Refeeding syndrome in a vegan patient with stage IV gastric cancer: a novel case

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The refeeding syndrome encompasses the complex physiologic state that occurs in malnourished patients who receive nutrition after a period of decreased oral intake. The hallmark of the syndrome is hypophosphatemia, though other electrolyte imbalances and severe fluid shifts are commonly involved.[1] Patients with newly diagnosed malignancies and those undergoing treatment for malignancies are at increased risk for developing the refeeding syndrome,[2] however there are few reported cases or other data in the oncology literature regarding this syndrome in cancer patients.

We report a case of a vegan woman with stage 4 gastric adenocarcinoma who developed the refeeding syndrome after the severe nausea caused by her primary tumor was alleviated with chemotherapy. The patient twice required admission for the treatment of severe hypophosphatemia, and phosphorus levels were resistant to intravenous and oral repletion. Further workup revealed severe vitamin D deficiency secondary to her 20-year history of veganism. After supplementation with vitamin D, her phosphorus levels stabilized and the refeeding syndrome did not recur. We believe that we are the first to report a case of severe vitamin D deficiency in association with a vegan diet as the cause of resistance to phosphate repletion in the refeeding syndrome. We seek to highlight the importance of recognizing the risk of the syndrome in the oncologic population and also of understanding the physiology of phosphate metabolism in treating this disorder.

Case presentation

A 35-year-old vegan woman presented with a 5-month history of heartburn, anorexia, fatigue, a 30-lb weight loss, and persistent vomiting with oral intake. The patient had been a vegan since she was 15 years old and did not consume any meat, fish, dairy, or egg products. She did not take any multivitamins or supplements. At the onset of her symptoms, she had an upper endoscopy that showed diffuse inflammation but no focal or gross abnormalities.

The patient continued to have progression of symptoms despite antacid therapy, and a subsequent endoscopy 3 months later revealed an infiltrative mass-like deformity throughout the entire stomach. Pathology was consistent with gastric adenocarcinoma, and the patient was diagnosed with stage IV disease due to concomitant peritoneal carcinomatosis detected on a computed tomography (CT) scan of the abdomen. She was started on modified docetaxel, cisplatin, and fluorouracil (mDCF) chemotherapy. An improvement in her symptoms with an increase in appetite was noted within the first week after the first cycle of chemotherapy.

The patient reported an increase in oral intake and began to consume a variety of different foods consistent with her vegan diet. Routine labs performed 10 days after the first cycle of chemotherapy revealed a phosphorus level of 0.4 mg/dL (normal range, 2.5-4.5 mg/dL) and a magnesium level of 1.7 mg/dL (normal range, 1.8-3.6 mg/dL). The patient was admitted to our institution for intravenous phosphorus infusions and discharged after improvement of the phosphorus level with intravenous infusions of potassium phosphate (Table 1). Two days after discharge, she presented with generalized muscle weakness and was again found to have hypophosphatemia with a phosphorus level of 1.2 mg/dL. She was readmitted to the hospital, but response to phosphorus repletion was not robust (Table 1). Further workup revealed severe vitamin D deficiency and elevated urinary phosphate excretion (Table 2).

Aggressive vitamin D supplementation was ini-

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TABLE 1 Patient phosphorus levels in response to treatment throughout admissions #1 and #2

Day	Phosphorus level, mg/dL[a]	Therapy[b]
	Admission #1	
Pre-chemotherapy	4.3	na
1	0.4	15 mmol IV KPO4
2		
Morning	1.5	15 mmol IV KPO4
Afternoon	1.4	15 mmol IV KPO4
3	2.8	na
	Admission #2	
1		
Morning	1.2	30 mmol IV KPO4 x 1 dose
Afternoon	1.8	na
2		
Morning	3.2	na
Afternoon	1.7	na
Overnight, between days 2 and 3: 60 mmol IV KPO4 x 1 dose		
3	4.0	KPO4 2 tablets[c] TID
4	1.5	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg daily, + ergocalciferol 50,000 IU weekly initiated
5	1.7	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
6	1.2	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
7	1.4	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
8	1.2	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
9	1.5	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
10	1.8	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
11	1.7	KPO4 2 tablets[c] TID, calctriol 0.25 mcg, + ergocalciferol 50,000 IU
12	2.6	KPO4 2 tablets[c] TID, calcitriol 0.25 mcg
	After discharge	
Discharged on KPO4 2 tablets[c] TID, calcitriol 0.25 mcg daily, + ergocalciferol 50,000 IU weekly, + calcium 500 mg with vitamin D 200u 2 tablets BID		
1 week	3.2	na
3 weeks	2.8	na

IU, international units; IV, intravenous; KPO4, potassium phosphate; na, not applicable; PO, orally; TID, 3 times a day;

[a]Normal range, 2.5-4.5 mg/dL. [b]Therapy in right column given in response to phosphorus level in same row. c1 KPO4 tablet contains: 250 mg phosphorus, 8 mmol phosphate, 1.1 mEq potassium, and 13mEq sodium.

tiated with calcitriol 0.25 mcg daily and ergocalciferol 50,000 units weekly. Phosphate supplementation was continued. About a week after initiation of vitamin D supplementation, the patient's phosphorus levels normalized and remained stable. She was continued on vitamin D supplementation and did not have any recurrences of the refeeding syndrome or hypophosphatemia.

