JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

Original Paper Open Access

MYELOPROLIFERATIVE DISORDER ASSOCIATED WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS - A CASE REPORT

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ABSTRACT

We report a rare case of focal segmental glomerulosclerosis (FSGS) with Myelofibrosis. A 57-year-old man with underlying Idiopathic Membranous Nephropathy (IMN) presented to us with chief complaints of frothy urine and leg swelling. Urine quantification showed nephrotic-range proteinuria. The patient underwent renal biopsy due to rapidly declining renal function and persistent proteinuria, in which the electron microscopy (EM) revealed the diagnosis of focal segmental glomerulosclerosis (FSGS) although initial light microscopy showed thickening of capillary loops which suggested MN. He was started on immunosuppressive therapy which consisted of calcineurin inhibitor and steroids, and his renal function and proteinuria improved. We wish to highlight the importance of incorporating EM as part of the routine histopathological assessment to yield a precise diagnosis.

Keywords: *Focal Segmental Glomerulosclerosis, Membranous Nephropathy, Myelofibrosis, Nephrotic syndrome, Electron Microscopy*

INTRODUCTION

FSGS is a clinical-pathologic syndrome of proteinuria associated with focal and segmental sclerotic glomerular lesions that are characterized by podocyte damage. The pathologic classification of FSGS is categorized as primary and secondary, the latter of which is caused by HIV-associated, drug toxicities, but also by structural-functional adaptations to glomerular hyperfiltration such as obesity, hypertension, reflux nephropathy, and so on. Several morphologic variants of primary and secondary focal sclerosis are now recognised, based on a 2004 Columbia classification system, including FSGS-not otherwise specified (NOS), perihilar, cellular, tip, and collapsing variants.

To date, the exact nature of FSGS superimposed on Idiopathic MN remains unclear. Uchika Gupta et al. suggested that FSGS may be secondary to membranous nephropathy and may be an indication of poor prognosis however the mechanism is still unknown. Glomerulopathy is even more unusual in myeloproliferative neoplasm (MPN). According to the literature, there are only a few reported cases of glomerular disease with myelofibrosis, hence we present an interesting case of focal segmental glomerulosclerosis with myelofibrosis

CASE REPORT

A 57 years old Malay Gentleman with underlying Idiopathic Membranous Nephropathy (IMN) was diagnosed in 2010. He is also obese with a BMI of 30 kg/m2. He was previously on mycophenolate mofetil (MMF) since 2010 and was off after achieving remission in 2014. But unfortunately, he had relapsed nephrotic syndrome in 2015 and MMF was restarted. At that time, he was offered cyclophosphamide but he refused. He was then on prednisolone tapered dose and T MMF 500mg BD. His urine protein creatinine index remains in the range of 1-3 grams per day. However, in early June 2021, he presented with abdominal distension

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JCTN (2023) Volume 2: Article no: 1

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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with splenomegaly and bone marrow aspiration and trephine was done which unfortunately he was diagnosed with myelofibrosis. He was started on thalidomide and ruxolitinib but thalidomide was stopped in April 2023 due to infection. Currently, he was on ruxolitinib and monthly blood transfusion. He was planned for allotransplant but unfortunately, he has no matched donor and was deemed not suitable for mud transplant due to his underlying glomerulopathy. He is currently still under haematology team follow-up.

In September 2022, he had relapsed nephrotic syndrome again with a urine protein of up to 9.1g per day. Therefore, he was counselled for re-biopsy and was restarted with high-dose prednisolone 60mg daily (1 mg/kg), and the MMF dose was increased to 1g BD. He underwent renal biopsy and light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) were performed. Light microscopic examination disclosed 35 glomeruli, 4 of which were globally sclerotic and 3 glomeruli disclosed segmental glomerulosclerosis associated with hyalinosis. 3 other glomeruli show periglomerular fibrosis with increased urinary space and mild wrinkling of glomerular tufts. There is the presence of global and diffuse thickening of the basement membrane and most of the glomeruli show mild mesangial hypercellularity and mesangial matrix expansion (Fig. 1).

