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Case Report

Collapsing Focal Segmental Glomerulosclerosis in a Patient with Juvenile Idiopathic Arthritis Treated with Leflunomide

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Keywords
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Abstract

Introduction: Collapsing glomerulopathy is a severe podocyte injury that causes massive proteinuria, renal failure and is resistant to therapy. This disease is most often seen in association with HIV infection. However a growing list of collapsing glomerulonephropathy has been reported to occur in association with other infections, drugs, autoimmune diseases or is classified as idiopathic.

Case presentation: We present the case of a patient with juvenile idiopathic arthritis treated with leflunomide who developed a full blown nephrotic syndrome with normal renal function. She underwent renal biopsy that showed collapsing focal segmental glomerulosclerosis. In the suspicion that leflunomide could be the cause of the glomerulopathy, we decided to stop the drug and to treat the patient with steroids and cyclosporin, achieving a significant reduction of proteinuria.

Conclusion: This is the first report about the development of collapsing glomerulopathy in a patient with juvenile idiopathic arthritis and we cannot exclude a role of the autoimmune disease in its pathogenesis. Remission of nephrotic syndrome was achieved with withdrawal of leflunomide and immunosuppressive treatment. We speculate that leflunomide could have induced the renal disease but the pathogenetic connection between the drug and the renal toxicity remains to be demonstrated.

ABBREVIATIONS

CG: Collapsing Glomerulopathy; JIA: Juvenile Idiopathic Arthritis.

INTRODUCTION

Collapsing focal segmental glomerulosclerosis (also known as collapsing glomerulopathy or CG) is a severe podocyte injury that causes massive proteinuria, renal failure and is resistant to therapy [1]. Most often seen in association with HIV infection, CG has also been increasingly recognized in non-HIV infected patients [2]. Most cases of CG not associated with HIV infection are idiopathic. However, CG has been reported to occur in association with a growing list of disease including other viral infections (hepatitis C, parvovirus B19 and cytomegalovirus) and autoimmune diseases such as systemic lupus erythematosus and mixed connective tissue disease [3-6].

An association has been noted between development of CG and therapy with the bisphosphonate pamidronate in patients treated with higher than recommended doses [7,8].

Anabolic steroids, anthracycline and the therapeutic use of INF-alpha, beta, and gamma have been associated with the development of CG [9].

We report a case of one patient affected by juvenile idiopathic arthritis who developed a CG while treated with leflunomide.

CASE PRESENTATION

A 26 year old woman was referred to our Renal Unit in August 2012 for edema due to severe nephrotic syndrome (proteinuria 18.4g/day) with normal renal function and blood pressure.

She has been diagnosed with juvenile idiopathic arthritis

(JIA) since the age of 16 and she was followed in the department of pediatric Rheumatology.

She had been treated with steroids and hydroxychloroquine without benefit. The patient had her first pregnancy from January to October 2009: the clinical course was uneventful, the rheumatic disease remained in complete remission and the delivery was at term. Due to exacerbation of arthritis after pregnancy she started leflunomide in April 2011 achieving good disease control.

At the time of admission she was continuing treatment with 20mg/day leflunomide.

Laboratory tests are shown in (Table 1).

Proteinuria was confirmed, C3 and C4 were normal, anti-DNA antibodies and P and C ANCA were negative, while ANA was positive. We decided to perform a kidney biopsy in August 2012.

At light microscopy 26 glomeruli were present. Seven of them showed global (Figure 1A) or segmental (Figure 1B) collapse and solidification of the glomerular tuft with wrinkling and folding of the glomerular basement membrane. The collapsed glomerular tuft was surrounded by hyperplastic and hypertrophic podocytes filling the urinary space forming pseudocrescent. At immunofluorescent microscopy only IgM (++) was present in 2 out of 8 glomeruli, with segmental mesangial and parietal distribution. The histological picture was compatible with CG and we decided to treat the patient with prednisone 1mg/kg/day, ACE inhibitor and statin. After two months of full dose steroids therapy nephrotic syndrome persisted (proteinuria 14g/die). In the suspicion that the CG could be secondary to leflunomide, in accordance with the Rheumatologists, in October 2012 we decided to stop the drug. The patient was treated with cholestryramine in order to remove leflunomide from the body. In November 2012 leflunomide was undetectable in the blood.

In January 2013, due to the persistence of nephrotic syndrome (proteinuria 11g/day), the patient started cyclosporine A (4mg/kg/day) in association with prednisone and ACE inhibitor.

During the following months proteinuria progressively decreased and serum albumin progressively normalised. From July 2013 serum albumin was in normal range (3.7g/dl) and proteinuria in non nephrotic range (2.3g/die).

A further reduction of proteinuria was documented at last observation in January 2014 (proteinuria 0.8 g/day). During the follow up renal function was persistently normal and the rheumatic disease was in clinical remission.

