

Chronic Interstitial Nephritis Induced by Deferasirox (Exjade): An Oral Iron-Chelating Agent in a Patient with Thalassemia Major

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ABSTRACT

We report on the development of chronic interstitial nephritis induced by Deferasirox (Exjade). The patient is a 40-year-old woman, with history of thalassemia major had developed progressive increase in serum creatinine up to 150 $\mu\text{mol/L}$ and proteinuria at 2 g/day over 6 months following 9 years-treatment with 500 mg/daily of Exjade as an oral iron chelating agent. Her kidney biopsy showed chronic interstitial inflammation and fibrosis with 73% secondary global glomerulosclerosis. In conclusion, patients treated with Exjade are at risk of irreversible kidney damage by interstitial inflammation and fibrosis.

Key words: Exjade, Thalassemia Major, Iron-Chelation, Interstitial Nephritis, Renal Failure.

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INTRODUCTION

For decades, patients with thalassemia major (TM) have depended on nightly Deferoxamine infusions for iron chelation. The latter resulted in improved survival with 25,000 deaths in 2013 compared to 36,000 in 1990.¹ Further achievement was the development of novel oral iron-chelators (IC) to improve patient's compliance. Initially, Deferiprone, in 1987 and Deferasirox (Exjade) in 2006. The latter is more convenient since it has long plasma half-life of 8-16 hours and hence can be administered once daily. Its renal side-effects were described as minimal and limited to vacuolar tubular degeneration after high doses in rats and marmosets.² Moreover, the initial phase 3 clinical evaluation and a recent 5-year follow up studies, showed only mild, dose-related, reversible rise in serum creatinine.^{3,4} In the post-marketing era, 2 cases of acute and reversible acute interstitial nephritis (AIN) were reported following few weeks of drug-use; 1 with Fanconi syndrome and the second with a histological evidence of AIN.^{5,6} In the present case report, we describe a patient with TM who presented with histological evidence of advanced renal interstitial fibrosis associated with a chronic use of the drug.

CASE PRESENTATION

A 40 year-old woman was referred for management of persistent rise in serum creatinine and proteinuria in the past 6 months. She denied shortness of breath, oedema, chest or abdominal pains, skin rash and joint disease. Past history was significant for TM and is requiring blood transfusions, every 2 months, since the age

of 3 years. She was started on Exjade 500 mg daily as a maintenance IC agent in 2005. She held the drug for 1 year, in 2012, after marriage and had conceived her first and only child. Subsequently, the drug was resumed for another 2 years. Subsequent, work up for in-vitro-fertilization revealed progressive rise in serum creatinine over a 6-months follow up that had reached 150 $\mu\text{mol/L}$. The drug was held for 2 months and serum creatinine had improved marginally to 130 $\mu\text{mol/L}$ yet had persistent proteinuria at 2 g/day. Retrospectively, the drug was tolerated well without any gastrointestinal side effect or liver abnormalities. During therapy, serum ferritin remained < 400. The patient did not have past history of other significant medical illness, surgery, allergy or chronic intake of medications especially NSAIDs. On her initial physical examination, she was conscious, oriented X3 and without distress of pain or shortness of breath. She was pale. Blood pressure was 160/90 mm Hg. She was afebrile with a body weight at 48 kg. She did not have lymphadenopathy, goiter, jugular venous distension or oedema. Systemic examination did not show abnormality. Laboratory investigations showed normal peripheral leucocytic and platelets counts. Hemoglobin was 78 g/L with MCV at 62 fL. Serum urea and creatinine were elevated at 9 mmol/L and 130 $\mu\text{mol/L}$, respectively. Serum sugar, electrolytes and liver functions were normal. Serum cholesterol and TSH were normal. Urine routine and microscopy were normal except for 3 (+) proteinuria yet without hematuria or pyuria. Chest x-ray and ECG were normal.

Abdominal and pelvic ultrasound was normal except for normal-sized kidneys with increase cortical echogenicity. Serum complements (C3 & C4), IgA level and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Kidney biopsy showed extensive interstitial fibrosis (Fig.1) which was more evident in the medulla (Fig.2) as compared to the cortex (Fig.3). The interstitium showed moderate interstitial infiltrate with plasma cells and lymphocytes (Fig.4). Approximately, 75% of the

glomeruli showed global sclerosis while the remaining ones were normal (Fig.5).