Immunofluorescence staining of glomeruli revealed granular staining of IgM (1+) within the mesangium and C3 accentuation at the area of sclerosis. There is non-specific deposition at C3, IgA, IgM, IgG and C1q. Kappa and lambda light chains were negative. Electron microscopy showed thickened basement with diffuse foot processes effacement (Fig. 2). There were no electron-dense deposits or fibrils.

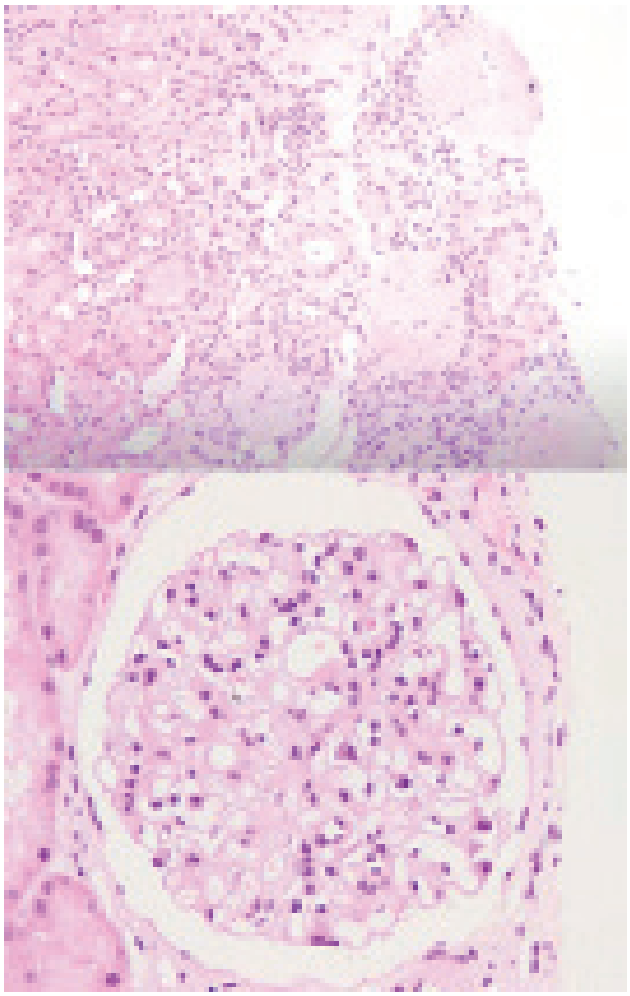

Fig. 1. The light microscopic appearance of a renal biopsy demonstrated global (top) glomerulosclerosis with thickened basement and mesangial hypercellularity (below) (H & E stains).

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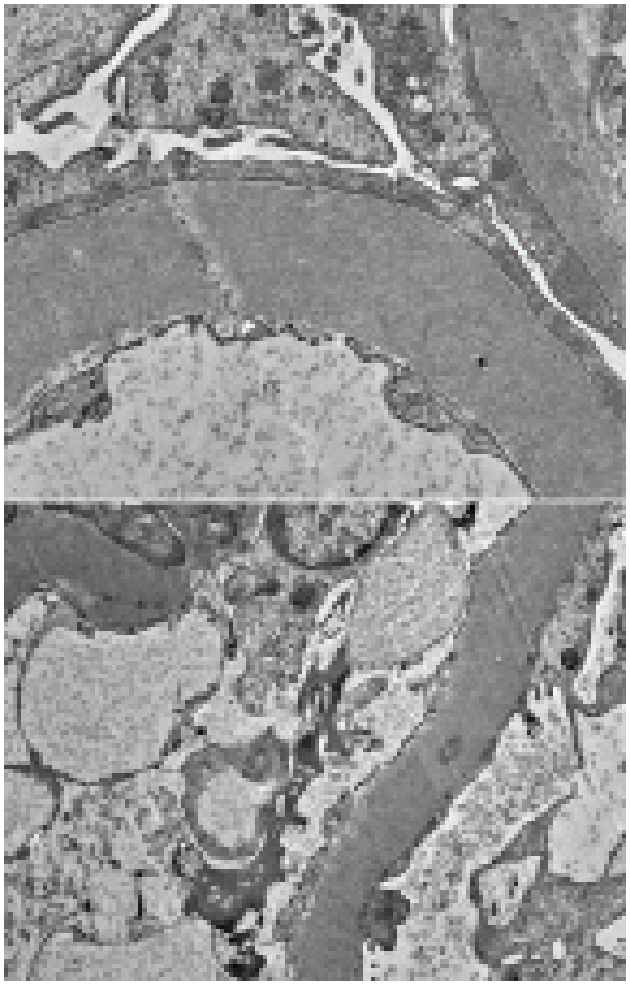

