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Extreme hypercholesterolemia presenting with pseudohyponatremia - a case report and review of the literature

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Abstract: Pseudohyponatremia has been reported in association with severe hypertriglyceridemia and hyperparaproteinemia, but its association with severe hypercholesterolemia is not well-known. We report a 43-year-old woman with refractory primary biliary cirrhosis who presented with asymptomatic hyponatremia (121 mmol/L; normal range: 135-145 mmol/L). She was ultimately found to have a total serum cholesterol level of 2415 mg/dL (normal range: 120-199 mg/dL) — secondary to accumulation of lipoprotein-X—causing pseudohyponatremia. The diagnosis was confirmed by measurement of serum osmolality (296 mOsm/kg H_2O; normal range: 270-300 mOsm/kg H_2O) and serum sodium by direct potentiometry (141 mmol/L). Furthermore, following 16 sessions of plasmapheresis over a 4-month period, there was marked lowering of serum cholesterol to 200 mg/dL and normalization of serum sodium (139 mmol/L) as measured by indirect potentiometry. This case shows that extreme hypercholesterolemia from elevation of lipoprotein-X particles in cholestasis can be a rare cause of pseudohyponatremia. It highlights the need to measure serum sodium with direct potentiometry in the setting of extreme hypercholesterolemia and consider this possibility before initiating treatment of hyponatremia.
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Introduction

Pseudohyponatremia is defined as a spuriously low serum sodium concentration in the setting of normal serum osmolality.[1–3] It is important to distinguish pseudohyponatremia from true hyponatremia lest injudicious treatment results in increased morbidity and mortality.[4] Pseudohyponatremia is usually seen in cases with extreme hypertriglyceridemia and hyperparaproteinemia[1–3,5–7] when serum sodium is measured using routine laboratory testing methods (ie, indirect potentiometry/flame photometry).[1,2,4,7,8] Pseudohyponatremia in association with severe hypercholesterolemia is extremely rare and is not well-recognized. We present an unusual case of a woman with primary biliary cirrhosis who presented with pseudohyponatremia secondary to extreme hypercholesterolemia caused by elevation of lipoprotein-X. This report emphasizes having a high index of suspicion for extreme hypercholesterolemia resulting in pseudohyponatremia.

Case report

A 43-year-old African American woman was admitted for evaluation and treatment after routine laboratory testing revealed low serum sodium (121 mmol/L; normal range:

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135-145 mmol/L). She complained of increasing fatigue, jaundice, and itching for several weeks before admission. Review of past laboratory testing showed normal serum sodium levels for the past 3 years; with slight reductions noted three months (133 mmol/L) and one month (131 mmol/L) before presentation. She had not been drinking excessive amounts of water, urine output was normal, and she had no mental status changes. She was taking amlodipine, azathioprine, cholestyramine, fenofibrate, hydroxyzine, losartan, ondansetron, prednisone, prochlorperazine, promethazine, ranitidine, sertraline, trazodone, and high doses of ursodiol (24 mg/kg/day). She reported no dose adjustments or changes in medications in the past 6 months that could explain her new-onset hyponatremia.

She was diagnosed with right-sided invasive ductal breast carcinoma associated with breast cancer 1, early onset (*BRCA1*) gene mutation one year before her current presentation, and was status post partial mastectomy and chemoradiotherapy, with no active disease. During evaluation of her breast cancer, she was noted to have elevated serum alkaline phosphatase level (503 U/L; normal range: 35-104 U/L) and was subsequently diagnosed with primary biliary cirrhosis—confirmed by liver biopsy and elevated antimitochondrial antibodies (titer ≥ 1:320; normal range: negative)—eight months before presentation. Her primary biliary cirrhosis has been refractory to medical therapy.

On physical examination, her vital signs were unremarkable and her skin turgor appeared normal. She had scleral icterus but had no hepatosplenomegaly, xanthelasmata, or xanthomata. Her laboratory results (Table 1) revealed hyponatremia, elevated bilirubin levels (10.2 mg/dL; normal range: 0.2-1.3 mg/dL) indicating worsening biliary disease, and very high cholesterol levels (total cholesterol 2415 mg/dL; normal range: 120-199 mg/dL). She also had hypokalemia (3.0 mmol/L; range 3.6-5.0 mmol/L) and hypochloremia (87 mmol/L; range 98-109 mmol/L).

