Hypercalcemia of advanced chronic liver disease: a forgotten clinical entity!

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Summary

Hypercalcemia caused by advanced chronic liver disease (CLD) without hepatic neoplasia is uncommonly reported and poorly understood condition. We are reporting two cases of advanced CLD who developed hypercalcemia in the course of the disease. This diagnosis of exclusion was made only after meticulous ruling out of all causes of hypercalcemia. The unique feature of this type of hypercalcemia is its transient nature that may or may not require treatment. This clinical condition in patients with CLD should be kept in mind while evaluating the cause of hypercalcemia in them.

KEY WORDS: hypercalcemia; cirrhosis; parathyroid hormone.

Introduction

Chronic liver disease complicated by hepatocellular carcinoma or cholangiocarcinoma is a known cause of hypercalcemia. Gerhardt et al. described a case series of 16 patients in 1987 who had hypercalcemia and CLD. Although 5 patients of this series also had hepatic tumor, the remaining 11 patients had no other cause explaining hypercalcemia in them. CLD per se as the cause of hypercalcemia in this subset of patients is not clearly established. In this article, we are describing two cases who developed hypercalcemia in the course of the advanced chronic liver disease. Extensive evaluation for classical etiology of hypercalcemia was unrevealing. This type of hypercalcemia is relatively easy to treat and requires minimal intervention.

Case report

Case 1
A 56-year-old male was diagnosed as cryptogenic chronic liver disease 8 years ago, when he was evaluated for upper gastrointestinal (GI) bleeding in the form of melena. He was found to have bleeding from esophageal varices and put on endoscopic variceal ligation protocol. Present admission in the hospital was because of de-compensation of liver disease in the form of ascites and upper GI bleed. On day 5th of admission, he was found to have increased ionized calcium. His albumin-corrected total calcium was also found to be high (Table 1). Despite extensive evaluation, no cause for hypercalcemia was identified (Table 2). This was a PTH-independent hypercalcemia with normal vitamin D metabolites. Magnetic resonance cholangio-pancreatiography (MRCP) of liver revealed chronic liver disease with a few regenerative nodules but no evidence of hepatoma. Serum immunofixation electrophoresis (IFE), serum and urine protein electrophoresis, urine for Bence Jones protein, and bone marrow examination were unremarkable. He was ambulatory and was not on thiazide diuretics or other medications that could have elevated his serum calcium levels. Skeletal survey with X-rays was unremarkable. He was managed with fluids and no specific medication was given for hypercalcemia. During the last week of hospital stay, his albumin-corrected calcium and ionized calcium levels were within normal limits.

Case 2
A 38-year-old male was diagnosed as ethanol-related chronic liver disease 5 years ago when he was evaluated for ascites. The present admission in the hospital was for thalamic bleed and de-compensation of liver disease in the form of hepatic encephalopathy. On day of admission, he was found to have high ionized and corrected total calcium (Table 3). Similar to case 1, this was a PTH-independent hypercalcemia with normal vitamin D metabolites (Table 2). Evaluation for any malignancy was unremarkable (MRCP liver and CECT abdomen, serum and urine electrophoresis, urine for Bence Jones protein, skeletal survey with X-rays). He was not on prolonged immobilization and had not used vitamin A supplementation, lithium or antacids. He was managed with fluids and no specific medication was given for hypercalcemia. During the last 10 days of hospital stay, albumin-corrected calcium and ionized calcium were within normal limits without any intervention for hypercalcemia.

Our patients were getting 1400-1600 kcal diets in the hospital with estimated calcium of 250-350 mg/day. Urinary calcium-to-creatinine ratio was normal in both the patients.
Advanced chronic liver disease is not a known cause of hypercalcemia except in the setting of hepatic neoplasia. Gerhardt et al. described an interesting pattern of hypercalcemia in 11 patients who had advanced chronic liver disease but no hepatic cancer (1). There were no obvious causes for hypercalcemia after extensive evaluation in them. The Authors suggested that hypercalcemia might be due to chronic liver disease per se. After extensive evaluation, no obvious cause for PTH-independent hypercalcemia was detected.

Our case 1 developed hypercalcemia acutely on 3rd day of hospital stay while case 2 was detected having hypercalcemia at the time of admission to the hospital. The duration of hypercalcemia could not be determined in the second case. In Gerhardt’s series, 7 patients were already hypercalcemic at the time of hospitalization while the other 4 developed hypercalcemia acutely in the hospital.

