Severe Hypophosphatemia in a Patient with a Relapsing Lymphoma

Xiaoying Deng MD, PhD , Edgar Guzman-Suarez MD, Anju Yadav MD, Rakesh Gulati MD

Division of Nephrology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, United States

Abstract

Hypophosphatemia in cancer patients is commonly ascribed to chemotherapy, renal wasting or malnutrition from anorexia and poor PO intake. We report a case caused by rapid cancer cell proliferation. 61-year-old woman with history of marginal zone lymphoma diagnosed in 2017 who presented with fatigue, poor oral intake and undetectable phosphate levels (Phos) for 5 days. Her outpatient medications included Acyclovir 400 mg by mouth daily, Allopurinol 100 mg PO daily and Enoxaparin 60 mg under the skin every 12 hours. Blood work revealed phosphate levels less than1 mg/dl (normal 2.4-4.5mg/dl). Her intact PTH level was normal. Her phosphate level further dropped to <0.3 mg/dl on admission. The initial white blood cell count (WBC) was 41000 cells per cubic millimeter of blood and her phosphate level was < 0.3 mg/dl compared to Phos of 3.3 mg/dl with WBC of 900 cells per cubic millimeter one week prior to the admission. This severe hypophosphatemia required aggressive IV Phosphate treatment of 15 mmol k-Phos every 2 hours for 3 doses and simultaneous PO phosphorus supplementation. 24 hour fraction excretion of Phos was only 1.8%, ruling out renal loss of phosphorus including acyclovir induced renal Phos wasting.. The hypophosphatemia correlated with hyperproliferation of cancerous cells. Therefore, hypophosphatemia might be surrogate biomarker of recurrence of rapidly proliferating hematological malignancy. Phosphate levels can serve as an excellent adjuvant widely available, non-invasive and cost-effective biomarker.

Introduction

- Hypophosphatemia occurs in 2% of hospitalized patients, can up to 10% in certain population esp. alcoholics.
- The common reasons for hypophosphatemia are : Recovery of DKA, acute alcohol intoxication, severe burns, TPN, refeeding syndrome after prolonged fast and severe respiratory alkalosis.
- Chronic hypophosphatemia are commonly seen: Hypothyroidism, Primary or secondary hyperparathyroidism, Cushing syndrome, hypothyroidism, Vit D deficiency, hypokalemia, hypo-magnesemia, Theophylline intoxication, diuretics use, Aluminum-containing antacids use in CKD.
- We have not seen any report on patient who presents with persistent hypophosphatemia, associated with lymphoma.

Case Presentation and Hospital Course

- 61 year old woman with PMH of Marginal Zone Lymphoma diagnosed in 2017, S/p Cytoxan complicated with Tumor lysis syndrome (TLS) requiring CVVHD 1 month prior, PE on Enoxaparin and Hypothyroidism developed progressive fatigue after taking Acyclovir for five days. Associated with decreased oral intake, only can eat 40% of her regular meals. Outpatient medications included Acyclovir 400 mg PO QD, Allopurinol 100 mg PO QD, Lovenox 60 mg Subcut Q 12 hrs.
- Blood work revealed phosphate (Phos) level <1 mg/dl (normal 2.4-4.5 mg/dl), admitted to hospital.
- iPTH: 17 ng/ml (normal 11-67ng/ml), Glucose: 116-119 mg/dl, last A1C 6%.
- Magnesium 1.8 -2.3 mg/dl , TSH 6.73 (normal 0.3-5) uIU/ml, Free T4 1.3 (normal 0.7-1.7) ng/dl.
- Phos level decreased from < 1 mg/dl to < 0.3 mg/dl (Figure 1). Acyclovir was d/ced after admission.
- Initial Lab work:

41.2	9.9 / 30.5	293
3.9	137 104 / 25	7 / 1.62 116
9.1	2.3 / <1.0	

- Spot U Cr :79 mg/dl, U Phos: <3 mg/dl, S Cr: 1.5mg/dl, S Phos: <0.3 mg/dl. The FE Phos:< 10%.
- Received IV K-Phos 15 mmol Q2hrs x 3 doses, then 15 mmol QD x 4 days and Neutrophos 250 mg PO BID x 5 days- fatigue resolved.
- Repeated CT scan revealed improved adenopathy in retroperitoneum and worsening adenopathy above the diaphragm; and repeated flowcytometry confirmed relapse of the lymphoma.
- The patient received Dexamethasone x 4 days., Her hypophosphatemia was converted to hyperphosphatemia 2nd to TLS (Figure 2).
- Her hyperphosphatemia was treated with IV fluid hydration and strict low phosphate diet.

