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Secondary hyperparathyroidism and symptomatic hypercalcemia: overlooked complications of chronic liver disease

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ABSTRACT

A 71-year-old female with biopsy-proven liver cirrhosis was brought to the ER due to confusion for 5 days. She was diagnosed with acute decompensated liver disease and hepatic encephalopathy. Investigations also revealed PTH-dependent hypercalcemia. Both of these entities could be causing her symptoms. Neck ultrasound did not reveal any parathyroid lesions. Alteration in mental status persisted even after the management and resolution of hepatic encephalopathy. Symptomatic resolution occurred after normalization of her calcium levels which required normal saline, cinacalcet as well as calcitonin over the course of 7 days. Hypercalcemia secondary to chronic liver disease should be considered in the differential diagnosis of patients with liver cirrhosis presenting with an altered mental status. Hypercalcemia of chronic liver disease is not always transient and managed with normal saline as previously reported; It could necessitate more aggressive therapy with calcitonin and cinacalcet as reported in this case.

Keywords: Chronic liver disease; Case report

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Background

Chronic liver disease is known to cause hypercalcemia when complicated by cholangiocarcinoma and hepatocellular carcinoma. However, there is no clear understanding of hypercalcemia resulting from advanced chronic liver disease in the absence of hepatic neoplasia.

The majority of the studies have shown a clear correlation between vitamin D deficiency and chronic liver disease. Other studies investigating the correlation between parathyroid hormone level, calcium level and chronic liver disease have shown inconsistent findings. Hypercalcemia and secondary hyperparathyroidism have been reported to be complications of chronic liver disease, each as an entity on its own. This is the first article that shows the coexistence of hyperparathyroidism and symptomatic hypercalcemia in a setting of chronic liver disease.

Case presentation

A 71-year-old female with a past medical history of hypertension, diabetes mellitus type 2, nonalcoholic liver steatohepatitis and biopsy-proven cirrhosis complicated by hepatic encephalopathy with esophageal varices presented with confusion for the past 5 days.

Investigations

She was diagnosed with decompensated liver disease and hepatic encephalopathy. Her MELDNa score was 19. She was also found to have an elevated albumin-corrected total calcium level of 13.9 mg/dL. Her baseline albumin-corrected total calcium level was between 10 to 11mg/dL since January 2018 and had not been previously investigated. Her ionized calcium was 1.71 mmol/L, PTH was elevated at a level of 72 pg/mL and 25-hydroxyvitamin D and 1-25 dihydroxyvitamin D were found to be low at 15 ng/mL and less than 8pg/mL respectively. Her PTH related peptide was unmeasurable. A morning cortisol was 18.6mg. Ultrasound of the thyroid and soft tissue of the neck showed no extrathyroidal lesions to suggest parathyroid adenoma. A sestamibi scan was ordered but not done. An abdominal ultrasound showed cirrhotic morphology of liver with possible hypoechoic nodule along the inferior left hepatic lobe and an alpha-fetoprotein level of 3.7 ng/mL. She was not taking thiazides, vitamin A, lithium or antacids that would cause an elevation in her serum calcium level. She was diagnosed with primary hyperparathyroidism with a component of secondary hyperparathyroidism.

