Exceptional Case

Acute kidney injury due to deferoxamine in a renal transplant patient

Christian Clajus¹, Jan U. Becker², Dirk O. Stichtenoth³, Jessica Wortmann¹, Anke Schwarz¹ and Jan T. Kielstein¹

¹Department of Nephrology, Hannover Medical School, Hannover, Germany, ²Institute for Pathology, Hannover Medical School, Hannover, Germany and ³Institute for Clinical Pharmacology, Hannover Medical School, Hannover, Germany

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Introduction

Deferoxamine is an iron-chelating agent, used in the treatment of acute iron intoxication and chronic iron overload secondary to multiple blood transfusions. Moreover it is currently recommended by the K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease (CKD) for treatment in symptomatic aluminium toxicity [1]. Deferoxamine is known to have many adverse effects, some of them potentially fatal, especially infections with siderophilic organisms like mucormycosis [2]. We report a case of acute tubular injury in a renal transplant recipient secondary to treatment with deferoxamine due to iron overload, in the context of autoimmune haemolytic anaemia.

Case report

A 58-year-old Caucasian male, with 21-year status post-cadaver kidney transplantation due to Goodpasture’s syndrome, presented with a sudden rise in serum creatinine from 120 µmol/L to 250 µmol/L (Figure 1). This decrease in renal function was detected during his regular outpatient control visits, as he was in his usual state of health and denied any complaints. Upon admission to the hospital the increase in serum creatinine and BUN was confirmed and a creatinine clearance of 31 mL/min as well as a proteinuria of 1.06 g/d was determined. Urine sediment was unremarkable. Initial laboratory studies further revealed a macrocytotic anaemia (haemoglobin, g/dL) [8,9] as well as iron overload (ferritin 1747 µg/L) due to an autohaemolytic anaemia (diagnosed 3 years earlier) and repeated blood transfusions. The trough level of cyclosporine A was well within the therapeutic range (90 ng/mL). His oral medications at the time of admission included cyclosporine A, prednisolone, candesartan, carvedilol, furosemide, verapamil, pantoprazole, benzbro- marone, pravastatin, ezetimibe and warfarin. He also received darbepoetin alfa s.c. His physical exam revealed a remarkably irregular rhythm and a 2/6 systolic murmur. He had thin, brownish-coloured vulnerable skin. An ultrasound examination of the allograft showed a normal-sized transplant with slightly smaller parenchyma, multiple calcifications of the parenchyma and an elevated resistance index.

To exclude delayed graft rejection a renal biopsy of the transplanted kidney was performed. Light microscopy did not show any signs of acute humoral or cellular rejection. There was about 15% of cortical tubular atrophy and interstitial fibrosis in a non-striped pattern. Partially flattened epithelium with attenuated brush borders indicated acute tubular damage of the remaining cortical tubules. Isometric vacuolization or microcalcification as signs of calcineurin inhibitor (CNI) toxicity was not found. Arterioles displayed marked cuff-like hyalinosis, indicating chronic vascular CNI toxicity. The biopsy contained only two glomeruli, both of which displayed slightly thickened basement membranes without any double contours. The specimen for transmission electron microscopy contained no glomeruli. The acutely damaged cortical tubular epithelial cells were remarkable for their degenerated mitochondria with myelin-like figures and loss of cristae (Figure 2). There was no swelling of the mitochondria or of the endoplasmic reticulum.

A secondary thorough history was taken, which revealed that he had started a subcutaneous deferoxamine therapy just 22 days before admission. A daily dose of 2.0 g deferoxamine was diluted in 100 mL normal saline and administered overnight via pump. Each dose was infused for 12 h overnight, followed by a 12-h daytime pause. In total the deferoxamine therapy was performed for 3 weeks, while in this cycle the patient interrupted the therapy for 2 days. This is an equal dose of 2.35 mg/kg/h and respectively...
Fig. 1. Plasma creatinine in a patient with acute kidney injury due to deferoxamine. Each triangle represents the subcutaneous administration of 2 g deferoxamine over 12 h via infusion pump.

