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LETTER TO THE EDITORS

Hemolytic anemia associated with severe hypophosphatemia in a renal transplant recipient

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Sirs,

Transient hypophosphatemia is a common complication in the early post-transplant period, and is moderate to severe in up to 90% of renal tranplant recipients [1,2]. Post-transplant hypophosphatemia is caused, at least partly, by inappropriately high levels of the phosphaturic hormones parathormone (PTH) and fibroblast growth factor-23 (FGF-23) [2]. Protracted hypophosphatemia has been associated with a progressive decrease in bone mineral density [1]. The clinically relevance of acute, transient hypophosphatemia in renal transplant recipients is less clear. In non-transplanted patients, severe hypophosphatemia, generally defined as a serum phosphorus level below 1 mg/dl, has been implicated as a cause of hemolytic anemia [3–5]. Hypophosphatemia may result in depletion of erythrocyte adenosine triphosphate levels, which in turn may trigger hemolysis by influencing cell membrane stability [3]. Especially, patients with rapidly falling or severely depressed (≤0.2 mg/dl) serum phosphorus concentrations seem at risk [3]. Renal transplant recipients clearly belong to the first category of patients [2]. However, to the best of our knowledge, no cases of hypophosphatemia-related hemolytic anemia have been reported so far. In this letter, we report a case of hemolysis associated with hypophosphatemia in a renal transplant recipient.

A 50-year-old Caucasian male with end-stage renal disease secondary to proliferative glomerulonephritis underwent a living donor renal transplantation. The graft was donated by his 60-year-old wife. The recipient's medical history included arterial hypertension, cerebrovascular disease and gout arthritis. Ten years ago, he received a first deceased donor renal graft, which was lost 9 years later due to transplant glomerulopathy. His panel-reactive anti-HLA antibody (PRA) count was 0% at all time points before his second transplantation. His blood group was A Rh(+). HLA phenotype was A2, A3, B35, B44, DR11, DR13. The donor's blood group was A Rh(+). HLA phenotype was A2, A31, B47, B60, DR13, DR13. Hematinics showed no signs of vitamin B12 or folate deficiency. Iron status appeared suboptimal (transferrin saturation 17%, ferritin 69 μg/l). Pretransplant serum parameters of mineral metabolism were as follows: albumin-adjusted calcium: 9.23 mg/dl; phosphorus: 7.9 mg/dl (normal range: 2.3–4.7 mg/dl); biointact PTH: 101.4 ng/l (4–40 ng/l); biointact FGF-23: 34424 ng/l (<50 ng/l); and calcitriol: 42.5 ng/l (on treatment with alphacalcidol 1 μg OD).

The patient's initial postoperative course was uncomplicated. He experienced immediate graft function with a rapid decline in his serum blood urea nitrogen and creatinine levels (serum creatinine of 1.27 mg/dl, measured creatinine clearance of 45.2 ml/min on day 6). Postoperative immunosuppression consisted of antibody induction with antithymocyte globulin in combination with mycophenolate mofetil 1000 mg BID, tacrolimus targeting trough levels of 10–15 ng/ml and methylprednisolone tapered down from 16 mg OD to 4 mg OD at month 3. He was also given antimicrobial prophylaxis including trimethoprim-sulfamethoxazole and valganciclovir. Physical examination revealed no abnormalities; the patient was afebrile. Hemoglobin (Hb) levels showed a steady decline in the immediate post-transplant period (Fig. 1). Blood examinations on day 6 showed signs of hemolysis: red blood cells (RBCs): 2 700 000/mm^3; Hb: 8.6 g/dl; lactate dehydrogenase (LDH): 427 mU/ml; total bilirubin: 0.7 mg/dl; and undetectable serum haptoglobin. Mean corpuscular Hb and volume were within normal range. There was no overt schistocytosis or thrombocytopenia, and a renal