Fig. 2. Electron microscopy showed thickened basement with diffuse foot processes effacement and without any depositions.

DISCUSSION

This is a case of a diagnostic challenge. This patient was diagnosed as MN earlier at another centre but unfortunately, we were not able to retrieve his slides and nor could we retrieve any prior Phospholipase A2 Receptor (PLA2R) antibody results in view of it was in different centre and more than 10 years. The current biopsy sample, although showed rigid capillary loops that were suggestive of IMN, the EM has failed to show any subepithelial deposits. Instead, the EM revealed features of FSGS. The patient's prior IMN could have resolved as evidenced by the dissolution of the immune deposits. Nevertheless, segmental glomerulosclerosis can occur in the course of membranous nephropathy. Several studies have reported the effect of lesions on the clinical characteristics and renal prognosis of Idiopathic MN patients with FSGS, but the conclusions varied. Some studies have shown that the incidence of FSGS in IMN patients is between 12.8% and 43% [1,2,3]. Several prognostic factors including age, sex, degree of proteinuria, the extent of tubulointerstitial changes, hypertension and stage of glomerular disease, have been identified in IMN patients [1,3].

Additionally, glomerular lesions also have been described in some malignant diseases especially myeloproliferative disorder [4]. MN is the most widely described glomerulopathy associated with solid organ tumours while FSGS associated with haematological tumours is infrequent and, when it occurs, it is not clear whether the occurrence of FSGS in these patients is related to the primary haematological disorder or just a coincidence. In our case, glomerulopathy was present at a later stage after diagnosis of myelofibrosis compared to a case described by Rajasekaran et al with early MPN-related glomerulopathy in a 60-year-old man. However, the pathogenesis of glomerulopathy in MPN is still unclear. The most prominent histological findings that are associated with myeloproliferative disorder included double-contoured glomerular basement membranes (71%), acute endothelial damage (68%), intracapillary platelet aggregation (62%), mesangiolysis (21%), thrombotic microangiopathy (24%), segmental glomerulosclerosis (66%), mesangial hypercellularity and sclerosis, extramedullary haematopoiesis (17%), and also IgA nephropathy (21%) and glomerulonephritis (GN) with features of infection-related GN (21%).

Therefore, this case highlights the importance to have EM to accurately diagnoses renal disease. In any case, the prognosis of MPN-related FSGS remains poor despite immunosuppressive therapy and treatment of underlying neoplasm. However, in our case, the patient improved after 2 months of steroid therapy. Long-term follow-up is required to better define the exact clinical course of glomerulopathy in MPN. It remains to be seen whether FSGS is a part of the wider spectrum of MPN-associated glomerulopathy.

CONCLUSION

The mechanism of development of FSGS lesions in IMN and associated with myelofibrosis is still uncertain. Therefore, more studies are needed to elucidate the overlap of these primary glomerulopathies and their association with malignancy.

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