CLINICAL REPORT

A Case of Transient Hyperphosphatemia and Hypoparathyroidism

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Case

A 28-year-old female with systemic lupus erythematosus was admitted with hemophagocytic lymphohistiocytosis (HLH). While being treated with mycophenolate and dexamethasone, her serum phosphorus levels were elevated to 6.5 mg/dl (reference range 2.3-4.4 mg/dl). Intact parathyroid hormone level was 10 pg/ml (reference range 11-51 pg/ml). At that time the endocrinology was consulted for the evaluation of hyperphosphatemia and possible hypoparathyroidism.

She had no history of prior problems with calcium or phosphorous. There was no history of kidney disease, neck surgery, parathyroid or thyroid disorders.

On initial consultation, vitals showed blood pressure 115/66 mmHg, pulse 96 beats per minute, temperature of 36.8° C, respiratory rate of 18 breaths per minute, and weight of 67.8 kilograms. Physical exam was remarkable for a chronically ill appearing woman with a negative Chvostek's sign, and diminished strength 2/5 in bilateral lower extremities.

At the time of initial consultation, laboratory values were notable for: creatinine 0.33 mg/dL (0.6-1.3 mg/dl), calcium 7.9 mg/dL (8.6-10.3 mg/dL), ionized calcium 1.11 mmol/l (1.09-1.29 mmol/l), phosphorus 6.5 mg/dl (2.3-4.4 mg/dl), magnesium 1.4 mEq/L (1.4-1.9 mEq/L), albumin 1.8 (3.9-5.0g/dl), intact parathyroid hormone (PTH) 10 pg/ml (11-51 pg/ml), vitamin D-25-hydroxy 6 pg/ml (20-50 ng/ml), and vitamin D-1,25-dihydroxy 6.7 (19.9-79.3 pg/ml). Review of prior laboratory values two weeks prior to consultation showed initial normal phosphorus level with gradual increase to a maximum of 6.5 mg/dL. Serum creatinine had been as high as 0.86 mg/dl, with a baseline level between 0.2-0.4 mg/dl.

Additional testing included negative parathyroid antibody levels and 24-hour urine phosphorus of 0.2 g (0.9-1.3 g), calcium of 36 mg (0-300mg), and creatinine 164 mg (1000-1800mg), with a volume of 411 mL.

Given the hyperphosphatemia, the patient was started on sevelamer 800mg with meals. Due to concern for hypoparathyroidism as the etiology of the hyperphosphatemia, calcitriol was also started. She was also on her third week of ergocalciferol 50,000IU weekly for vitamin D-25-hydroxy level of 5 ng/ml (reference range 20-50 ng/ml).

Over the next week, serum phosphorus levels returned to the normal range, and calcitriol and sevelamer were subsequently discontinued.

Once phosphorous levels were normal, laboratory values were reassessed one week after initial consultation. These included: Calcium 7.6 mg/dL (8.6-10.3 mg/dL), ionized calcium 1.22mmol/l (1.09-1.29 mmol/l), magnesium 1.8 mEq/L (1.4-1.9 mEq/L), phosphorus 3.1 mg/dl (2.3-4.4 mg/dl), albumin 1.9 (3.9-5.0g/dl), intact parathyroid hormone level 45pg/ml (11-51 pg/ml), vitamin D-25-hydroxy 9 pg/ml (20-50 ng/ml), and vitamin D-1,25-dihydroxy 29.7 (19.9-79.3 pg/ml).

Discussion

The etiology of hyperphosphatemia can be due to impaired renal phosphate excretion or due to increased extracellular phosphate. Causes of impaired renal phosphate excretion include renal insufficiency and endocrinopathies, including hypoparathyroidism. Causes of increased extracellular phosphate include rapid administration of phosphorus as with liposomal amphotericin B, from cellular break down (as in crush injuries or cellular lysis hemolytic anemia or tumor lysis syndrome), or from cellular shifts, as in metabolic acidosis.[1]

This patient did not have a clear cause of increased extracellular phosphate. Her medication history did not include exogenous phosphorus intake. Laboratory values did not show cellular break down or increased cellular shifts.

She had acute kidney injury earlier in her illness. Her low serum creatinine reflected overall deconditioning and lack of muscle mass. The 24-hour urine collection showed low phosphorus excretion, suggestive of impaired renal excretion. However, the 24-hour urine collection had low volume and low creatinine, suggesting overall impaired renal function, making difficult interpretation of the 24-hour urine collection results.

The high initial phosphorus occurred in conjunction with low parathyroid hormone suggestive of hypoparathyroidism. However, both calcium corrected for the low albumin and ionized calcium were normal and hypocalcemia is considered a defining feature of hypoparathyroidism.

