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Life Threatening Rapid Onset of Hypophosphatemia Developed due to Intravenous Iron Replacement Following Pulmonary Resection; A Case Report

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Pulmoner Rezeksiyon Sonrası İntravenöz Demir Replasmanı Nedeniyle Gelişen, Yaşamı Tehdit Eden Hipofosfatemi, Olgu Raporu

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ABSTRACT

Severe hypophosphatemia is a rare electrolyte disturbance among surgical patients associated with severe fatigue, impaired cardiac and respiratory functions. Although mild hypophosphatemia is common after parenteral administration of intravenous iron replacement, severe hypophosphatemia is not usual in perioperative period. We present a case of 76-year-old female who underwent surgery for a left paramediastinal mass. Laboratory examination showed hypochromic microcytic anemia. A total dose of parenteral 1000 mg ferric carboxymaltose was administered two days prior to the operation with the aim of achieving a rapid increase in hemoglobin. We performed a wedge resection for the mass originating from the left upper lobe. The patient developed dyspnea and fatigue with severe hypophosphatemia on postoperative third day. The clinical status of the patient could be only improved with parenteral administration of high dose of sodium phosphate. We tried to emphasize this unexpected complication of intravenous iron replacement and the features of its management.

Keywords: *hypophosphatemia, iron replacement, cardiothoracic surgery*

ÖZ

Şiddetli hipofosfatemi, cerrahi hastalar arasında ender görülen; ciddi yorgunluk, bozulmuş kalp ve solunum fonksiyonları ile ilişkili bir elektrolit bozukluğudur. İntravenöz demir replasmanı sonra hafif hipofosfatemi görülmekle birlikte, ciddi hipofosfatemi beklenmemektedir. Bu makalede, sol paramediastinal kitle nedeniyle ameliyat edilen 76 yaşında bir kadın olgu sunuldu. Laboratuvar incelemesinde hipokromik mikrositik anemi saptandı. Aneminin düzeltilmesi amacıyla ameliyattan 2 gün önce 1.000 mg parenteral 1.000 mg ferrik karboksimaltoz uygulandı. Sol üst lobdan çıkan kitle için wedge rezeksiyon uyguladık. Ameliyat sonrası üçüncü günde hastada şiddetli hipofosfatemi ile birlikte yorgunluk, nefes darlığı ve hipoksi gelişti. Hastanın kliniği ancak yüksek doz parenteral fosfor replasmanı ile düzeltilebildi. İntravenöz demir replasmanının bu beklenmedik komplikasyonunu ve yönetiminin özelliklerini vurgulamaya çalıştık.

Anahtar kelimeler: *hipofosfatemi, demir replasmanı, kardiyotorasik cerrahi*

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INTRODUCTION

IIntravenous iron therapy (IIT) is an alternative to oral replacement for iron deficiency. IIT is recommended to be used for patients undergoing surgery, when there is less than 6 weeks left up to surgery [1]. This is particular significant and suggested as a component of preoperative anemia mana-

gement for patients who are candidates for cancer surgery [2].

Hypophosphatemia after IIT is not an uncommon complication which was first described by Okada M. et al in 1983 [3]. A randomized trial with 1000 patients has reported that 50.8 % of patients had hypophosphatemia below 2 mg/dL following IIT. In recent studies, mechanism of hypophosphatemia and phosphorus metabolism after IIT has been widely investigated. It has been shown that hypophosphatemia generally occurs two weeks after IIT [4].

We herein present a case of female patient, who received IIT two days prior to surgery. She developed severe hypophosphatemia in the early postoperative period on the postoperative day 2 and recovered with intravenous sodium phosphate therapy.

CASE REPORT

AA 76-year-old female patient with symptoms of fatigue who was radiologically diagnosed to have a paramediastinal mass was admitted to our clinic. She had a history of 40 pack-year smoking. She also had hypertension and diabetes mellitus which were treated with indapamide and oral antidiabetics, respectively. She had undergone cholecystectomy for acute cholecystitis, and hysterectomy for uterine myoma.

Physical examination did not show any abnormality. Chest X-ray showed a central mass. Computed tomography detected the mass measuring 44x55x45 mm with eccentric calcification and lobulated shape in the anterior mediastinum. Fluorine-18-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET-CT) revealed that the mass had a maximum standardized FDG uptake value (SUV max) of 2.71. The possible radiological diagnoses included thymoma, germ cell tumor or mature teratoma. Laboratory examination revealed that levels of lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), beta subunit human chorionic gonadotropin (ß-hcg) were within normal limits. However, hemoglobin level and mean corpuscular volume (MCV) were as low as 10.5 g/dL and 76 fL, respectively consistent with a microcytic anemia. Electrolyte levels were within the normal range including the blood phosphorus level, which was 3.26 mg/dL (range; 2.7-4.5 mg/dL). Electromyography revealed polyneuropathy resulting from diabetes mellitus. However, neurological examination showed no evidence of myasthenia gravis or other neurological pathology. The patient was scheduled for an emergency surgery because she had a possible malignant tumor in the anterior mediastinum. Operative blood loss was preoperatively discussed and assessed to be approximately 400 mL. Conforming to patient blood management of our institution, preoperative iron replacement was defined as the first- line treatment and initiated as recommended in enhanced recovery after lung surgery [1,2]. We administrated intravenous iron with a total dose of 1000 mg ferric - carboxymaltose (FERINJECT, Vifor France SA) for iron deficiency anemia.

