Undetected Iatrogenic Drug-Induced Complications in a Hemodialyzed Anuric Patient: A Case Report and Review of the Literature

Edouard Cubilier  Mohamed Tayeb Salaouatchi  Maxime Taghavi  Saleh Kaysi  Joëlle Nortier  Maria do Carmo Filomena Mesquita

Nephrology Clinic, Department of Internal Medicine, Brugmann University Hospital, Université Libre de Bruxelles, Brussels, Belgium

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Abstract
Anuric hemodialyzed end-stage renal disease patients are prone to multiple complications and comorbidities and are therefore often treated with various medications. Adverse drug reactions and risk factors leading to them can be difficult to discern in such polymedicated patients. Most problems regarding low phosphate levels are frequently underdiagnosed in clinical practice and sometimes overlooked in these regularly hyperphosphatemic patients. Hemodialysis vascular accesses are frequently subject to infections and therefore require adapted antibiotic treatments. We report a case of an occult severe multifactorial hypophosphatemia in an anuric hemodialyzed patient with multiple comorbidities who required two hospitalizations for encephalopathy, seizures, and cardiac failure. Retrospective analysis of the medical record revealed several underlying causes of hypophosphatemia, as well as undetected risk factors for adverse drug reactions related to cephalosporins. A global approach to these concerns in routine clinical practice would raise awareness of often disregarded issues related to hypophosphatemia and drug prescription in these patients.

Correspondence to:
Maria do Carmo Filomena Mesquita, maria.mesquita@chu-brugmann.be
Introduction

Phosphorus is a ubiquitous ion of the human body widely present in mineralized and soft tissues and to a lesser extent in extracellular fluids where it appears as inorganic phosphate. In adults, normal serum phosphorus levels range from 2.5 mg/dL (0.8 mmol/L) to 4.5 mg/dL (1.45 mmol/L) [1]. Phosphorus metabolism depends on dietary content, intestinal absorption, plasma pH, phosphatase levels such as fibroblast growth factor 23 (FGF23), and circulating levels of parathormone (PTH), calcitriol (1,25(OH)-vitamin D3), glucose, insulin, glucagon, calcitonin, and catecholamines [1, 2]. Many key physiological mechanisms depend on phosphorus, such as cellular signalization, oxidative phosphorylation, adenosine triphosphate synthesis, extracellular acid-base homeostasis, oxygen transportation by hemoglobin (Hb), consolidation of mineralized tissues, and formation of RNA and DNA bases [1].

Phosphate levels are tightly balanced by renal reabsorption through proximal tubule sodium-phosphate cotransporters NaPi2a and NaPi2c [3], and renal phosphate loss is the main mechanism responsible for hypophosphatemia in the general population [1]. Severe hypophosphatemia is defined as serum phosphate levels below 1.0 mg/dL (0.32 mmol/L), and these may provoke serious musculoskeletal, neurological, cardiac, and respiratory complications, thus increasing mortality [4]. However, non-severe hypophosphatemia is often expressed clinically by nonspecific symptoms such as global weakness [1, 4].

Because anuric end-stage renal disease (ESRD) patients fail to excrete phosphate in urine, they rarely present hypophosphatemia but often present hyperphosphatemia and therefore require phosphate removal therapies like hemodialysis (HD) or oral phosphate binders [5]. ESRD patients are also susceptible to anemia as a consequence of low renal erythropoietin production, uremia-induced erythrocyte longevity reduction, and platelet malfunction [6]. Moreover, hemodialyzed ESRD anuric patients, often anticoagulated during HD, are also prone to iron deficiency-related anemia (IDA) via discreet blood loss in the dialysis circuit and in the gastro-intestinal tract [6, 7]. Hence, they frequently receive intravenous iron supplementation (IVIS) [6, 7] which was originally labeled with mild transient hypophosphatemia but lately has been associated with sometimes severe and prolonged hypophosphatemia when formulations like ferric carboxymaltose (FCM) are administered [8]. We report a case of an undetected, progressive, multifactorial hypophosphatemia that acutely dropped twice in the context of FCM and ceftazidime use and was responsible for two life-threatening complications requiring hospitalizations.

