A Rare Case Of Liver Disease Induced Hypercalcemia: Case Presentation And Review Of The Literature

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Abstract

Hypercalcemia induced by advanced chronic liver disease without hepatoma is an exquisitely rare condition, poorly understood, with only 17 cases described to date in the literature. We describe the case of a 36 year old African American man with sickle cell disease, chronic liver disease secondary to sickle cell hepatopathy complicated by acute liver failure induced by congestive hepatopathy following a severe episode of sickle cell crisis. The patient was transferred to our center to be evaluated for liver transplantation. While in the hospital he developed hypercalcemia. Our extensive search for a "classical" etiology of hypercalcemia was negative. The calcium rapidly returned to normal with calcitonin followed by a small dose of bisphosphonate and recovering of the liver function. Liver disease induced hypercalcemia is a diagnosis of exclusion and responds well to bisphosphonate treatment.

INTRODUCTION

The case of a 36 year old African American man with sickle cell disease who developed acute liver failure caused by congestive hepathopathy after a severe episode of sickle cell crisis is presented. While in the hospital to be evaluated for possible liver transplantation, he developed hypercalcemia that was deemed to be caused by the liver failure after excluding all the usual causes of hypercalcemia. With minimal treatment and as the liver disease improved, hypercalcemia resolved.

CASE REPORT

A 36 year old African American man with sickle cell disease with frequent episodes of sickle cell crises was transferred to the University of Nebraska Medical Center to be evaluated for possible liver transplantation. His acute liver disease diagnosed by liver biopsy was caused by congestive hepathopathy (intrahepatic cholestasis) with sinusoidal dilatation and congestive cholestasis induced by sickle cell crisis on a background of chronic liver lesions induced by sickle cell disease. Other possible etiologies for his chronic liver disease were ruled out by a negative ANA, negative hepatitis A, B, C panel and anti-smooth muscle antibody. Alpha -1 antitrypsin level was normal as well as his hemochromatosis genotype. A liver MRI revealed a heterogenous nodular liver with atrophy of the right lobe and hypertrophy of the left lobe. There were multiple liver

lesions consistent with dysplastic nodules. On admission he had nonologuric acute renal failure with a creatinine of 2.2 increasing from his baseline of 1.2. The acute renal failure was caused by contrast induced nephropathy and the use of nonsteroidal antiinflammatory medications.

The patient was in mild distress because of generalized malaise. On the physical examination he was severely jaundiced, hepatomegaly was present but no ascites was found.

At the time of the transfer his serum total calcium was 9.8 mg/dL, and serum albumin was 2.7 g/dL. Thus his corrected serum calcium was 10.9 mg/dL. The patient denied any previous episode of hypercalcemia.

His past medical history is significant for sickle cell disease with frequent crises treated with multiple exchange transfusions, avascular necrosis of the hip requiring partial resection, cholecystectomy, chronic renal failure with baseline creatinine of 1.2-1.4, iron overload caused by multiple blood transfusions and hypertension.

His medications consisted of hydroxyurea, famotidine, folic acid, oxycodone, morphine sulfate, ursodiol, metoprolol, cefepime, multivitamin. He denied any over the counter or herbal medications.

LABORATORY DATA

On admission his sodium was 137 mmol/L, potassium 3 mmol/L, chloride 107 mmol/L, carbon dioxide 24 mmol/L. BUN 30 mg/dL, creatinine 2.2 mg/dL, total Calcium 9.8 mg/dL, phosphorus 4.6 mg/dL, albumin 2.7 g/dL, total proteins 6.5 g/dL, total bilirubin 36.3.mg/dL, hemoglobin 7.4 g/dL, hematocrit 20.5 %.

Protein and urine electrophoresis did not show any evidence of monoclonal gammopathy.

Hepatitis panel was negative. HIV negative. A fetoprotein was 3.5 ng/mL (normal range <15 ng/mL).

An adequate 24 h urine collection showed 2.8 g of proteins a day and 187 mg of urinary calcium a day.

Abdominal MRI showed heterogenous nodular liver with atrophy of the right lobe and hypertrophy of the left lobe with dysplastic nodules but no evidence of hepatoma.

HOSPITAL COURSE

After admission his Ca level started to increase reaching a level of 11.2 mg/dL (12.4 mg/dL after correction for hypoalbuminemia) and iCa 1.61 mmol/L. The usual causes of hypercalcemia were investigated and the following results were found:

PTH <3 pg/ml(normal range 10-69 pg/ml), PTH rp 0.2pmol/L (normal range <2 pmol/L), vitamin D 25 OH 17 ng/ml (normal range 20-57 ng/ml), vitamin D 1,25 OH 5 U/ML (normal range 15-75 U/ML), TSH 0.897 mcIu /ml (normal range 0.40-5.00 mcIU/ML), T3 90nG/DL (normal range 70 -150 ng/DL), Free T4 0.6 ng/dl (normal range 0.8-2 ng/dl), A.M. cortisol level was 7.7mcg/dL (normal range-5-25 mcg/dL) while the patient was in no acute distress.