Fig. 2. Ultrastructure of a representative tubular epithelial cell: degenerated mitochondrium (short arrow) with diminished cristae and myelin-like inclusions (long arrows). Transmission electron micrograph, original magnification ×10 000.
178.28 mg/kg/week. The last application took place 1 day prior to hospital admission (Figure 1). With supportive treatment alone, serum creatinine levels returned to 135 µmol/L and urinary protein excretion decreased to 0.22 g/day.

To our knowledge, this is the first case of acute kidney injury due to deferoxamine in a patient with renal disease. Moreover, for the first time, the work-up for alleged deferoxamine toxicity included a renal biopsy.

Originally produced as a ferric compound, deferoxamine has the iron component chemically removed, resulting in an iron-free ligand. Approved by the FDA in 1968, it is utilized to bind excess ferric ions in iron poisoning or iron overload associated with transfusion-dependent anaemia. Deferoxamine also chelates aluminium and increases its renal clearance, and the drug can be used as a diagnostic test for aluminium overload. Ferric ions bind to the three hydroxamic groups of deferoxamine, creating ferrioxamine, a stable, water-soluble complex that is then readily excreted by the kidneys.

Several case reports [3,4] and a small case series [5] in patients with thalassemia highlighted the problem of reversible renal failure as early as 1975 [6]. Therefore deferoxamine is contraindicated for use in patients with anuria or severe renal disease, as the drug and the iron chelate are eliminated primarily by the kidneys. Koren et al. [7] proposed two mechanisms by which deferoxamine might mediate its nephrotoxicity, that is (i) acute decrease in renal perfusion in the absence of systemic blood pressure changes as well as (ii) inhibition of tubular reabsorption resulting in solute diuresis. The decrease in renal perfusion is thought to be caused by a decrease in prostaglandine synthesis [8].

Preclinical studies in dogs showed an impressive fall in glomerular filtration rate (GFR) and renal plasma flow [7]. A subsequent clinical study in patients with thalassemia revealed that 80% of the 27 patients had a (reversible) fall in GFR after s.c. administration of deferoxamine [5]. Interestingly, the iron chelate ferrooxamine increases the fractional excretion of sodium and chloride, leading to increased diuresis and subsequent volume contraction. These results are consistent with a study in thalassemic patients receiving deferoxamine, indicating impaired tubular function by an increase in urinary beta-2-microglobulin growth hormone excretion [9]. At an ultrastructural level, the cortical tubular epithelial were remarkable for their degenerated mitochondria (Figure 2). Although deferoxamine can stabilize mitochondria, direct toxic effects, especially on complex II activity, have been reported [10]. This effect is probably caused by chelation of mitochondrial iron, leaving behind an iron-depleted, nonfunctioning complex II that results in ATP depletion of tubular epithelial cells. This mechanism has been demonstrated in cell culture [10,11]. In these experiments, even morphologic alterations in mitochondria were reported. However, in contrast to our findings in tubular epithelial cells, the authors reported elongated mitochondria and no myelin figures in the immortalized hepatocyte cell line they examined [11].

This toxic effect on mitochondria with ATP depletion could explain the acute tubular damage, dysfunction and the increased fractional excretion of sodium. The ultrastructural morphology of the tubular epithelial cells in this case seems distinct and could help to define a specific morphologic pattern of deferoxamine-induced damage in tubular epithelial cells. The mitochondrial alteration described in this case are clearly different from the pattern of acute tubular damage ‘common type’ as described by Olson et al. [12]. Although CNIs can also cause structural damage in mitochondria of tubular epithelial cells, neither the typical giant mitochondria nor a dilatated endoplasmic reticulum specific for CNI-induced damage was found. Still it is conceivable that a synergistic toxicity of both drugs targeting mitochondria caused the acute tubular damage. Further studies in animal models and in biopsy cases are needed to precisely define the morphologic alternations caused by deferoxamine. Nevertheless, deferoxamine is widely considered to be a safe drug and, apart from its use in iron overload, is recommended to treat aluminium-related bone disease in patients with CKD stage 4. Moreover, patients with iron overload are not routinely monitored for renal impairment and deferoxamine is considered a safe alternative to deferasirox, which had been repeatedly shown to cause acute renal failure [13]. Despite all the limitations of this single report, which does not prove causality, this case as well as the existing literature suggests that the off-label use of deferoxamine in patients with renal impairment should be accompanied by a close monitoring of renal function.

Conflict of interest statement. None declared.

References


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