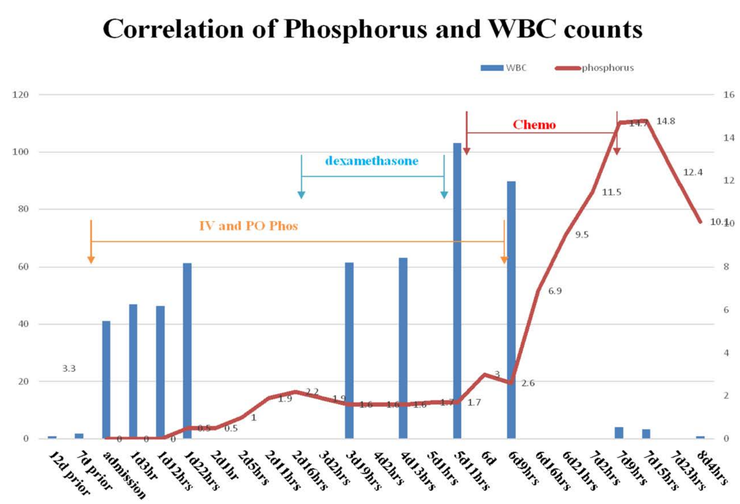

Figure 1

- Acyclovir was resumed, and it did not cause any recurrent hypophosphatemia.
- During the hospitalization, her BUN and creatinine remain stable, no AKI (Figure 3).
- Her pattern of hypophosphatemia and hyperphosphatemia are closely associated with WBC count changes (Figure 1).

Discussion

- The patient had undetectable Phos in urine, there is no renal Phos wasting, which is a key pathophysiology for FGF-23 and other phosphotonin to induce hypophosphatemia. The patient is ruled out of those conditions, including alcohol abuse, drugs, toxins, RTA, Fanconi's syndrome, or hereditary hypophosphatemia rickets with hypercalciuria.
- The patient's clinic course does not support a hypophosphatemia from cellular phosphate shifting due to hyperglycemia, IV iron infusion, IVF volume expansion, or any diuretics use.
- The patient's normal calcium levels does not suggest any involvement of Vitamin D. The patient did not have any exposure to tyrosine-kinase inhibitors, mTOR inhibitors and VEGF inhibitors, which could cause hypophosphatemia.
- Our case clearly revealed a close association between serum phosphate levels and lymphoma cell tumor burden/proliferation.
- Phos is essential component for synthesis of nucleic acid, phospholipids and ATP via Krebs cycle. Rapidly growing and dividing normal/cancer cells require continuous supply of phosphate.
- Tumor and cancers are found of sequestering phos and accumulate up to twice as much Phos as normal cells. A high Phos cellular environment induce tumor neovascularization and angiogenesis; modulate tumor metabolism and metastasis. Dietary Phos overload can stimulate cancer growth in patient's lung, increase risk for prostate cancer, promote tumorigenesis in animals.
- Further research is required to clarify the pathogenesis of the phosphate in the modulation of cancer growth and proliferation.

Conclusion

- The hypophosphatemia correlated with hyperproliferation of cancerous cells.
- Phosphate level can be an excellent surrogate biomarker of recurrence of rapidly proliferating hematological malignancy.
- Phosphate levels can serve as an excellent adjuvant widely available, non-invasive and cost-effective biomarker.

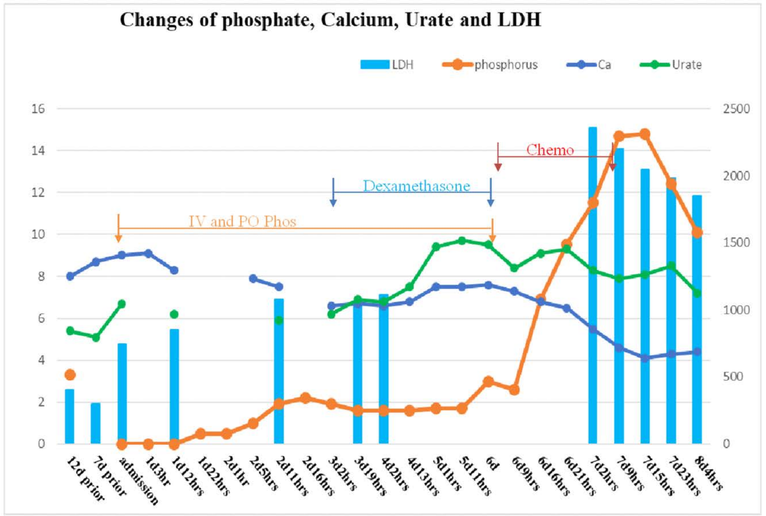

Figure 2

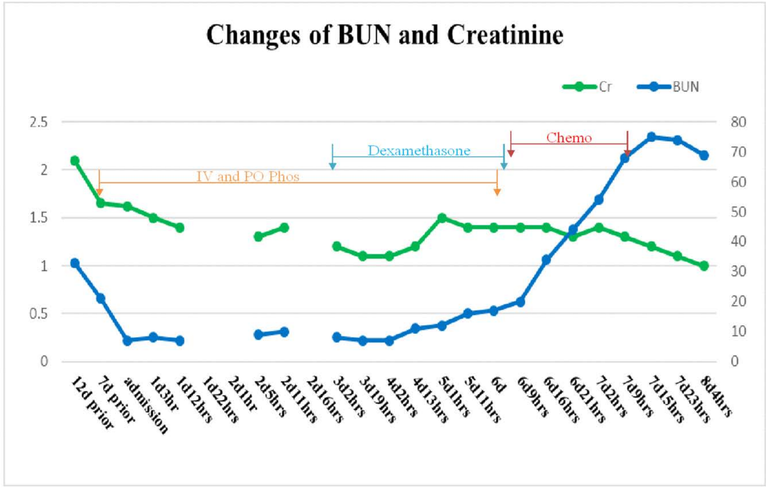

Figure 3

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