Abbreviations: AME, apparent mineralocorticoid excess; CDCA, chenodeoxycholic acid; CT, computed tomography; DRC, direct renin concentration; ERCP, endoscopic retrograde cholangiopancreatography; HSD11B2, 11 β-hydroxysteroid dehydrogenase type 2; MR, mineralocorticoid receptor; PAC, plasma aldosterone concentration.

Introduction

The enzyme 11 β-hydroxysteroid dehydrogenase type 2 (HSD11B2), located in the distal nephron, catalyzes the conversion of active cortisol to its inactive form, cortisone. This conversion ensures that only aldosterone, rather than cortisol (which also has a high affinity for the mineralocorticoid receptor [MR]), activates the MR [1-3].

The activity of HSD11B2 is greatly influenced by endogenous and exogenous steroidal compounds, known as glycyrrhetinic acid-like factors, which act as inhibitors or activators. Among these substances are bile acids, as well as licorice, gossypol, phthalates, organotins, alkylphenols, perfluorinated compounds, and carbenoxolone [3-5]. These substances can lead to sodium retention, renal losses of potassium, and suppression of aldosterone and renin levels [3, 4].

In this report, we present a case of apparent mineralocorticoid excess (AME) resulting from HSD11B2 inhibition caused by elevated bile acids secondary to malignant obstruction of the biliary tract.

Case Presentation

A 61-year-old woman was admitted for evaluation of painless jaundice that had developed over the previous 3 days.

On physical evaluation, jaundice, cachexia (body mass index, 16.2 kg/m^2), and mild hypertension were noted (142/81 compared to 90/60 mm Hg 10 weeks earlier). The rest of the examination showed no relevant findings.

Computed tomography (CT) demonstrated a pulmonary and a pancreatic tumor, along with multiple metastases involving mediastinal lymph nodes, subepicardial and cardiac regions, adrenal glands, thyroid, perinephric area, peritoneal carcinomatosis, and dilated bile ducts.

The right adrenal lesion showed central necrosis. A ^{68}Galium (DOTA)-octreotate positron emission tomography/CT (^{68}Ga-DOTATATE positron emission tomography/CT) was performed, showing mild uptake by the adrenal nodules. A targeted study was recommended, but given the clinical conditions, a CT-guided biopsy was ruled out [6].

Laboratory studies revealed metabolic alkalosis, hypokalemia, and elevated cholestatic enzymes. Hypokalemia reached 2.8 mmol/L (2.8 mEq/L) despite high enteral and parenteral potassium supplementation (up to 6.4 mmol/kg/day) (Fig. 1). Electrocardiographic findings were unremarkable.

Further evaluation of urinary markers indicated an inappropriately high potassium excretion, with a potassium/creatinine ratio of 56.2 mmol/g and a transtubular potassium gradient of 7.4, which are highly suggestive of mineralocorticoid activity in the distal convoluted tubule [7].

Diagnostic Assessment

As part of the study of hypokalemia [8], digestive losses were excluded clinically. Magnesium levels were consistently found to be within normal limits. The possibility of covert diuretic use was also ruled out because all of the patient's medication was