Cadranel et al. described a case of hypercalcemia associated with chronic hepatitis caused by hepatitis B virus (2). After excluding all possible causes of hypercalcemia, they suggested that hypercalcemia could be a metabolic feature in some patients of chronic liver disease irrespective of the cause of the liver disease. They also demonstrated that the hypercalcemia was resorptive in nature based on calcium absorption tests (3). As these patients have acute decompensation of chronic liver disease, some inflammatory substances elaborated could be the cause for increased resorp-

### Table 1 - Parameters of case 1 during the hospital stay.

| Parameter          | Day 01 | Day 05 | Day 10 | Day 15 | Day 20 | Day 25 | Day 35 | Day 45 | Normal Values |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|---------------|
| Total Calcium (mg/dL) | 9.7    | 10.0   | 10.9   | 11.8   | 10.8   | 9.9    | 10.3   | 9.2    | 8.4-10.2      |
| Serum Albumin (g/dL)    | 3.2    | 3.0    | 2.9    | 3.2    | 3.3    | 2.9    | 2.9    | 2.9    | 3.5-5.0       |
| Corrected Calcium* (mg/dL) | 10.3   | 10.8   | 11.7   | 12.4   | 11.3   | 10.8   | 11.2   | 10.0   | 8.4-10.2      |
| Ionized Calcium (mmol/L) | 1.25   | 1.41   | 1.36   | 1.50   | 1.41   | 1.38   | 1.32   | 1.24   | 1.15-1.29     |
| Serum Phosphorus (mg/dL) | 3.8    | -      | 3.1    | 4.2    | -      | 3.6    | 3.5    | 3.8    | 2.5-4.5       |
| Total Bilirubin (mg/dL) | 2.5    | 3.5    | 40.3   | 48.0   | 42.1   | 34.3   | 16.9   | 8.8    | 0.2-1.3       |
| AST (U/L)             | 90     | 115    | 130    | 127    | 122    | 120    | 108    | 93     | 17-59         |
| ALT (U/L)             | 44     | 44     | 48     | 49     | 51     | 65     | 50     | 37     | 21-72         |
| ALP (U/L)             | 161    | 206    | 200    | 173    | 187    | 160    | 168    | 165    | 30-120        |
| PT (seconds)          | 12.6   | 12.9   | 14.6   | 14.2   | 14.9   | 15.6   | 14.9   | 12.1   | 8.8-12.3      |
| Serum Creatinine (mg/dL) | 1.0    | 1.4    | 2.8    | 2.1    | 1.5    | 1.3    | 1.0    | 0.8    | 0.8-1.5       |

*Corrected calcium = [0.8 x (4 - serum albumin)] + serum calcium

### Table 2 - Parameters of case 2 during the hospital stay.

| Parameter          | Day 01 | Day 03 | Day 05 | Day 07 | Day 09 | Day 11 | Day 15 | Day 25 | Normal Values |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|---------------|
| Total Calcium (mg/dL) | 10.2   | 11.5   | 12.2   | 11.7   | 10.2   | 10.0   | 10.9   | 9.0    | 8.4-10.2      |
| Serum Albumin (g/dL)    | 2.8    | 2.2    | 3.1    | 2.7    | 2.3    | 3.0    | 3.0    | 3.0    | 3.5-5.0       |
| Corrected Calcium* (mg/dL) | 11.2   | 12.9   | 12.9   | 12.7   | 11.6   | 10.8   | 11.7   | 9.8    | 8.4-10.2      |
| Ionized Calcium (mmol/L) | 1.39   | 1.47   | 2.12   | 1.70   | 1.28   | 1.31   | 1.39   | 1.18   | 1.15-1.29     |
| Serum Phosphorus (mg/dL) | 4.0    | 3.5    | 3.1    | 3.2    | 2.4    | 2.6    | 3.7    | 3.6    | 2.5-4.5       |
| Total Bilirubin (mg/dL) | 2.2    | 2.8    | 3.8    | 4.7    | 4.5    | 5.4    | 6.8    | 5.6    | 0.2-1.3       |
| AST (U/L)             | 50     | 41     | 45     | 59     | 55     | 44     | 43     | 50     | 17-59         |
| ALT (U/L)             | 31     | 22     | 18     | 21     | 26     | 23     | 18     | 26     | 21-72         |
| ALP (U/L)             | 258    | 139    | 137    | 126    | 161    | 117    | 121    | 129    | 30-120        |
| PT (Seconds)          | 20.4   | 19.6   | 23.3   | 25.5   | 23.9   | 23.3   | 21.8   | 23.0   | 8.8-12.3      |
| Serum Creatinine (mg/dL) | 0.7    | 0.6    | 0.5    | 0.5    | 0.6    | 0.7    | 0.5    | 0.4    | 0.8-1.5       |

*Corrected calcium = [0.8 x (4 - serum albumin)] + serum calcium

### Discussion

Advanced chronic liver disease is not a known cause of hypercalcemia except in the setting of hepatic neoplasia. Gerhardt et al. described an interesting pattern of hypercalcemia in 11 patients who had advanced chronic liver disease but no hepatic cancer (1). There were no obvious causes for hypercalcemia after extensive evaluation in them. The Authors suggested that hypercalcemia might be due to chronic liver disease per se. After extensive evaluation, no obvious cause for PTH-independent hypercalcemia was detected.

