Multifactorial Causes of Hypocalcemia

Javvaji A, Reddy V, Naran J, Barnes C, Raza M, Haytoglu T, Can A

Case Report

A 61 year old male with a significant history of stage IV metastatic clear cell renal cancer, status post right nephrectomy with metastasis to the bone had been receiving systemic chemotherapy. Since starting chemotherapy, he developed chronic diarrhea (2 years). Of note, on physical examination patient has 2+ pitting edema secondary to low albumin with poor oncotic pressure. Initially he was being treated for his cancer with Pazopanib 800mg and Zometa 4mg IV monthly consistently for 1 year (table 1). He was on Pazopanib 800mg tablet daily from August 2017 to July 2018. Because there was progression of the disease noted on imaging, he was switched to Nivolumab 480mg on 7/25/18 and received nine monthly infusions until March 7th 2019 when he was admitted with severe diarrhea with lymphocytic microscopic colitis. Along with chemotherapy he received 20 monthly infusions of zoledronic acid 4mg IV from Aug 2018 to March 2019.

On admission he was found to have diarrhea of >15 loose watery bowel movements and had lost 20lbs over the previous month. He also had nausea & vomiting with upper abdominal pain. GI team was consulted and performed a colonoscopy that did demonstrate lymphocytic microscopic colitis. He was started on Imodium, Questran, Lomotil which provided him with some relief. Of note patient did have a non chloremic anion gap metabolic acidosis secondary to prolonged diarrhea as well as prerenal AKI. Nephrology team was consulted and placed the patient on bicarbonate infusion as the bicarbonate level was critically low at 9. Patient was continued on bicarbonate as underlying diarrhea continued. At the time of initiation of bicarb the serum calcium was 7.6mg/dL.

Corticosteroids were also initiated shortly after admission with the recommendation of the oncologist to reduce inflammation and help control episodes of diarrhea and were continued till 3/21/19. It appears the diarrhea continued throughout the hospitalization until infliximab was initiated by the GI team. Octreotide and TPN was also started at one point but shortly discontinued. Hypocalcemia was noted at 7.6mg/dL at the time of prednisone initiation. Serum calcium did fall to the levels of 4.2 at the lowest point. IV infusion of calcium gluconate was then changed to IV calcium chloride.

Ultimately patient's calcium did respond to IV calcium, calcitriol, cholecalciferol, and oral calcium. Calcium levels did normalize to 8.4 mg/dL and was discharged on calcitriol, cholecalciferol, and oral calcium.

TABLE 1

Medications/ Dosage	Dates
Pazopanib 800 mg daily	8/30/2017-6/21/2018
Nivolumab 480 mg IV	7/25/2018-3/7/2019
Cabometyx 40 mg daily	6/10/2019-unknown
Zoledronic 4mg IV	8/30/2017-3/7/2019

Discussion

We present a case of hypocalcemia due to multiple etiologies. We discuss various causes of hypocalcemia pertaining: including severe vitamin D deficiency, long term use of zoledronic acid, bicarbonate use, steroid use, malabsorption secondary to diarrhea, nivolumab therapy, acute renal insufficiency, hypomagnesemia, bone metastasis.

Vitamin D deficiency is associated with rickets and can lead to hypocalcemia. Can be caused by multiple etiologies including poor intake or malabsorption coupled with reduced exposure to ultraviolet light, decreased 25-hydroxylation of vitamin D to form 25-hydroxyvitamin D (calcidiol) in the liver, increased metabolism to inactive metabolites, decreased 1-hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidney, and decreased 1,25-dihydroxyvitamin D action. We think in our case hypocalcemia is primarily due to secondary to low vitamin D level due to poor intake with malabsorption. Diminished vitamin D absorption leads to a decreased absorption of calcium in the intestines.

Bone metastasis- osteoblastic metastases can contribute to a low serum calcium (1) however given his previous imaging showed osteolytic lesions, more of a hypercalcemic picture is expected. Direct bone metastasis is not likely the cause of hypocalcemia in this patient.

Steroid use is likely another cause of hypocalcemia in this patient as the levels were 7.6mg/dL on admission and steroids were initiated and levels did drop to 4.2 at the lowest point. Eventually the steroids were tapered and there was an improvement of serum calcium levels.

Bisphosphonates are pyrophosphate analogues bind to hydroxyapatite in bone, and inhibits osteoclast activity. Hypocalcemia caused by inhibition of osteoclast activity is avoided secondary to compensatory mechanisms (2). PTH secretion is increased to compensate for hypocalcemia as seen in this case with elevated PTH level at 229.6. Compensatory mechanisms have been blocked due to underlying low vitamin D levels and prior prolonged bisphosphonate therapy in our case. It is recommended to evaluate for vitamin D deficiency (3) prior to initiating osteoclast inhibitor and periodically during bisphosphonate treatment. Vitamin D 25 dihydroxy level was 9.5mg/mL indicating vitamin D deficiency. The setting of bisphosphonate use in Vitamin D deficiency is associated with worsening hypocalcemia. It may be possible that 20 doses of zoledronic acid has suppressed his osteoclast activity to the point that there is difficulty in maintaining calcium metabolism. Bone turnover revealed very low osteocalcin, 1 (normal 9-42). and initial suspicion of decreased bone formation and adynamic bone disease, normal beta cross labs, 369 (normal 40-840).

Renal insufficiency is associated with worsening hypocalcemia. The compounding effect of Vitamin D deficiency with renal insufficiency is likely one of the causes of severe hypocalcemia in this case. It is the combination of low vitamin D level and acute renal insufficiency that worsened acute hypocalcemia and previous long-term bisphosphonate therapy prevented recovery from hypocalcemia. Acute renal failure can lead to defective alpha 1 hydroxylation of 25 hydroxy vitamin D decreased calcium levels further. It remains unclear the level of contribution of renal insufficiency leading to hypocalcemia relative to the other causes in this case.

Various chemotherapeutic drugs, most commonly cisplatin can lead to hypocalcemia. Many endocrinopathies are noted to occur with immune checkpoint inhibitors including **Nivolumab** (a humanized antibody against PD-1). Hypoparathyroidism leading to hypocalcemia has been reported in one rare case with Nivolumb (4). In our case the cause of hypocalcemia is not secondary to hypoparathyroidism as PTH level was appropriately high. Of Note, Opdivo (Nivolumab) was given to the patient with monthly infusions for a total of 9 cycles.

Sodium Bicarbonate is another cause for hypocalcemia in this case. Initially was started for metabolic acidosis secondary to significant GI losses and diarrhea leading to non hypochloremic metabolic acidosis. Upon initiation of bicarbonate drip patient continued to have more drop in serum calcium levels to a critical level of 4.1mg/dL. Given the metabolic acidosis was severe and patient continued to have episodes of diarrhea, bicarbonate therapy was continued.

Patient had diarrhea throughout the hospitalization. Once infliximab and octreotide was started then only did his diarrhea subside. Patient did have of 20lbs weight loss. Ultimately lack of absorption of vitamin D and calcium with protein calorie malnutrition compounded the hypocalcemia further.

Hypomagnesemia (5) can reduce PTH secretion or cause PTH resistance and is therefore associated with normal, low, or high PTH levels. Our patient did have decreased magnesium levels to as low as 1.5mg/dL. Given the PTH levels were appropriately elevated, there may have been an underlying PTH resistance noted. Once hypomagnesemia was corrected serum calcium did improve.

Conclusion

Hypocalcemia can be caused by multiple etiologies. The clinicians such be aware of each cause of hypocalcemia in differential diagnosis.

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