She was initially thought to have hypovolemic hyponatremia and was given intravenous normal saline; however, a repeat sodium level test was unchanged (121 mmol/L) after five hours.

Review of her medical records revealed a much lower total serum cholesterol level of 322 mg/dL 2 years ago. The marked increase in serum cholesterol suggested rapid progression of primary biliary cirrhosis resulting in accumulation of lipoprotein-X and development of pseudohyponatremia secondary to lipoproteinemia. The diagnosis of pseudohyponatremia was confirmed by measurement of serum osmolality (296 mOsm/kg H_2O; normal range: 270-300 mOsm/kg H_2O) and measurement of serum sodium by direct potentiometry (141 mmol/L; normal range: 135-145 mmol/L). Lipoprotein electrophoresis confirmed a major presence of lipoprotein-X (Fig. 1 and Table 2). Serum apolipoprotein B level was 218 mg/dL (normal range: 48-124 mg/dL).

Her serum sodium by indirect potentiometry ranged from 120 to 125 mmol/L for the next 2 days and she was discharged without any additional lipid-lowering drugs.

Table 1 Initial laboratory studies showing extreme elevation of cholesterol and low sodium, along with low potassium and chloride

Laboratory test	Value	Normal range
Sodium	121 mmol/L	135-145 mmol/L
Potassium	3 mmol/L	3.6-5 mmol/L
Chloride	87 mmol/L	98-109 mmol/L
Carbon dioxide	23 mmol/L	22-31 mmol/L
Anion gap	11	6-16
Blood urea nitrogen	16 mg/dL	6-23 mg/dL
Creatinine	0.98 mg/dL	0.51-0.95 mg/dL
Albumin	2.6 g/dL	3.5-5.2 g/dL
Protein, total	6.7 g/dL	6.6-8.7 g/dL
Aspartate aminotransferase	120 U/L	10-35 U/L
Alanine aminotransferase	107 U/L	10-35 U/L
Alkaline phosphatase	507 U/L	35-104 U/L
Bilirubin, total	10.2 mg/dL	0.2-1.3 mg/dL
Glucose	82 mg/dL	65-200 mg/dL
Calcium	9.5 mg/dL	8.4-10.2 mg/dL
Cholesterol, total	2415 mg/dL	120-199 mg/dL
Triglycerides	299 mg/dL	50-150 mg/dL
High-density lipoprotein cholesterol	42 mg/dL	45-65 mg/dL
Low-density lipoprotein cholesterol (calculated)	Not reported	≤99 mg/dL

Low-density lipoprotein cholesterol not reported because of interference with assay.

For intractable itching secondary to elevated bile acids (>180 μmol/L; normal range: ≤10 μmol/L) despite maximal medical therapy, plasmapheresis was initiated 2 months after discharge because she was not a candidate for

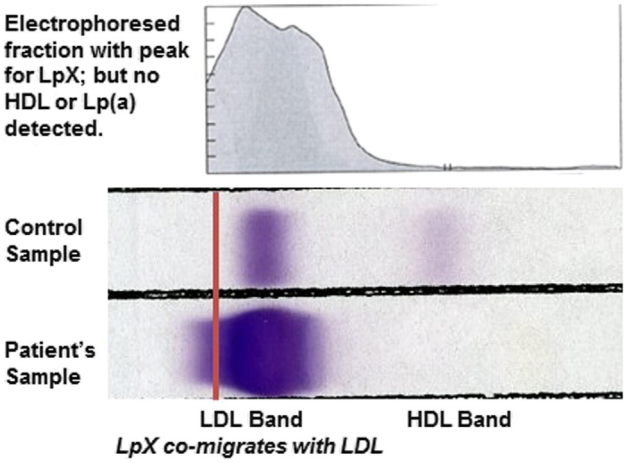

Figure 1 Lipoprotein electrophoretogram showing broad lipoprotein-X (LpX) banding. The bottom fraction after ultracentrifugation, normally containing only low-density lipoprotein (LDL), high-density lipoprotein (HDL), and sometimes lipoprotein(a), was electrophoresed. The atypical pattern of the patient's sample (ie, the reverse migration from the application point, marked by the vertical line), indicates the presence of LpX as opposed to LDL.