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Table 3 - Biochemical parameters of case 1 and case 2 for excluding other causes of hypercalcemia.

| Parameter            | Case 1         | Case 2         | Normal value |
|----------------------|----------------|----------------|--------------|
| iPTH (pg/mL)         | 16.1, 19.8     | 10.3, 16.6     | 15-68.3      |
| 25(OH)D (ng/mL)      | 19.3, 25.4     | 51.3, 24.4     | 20.0-50.0    |
| 1,25(OH)_{2}D (pmol/L)| 24.57 | 55.9 | 39.0-193.0 |
| PTH-rp (pg/mL)       | 16.0           | 13.0           | 14.0-24.0    |
| ACE (μU/mL)          | 11.0           | 15.0           | 8.0-65.0     |
| Free T4 (ng/dL)      | 1.61           | 1.91           | 0.78-2.19    |
| AFP (μU/mL)          | 4.0            | 4.4            | 0.0-4.4      |
| CEA (ng/mL)          | 1.3            | 9.4            | 0.0-3.0      |
| CA 19-9 (U/mL)       | 82             | 78             | 0.0-37.0     |
| PSA (ng/mL)          | 0.09           | 0.07           | 0.0-4.0      |
| Morning Cortisol (μg/dL) | 16.1 | 20.1 | - |

iPTH (Intact parathyroid hormone), 25(OH)D (25-hydroxy vitamin D), 1,25(OH)_{2}D (1,25-dihydroxy vitamin D), PTH-rp (PTH-related peptide), ACE (angiotensinogen converting enzyme), TSH (thyroid stimulating hormone), T4 (thyroxine), AFP (Alpha-fetoprotein), CEA (carcinoembryonic antigen), CA-19-9 (carbohydrate antigen 19-9), PSA (prostate specific antigen).

Discussion

Bone resorption increases with immobilization leading to hypercalcemia in patients who are bedridden for at least 4 weeks if the renal functions are impaired and up to 6 weeks if the renal functions are normal (8). Seven out of 11 patients in Gerhardt’s series had received vitamin D supplementation orally, intravenously or intramuscularly in the near past. Despite that all the patients had lower serum 25OHD and 1,25(OH)_{2}D levels. None of our patients received vitamin D supplementation and both vitamin D metabolites were on lower side.

Conclusions

When hypercalcemia is encountered in a patient with chronic liver disease, the diagnosis of hypercalcemia of advanced chronic liver disease can be made after exclusion of usual causes of parathyroid hormone-independent hypercalcemia. This type of hypercalcemia is relatively easy to treat and may respond to calcitonin therapy. Much work is needed to dissect this clinical condition fully.

References

1. Gerhardt A, Greenberg A, Reilly J, Van Thiel D. Hypercalcemia, a complication of advanced chronic liver disease. Arch Intern Med. 1987; 147:274-277.
2. Cadranel JF, Cadranel J, Buffet C, Ink O, Pelletier G, Bismuth E, et al. Hypercalcemia associated with chronic viral hepatitis. Postgraduate Medical Journal. 1989;65:678-680.
3. Meynier A, Valeyre D, Bouillon R, Paillard F, Battesti JP, Georges R. Resorptive versus absorptive hypercalcemia in sarcoidosis: correlation with 25 hydroxy vitamin D3 and 1,25 dihydroxy vitamin D3 and parameters of disease activity. Q J Med. 1985;54:269-281.
4. Mundy GR, Ibbotson KJ, D’Souza SM, Simpson EL, Jacobs JW, Martin TJ. The hypercalcemia of cancer: clinical implications and pathogenic mechanisms. N Engl J Med. 1984;310:1718-1727.
5. Mundy GR. Hypercalcemia of malignancy revisited. J Clin Invest. 1988;82:1-6.
6. Marius CF, Fillaus J, Groggel G. A rare case of liver diseases induced hypercalcemia. Case presentation and review of the literature. The Internet journal of Nephrology. 2009;5:1.

7. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE. Calcium homeostasis in immobilization: an example of resorptive hypercalcia. N Engl J Med. 1982;306:1136-1140.

8. Evans RA, Bridgeman M, Hills E, Dunstan CR. Immobilization hypercalcemia. Miner Electrolyte Metab. 1984;10:244-248.