DISCUSSION

We present the case of a patient with JIA who developed nephrotic syndrome with normal renal function and an histological renal picture of collapsing focal segmental glomerulosclerosis. The nephrotic syndrome appeared after more than one year of therapy with leflunomide. In the suspicion that the renal disease was secondary to leflunomide therapy the drug was withdrawn. The patient was treated with steroid and cyclosporin with remission of nephrotic syndrome.

JIA is a complex disease that can affect multiple organ systems, its pathogenesis is unclear and JIA may represent not a single disease but a syndrome with different etiologies. Renal involvement is an unusual finding. That may be attributed to the disease itself, as well as caused by drugs, either nonsteroidal anti-inflammatory or antirheumatic drugs. Mesangial glomerulonephritis, renal amyloidosis and exceptionally, rapidly progressive crescentic glomerulonephritis have been reported in association with JIA [10]. However association between this disease and CG have never been reported. Instead CG have been described in other autoimmune diseases such as systemic lupus, still disease and mixed connective tissue diseases [4-6].

Our patient was treated with leflunomide which acts inhibiting pyrimidine synthesis, resulting in antiproliferative and anti-inflammatory effects. No cases of CG during treatment with leflunomide have been described. However an association has been described between development of CG and some drugs [7-9].

Table 1: Laboratory test at diagnosis of Collapsing glomerulophaty, during the follow-up and at last observation.

Test	Start therapy with prednisone	Leflunomide blood dosage:0	2 months after CsA therapy	last observation
Data	9/8/2012	20/11/2012	25/3/2013	9/1/2014
Serum Creatinine	0.7 mg/dl	0.63 mg/dl	0.64 mg/dl	0.87 mg/dl
Azotemia	24 mg/dl	33 mg/dl	-	32 mg/dl
proteinuria 24h	18.4 g/24h	11 g/24h	10.9 g/24h	0.832 g/24h
Total cholesterol	308 mg/dl	338 mg/dl	-	115 mg/dl
HDL cholesterol	45 mg/dl	-	-	58 mg/dl
Triglycerides	121 mg/dl	131 mg/dl		69 mg/dl
Total protein	4 g/dl	4.5 g/dl	4.9 g/dl	6.6 g/dl
Albumin	2.3 g/dl	2.9 g/dl	2.8 g/dl	4.2 g/dl
Electrophoresis	↑α2	↑α1 and α2 ↓ γ	↑α1 and α2 ↓ γ	Normal
Hemoglobin	9.7 g/dl	11.6 g/dl	10.5 g/dl	10.2 g/dl
White blood cells	5010	8630	11370	8950
Platelets	217000	246000	222000	363000

Abbreviations: CsA: cyclosporine

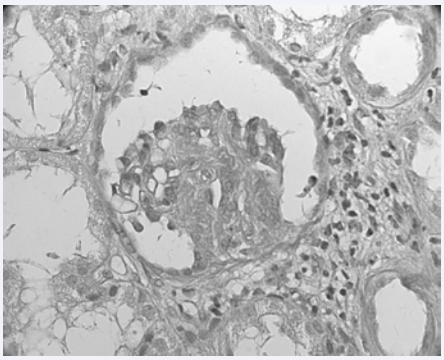

Figure 1a One glomerulus with global collapse and solidification of the tuft surrounded by hyperplastic and hypertrophic podocytes.

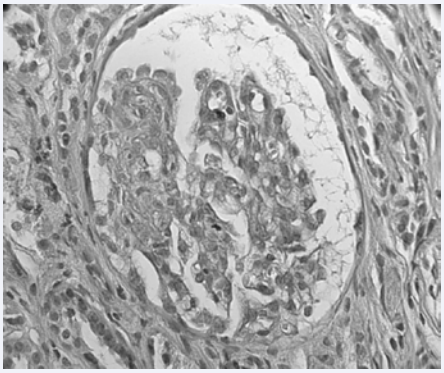

Figure 1b One glomerulus with segmental collapse and solidification of the glomerular tuft surrounded by hyperplastic and hypertrophic podocytes filling the urinary space forming pseudocrescent.

Patients with CG usually present with renal failure and massive proteinuria that is frequently not responsive to therapy. Thirteen cases of CG in lupus patients have been treated with pulse steroids followed by oral steroids alone or in association with mycophenolate mofetil, IVIg, azathioprine and plaquenil [4]. Of them seven progressed to end stage renal disease, five achieved partial response and one complete remission. In one study only renal dysfunction partially reversed after stop of pamidronate with or without steroid therapy [8].

Our patient did not have renal failure at presentation but severe nephrotic syndrome and at last observation continued to have a good renal function and a significant reduction of proteinuria.

This is the first work that suggests an association between use of leflunomide and CG in a patient with JIA. However, in our patient the achievement of a significant remission of proteinuria may be either secondary to discontinuation of leflunomide or a response to therapy with steroids and cyclosporin. The pathogenetic hypothesis of cause and effect between the drug and the glomerulopathy remains to be demonstrated.

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