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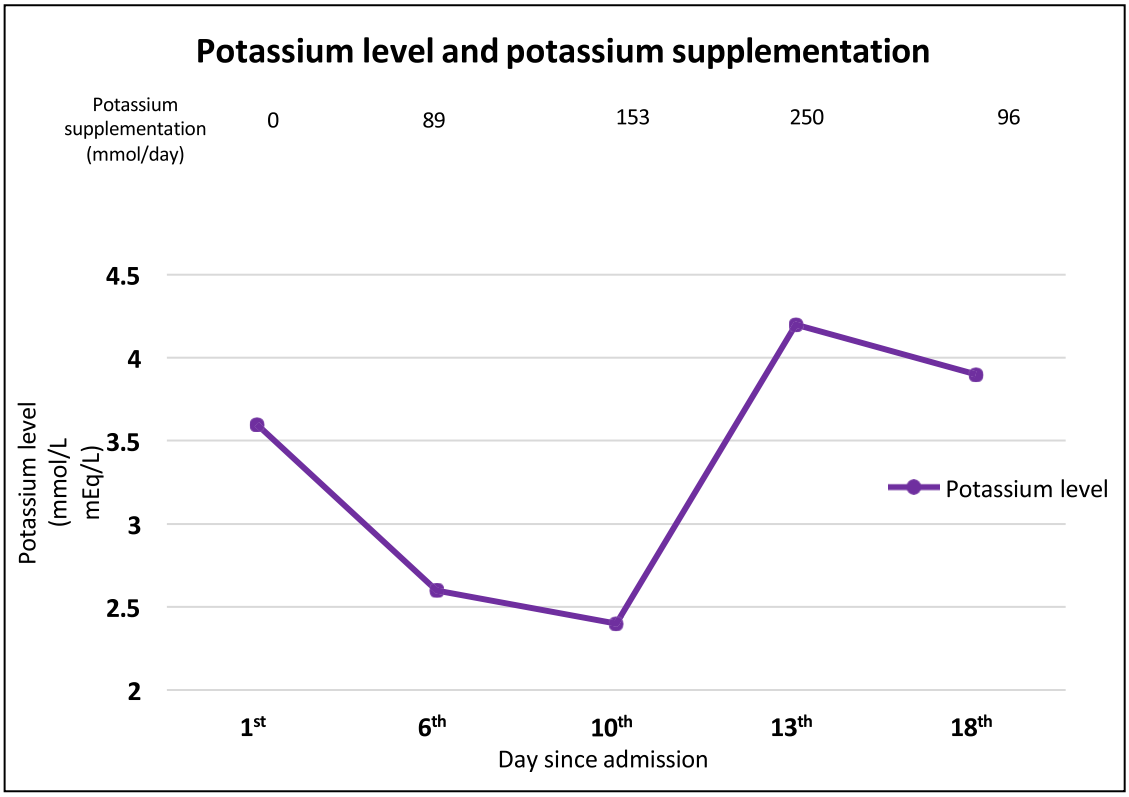

Figure 1. Evolution of potassium level and supplementation. Evolution of kalemia (mmol/L; mEq/L) and potassium supplementation (mmol/day) throughout the patient's hospitalization. On the 10th day of admission, the patient presented the lowest kalemia value: 2.4 mmol/L (mEq/L) despite receiving 153 mmol/day of potassium. On the 7th day of admission, an endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and placement of a metallic biliary stent was performed. As a result of this procedure, cholestatic enzyme levels and the associated hypokalemia gradually normalized, which allowed for a reduction in potassium supplementation.

supervised. Genetic conditions such as Bartter, Gitelman, Liddle, and Geller syndrome were also excluded because of the lack of ionic alterations before admission and the absence of relevant family or personal history. Deficiency of 11 β-hydroxylase and/or 17 α-hydroxylase were considered unlikely because of the absence of signs of hyperandrogenism or previous clinical manifestations. However, we did not determine the levels of 11-deoxycortisol, deoxycorticosterone, testosterone, adrenal androgens, 17-hydroxyprogesterone, or the urinary metabolites 17-hydroxysteroid and 17-ketosteroid.

Additional endocrine testing provided further insights. The concentration of ACTH was 5 pg/mL (1.1 pmol/L) (reference range, 5-46 pg/mL [1.1-10.12 pmol/L]), and morning serum cortisol level was 29.1 micrograms/dL (802.87 nmol/L) (reference range, 5.3-22.5 micrograms/dL [146.2-620.69 nmol/L]). Cushing syndrome was excluded by clinical evaluation. Syndromes associated with altered cortisol metabolism or receptor function, such as glucocorticoid resistance, were excluded based on the absence of a relevant family history and the normal ACTH levels. Urinary cortisol and cortisone measurements could not be conducted because of the urgent need to initiate dexamethasone treatment.