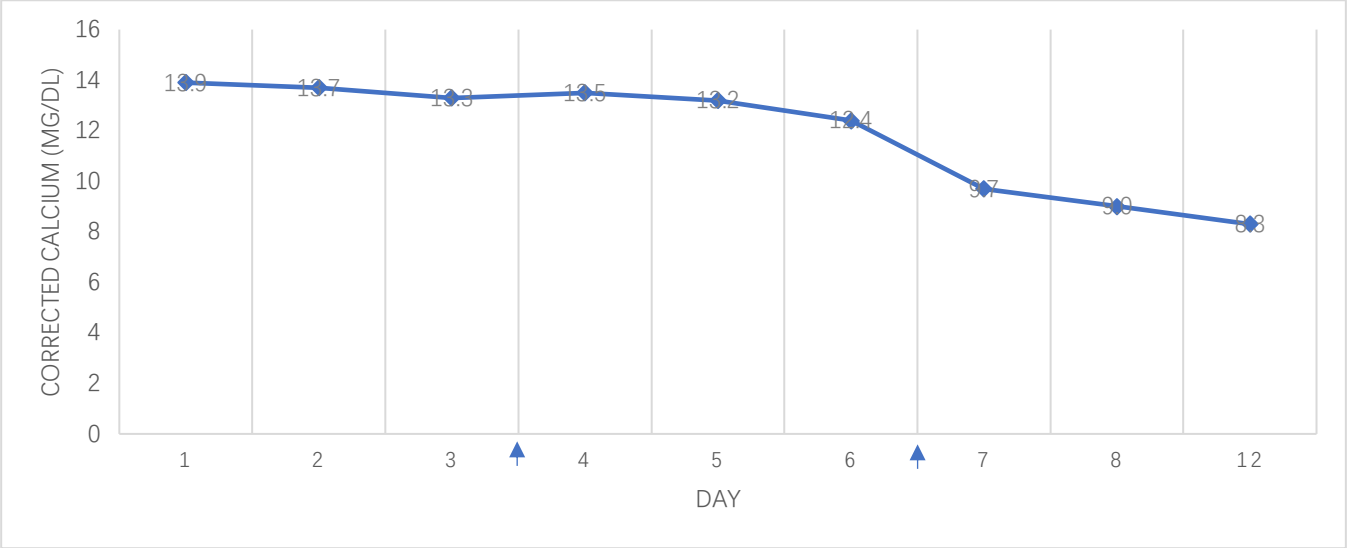
Differential Diagnosis

The first important step in determining the etiology of this individual's hypercalcemia was checking a parathyroid hormone (PTH) level. The PTH was elevated mitigating against exogenous calcium intake, granulomatous or tumor mediated hypercalcemia and consistent with hyperparathyroidism. In this case, the hypercalcemia was attributed to primary hyperparathyroidism which was worsened by correcting her previous vitamin D deficiency. A neck ultrasound failed to reveal parathyroid enlargement. A 24-hour urine for creatinine clearance and calcium excretion were done to rule out familial hypocalciuric hypercalcemia after stopping diuretics for three days and was normal. Her renal function was normal and thus tertiary hyperparathyroidism was not a consideration.

Treatment

On day 2, her albumin-corrected total calcium level and ionized calcium increased to 13.5 mg/dL and 1.7 mmol/L respectively. She was managed with normal saline. Furosemide and spironolactone were held because of non-oliguric acute renal failure with a creatinine level of 1.56 mg/dL. Diuretics were held which allowed a urine sample for calcium and creatinine to be obtained to rule out familial hypocalciuric hypercalcemia. Her 24-hour urine calcium level was 344 mg/24hr and urine creatinine was 0.8 gm/24hr. On day 3, she was started on 30 mg of cinacalcet twice a day because her albumin-corrected calcium levels remained elevated even after hydration (figure 1).

Figure 1: Serial measurement of serum albumin-corrected calcium levels after initiation of Cinacalcet on day 3 and a dramatic decrease in this level after doubling the dose of Cinacalcet and initiation of Calcitonin on day 6.



On day 5 of admission, her albumin-corrected total calcium level increased to 13.3 mg/dL and ionized Ca+ 1.77 mmol/L. Despite normalization of liver function tests the patient still had an alteration in her mental status. The dose of cinacalcet was increased from 30 to 60mg twice a day and two doses of calcitonin 300U subcutaneously every 12 hours were given after the urine was collected on day 6. Her calcium-creatinine clearance ratio (CCCR) was shown to be 4% which supported the diagnosis of primary hyperparathyroidism rather than familial hypocalciuric hypercalcemia. Her calcium levels normalized on day 7 of admission. On the day of discharge her albumin-corrected total calcium level was 8.3 mg/dL and ionized calcium was 1.00 mmol/L. A summary of the patient's pertinent laboratory values reported from day of admission until day of discharge is presented in (Table 1).

Table 1: Pertinent laboratory values during hospitalization

Parameter \ Day	1	2	3	4	5	6	7	8	12	Reference Range
Total calcium (mg/dL)	12.9	12.6	12.4	12.6	12.2	11.3	8.6	7.7	6.8	8.5-10.5
Serum albumin (g/dL)	2.8	2.6	2.9	2.9	2.7	2.6	2.6	2.4	2.1	3.6-5.0
Corrected calcium (mg/dL)	13.9	13.7	13.3	13.5	13.2	12.4	9.7	9.0	8.3	8.5-10.5
Ionized calcium (mmol/L)		1.71	1.68	1.69	1.75	1.69	1.26	1.2	1.0	1.15-1.30
Serum phosphorus (mg/dL)		2.7	2.1	2.2	2.4	1.8	1.8	3.1	3.0	2.5-4.7
Total Bilirubin (mg/dL)	4.0	3.7	3.0	3.4	2.9	2.6	2.4	2.3	1.8	0.2-1.4
AST (U/L)	41	38	45	49	54	43	43	40	40	10-40
ALT (U/L)	26	24	25	28	26	26	30	27	28	7-35
ALP (U/L)	153	133	122	135	117	124	165	159	136	30-110
PT (seconds)								18	17.7	9.7-13.1
Serum creatinine (mg/dL)	1.56	1.52	1.56	1.47	1.54	1.22	1.28	1.34	1.63	0.6-1.4

Outcome and follow-up

After complete workup, the options of parathyroidectomy versus medical therapy with cinacalcet 90mg twice a day were discussed with the family. Indications for surgery were explained including a calcium level that is 1mg/dL above the upper limit of normal, the presence of osteoporosis, and a decrease in glomerular filtration rate (GFR) consistent with renal dysfunction. While surgery would be appropriate based on these criteria, the underlying liver disease was progressive and it was elected to use cinacalcet to block PTH. Since this medication requires several days to lower calcium level,

calcitonin was also used for 72 hours to lower her calcium quickly. While this regimen was very effective for lowering the calcium level into the normal range and allowed the individual to be discharged, the underlying liver disease progressed and she expired within 6 weeks of discharge. Her calcium prior to her death was normal on cinacalcet.