Hypoparathyroidism most frequently occurs after neck surgery, especially thyroidectomy if the parathyroid glands are temporarily or permanently injured. Other less common causes include radiation, metastatic infiltration, or deposition in hemochromatosis or Wilson's disease. There are a number of rare genetic causes of hypoparathyroidism, such as DiGeorge syndrome. Autoimmune disorders can also affect the parathyroid glands. One example is autoimmune polyglandular syndrome type 1 (APS1), which typically presents in childhood, is commonly characterized by hypoparathyroidism. Acquired autoimmune hypoparathyroidism can also be due to antibodies to the calcium-sensing receptor, which has been associated with other autoimmune diseases such as Grave's disease and primary adrenal insufficiency. Hypoparathyroidism can occur transiently in the setting of hypomagnesemia or hypermagnesemia, since proper levels of magnesium are required for secretion and action of PTH.[2]

On initial consultation, we considered an autoimmune process given the patient's significant history of lupus. Autoimmune hypoparathyroidism is a rare entity. Autoimmune hypoparathyroidism as a part of APS1 has been reported as frequently as 1 in 25,000 in Finland to 1 in 10 million in Japan. Idiopathic autoimmune hypoparathyroidism has been described in case reports. There are few studies assessing the sensitivity of parathyroid antibodies, and depending on the assay are reported positive in 38-100% of patients with hypoparathyroidism.[3] Our patient had negative parathyroid antibodies.

Interestingly, our patient's phosphorus levels normalized with minimal intervention. Furthermore, the initial low parathyroid hormone level resolved on subsequent evaluation. While the vitamin D-25-hydroxy levels remained low despite supplementation, the low vitamin D-1,25-dihydroxy level returned to the normal range, likely from improved parathyroid hormone levels and improved conversion from vitamin D-25-hydroxy to vitamin D-1,25-dihydroxy.

Given the self-resolution of the hyperphosphatemia, we ultimately favored hyperphosphatemia due to an inflammatory response in the setting of her autoimmune disease. This is likely a unique situation. A number of studies of critically ill patients documented vitamin D-25-hydroxy deficiency with hypocalcemia and secondary hyperparathyroidism.[4,5]

Patients with rheumatoid arthritis have markedly decreased PTH release in the setting of induced hypocalcemia, and the release of PTH has a strong inverse relationship to the degree of inflammatory activity.[6]

Conclusion

We reviewed the etiologies of hyperphosphatemia and hypoparathyroidism. Our patient's hyperphosphatemia and hypoparathyroidism spontaneously resolved. One possible mechanism is transient, acquired hypoparathyroidism in the setting of autoimmune disease.

REFERENCES

1. **Bringhurst FR, Demay MB, Kronenberg HM.** Hormones and disorders of mineral metabolism. In: Melmed S, Polonsky K, Larsen PR, Kronenberg HM, editors. Williams Textbook of Endocrinology. Philadelphia: Elsevier; 2016. p. 1304-1305.
2. **Al-Azem H, Khan AA.** Hypoparathyroidism. *Best Pract Res Clin Endocrinol Metab*. 2012 Aug;26(4):517-22. doi: 10.1016/j.beem.2012.01.004. Epub 2012 May 31. Review. PubMed PMID: 22863393.
3. **Betterle C, Garelli S, Presotto F.** Diagnosis and classification of autoimmune parathyroid disease. *Autoimmun Rev*. 2014 Apr-May;13(4-5):417-22. doi:10.1016/j.autrev.2014.01.044. Epub 2014 Jan 11. Review. PubMed PMID: 24424178.
4. **Nair P, Lee P, Reynolds C, Nguyen ND, Myburgh J, Eisman JA, Center JR.** Significant perturbation of vitamin D-parathyroid-calcium axis and adverse clinical outcomes in critically ill patients. *Intensive Care Med*. 2013 Feb;39(2):267-74. doi: 10.1007/s00134-012-2713-y. Epub 2012 Oct 13. PubMed PMID: 23064465.
5. **Hu J, Luo Z, Zhao X, Chen Q, Chen Z, Qin H, Qin Y, Liang X, Suo Y.** Changes in the calcium-parathyroid hormone-vitamin d axis and prognosis for critically ill patients: a prospective observational study. *PLoS One*. 2013 Sep 20;8(9):e75441. doi: 10.1371/journal.pone.0075441. eCollection 2013. PubMed PMID: 24073266; PubMed Central PMCID: PMC3779172.
6. **af Ekenstam E, Benson L, Hällgren R, Wide L, Ljunghall S.** Impaired secretion of parathyroid hormone in patients with rheumatoid arthritis: relationship to inflammatory activity. *Clin Endocrinol (Oxf)*. 1990 Mar;32(3):323-8. PubMed PMID: 2111747.

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