Case Presentation

We present the case of a 44-year-old anuric woman of African descent with a 23-year history of HD for ESRD due to a congenital malformative structure and a neurogenic bladder-related chronic pyelonephritis. The patient also presents a polymalformative syndrome characterized by a cervical syringomyelia with myelomeningocele, a thoracolumbar scoliosis, and a congenital paraplegia. In 1999, she underwent a total parathyroidectomy for tertiary hyperparathyroidism, with a presternal graft implantation. In 2002, she developed multifocal epilepsy and presented with her most recent seizure in 2016. In the context of severe left ventricular hypertrophy attributed to chronic severe arterial hypertension, she developed a biparieto-temporal stroke in 2012 which led to mild aphasia as a sequela. Medical history also includes several episodes of cardiac failure with pleuro-pericardial effusions, gastroesophageal reflux, hiatal hernia, and gastritis (i.e., antritis and bulbitis).

The patient’s daily medications comprise amlodipine 10 mg, bisoprolol 5 mg, dihydralazine mesylate 150 mg, levetiracetam 750 mg, esomeprazole 40 mg, magaldrate 1,600 mg,
sodium bicarbonate 3 g, calcium polystyrene sulfonate 30 g, and lormetazepam 1 mg. When necessary, she has also used picosulfate sodium 22.5 mg, domperidone 10 mg, and paracetamol 1 g. On dialysis, she receives intravenous (IV) epoetin beta thrice weekly, oral cholecalciferol 25,000 UI once weekly, and IV FCM 500 mg approximately once monthly.

On July 19, 2021, in HD, the patient presented with fever and considerable inflammation with a C-reactive protein (CRP) level of 265 mg/L (normal range <10 mg/L) and was treated empirically by IV ceftazidime (Glazidim®) 2 g per day of dialysis in one dose after HD for a total of 2 weeks. No pathogen was revealed by microbiological work up, and CRP levels dropped favorably within 4 days. 18F-Fluorodeoxyglucose positron emission tomography integrated with computed tomography revealed a moderate focal hyper-metabolism on the HD catheter’s internal extremity, suggesting a catheter infection as responsible for the inflammation. Five days after initiation of ceftazidime, the patient manifested 10 days of fluctuant speech and praxic limitations, leading to a seizure and the first hospitalization for neurological work up. On admission, physical examination unveiled signs of palilalia, perseverations, and dyspraxia. Cerebral computed tomography showed an important and stable hydrocephalus with no recent intracranial hemorrhage compared to previous imageries (Fig. 1a), and chest radiography revealed small bilateral pleural effusions with an extension of the cardiac silhouette. cerebral computed tomography showed an important and stable hydrocephalus with no recent intracranial hemorrhage compared to previous imaging (Fig. 1a), and chest radiography revealed small bilateral pleural effusions with a known extension of the cardiac silhouette (Fig. 1b). While antiepileptic treatments were adjusted, electroencephalography tracings showed evidence of focal epilepsy on the first day, followed by 2 days of status epilepticus, then moderate to mild encephalopathy in the following days. Hetero-anamnesis provided by family members uncovered a peculiar behavior and an inadequate intake of her antiepileptic treatment several days before this episode. She was discharged from hospital after neurological stabilization.

Phosphate levels progressively declined over a period of 3 months before dropping into severely low ranges 1 week prior to the first hospitalization. PTH and low calcium levels remained relatively stable, as displayed in Figure 2. During that period, FCM administrations, represented by vertical arrows in Figure 2, were given while transferrin saturation (TFsat), Hb, and ferritin levels were normal to high. Hb levels then progressively declined, which led to an increase in FCM administrations that in turn raised both ferritin levels and TFsat. FCM administrations were then stopped before the first hospitalization until the end of the whole study period. During hospitalization, phosphate briefly returned to normal levels with oral sodium diphosphate supplementation before decreasing again.
in hypophosphatemia. Concordant spikes in CRP and ferritin levels were observed while TFSat dropped abruptly.