Discussion:

Vitamin D holds significance in the maintenance of calcium homeostasis through its vital role in the Ca-PTH axis. However, it is still not well understood how this axis shifts in chronic liver disease (CLD). [1] Previous studies have shown a wide prevalence of hypovitaminosis D in patients with CLD due to a variety of causes. [1,2] Conversely, some studies show no association between hypovitaminosis D and CLD due to hemochromatosis, [3] non-alcoholic fatty liver disease, [4] non-cirrhotic viral liver disease, [5] and liver cirrhosis. [6,7]

In past studies, vitamin D deficiency and severity of liver disease were not consistently shown to be correlated, [8,9] whereas some studies have shown that vitamin D levels decrease as liver damage progresses. [1,10,11] The severity of vitamin D deficiency was found to strongly correlate with higher CTP and MELD scores, which may indicate an impairment in vitamin D metabolism among patients with liver cirrhosis. [1-10]

There are conflicting studies on the association between calcium levels and liver cirrhosis. A recent study conducted by Narayanasamy et al. published in 2018 reported that 85.59% of patients with CLD have hypocalcemia, as well as hypovitaminosis D in 69.3% of the hypocalcemic patients. [1] The study by Duarte et al. reports that cirrhotic patients show a clear decline in serum calcium levels as opposed to noncirrhotic patients. [6] Conversely, the study conducted by Miroliaee, A et al. in 2010 found that liver disease, cirrhotic and noncirrhotic, holds no association to serum calcium levels. [10]

CLD is known to cause hypercalcemia when complicated by cholangiocarcinoma and hepatocellular carcinoma. However, there is not a clear understanding of hypercalcemia resulting from advanced CLD in the absence of hepatic neoplasia. As shown by Gerhardt et al., eleven patients with advanced CLD in the absence of hepatic cancer showed a remarkable pattern of hypercalcemia. After evaluating those patients, nothing was shown to cause hypercalcemia. [12] Another study conducted by Kuchay, M. S. et al also describes two cases of advanced CLD in which hypercalcemia had developed without any identifiable cause [13]; it was suggested that chronic liver disease as an entity on its own, causes hypercalcemia. The correlation between PTH levels and liver cirrhosis remains undetermined, as secondary hyperparathyroidism proved to be uncommon among patients with hypovitaminosis D and liver cirrhosis. [10]

Presently, no association is shown between PTH levels and the severity of CLD. Miroliaee, A et al showed that, out of 61 patients with both CLD and vitamin D deficiency, only 6 had increased PTH levels. There are currently no known causes of the normal to low PTH levels in vitamin D deficiency. One possibility is that PTH secretion is suppressed by specific vitamin D receptor gene polymorphisms. [10] A study conducted in 1989 measured the levels of intact, aminoterminal, and mid-region PTH of 11 patients with severe liver disease and compared them to 8 age-matched controls. They found that serum PTH levels were normal in all assays. [14] These studies conflict with the previous studies conducted to test whether secondary hyperparathyroidism occurs due to impaired liver function. The study conducted in 1980 by Louboutin JY et al. revealed a statistically significant increase in amino-terminal PTH in patients with decompensated liver cirrhosis compared to patients with non-decompensated liver cirrhosis. They've also noted no increase in the terminal C fraction of PTH. [15] Atkinson MJ,et al. conducted a study in 1983 and found an increase in intact-PTH and a decrease in carboxylregional PTH concentrations. They've hypothesized that the elevation of intact PTH in patients with primary biliary cirrhosis is due to defective Kupffer cell-mediated cleavage of the hormone. [16] The study conducted by Kirch et al. in 1990 revealed that

although the level of albumin-corrected total calcium levels of patients with liver cirrhosis were on the lower limit of normal, the corrected calcium and PTH were positively correlated, which signifies that the elevated levels of PTH is not reactive to calcium depletion. They've concluded that the midregion PTH fragments are increased in patients with liver cirrhosis rather than the intact hormone. [17]

On another note, more research is required to further clarify whether correcting low levels of Vitamin D will alter the severity of CLD. The effect of vitamin D supplements on the progression and severity of liver fibrosis in NAFLD patients will be determined for the first time by the randomized controlled trial conducted by Ebrahimpour-Koujan, S. et al. [18]

We describe a patient with liver cirrhosis due to nonalcoholic fatty liver disease who was found to have significant hypercalcemia causing an alteration in her mental status, an inappropriately elevated PTH level and a low Vitamin D level. She was managed with cinacalcet and calcitonin over the course of her admission; albumin-corrected total calcium level, as well as ionized calcium level, returned to normal limits by the 7th day of admission.

Learning points

- This is an atypical presentation of a forgotten clinical entity.
- Consider hypercalcemia secondary to chronic liver disease in the differential diagnosis of patients presenting with liver cirrhosis and altered mental status.
- Hypercalcemia of chronic liver disease is not always transient and managed with normal saline as previously reported. It could necessitate more aggressive therapy with calcitonin and cinacalcet as reported in this case.
- More studies are required to determine the correlation between PTH and calcium levels in patients with advanced chronic liver disease.

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