We measured the plasma aldosterone concentration (PAC) and the direct renin concentration (DRC) levels without any hypotensive medication that could interfere, obtaining a PAC of 0.97 ng/dL (26.91 pmol/L) (reference range, 2.21-25.30 ng/dL [61.31-701.82 pmol/L]), and a DRC of 3.9 mIU/L (2.1 ng/L) (reference range, 4.4-46.1 mIU/L [2.53-27.42 ng/L]), resulting in a ratio of 0.2 ng/dL-mUI/L (normal reference range < 3.7 ng/dL-mUI/L). Therefore, primary hyperaldosteronism was excluded as a potential cause. The findings pointed towards a case of AME.

Treatment

On the 7th day of admission, an endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and placement of a metallic biliary stent was performed. This procedure led to a progressive normalization of the cholestatic enzymes and the associated ionic alterations, with normalization of pH and potassium levels, and allowing for a gradual reduction in potassium supplementation (Figs. 1 and 2).

Outcome and Follow-up

The final diagnosis for the patient was a well-differentiated neuroendocrine tumor, G2, with a Ki-67 index of 7%, of unknown origin, classified as stage IV. The patient started treatment with everolimus and lanreotide following the recommendations of the oncology department.

Retrospectively, the diagnosis of AME syndrome was made due to the inhibition of HSD11B2, caused by the elevation of bile acids secondary to malignant obstruction of the biliary tract. The patient presented with hypertension, hypokalemia, metabolic alkalosis, and suppression of PAC and DRC. These abnormalities resolved as cholestatic enzyme levels normalized post-ERCP intervention.

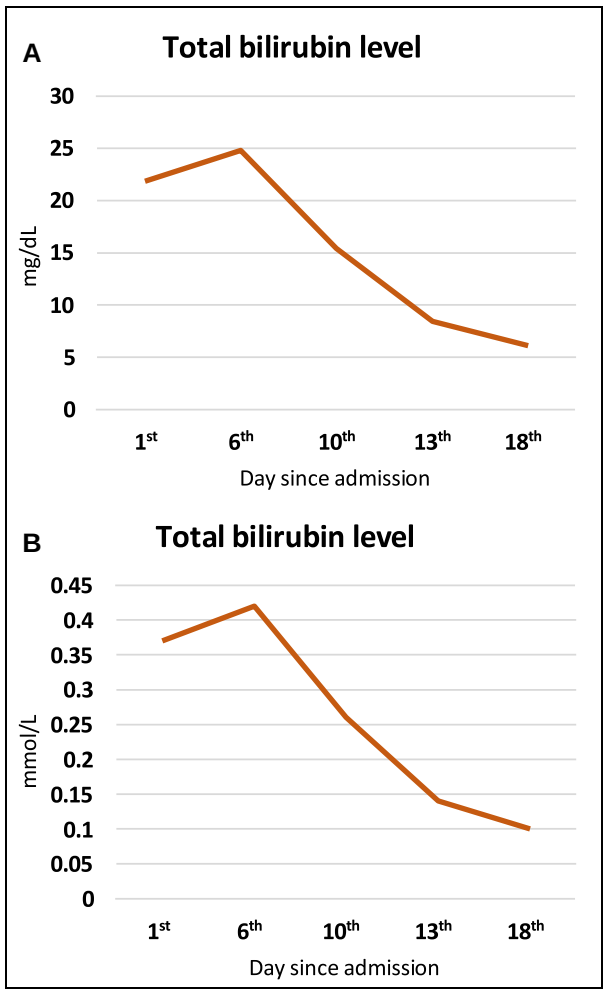

Figure 2. Evolution of total bilirubin level. Evolution of total bilirubin level (A, mg/dL); (B, mmol/L) throughout the patient's hospitalization. On the 7th day of admission, an endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and placement of a metallic biliary stent was performed. As a result of this procedure, cholestatic enzyme levels and the associated hypokalemia gradually normalized, which allowed for a reduction in potassium supplementation.