Immunofluorescent stains were negative in the glomeruli and tubules. Blood vessels did not show significant abnormality. Stainable iron was limited only to the luminal surface of tubules and not detected in the interstitium and (Fig.6). The patient was instructed to avoid further exposure to oral IC and to be maintained on Deferoxamine-infusions. Two months later, serum creatinine fell to 110 $\mu\text{mol/L}$.

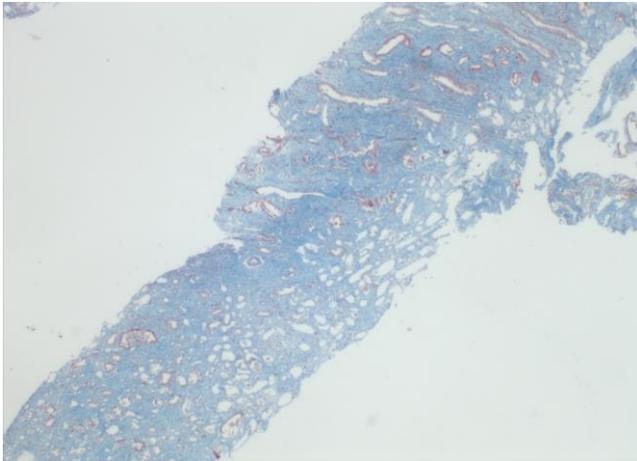


Fig 1: Photomicrograph of kidney biopsy showing extensive kidney fibrosis (Trichrome stain X100)

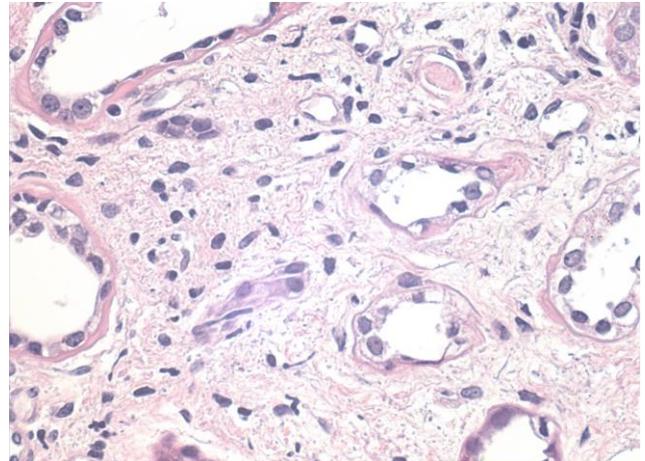


Fig 2: Photomicrograph of medulla showing advanced fibrosis with fibroblasts, atrophic tubules (HE X400).

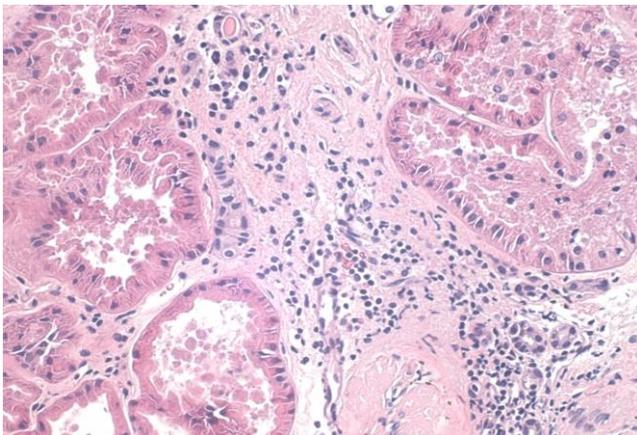


Fig 3: Photomicrograph of cortical area with globally sclerosed glomeruli and interstitial infiltrate with early fibrosis (HE X160)

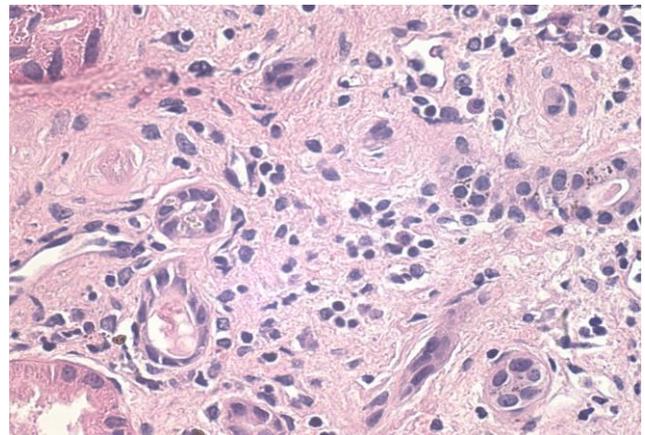


Fig 4: Photomicrograph showing cortical area of fibrosis containing plasma cells and lymphocytes (HE X200).

