Exceptional Cases

FSGS permeability factor-associated nephrotic syndrome: remission after oral galactose therapy

Eric De Smet, Jean-Philippe Rioux, Hélène Ammann, Clément Déziel and Serge Quérin

Nephrology and Medical Biology Divisions, Hôpital du Sacré-Coeur and Université de Montréal, Montreal, QC, Canada

Correspondence and offprint requests to: Serge Quérin; E-mail: serge.querin@umontreal.ca

Abstract

Some cases of nephrotic syndrome in focal and segmental glomerulosclerosis (FSGS) are associated with a circulating factor, the FSGS permeability factor (FSPF). Galactose has a high affinity for FSPF, and experimental data suggest that it could reduce its activity. We describe the case of a 48-year-old male with a nephrotic syndrome found to be resistant to corticosteroids, immunosuppression and plasmaphaeresis. The patient was given oral galactose as a last resort treatment, which was followed by a remission of his nephrotic syndrome that correlated with a reduction of FSPF activity. This case is the first report of a long-standing remission of an FSPF-associated nephrotic syndrome on oral galactose therapy.

Keywords: focal segmental; galactose; glomerulosclerosis; nephrotic syndrome; permeability factor

Introduction

Proteinuria in focal segmental glomerulosclerosis (FSGS) is sometimes associated with a circulating factor, the FSGS permeability factor (FSPF) [1]. This concept is supported by the recurrence of FSGS after transplantation [2], by the response to therapy with plasmaphaeresis [3] or immunoadsorption [4] and by a case of transient nephrotic syndrome in a newborn whose mother had FSGS [5]. Testing for permeability to albumin (Palb) of rat glomeruli that have been incubated with the serum from a suspected case, compared to a control, is believed to be correlated with FSPF activity [6]. $P_{\text{abl}}$ with pooled normal human serum is taken as 0, values between 0.2 and 0.5 are nonspecific and common in patients with renal disease, and values > 0.5 have been associated with a high incidence of recurrence of FSGS following kidney transplantation [6].

Galactose is a sugar that has been shown to have a high in vitro affinity for FSPF in chromatographic studies [1]. In vivo, administration of intravenous or oral galactose has also been associated with a significant decrease of $P_{\text{abl}}$ in a patient with an FSPF-associated nephrotic syndrome; however, no improvement of proteinuria has been noted, as the patient was already dialysis dependent [1]. The effect of galactose administration in reducing FSPF-associated proteinuria at an earlier disease stage has never been described.

Case report

A 48-year-old male was admitted in February 2004 complaining of progressive acral and facial oedema for 1 month. His past medical history included dyslipidaemia, mild asthma, thalassaemia minor and an allergy to trimethoprim–sulfamethoxazole. Physical examination revealed a blood pressure of 145/90 mmHg, evidence of ascites and ankle oedema. The body mass index was 24.7 kg/m² after control of the oedema with diuretics. Blood chemistry showed the following: creatinine 5.19 mg/dL (459 µmol/L), total protein 3.4 g/dL (34 g/L), albumin 1.3 g/dL (13 g/L), total cholesterol 445 mg/dL (11.5 mmol/L) and fasting glucose 104 mg/dL (5.8 mmol/L). Complete blood count, liver enzymes and C-reactive protein were normal. Urine sediment showed 5–10 red blood cells per high-power field, and proteinuria was 19.8 g/24 h. Kidney ultrasound was normal as well as chest radiography. A kidney biopsy was performed and was consistent with minimal change disease. There were five glomeruli in the mostly cortical sample examined with light microscopy. All were of normal diameter, one showed global sclerosis and the other four were optically normal. The interstitium, tubules and vessels were normal. Indirect immunofluorescence only showed slight granular deposits of IgM in the mesangium and peripheral capillary loops in a focal and segmental fashion. In the three glomeruli found in the sample for electron microscopy, diffuse effacement of the epithelial foot processes was observed, without any other lesion. Further investigation was negative including hepatitis B and C serological screening, search for the antineutrophil cytoplasmic antibody and the antiglomerular basement membrane antibody and serum C3 and C4 levels.

The patient was initially treated with prednisone 80 mg (1 mg/kg) daily started in February 2004. Cyclophosphamide 125 mg (1.5 mg/kg) daily was added 6 weeks later.
later. The patient developed severe *Pneumocystis jirovecii* pneumonia in April 2004 requiring prolonged hospitalization in the intensive care unit and withdrawal of immunosuppression. The latter was reintroduced in January 2005 with mycophenolate mofetil (500 mg twice daily). Due to persistent proteinuria (11.68 g/24 h), cyclosporine in microemulsion capsules was added in April 2005 at an initial dosage of 50 mg twice daily that was later increased to 75 mg twice daily. As proteinuria remained at 13.31 g/24 h, both immunosuppressive agents were discontinued and cyclophosphamide reintroduced (up to 100 mg daily) in July 2005. Finally, the patient had three times weekly, and ultimately once every two weeks, plasma exchanges between December 2005 and July 2006 (34 treatments in all). Despite plasmapheresis and the replacement of cyclophosphamide by cyclosporine in May 2006, this time at a starting dosage of 175 mg twice daily, proteinuria was still 4.5 g/24 h in July 2005. The patient was on oral prednisone (5 mg daily), proteinuria still remained at 1.23 g/24 h. Blood pressure was 105/70 mmHg, serum creatinine was stable at 1.75 mg/dL (155 µmol/L) and serum albumin concentration had risen to 3.5 g/dL (35 g/L). As of January 2009, with the patient still on oral galactose therapy but at an increased dosage of 15 g BID on the basis of a recent report [1], proteinuria remained at 1.14 g/24 h and serum creatinine at 1.75 mg/dL (155 µmol/L). No side effects of this prolonged treatment have been observed.