On August 19, 2021, 8 days after discharge, the patient was re-hospitalized for dyspnea, severe arterial hypertension, and lung crackles on physical examination. The work up was suggestive of pleuro-pericardial effusions due to a heart failure, with increased cardiac silhouette, lung hilum turgor, and interstitial tissue thickening on chest radiography (Fig. 1c). Laboratory results showed an acute drop of phosphate levels into severely low ranges on admission that normalized within 2 days and a spike in CRP levels that rapidly decreased during hospitalization. In the context of anemia and persisting heartburn symptoms, the esophagogastroduodenoscopy performed revealed a normal mucosal aspect and no sign of bleeding from the upper gastrointestinal tract. Phosphate levels were corrected with oral sodium diphosphate supplementation, and the patient’s clinical status improved over 1 week of daily ultrafiltrations in HD. She was then discharged from hospital and continued ambulatory intermittent HD. During the whole period of observation, magnesium levels ranged from a maximum of 1.22 mmol/L to a minimum of 0.67 mmol/L (0.65 mmol/L < normal range < 1.05 mmol/L), and IV phosphate supplementation was not administered.

**Discussion**

In our patient, several etiologies for hypophosphatemia have been diagnosed. Chronic use of oral antacids for alleviation of gastro-intestinal symptoms has previously been described to induce hypophosphatemia in HD patients [9, 10]. Among them, magaldrate (Riopan®) has a crystal molecular structure containing aluminum and magnesium hydroxide, which binds to biliary salts and pepsin to temporarily neutralize gastric pH, but it also binds to dietary phosphate which inhibits its intestinal absorption [10]. Lifestyle modifications such as head-of-bed elevation were advised, and H2 blockers were not administered since they have been withdrawn from the Belgian market. Considering the patient’s persisting heartburn
symptoms with normal endoscopy findings under adequate double acid suppression therapy, magaldrate should have been withdrawn given the severe hypophosphatemia, and a pH monitoring could have been proposed in order to test the correlation between symptoms and acid reflux [11].

FCM (Injectafer®), involved in this case, is one of the three IVIS types available in Belgium, the others being ferric dextran (Fercaryl®) and ferric saccharose (Venofer®). All types of IVIS reduce global FGF23 production, but FCM, unlike the others, inhibits the cleavage of the intact FGF23, the active form of FGF23 [1, 12]. Excess of intact FGF23 inhibits 1-α-hydroxylase transcription, which in turn reduces 25-hydroxyvitamin-D conversion into calcitriol, its active form. It also activates 24-hydroxyvitamin-D-hydroxylase, responsible for calcitriol degradation, and therefore hinders intestinal absorption of calcium and phosphate [1, 12]. For this reason and because of chronic oral antacid use in our patient, both intestinal phosphorus availability and absorption were disabled. We also note low calcium levels with rather high PTH levels considering the patient’s partial parathyroidectomy status, also probably because of low calcitriol.

Moreover, FCM appears to be a major risk factor for developing hypophosphatemia when compared to other IVIS formulations. Hypophosphatemia induced by FCM also seems to last longer than when induced by other IVIS. Risk factors leading to this complication include but are not limited to black compared to white phenotype patients, lower body weight, and high baseline Hb levels [13]. These preexisting risk factors were present in our patient. We suggest that the presence of such risk factors for hypophosphatemia prior to the administration of an IVIS should always lead to the prescription of alternative treatments.

In our dialysis center, IVIS is administered depending on patient’s monthly blood tests and according to KDIGO 2012 guidelines [14], with aimed values of Hb between 10 and 12 g/dL, TFsat above 30%, and ferritin level below 500 ng/mL. ESRD patients undergoing HD are often treated for IDA with IVIS which raises ferritin levels and restores the body’s iron pool but also raises hepcidin levels which disables access to stored iron [6, 7]. Moreover, lower maintenance IVIS doses of 100–200 mg/month were proved sufficient in anemia management while reducing IVIS toxicity [7]. Considering her rather high initial ferritin and Hb levels and the ineffectiveness of cumulated FCM administration to maintain adequate Hb levels, and taking into account her risk factors for FCM-induced hypophosphatemia, it appears that our patient has been overtreated with FCM, while she should have received more erythropoietin stimulating agent instead.