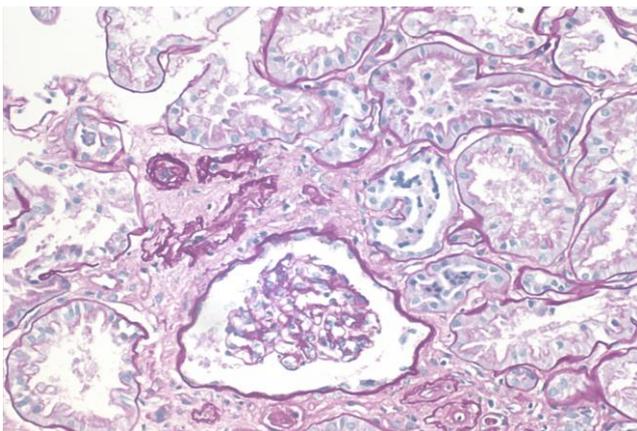


Fig 5: Photomicrograph showing normal glomeruli surrounded by interstitial fibrosis (PAC X400)

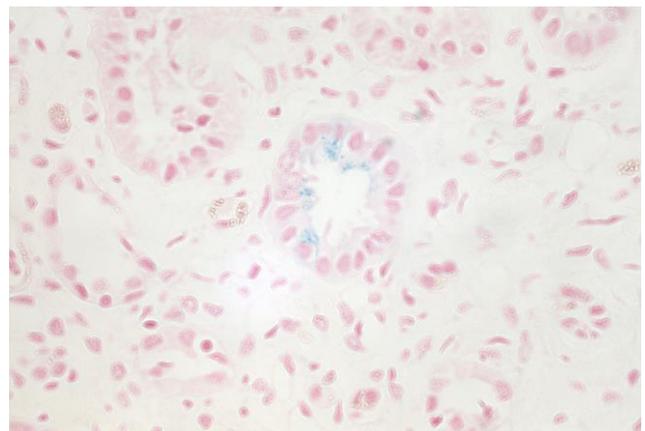


Fig 6: Photomicrograph showing part of the medulla with stainable iron limited only to the luminal surface of a tubule (Perl's Prussian blue stain X200).

DISCUSSION

The persistent azotemia and proteinuria, without any clinical evidence of infection or autoimmune disease, indicated kidney biopsy in our patient. The normal appearance of the 25% unaffected glomeruli with diffuse interstitial fibrosis in the medulla and chronic interstitial disease in the cortex indicated that the initial mechanism of injury was a chronic interstitial nephritis.⁷ The normal serum ferritin and lack of stainable iron in the interstitium were against iron as the culprit and the decrease in serum creatinine following discontinuation of Exjade incriminates the latter. Recent large and prospective postmarketing studies with a 5-year follow up, described only mild and reversible azotemia with Exjade-use and never a permanent damage.⁴ Significant kidney disease was reported once in a patient with slow yet progressive rise in serum creatinine from 141 $\mu\text{mol/L}$ in May 2007 to 194 one month later to 265 four months later.⁶ It showed AIN with 40% interstitial fibrosis. In our patient, an isolated idiosyncratic reaction is a possible hypothesis yet the frequency of raised serum creatinine encountered in most longitudinal studies is of a major concern. Moreover, and as in our patient, mild azotemia may underestimate the extent of the chronic interstitial fibrosis. The potential toxicity of Exjade is inherent with its ability to enter cells owing to its lipophilic character and hence the formation of highly charged complex with iron.⁸ The latter has been shown in cultured heart muscle.⁹

Untreated or poorly transfused TM patients develop growth retardation, hepatosplenomegaly, leg ulcers, deforming skeletal masses from extramedullary hematopoiesis, cholelithiasis and splenectomy-associated infections. On the other hand, treatment with regular blood transfusions leads to iron overload-related complications that include multiple endocrine complications, cardiomyopathy and liver fibrosis. For such disease, bone marrow transplantation is the ideal treatment yet identical donors are rare.¹⁰ Therefore, strategies to reduce post-transfusional diseases by improving ICs are of highest priority. The latter includes meticulous follow up to avoid replacing one disease with another.

CONCLUSION

Nephrologists, hematologists and internists should be aware of the potential risk of chronic interstitial fibrosis associated with Exjade.

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