Exceptional Case

Acute interstitial nephritis due to deferasirox: a case report

Godela Brosnahan\textsuperscript{1,2}, Neriman Gokden\textsuperscript{3} and Sundararaman Swaminathan\textsuperscript{1}

\textsuperscript{1}Division of Nephrology, Department of Internal Medicine, University of Arkansas for Medical Sciences, \textsuperscript{2}Central Arkansas Veterans Healthcare System and \textsuperscript{3}Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Abstract

Deferasirox is a new oral iron chelator used to treat transfusional iron overload. Pre-marketing clinical trials revealed little organ-specific toxicity. Increases in serum creatinine were noted in one-third of patients but were mild and non-progressive. We describe a 62-year-old man with myelodysplastic syndrome who developed a progressive decline in renal function after starting deferasirox. A kidney biopsy showed acute interstitial nephritis with increased eosinophils, suggesting drug hypersensitivity. Deferasirox was discontinued and renal function returned to baseline. This is the first pathological description of deferasirox-related acute kidney injury in humans, which differs from tubular vacuolization observed in animals.

Keywords: acute interstitial nephritis; deferasirox; iron chelation

Background

Iron overload due to red blood cell transfusions is an important health problem worldwide, particularly in countries where thalassemia major or sickle cell diseases are common. Desferrioxamine, an iron-chelating agent, has been available since the early 1960s and its use has led to an increase in survival in these patients [1]. However, it is cumbersome to use because it must be administered as a continuous subcutaneous or intravenous infusion, which makes effective iron chelation very difficult.

Two oral iron chelators have been developed. Deferiprone was approved for use in India in 1995 and in Europe in 1999 [2]. More recently, deferasirox was approved in the United States in 2005 and remains the only oral iron chelator available in this country [2]. The main adverse events in the initial clinical trials were transient gastrointestinal complaints and skin rashes; about one-third of patients developed mild and reversible increases in serum creatinine [3,4]. Post-marketing surveillance, however, revealed the occurrence of fatal acute renal failure; the decrease in renal function was not always reversible, and older patients were particularly at risk [1,2,5]. Nephrotoxicity in animals has been attributed due to tubular toxicity but, to our knowledge, there are no renal biopsy data in humans. Here we report histologically proven acute interstitial nephritis (AIN) in a patient treated with deferasirox in the context of a myelodysplastic syndrome.

Case report

The patient is a previously healthy 62-year-old Caucasian man with myelodysplastic syndrome diagnosed in June 2006. He received multiple red cell transfusions during 2006 and 2007 at an outside institution. In May 2007, he presented to our institution for re-evaluation. A repeat bone marrow biopsy showed myelodysplastic/myeloproliferative disease and increased iron stores. Serum ferritin was 2968 µg/L and iron saturation was 102%. He was started on deferasirox 2 g daily.

He was first seen in the renal clinic in July 2007 for worsening renal function, with an increase in creatinine from 141 to 194 µmol/L (1.6 to 2.2 mg/dL). He did not have a prior history of kidney disease, nor of hypertension or diabetes. He did not take non-steroidal or other nephrotoxic drugs. Imaging revealed normal kidneys. The patient had proteinuria of ∼1 g/day, with bland urine sediment. Serological tests were all negative. By September 2007 his creatinine had increased to 265 µmol/L (3.0 mg/dL). Urinalysis showed 3–5 red cells and 3–5 white cells per high-power field. There were no urinary eosinophils and no blood eosinophilia. A renal biopsy was performed.

Light microscopy showed 15 glomeruli, one of which was globally sclerosed, but the others were unremarkable. There was diffuse interstitial mononuclear cell infiltration admixed with neutrophils and increased numbers of eosinophils and interstitial oedema (Figure 1). There were no granulomas. The immunohistochemical panel was negative for any leukaemic infiltrates. Arteries and arterioles were unremarkable. There was ∼40% interstitial fibrosis with proportional tubular atrophy.
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**Fig. 1.** Renal biopsy showing acute interstitial nephritis. There are interstitial mononuclear infiltrates and increased numbers of eosinophils, H&E, 400×.

An immunofluorescence panel including IgG, IgA, IgM, C3, C1q, kappa and lambda light chains and fibrinogen was negative. Electron microscopy revealed unremarkable glomeruli with no evidence of deposits in any location.

The diagnosis of AIN with increased eosinophils, suggestive of drug hypersensitivity, on a background of chronic interstitial nephritis was rendered. Deferasirox was discontinued and subsequently creatinine levels improved to 115 µmol/L (1.3 mg/dL).

**Discussion**

This patient presented to the renal clinic with progressive renal failure, with non-specific findings on urinalysis and non-nephrotic proteinuria. He did not report any episodes of hypotension, and there were no signs of hypovolaemia or of infection leading to acute tubular necrosis (ATN). The urinalysis did not suggest glomerulonephritis, and the patient had no signs or symptoms of vasculitis.

The finding of AIN was unexpected. The patient had no suggestive findings such as leukocyturia with eosinophils, nor any systemic signs of hypersensitivity. This non-specific presentation has been reported before in many cases of drug-induced AIN [6,7].

AIN has many potential etiologies. The most common is a drug hypersensitivity reaction [6,7]. In the classical case of methicillin-induced AIN, intense staining of the tubular basement membranes for IgG was observed, suggesting an antibody-mediated mechanism [8]. In most other reports of drug-induced AIN there were no immune deposits; cell-mediated immunity is believed to be the cause of the injury [7]. Drugs most commonly implicated are penicillins and other antibiotics, non-steroidal drugs, proton pump inhibitors and H2-receptor blockers [6,7]. Granuloma formation can be observed in drug-induced AIN.

AIN can occur during an infection with bacteria, viruses and protozoa, either by direct invasion of the microorganism such as in pyelonephritis or as a hypersensitivity reaction to the infection [9]. Viruses can also directly invade the kidney and evoke an inflammatory interstitial reaction; a pathognomonic finding in these cases is intranuclear inclusions in tubular cells, as is seen in adenovirus- and cytomegalovirus-related AIN. The BK virus causes AIN in transplanted kidneys. AIN often accompanies glomerulonephritis or can be part of a systemic autoimmune disease. The differential diagnosis of granulomatous AIN is drugs, sarcoidosis, Wegener’s granulomatosis, tuberculosis, fungal infection such as disseminated histoplasmosis or tubulointerstitial nephritis with uveitis (TINU) syndrome. Lastly, idiopathic tubulointerstitial nephritis due to anti-tubular basement membrane antibodies has been described. All of these causes had been ruled out in our patient, leaving deferasirox as the most likely etiology.

To our knowledge, this is the first biopsy report on deferasirox-induced nephrotoxicity in humans and it clearly differs from the findings in rats and marmosets, where tubular toxicity with vacuolar tubular degeneration was observed after high doses of deferasirox. Our patient developed a hypersensitivity reaction manifesting as AIN. Cases of leukocytoclastic vasculitis, another manifestation of hypersensitivity, have also been reported. Knowledge of the potential for renal adverse effects is important because the incidence of myelodysplastic syndrome is increasing and patients with haemolytic anemias are living longer. Therefore, the use of iron-chelating agents will likely increase,
also. Iron chelation is also being considered for various neurodegenerative diseases such as Alzheimer’s dementia and Parkinson’s disease [10].

In summary, we report a case of biopsy-proven AIN in a patient treated with deferasirox, whose renal dysfunction improved after the drug was discontinued. Although the association of deferasirox with renal dysfunction had been reported before, this is the first biopsy data in humans.

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Conflict of interest statement. None declared.

References


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