After discharge, the patient showed normal potassium levels without supplementation. No antihypertensive medication was needed during follow-up. The patient passed away 18 months after the initial diagnosis.

Discussion

Studies have reported that patients with biliary obstruction exhibit highly elevated concentrations of chenodeoxycholic acid (CDCA), cholic acid, and deoxycholic acid in their urine [9]. Some experiments show that both CDCA and deoxycholic acid inhibit HSD11B2 with micromolar half-maximal inhibitory concentration values [9]. These bile acids, specially CDCA, also promote cortisol-dependent nuclear translocation and increased transcriptional activity of the MR [9-11].

In adrenalectomized rats, CDCA infusion has been shown to elevate blood pressure, promote sodium retention, and increase renal potassium excretion, which are reversed using treatment with mineralocorticoid receptor antagonists [12, 13].

In cholestatic patients, the 5α-tetrahydrocortisol + tetrahydrocortisol/tetrahydrocortisone ratio (a urinary marker reflecting combined renal proximal and distal HSD11B2 activity) is significantly increased. This alteration normalized following surgical removal of the biliary obstruction and subsequent normalization of serum bile acid concentrations [9-14].

Clinically, cases have also been reported of patients with sodium retention and potassium loss in the context of cholestatic liver cirrhosis [15]. Additionally, the inhibition of HSD11B2 by bile acids may play a role in the etiology of ascites, pleural effusion, and edema observed in liver cirrhosis [10, 15].

Conditions that inhibit HSD11B2 activity, such as hyperuricemia, gut dysbiosis, elevated inflammatory cytokines, or licorice intake, may represent risk factors for AME in patients with cholestasis [4, 16]. However, unconjugated and conjugated glycyrrhetinic acid-like factors exhibit distinct inhibitory properties and cause different effects on hormonal receptors, depending on their concentrations and compositions in different tissues and pathological states [4]. The complex interplay among steroid substrates, their metabolites, and bile acids forms a "cloud" of biologically active compounds that influence the catalytic efficiency of 11 β-hydroxysteroid dehydrogenase isoforms. This dynamic cloud varies in size, dimension, and composition, complicating the identification of risk factors for AME development in cholestatic patients [4].

In conclusion, bile acid-induced AME syndrome is a rare condition requiring high clinical suspicion for timely diagnosis and treatment of secondary hypokalemia, metabolic alkalosis, and hypertension. This treatment involves addressing the underlying cause of bile acid elevation. In our case, the placement of a metal biliary stent via ERCP allowed the normalization of cholestatic enzymes and resolved the condition.

Learning Points

- When evaluating hypokalemia, it is essential to assess its severity, speed of onset, and potential secondary complications. The status of acid-base balance and urinary parameters should also be evaluated.
- The differential diagnosis of hypokalemia with renal potassium loss should include apparent mineralocorticoid excess syndrome. This rare condition may have either a genetic origin or an acquired cause, often from inhibition of the enzyme 11 β-hydroxysteroid dehydrogenase type 2 by various substances, with licorice being one of the most studied inhibitors.
- Bile acids can also cause this inhibition, so we should suspect it in patients with cholestasis who present with hypertension, hypokalemia, metabolic alkalosis, and suppressed aldosterone and renin levels.
- Treatment should focus on addressing the underlying cause of cholestasis to resolve the associated abnormalities.

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Contributors

All authors made individual contributions to authorship. I.B.S. and O.M.D. contributed to manuscript preparation, graphic design, and submission. I.B.S., Y.H.P., B.R., and C.V.C. were

involved in the diagnosis and management of the patient. I.B.S, P.P.R., and O.M.D. were involved in the physiopathology section. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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