Hypercalcemia responded rapidly to subcutaneous calcitonin and 3 days later to a small dose of 15 mg i.v. pamidronate. On the day of discharge his total calcium was 8.5 mg/dL.

Of note the patient was ambulating, spending most of the time out of bed throughout the hospitalization.

DISCUSSION

As previously described, advanced chronic liver disease with elevated bilirubin can be a rare cause of hypercalcemia [1]. We found only 2 articles in the literature describing liver disease as a cause of hypercalcemia presenting a total of 17 cases [1,2]. Our patient's bilirubin level was elevated in the same range found in the previous articles.

In the present case, the common causes of hypercalcemia were excluded by laboratory data.

Hyperparathyroidism as a cause of hypercalcemia was rejected by the appropriately decreased level of PTH in the setting of hypercalcemia. PTHrp (Parathyroid Hormone related peptide) was decreased ruling out humoral hypercalcemia of malignancy as a cause of hypercalcemia [3,4,5,6,7]. Vitamin D toxicity was excluded by low levels of 25 OH and 1, 25 OH vitamin D and the lack of high dose of vitamin D supplementation. He was on a multivitamin preparation for many years [8,9,10,11,12]. A possible hyperproduction of 1, 25 OH vitamin D by granulomatous tissue as might be found in infections (TB, Histoplasmosis), Wegener's granulomatosis or Crohn's disease was also rejected by the low serum level of this metabolite [13]. The patient did not receive vitamin A, retinoic acid or cis-retinoic acid that are known to cause hypercalcemia if taken in high doses [14,15,16,17,18]. Prolonged immobilization was not the cause of hypercalcemia in our patient. He was out of bed most of the time and many times out of the room during his admission. Prolonged immobilization as a cause of hypercalcemia was described in patients that were bedridden for at least 4 weeks if the renal function was impaired and up to 16 weeks if the renal function was normal [19].

Hyperthyroidism [20, 21] was excluded by normal Thyroid Stimulating Hormone, T3 and free T4. Adrenal insufficiency was excluded by a normal morning cortisol level while he was in no acute distress. He did not have any history of antacids, heavy milk consumption to suggest milk alkali syndrome [22, 23]. Patient was on no medications such as lithium [24] hydrochlorothiazide, theophylline [25] which could cause the elevation of his serum calcium.

Familial hypocalciuric hypercalcemia was excluded by a negative history of hypercalcemia in the patient as well as in the patient's family.

He had 2 chest X rays, head CT, abdominal MRI and none found any bone lesions that could be consistent with bone metastases. The normal alfa fetoprotein, lack of bone pain and young age made the diagnosis of widespread bone metastasis from an unknown malignancy very unlikely.

No association between sickle cell disease and hypercalcemia was found despite our extensive search of the literature.

We hypothesize that the liver disease caused increased bone

resorption and this concurred with the episode of acute renal failure that decreased the ability of the kidneys to excrete calcium and this was the mechanism for the development of hypercalcemia. In our patient hypercalcemia developed while he was in the hospital, was rapidly diagnosed and treated, initially with calcitonin and later with a small dose of pamidronate (15 mg) with good results. His urinary calcium excretion was within normal limits even while being in renal failure. This is consistent with an increased bone resorption as the source of hypercalcemia.

After excluding all the usual causes of hypercalcemia we are left with the liver failure as the most likely cause of hypercalcemia in this patient.

The association between significant elevations of bilirubin, acute renal failure and hypercalcemia was described in the previous articles of liver disease induced hypercalcemia. The role of hyperbilirubinemia in the pathogenesis of hypercalcemia is unclear. In the single case series in the literature ([1]) the total bilirubin was very elevated with a mean of 29.5 mg/dL as well as in another case presentation ([2]). It is also unclear if hyperbilirubinemia is a pathogenic factor for hypercalcemia or just a marker of severe liver disease.

Our case is unique because the chronic liver disease was not as advanced as the cases previously described ([1], [2]). His liver disease had an episode of acute worsening induced by the sickle cell crisis. While the liver disease worsened, the episode of hypercalcemia occurred and then improved rapidly with minimal treatment when the acute liver disease resolved. The severity of his chronic liver disease did not require liver transplantation.

The pathogenesis of increased bone resorption induced by liver disease is unknown. We can hypothesize that in liver failure the catabolism of metabolites stimulating bone resorption is decreased with the subsequent stimulation of osteoclastic activity. Renal failure that is often associated [found in 87 % of patients ([1])] with the development of hypercalcemia is most likely a contributory factor by decreasing the renal ability to excrete Ca.

CONCLUSION

In summary hypercalcemia induced by advanced chronic liver disease is a diagnosis of exclusion. It is associated with high bilirubin levels and the serum calcium can reach very high levels. It is presumed to be mediated by increased bone resorption and is responsive to bisphosphonate treatment.

Our case also suggests that hypercalcemia resolves as the liver function improves.

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