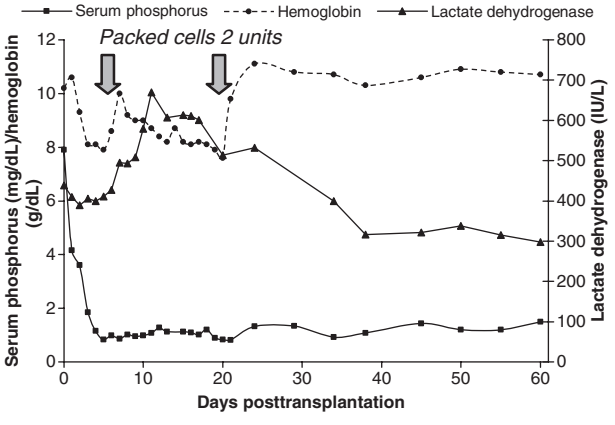

Figure 1 Evolution of serum phosphorus, hemoglobin and lactate dehydrogenase in the early post-transplant period.

biopsy on day 20 formally excluded thrombotic microangiopathy, generally considered the most frequent cause of post-transplant hemolysis [6]. As patient's and recipient's blood group were identical, acute hemolysis due to anti-erythrocyte auto-antibodies was unlikely, though should be considered in the case of an ABO-compatible, although ABO-nonidentical (usually O blood group) donor organ [7]. Moreover, Coombs test, and screening for irregular antibodies were negative, which also excluded other forms of immune-mediated hemolysis. Besides a marked hypophosphatemia (0.99 mg/dl), biochemistry did not reveal other relevant abnormalities. Transfusion of two units of packed cells was administered on day 6 and day 20. The patient did not receive phosphate supplements and antimicrobial prophylaxis was continued up to month 3. From day 12 on, signs of hemolysis gradually waned to disappear completely by day 60. Blood examinations on day 60 showed RBCs: 3 360 000/mm^3; Hb: 10.7 g/dl; LDH: 298 mU/ml; total bilirubin: 0.2 mg/dl; and serum haptoglobin: 0.45 g/l. Serum phosphorus slowly but steadily increased over time, but remained below the lower normal limit (1.5 mg/dl on day 60).

As stated, thrombotic microangiopathy and immune-mediated hemolysis were formally excluded. Additionally, drug-induced hemolysis was considered rather unlikely because most drugs (especially trimethoprim-sulfamethoxazole) were continued until day 90, whereas signs of hemolysis would appear completely absent by day 60. It is important to notice that ultrasound failed to reveal intra-abdominal collections, as a postoperative hematoma could also explain the Hb fall and biochemical signs of hemolysis. Furthermore, a closer look at the biochemistry data revealed a clear temporal relationship between the marked drop of the serum phosphate levels, from 7.9 mg/dl [day 0] to 0.83 mg/dl [day 5], and the occurrence of hemolysis. Severe hypophosphatemia persisted for 21 days, whereas LDH levels, i.e., a sensitive but aspecific marker of cell lysis, already started to decline from day 12 on. Altogether these data suggest that, in agreement with non-transplanted cases, a rapidly and profoundly falling phosphorus level rather than severe hypophophatemia *per se* can trigger hemolysis post-transplantation. Given the prevalence and severity of post-transplant hypophosphatemia, one might raise the hypothesis that (low-grade) hypophosphatemia-mediated hemolytic anemia is an under-recognized cause of anemia in the early post-transplant period.

Controversy exists on the serum phosphorus level below which therapy should be initiated. In non-transplanted patients, it is generally advised to start phosphorus supplements once serum phosphorus drops below 1 mg/dl or in the presence of suggestive clinical signs [3,8]. There are no specific treatment guidelines for treating hypophosphatemia in renal transplant recipients. Intervention studies are scarce and results were not unequivocal [9,10]. As phosphorus supplements could maintain the problem of persistent hyperparathyroidism [9] and hyperphosphatoninism and confer a risk of nephrocalcinosis, we suggest to restrict phosphate supplements to patients with complicated (e.g., cell dysfunction) and severe hypophosphatemia (<1 mg/dl) in whom causal treatment is contraindicated (e.g., parathyroidectomy) or unavailable (e.g., calcimimetics).

In summary, our case report warrants an increased awareness for severe hypophosphatemia as a potential trigger for hemolytic anemia in the early post-transplant period.

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