**Discussion**

Oral galactose therapy seems to have induced a remission of our patient’s nephrotic syndrome, which has been sustained for more than 2 years. This remission is correlated with a decrease in permeability factor activity (P_{\text{ab}}). Reduction of P_{\text{ab}} after galactose administration has already been described [1], but this is the first reported case of a sustained remission of an FSPF-associated nephrotic syndrome following oral galactose administration. Although we have no histological proof of a transformation from minimal change disease to FSGS in our patient, his clinical course, the presence of focal and segmental IgM deposits in the initial (mostly cortical) biopsy, resistance to therapy and high levels of P_{\text{ab}} argue strongly in favour of this diagnosis. In any case, we propose to label this patient as having an FSPF-associated nephrotic syndrome, since postulated pathophysiology rather than histology guided the experimental therapy that was attempted.

Savin *et al.* have hypothesized that FSPF might induce the nephrotic syndrome by interacting with galactose of the glomerular glycocalyx. Administration of large amounts of galactose to patients with an FSPF-associated nephrotic syndrome might induce formation of circulating complexes of free galactose and FSPF that could be cleared by the liver or other cells, hence preventing FSPF from interacting with the glycocalyx [1].

Our case lends credit to this hypothesis, which incidentally may not be entirely specific for FSGS. However, spontaneous remissions do occur in FSGS. Moreover, in our patient, although proteinuria appeared to have stabilized around 5 g/24 h after 9 months of cyclosporine before galactose was added to the therapeutic regimen and proteinuria only decreased to subnephrotic levels during the following months, a late contribution of cyclosporine to this apparent beneficial effect of galactose cannot be excluded. Clearly, the effect of galactose (if any) should be studied in more subjects, with biopsy-proven FSGS, to support our observation. A pilot study (NCT00816478) is presently recruiting patients with primary FSGS to determine if oral administration of galactose for 28 days can lower the circulating level of the FSGS permeability factor. Longer prospective trials should eventually be conducted if this pilot study is found to be conclusive. Should more evidence of its effectiveness be obtained, galactose could be a significant adjunct to the treatment of established FSGS and the prevention of post-transplantation FSGS recurrence. Galactose appears nontoxic, has been extensively used as a contrast ultrasound agent per IV [7] and more recently as therapy for the cardiac variant of Fabry’s disease for more than 2 years in one patient [8].

*Conflict of interest statement.* None declared.
A case of sulphasalazine-induced DRESS syndrome with delayed acute interstitial nephritis

Jean-François Augusto1,2,3, Johnny Sayegh1, Amélie Simon1, Anne Croue4, Jean-Marie Chennebault5, Maud Cousin1,3 and Jean-François Subra1,3

1Service de Néphrologie-Dialyse-Transplantation, 2Service de Réanimation Médicale et Médecine Hyperbare, CHU Angers, F-49933, 3UPRES EA 3863, University of Angers, F-49035, 4Département de Pathologie Cellulaire et Tissulaire et 5Département de Maladie Infectieuses et Tropicales, CHU Angers, F-49933, Angers, France

Abstract
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a rare and severe drug-induced hypersensitivity reaction characterized by haematological abnormalities (hypereosinophilia and/or mononucleosis) and multiorgan involvement. Renal failure has been rarely described. We report the case of a 77-year-old female with sulphasalazine-induced DRESS syndrome who improved rapidly on corticosteroid treatment. After prednisone withdrawal, the patient developed renal failure that necessitated a session of haemodialysis. A kidney biopsy showed acute tubulointerstitial nephritis with an intense lymphocytic infiltrate and tubular necrosis. Kidney function normalized after a further 2 weeks of corticosteroid treatment. This is the first histologically proven case of acute tubulointerstitial nephritis in the setting of sulphasalazine-induced DRESS syndrome.

Keywords: acute tubulointerstitial nephritis; DRESS syndrome; HHV-6; sulphasalazine

Introduction
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a rare and severe drug-induced hypersensitivity reaction characterized by skin rash, fever, eosinophilia and organ involvement [1]. Hepatitis and pneumonitis are frequent visceral manifestations, while kidney involvement is uncommon and has been rarely described. We report a case of typical sulphasalazine-induced DRESS syndrome with delayed onset of renal involvement.

Case report
A 77-year-old women was admitted to hospital with fever (39°C), dyspnoea and a diffuse exanthematous maculopapular rash, 4 weeks after the initiation of sulphasalazine. The patient had no significant past medical history. She developed bilateral ankle pain resistant to an association of paracetamol (3 g/day) with tramadol (300 mg/day) 2 months before admission to hospital.

References

Received for publication: 26.4.09; Accepted in revised form: 19.5.09