Pseudohyponatremia Secondary to Hypercholesterolemia in the Setting of Intrahepatic Cholestasis due to Metastatic Liver Disease: A Case Report and Review of the Literature

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Abstract

Objective. We describe a rare case of pseudohyponatremia in the setting of hypercholesterolemia caused by cholestasis due to metastatic liver disease and provide a review of the published cases in the literature. Case Report. We report a case of pseudohyponatremia in a 60-year-old man with rectal cancer with extensive metastasis to the liver. While assessing the patient for hyponatremia, extremely elevated serum cholesterol with normal serum osmolality was detected leading to the diagnosis of pseudohyponatremia. This is one of very few reports of pseudohyponatremia in patients with elevated cholesterol in cholestatic liver disease. Conclusion. Hypercholesterolemia is an exceedingly rare cause for pseudohyponatremia. Although pseudohyponatremia per se does not carry a risk to the patient, the delay in diagnosis and treatment plans may pose additional risks. Pseudohyponatremia needs to be considered in patients with low sodium and co-existing cholestasis from metastatic liver disease.

Key Words: Hyponatremia • Cholestasis • Osmolality • Pseudohyponatremia.

Introduction

Hyponatremia is one of the most common electrolyte disturbances in an acute hospital setting (1). However, it is prudent for clinicians to be aware of the pseudohyponatremia phenomenon that indicates a spurious low sodium level resulting from decreased relative proportion of water from elevation of either lipids or proteins in plasma (2). Accordingly, the initial step in evaluating a patient with a low sodium level is exploring the possibility of pseudohyponatremia by checking serum osmolality. Pseudohyponatremia is an artificial sodium level of less than 135 mmol/L when measured with the indirect ion-selective electrode method in conjunction with a normal serum osmolality (3). Pseudohyponatremia is typically associated with hyperlipidemia and hyperproteinemia, where the water component is replaced by non-aqueous materials. The condition is rarely reported in patients with hypercholesterolemia, particularly in conjunction with cholestasis (4).

In this report, we describe a patient with pseudohyponatremia in the presence of intrahepatic cholestasis, which was caused by extensive metastatic liver involvement.

Case Presentation

A 60-year-old African American man was admitted to the hospital with worsening abdominal pain and declining functional status. He had become progressively weaker after receiving the first round of chemotherapy for advanced rectal adenocarcinoma with extensive metastasis to the liver, lungs and spine. On the day of admission, the hematologic analysis was significant for hemoglobin of 11.6 g/dL, platelets of 555/nL, and a white blood cell count of 7.4/nL. Blood work was significant for random glucose of 114 mg/dL, creatinine of 1.1...
mg/dL, blood urea nitrogen of 20 mg/dL, potassium of 4.9 mmol/L, alanine aminotransferase of 215 U/L, aspartate aminotransferase of 180 U/L, alkaline phosphatase of 1,178 U/L, total bilirubin of 10.8 mg/dL, and serum sodium of 127 mmol/L. His serum sodium concentration 4 months earlier had been 137 mmol/L.

Magnetic resonance cholangiopancreatography was performed to evaluate the possibility of palliative stenting for his progressive cholestasis and showed liver enlargement with numerous mildly T2 hyperintense/T1 hypointense metastatic lesions throughout the liver. There was intrahepatic biliary ductal dilation, which was not amenable to palliative stenting.

Hypovolemic hyponatremia was suspected because of the patient's serum sodium of 127 mmol/L, his poor oral intake, and the presence of dry mucosal membranes on exam. Serum was sent to an outside laboratory to assess osmolality. Intravenous fluid boluses were given, and maintenance fluid was started. Despite adequate fluid resuscitation, on the third hospital day, the patient's serum sodium level further decreased to 125 mmol/L; thus, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was suspected. Fluid intake was restricted to 1.2 L/day, and the patient's serum sodium was 126 mEq/L on the following day. As a result of this improvement, therapy for SIADH was escalated with salt tablets. However, the serum sodium decreased to 121 mmol/L by the sixth day. At this time the result of serum osmolality became available revealing a normal level of 288 mOsm/kg, leading to a diagnosis of pseudohyponatremia.

Repeated laboratory tests showed worsening alkaline phosphatase levels at 1,698 U/L and total bilirubin at 15.3 mg/dL; random urine sodium was 63 mmol/L. A serum lipid profile workup revealed a total serum cholesterol of 816 mg/dL with triglyceride levels of 382 mg/dL and high-density lipoprotein of 9 mg/dL; the low-density lipoprotein levels were unmeasurable because the total cholesterol was >500 mg/dL. Interestingly, the patient’s lipid profile 4 weeks earlier showed total cholesterol of only 213 mg/dL, triglycerides at 115 mg/dL, high-density lipoprotein at 36 mg/dL, and low-density lipoproteins at 153 mg/dL. No further treatment for hyponatremia was further offered as it was determined a laboratory artifact secondary to severe hypercholesterolemia.