Central nervous system (CNS) serious adverse drug reactions (ADR) related to β-lactam antibiotics, and especially cephalosporins, are an often underdiagnosed entity clinically expressed by neuropsychiatric manifestations, i.e., encephalopathy, convulsion, confusion, or myoclonia [15]. Proneness to CNS serious ADR due to cephalosporins and notably ceftazidime (Glazidim®) has previously been linked to risk factors such as older age, interactions with other medications, renal impairment, and a medical history of CNS disorders [15]. Apart from older age, predisposing factors for CNS serious ADR related to ceftazidime were present in our patient. Additionally, severe hypophosphatemia, as present in this case, may provoke paresthesia, neuropathy, altered mental status, encephalopathy, and seizures [10]. The combination of ceftazidime use and severe hypophosphatemia presumably altered her mental status and behavior in terms of adequate medication intake, induced encephalopathy, and seizures. The real implication of mild to moderate hypophosphatemia in neurological alterations for hemodialyzed patients is to our knowledge not known and would require further exploration.

Moreover, ESRD anuric HD patients tend to accumulate aluminum in the context of chronic magaldrate use because of its poor removal by HD [16] and since 95% of normal aluminum elimination is urinary [17]. Nowadays, severe aluminum toxicosis is uncommon in
these patients [16], but aluminum accumulation is known to induce encephalopathy [17] and may have been involved in our patient but has not been tested during the period of observation. High aluminum levels (≥6 ng/mL) have also been associated with higher mortality in these patients, who would benefit from annual aluminum level assessment irrespective of severe aluminum toxicosis signs [16]. This particularity should be taken into account by the clinician in the follow-up of such patients.

Acute and severe hypophosphatemia is also accountable for cardiac function alteration [2, 10] and could be associated with arrhythmia [10]. Additionally, hemodialyzed patients are prone to hypocalcemia which may induce sudden death as a consequence of arrhythmia and myocardial contractility dysfunction [18]. Moreover, a clinical reduction of the patient’s lean body mass secondary to the catabolic state related to the first hospitalization most probably favored an increase in extracellular volume. Given the patient’s relatively low tolerance for hemodynamic fluctuations and propensity for cardiac failure, the combination of lean body mass reduction, chronic hypocalcemia with the second acute drop in severe hypophosphatemia most probably catalyzed the cardiac failure, leading to the second hospitalization. These drug-induced adverse reactions are probably underestimated, and clinicians involved in the treatment of IDA should be aware of such complications, their pathophysiology, and how to prevent and treat them.

**Conclusion**

Phosphate levels are often elevated in anuric HD patients but can drop for several reasons. IVIS such as FCM is frequently administered during dialysis for IDA, is regularly overused in clinical practice, and can lead to hypophosphatemia. However, the link between this treatment and its potentially severe complications may remain undetected by clinicians.

With this case presentation, we want to highlight the need for a global clinical and biological overview of the patient before drug prescription. FCM prescription requires screening for potential risk factors for FCM-induced hypophosphatemia and should often be given at reduced doses. Alternative options such as the use of other types of IVIS, increased doses of erythropoietin stimulating agent, or blood transfusions should be considered in certain patients to prevent serious outcomes.

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**Statement of Ethics**

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images.

**Conflict of Interest Statement**

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Author contributions

Edouard Cubilier first drafted the manuscript and wrote its content. Maria do Carmo Filomena Mesquita selected the clinical case, first drafted the manuscript, supervised its conception, and gave final approval of the manuscript for submission. Mohamed Tayeb Salauouatchi collected data for the conception of the graphics and commented on the manuscript. Maxime Taghavi commented and reviewed the manuscript. Saleh Kaysi and Joëlle Nortier supported the preparation and conception of the manuscript.

Data Availability Statement

All data supporting this work are included in this article. Any further inquiries can be directed to the corresponding author.

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