Discussion

The refeeding syndrome is a complex physiologic state in which there are severe metabolic and hormonal changes caused by the rapid refeeding of malnourished patients.[1-5] After 72 hours of starvation, metabolic pathways begin to obtain energy from ketones, which are produced by fatty acid oxidation.[6] Liver gluconeogenesis decreases and there is a decrease in the basal metabolic rate, a reduction in the secretion of insulin, and increased use of free fatty acids by the brain.[6]

When refeeding occurs, there is a shift back to the use of glucose as the main energy source and an increase in the demand for the phosphorylated intermediates of glycolysis.[6] Insulin secretion increases, and cells begin to uptake glucose.[6] There is an intracellular movement of phosphate, magnesium, and potassium, and an increased use of the cofactor thiamine.[6] The fluid and electrolyte imbalances that ensue can cause fatal cardiopulmonary dysfunction and can have adverse effects on most other organ systems.[6] Hypophosphatemia is usually defined as mild when levels are 2-2.5 mg/dL, moderate when 1-2 mg/dL, and severe when < 1 mg/dL (normal range, 2.5-4.5 mg/dL).[2] Treatment is aimed at intravenous and oral phosphate and electrolyte repletion.[2]

Body phosphate metabolism is regulated through plasma inorganic phosphate, with the kidney and the small intestine being the major organs that participate in phosphate homeostasis. 1,25-dihydroxyvitamin D3 enhances renal tubular phosphate reabsorption and mediates intestinal phosphate absorption, and thus vitamin D plays a critical role in phosphate metabolism.[7] Vitamin D deficiency can further exacerbate hypophosphatemia by inducing hypocalcemia and secondary hyperparathyroidism, which causes increased urinary phosphate excretion.[8]

Any patient with marasmus or cachexia is at risk for the refeeding syndrome.[1] It is recommended that enteral or parenteral nutrition be started at a reduced rate of 25%-50% of total estimated caloric requirements.[9] Serum phosphate, magnesium, calcium, potassium, urea, and creatinine concentrations should be measured before refeeding and are to be repeated daily for 4 days after feeding has been initiated.[10] In a prospective, hospital-based cohort study, the refeeding syndrome occurred in 3 out of 243 participants who had been identified at risk and treated with recommended hypocaloric feeding. Risk

TABLE 2 Patient vitamin D and electrolyte levels compared with normal ranges

Measurements	Patient level	Normal range
Vitamin D, 25	< 6.0 ng/ml	25-90 n/ml
Vitamin D 1,25	< 8.0 pg/ml	18-78 pg/ml
Fractional excretion of PO4	29%	10%-15%
Intact PTH	32 pg/ml	9-76 pg/ml
Calcium[a]	7.6 mg/dL	8.6-10.4 mg/dL
Ionized calcium	4.4 mg/dL	4.6-5.3 mg/dL

PO4, phosphate; PTH, parathyroid hormone

[a]Calcium level at time of intact PTH measurement.

factors distinct to these patients included a history of starvation and baseline low serum magnesium concentration.[9]

Risk factors for the refeeding sydrome in patients with malignancies are vast. Those undergoing chemotherapy may have nausea, vomiting, stomatitis, mucositis, and dysguesia that limit oral intake.[2,11] An increased release of anorexic cytokines such as tumor necrosis factor and interleukin-2 can cause loss of appetite and skeletal muscle wasting, which also precipitates phosphate depletion.[2,11] From a mechanical standpoint, those with brain metastases, malignant bowel or gastric-outlet obstruction, and visceral involvement may experience frequent vomiting. Those with malignancy may be receiving other medications, such as diuretics, that compound electrolyte imbalance.[6,8,11]

A nationwide poll conducted in 2006 found that 1.6% of Americans follow a vegan diet, which means that they do not consume any meat, fish, dairy products, or eggs.[12] In a study that assessed the nutrient adequacy of a very low-fat vegan diet, mean dietary intake of all of the analyzed vitamins and minerals met the recommended Dietary Reference Intake with the exception of vitamin D, for which a less-than-adequate intake was observed.[13] Another study found that concentrations of plasma 25-hydroxy vitamin D were lower in vegetarians and vegans than in meat and fish eaters, with vegans having the lowest concentrations of all the groups.[13,14]

We highlight a novel case of the refeeding syndrome in a vegan patient who had undergone a period of starvation because of the symptoms of her malignancy. It is important to recognize the risk factors for the refeeding syndrome in the oncology population, and to understand the interplay of phosphate, vitamin D, and calcium in mediating phosphate absorption. Furthermore, it is critical to recognize the variety of diets in the United States and the effects that these diets can have on different disease states and metabolic processes.

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