**Discussion**

It is important to note that the commonly used laboratory measure reports plasma sodium level. Plasma typically contains 7% lipids and proteins, but elevated lipids/proteins reduce the amount of electrolytes per unit volume of plasma. Hence, the measured plasma sodium decreases when lipid/protein levels increase, but the concentration of sodium in plasma water, which is the physiologically important value, remains the same. Sodium levels measured using an indirect ion-selective electrode can result in a laboratory artifact, called pseudohyponatremia, because this method uses a dilution step before sodium is measured and estimates serum sodium on the basis of the presumed typical proportion of water in plasma. However, measurements with an ion-selective direct electrode do not require a dilution step and will report accurate levels in the setting of elevated lipid or proteins (4). This method is commonly used in point-of-care devices (5), whereas central laboratories use the indirect method because of its substantially larger capacity.

One of the most common causes of pseudohyponatremia is hypertriglyceridemia (>1,500 mg/dL) but it can occur as a result of hyperproteinemia in patients with plasma cell dyscrasias, intravenous immunoglobulin therapy, or, very rarely, elevated cholesterol (6). Pseudohyponatremia due to hypercholesterolemia is highly uncommon, with a few reported cases (6). The patient described in this report had hypercholesterolemia-induced pseudohyponatremia as a result of cholestatic obstruction from metastatic liver disease. A review of the literature for reported adult patients with pseudohyponatremia in the setting of hypercholesterolemia revealed 14 additional cases, summarized in Table 1.

The reported underlying mechanisms included cholestasis secondary to graft-versus-host disease
after bone marrow transplantation in four patients (6-8), primary biliary cirrhosis in three patients (9-11), medication-induced obstructive jaundice in three patients (12-14), hepatitis C infection (15), chronic pancreatitis (16), autoimmune pancreatitis and lymphoplasmacytic sclerosing cholangitis (17), and pancreatic cancer (18) in one patient each.

Interestingly, all these patients presented with extreme cholestasis. Cholestasis can cause hyperlipidemia by increasing serum Lipoprotein X. Lipoprotein X, a major cholesterol transporter in the plasma, is formed when serum incubates with bile lipoproteins from unesterified cholesterol and phospholipids released from the bile ducts into the bloodstream (19). Lipoprotein X is the common factor in patients with cholestasis-induced hypercholesterolemia. The high level of this lipoprotein, which has a high phospholipid and free cholesterol content, contributes to the pathophysiology of pseudohyponatremia (6). Cholesterol levels are inversely correlated with serum sodium levels; therefore, severe hypercholesterolemia can exacerbate pseudohyponatremia (6).

### Conclusion

We present a rare case of hypercholesterolemia-induced pseudohyponatremia in the setting of metastatic liver disease with subsequent cholestatic obstruction. This case highlights the importance of checking serum osmolality before addressing the hyponatremia. Although patients with cholestasis disorder and hyponatremia can have hypovolemic hyponatremia because of volume depletion secondary to vomiting and poor oral intake, it is essential to establish the presence of a