We performed a partial upper sternotomy which showed that the mass was originated from left upper lobe parenchyma and extended to the anterior mediastinum. We proceeded with a pulmonary wedge resection for a frozen-section diagnosis, which revealed that the mass was a chondromatous hamartoma. The patient was extubated after two hours of surgery without any perioperative complication and transferred to the surgical ward.

The patient was asymptomatic and blood calcium level was within the normal range on the first postoperative day (POD). However, blood phosphorus level was as low as 2 mg/dL, thus we initiated 250 mg oral phosphorus therapy four times a day. Arterial blood gas analysis showed normal pH levels, and the blood sugar level was 120 mg/dL. Further examinations of blood parathyroid hormone, 25-Hydroxyvitamin-D and calcium levels showed that they were all within normal limits.

Blood phosphorus level had a tendency to decrease,

and was measured as 0.82 mg/dL on the second postoperative day. The patient developed symptoms of severe fatigue and respiratory distress. We switched to intravenous replacement with potassium phosphate. We administered 24 mmol phosphorus in eight hours according to the recommended dose of phosphorus replacement, which is 0.25-0.50 mmol/kg.

Sodium, potassium, creatinine, calcium and phosphorus levels were within normal range in spot urine on postoperative 3rd day . In addition, levels of total phosphorus and phosphorus concentrations in 24h urine were 917 mg/day (400-1300 mg/day) and 36.7 mg/dL (5.0-190.0 mg/dL), respectively. Tubular phosphate excretion was as high as 10 percent. Despite intravenous potassium phosphorus therapy, level of phosphorus continued to decrease to 0.56 mg/dl and blood potassium increased up to 5.78 mmol/L. We decided to switch the management to sodium phosphate (Glucophos, Fresenius Kabi, Germany). We increased phosphorus dosage to a high dose of 1 mmol/kg, and we monitored phosphorus levels every six hours. On the 4th postoperative day, symptoms were relieved when the blood phosphorus level reached up to 2 mg/dL. We discharged the patient on the 6th postoperative day with oral therapy.

DISCUSSION

PPhosphorus is an essential element that is usually found in nature combined with oxygen as phosphate. The total body phosphorus content is around 700 g and most of the body phosphorus is contained in the skeleton as crystalline hydroxyapatite. The intracellular/extracellular ratio of phosphorus is estimated to be as 100. Most intracellular phosphate exists as organic phosphate compounds such as creatine phosphate and adenosine triphosphate (ATP), which is the main resource of biochemical energy [5]. Another intracellulare phosphate store is the 2, 3 – diphosphoglycerate in the erythrocytes, which modulates oxygen transfer from hemoglobin to tissues. The decreased levels of phosphorus, namely, hypophosphatemia might result in adverse physiological outcomes such as impaired diaphragmatic contraction, rhabdomyolysis, erythrocyte dysfunction, hemolysis and central nervous system dysfunction. Regulation of hypophosphatemia might prevent above- mentioned impairments and possible related complications in patients undergoing surgery.

Hypophosphatemia might be observed up to 5 % in all hospitalized asymptomatic patients. In addition, some reports show that this rate increases up to 56 % after cardiothoracic surgery [6]. However, severe hypophosphatemia below 1.5 mg/dL is very rare and occurs in only 0.3 % of the patients.

Three important mechanisms have been suggested for hypophosphatemia [5]. The first and the most common mechanism is related to impaired internal redistribution resulting from refeeding syndrome, diabetic ketoacidosis and acute respiratory alkalosis. The second mechanism is decreased intestinal absorption, and the last mechanism is increased renal excretion. Iron deficiency increases transcription of fibroblast growth factor 23 (FGF23), however iron replacement also inhibits cleavage of FGF23, thereby resulting in an inappropriate phosphate excretion. Our patient had normal pH levels on blood gas analysis without any findings of ketoacidosis or respiratory alkalosis. In addition, she has not been on any medication which might cause hypophosphatemia. However, our patient had a level of urine phosphorus as 36 mg/dL, urine creatinine as 98 mg/dL, serum phosphorus as 0.56 mg/dL and serum creatinine as 0.8 mg/dL. Her renal excretion was compatible with increased excretion and calculated as high as 10 percent. Other causes of increased phosphorus excretion such as Vitamin D deficiency and hyperparathyroidism were excluded because they were within the normal limits in our patient. Another cause of increased phosphorus excretion might be a mesenchymal tumor secreting fibroblast growth factor 23 (FGF23), which results in a paraneoplastic syndrome and eventual hypophosphatemia [5].

However, phosphorus level in our patient was normal in the preoperative period. Thus, we concluded that hypophosphatemia had resulted from intravenous iron replacement in our case.

Hypophosphatemia after IIT most commonly reaches to its lowest level at postoperative second week [4]. However, our patient developed the lowest level of hypophosphatemia on the 5th day following iron replacement therapy. We started an oral treatment of phosphorus which was not sufficient for our patient. Thus, we initiated an intravenous treatment for hypophosphatemia first with potassium phosphate. However, the potassium levels exceeded the upper limits during this treatment. We could have managed the patient with an alternative treatment with high doses of sodium phosphate.

In conclusion, IIT is recommended especially for patients with iron deficiency anemia, who do not have sufficient time for oral replacement before surgery. Blood transfusion is not considered in the treatment of chronic anemia unless there is any symptom of acute impaired oxygen delivery (ECG abnormalities, acidosis, oliguria, decreased central venous oxygen saturation etc).

This treatment provides effective replacement in a short interval; however, the common side effects are less known, and can be life-threatening resulting in myocardial dysfunction and respiratory failure. Surgeons should consider hypophosphatemia in the differential diagnosis of patients with respiratory distress in the postoperative period following IIT, which should be treated with an appropriate management.

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