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**Table 1. Literature Review of Pseudohyponatremia Cases Secondary to Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Author/Reference number</th>
<th>Age (Year), Sex</th>
<th>Underlying condition</th>
<th>Sodium indirect method</th>
<th>Sodium direct method</th>
<th>Serum osmolality</th>
<th>Total cholesterol</th>
<th>Publication year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hickma et al. (9)</td>
<td>62, F</td>
<td>Primary biliary cirrhosis</td>
<td>115</td>
<td>134</td>
<td>NR†</td>
<td>3,011</td>
<td>1989</td>
</tr>
<tr>
<td>Ko et al. (11)</td>
<td>27, M</td>
<td>Primary biliary cirrhosis</td>
<td>116</td>
<td>132</td>
<td>304</td>
<td>1,830</td>
<td>1997</td>
</tr>
<tr>
<td>Turchin et al. (8)</td>
<td>64, F</td>
<td>Cholestasis due to chronic graft-versus-host disease</td>
<td>124</td>
<td>135</td>
<td>NR§</td>
<td>1,836</td>
<td>2005</td>
</tr>
<tr>
<td>Turchin et al. (8)</td>
<td>37, M</td>
<td>Cholestasis due to chronic graft-versus-host disease</td>
<td>129</td>
<td>135</td>
<td>NR§</td>
<td>977</td>
<td>2005</td>
</tr>
<tr>
<td>Le Riche et al. (14)</td>
<td>29, F</td>
<td>Drug-induced intra-hepatic cholestasis</td>
<td>116</td>
<td>NR§</td>
<td>NR§</td>
<td>2,815</td>
<td>2005</td>
</tr>
<tr>
<td>Inamoto et al. (7)</td>
<td>55, F</td>
<td>Cholestasis due to chronic graft-versus-host disease</td>
<td>101</td>
<td>139</td>
<td>273</td>
<td>4,091</td>
<td>2005</td>
</tr>
<tr>
<td>Klinke et al. (13)</td>
<td>36, M</td>
<td>Quetiapine-associated cholestasis</td>
<td>119</td>
<td>NR§</td>
<td>NR§</td>
<td>1,691</td>
<td>2010</td>
</tr>
<tr>
<td>Sivakumar et al. (18)</td>
<td>61, F</td>
<td>Obstructive biliary cholestasis secondary to pancreatic cancer</td>
<td>108</td>
<td>127</td>
<td>296</td>
<td>1,713</td>
<td>2011</td>
</tr>
<tr>
<td>Vo et al. (15)</td>
<td>41, F</td>
<td>Acute hepatitis C</td>
<td>120</td>
<td>135</td>
<td>297</td>
<td>2,621</td>
<td>2013</td>
</tr>
<tr>
<td>Ravella et al. (17)</td>
<td>40, M</td>
<td>Lymphoplasmacytic sclerosing cholangitis</td>
<td>121</td>
<td>138</td>
<td>297</td>
<td>2,109</td>
<td>2015</td>
</tr>
<tr>
<td>Hussain et al. (10)</td>
<td>43, F</td>
<td>Primary biliary cirrhosis</td>
<td>121</td>
<td>141</td>
<td>296</td>
<td>2,415</td>
<td>2015</td>
</tr>
<tr>
<td>Igbinonedion et al. (16)</td>
<td>44, M</td>
<td>Obstructive Biliary Cholestasis in setting of chronic pancreatitis</td>
<td>110</td>
<td>132</td>
<td>302</td>
<td>2,247</td>
<td>2017</td>
</tr>
<tr>
<td>Song et al. (6)</td>
<td>41, M</td>
<td>Cholestasis due to chronic graft-versus-host disease</td>
<td>121</td>
<td>144</td>
<td>309</td>
<td>1,449</td>
<td>2018</td>
</tr>
<tr>
<td>El Hage et al. (12)</td>
<td>69, M</td>
<td>Drug-induced cholestatic hepatitis</td>
<td>119</td>
<td>132</td>
<td>283</td>
<td>1,340</td>
<td>2019</td>
</tr>
<tr>
<td>Pourafkari et al.</td>
<td>60, M</td>
<td>Cholestasis in setting of metastatic liver disease</td>
<td>127</td>
<td>NR†</td>
<td>288</td>
<td>816</td>
<td>2022</td>
</tr>
</tbody>
</table>

*mmol/L; †mOsm/kg; ‡mg/dL; §Not reported; ||Current case.
true hypo-osmolar state. In our case, technical issues delayed the serum osmolality results and thus recognition of pseudohyponatremia. Attempts at correcting sodium levels in patients with pseudohyponatremia may lead to unnecessary treatment with dreadful consequences.

What Is Already Known on This Topic:
Pseudohyponatremia is a laboratory artifact in which low measured serum sodium level is accompanied with a normal serum osmolality. Hypertriglyceridemia and hyperproteinemia are two common causes of pseudohyponatremia. Hypercholesterolemia is an exceedingly rare cause of pseudohyponatremia and has been reported in the setting of cholestatic liver disease and subsequent elevation in lipoprotein X.

What This Case Adds:
A literature review identified 14 cases of pseudohyponatremia in adult patients with hypercholesterolemia. Pseudohyponatremia needs to be considered in patients with low sodium levels and cholestasis in the setting of extensive liver metastases.

Authors’ Contributions:
Concept and design: LP, SKY and CC; Acquisition and interpretation of data: LP, SKY, CC and NN; Literature review: LP, SKY, CC, and NN; Drafting and Conception and design: LP, SKY and CC; Acquisition and interpretation of data: LP, SKY, CC and NN; Literature review: LP, SKY, CC, and NN; Drafting and CC; Acquisition and interpretation of data: LP, SKY, CC and NN; Approval of final version: LP, SKY, CC and NN.

Conflict of Interest: The authors declare that they have no conflict of interest.

References