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Multiple Myeloma in a Patient with Focal Segmental Glomerulosclerosis: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 48
Final Diagnosis: Multiple myeloma
Symptoms: Back pain
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease
Background:





Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in adults, which can be primary, or secondary to various causes. Unlike membranous nephropathy, FSGS is less likely to be associated with malignancy. Few cases have been reported of the occurrence of FSGS with hematological malignancies like multiple myeloma (MM).

Case Report: A 48-year-old man presented with nephrotic syndrome and renal impairment and was diagnosed with primary FSGS after kidney biopsy, which showed a segmental scar with diffuse effacement of foot processes on electron microscopy. Treatment with steroids reduced proteinuria and stabilized the renal function. A few months later, the patient presented with acute Kidney Injury, bone pain, and anemia. A diagnosis of MM was made based on the bone marrow biopsy. Treatment of MM decreased proteinuria and improved renal function.

Conclusions: There is an association between FSGS and MM through an unclear mechanism.

MeSH Keywords: Glomerulosclerosis, Focal Segmental • Hematologic Neoplasms • Multiple Myeloma • Proteinuria

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Background

Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of idiopathic nephrotic syndrome in adults, but the mechanism is not well understood [1]. FSGS can be idiopathic, inherited [2], or secondary. The list of secondary FSGS causes is long, including: hypertension, obesity, infections such as human immunodeficiency virus (HIV), drugs such as bisphosphonate, and other causes [3]. Most recently, a few case reports were published documenting an association between multiple myeloma (MM) and FSGS, which is not common [4,5].

MM, or plasma cell myeloma, is a clinicopathologic malignancy, which is characterized by increased production of monoclonal plasma cells from the bone marrow and an associated production of monoclonal immunoglobulin in serum and urine. The clinical features usually include bone pain, lytic bone lesions, anemia, hypercalcemia, recurrent infections, and renal injury. Renal dysfunction can be due to direct injury from light chain deposition or because of toxicity from therapeutic drugs commonly used to treat MM [6]. Glomerulonephritis (GN) is uncommon in patients with MM. However, most of the cases of nephrotic syndrome in patients with MM are related to deposition of amyloid but rarely due to GN, like FSGS, fibrillary, proliferative crescentic, or membranous nephropathy [7–9].

As in other types of GN, nephrotic syndrome can precede the development of malignancy and can be the initial presenting scenario in which MM can present after GN diagnosis [8].

Here, we present a unique and interesting patient who developed MM 6 months after the diagnosis of FSGS. The clinicopathologic features are presented along with a discussion of this rare association.

Written informed consent was obtained from the patient for the publication of this case report.

Case Report

A 48-year-old, non-smoker male presented with a 2-week history of elevated blood pressure on routine checkup. The patient denied any respiratory, gastrointestinal, urinary, or musculoskeletal symptoms. He was not on any long-term therapy. His physical examination at presentation showed a body mass index of 29 kg/m², blood pressure of 123/80 mmHg (on Metoprolol 100 mg daily), heart rate 62 bpm/regular, no fever, pale conjunctiva, unremarkable chest/abdomen/pelvic examination, and mild lower-limb edema with no skin rash. His laboratory tests showed serum creatinine of 240 µmol/l (normal range, 53–97 µmol/l), +3 protein on urine analysis, no red blood cells

or casts, and a 24-h urine collection showed 8 g of protein. The fasting blood sugar and hemoglobin A1c were within normal limits and the antinuclear antibody, anti-neutrophil cytoplasmic antibody, complements (C3 and C4), hepatitis profile, and HIV results were all negative. Renal ultrasound showed normal-size kidneys (right 11.0 cm, left 11.5 cm).

Renal biopsy showed 16 glomeruli, none of which were globally sclerosed. One glomerulus showed a segmental scar with adhesion to the Bowman's capsule. There was no increase in mesangial matrix or cellularity. There was no endocapillary hypercellularity or crescents. There was mild interstitial fibrosis and tubular atrophy with no abnormal casts. The interstitium showed mild edema and mononuclear cell infiltrate composed mainly of lymphocytes. The blood vessels looked normal, with no hyaline arteriosclerosis or arterial sclerosis. Congo red staining was negative. The immunofluorescence sample contained 14 glomeruli, with negative staining for IgG, IgA, IgM, C3, C4, Kappa, and Lambda.

Electron microscopy showed segmental sclerosis, with diffuse foot processes effacement and microvillous transformation (Figure 1). There were no electron-dense deposits or fibrils and the adjacent tubules showed evidence of epithelial damage in the form of loss of apical membrane and swelling of cells.

The patient was started on tapering-dose steroid of 1.0 mg/kg as a case of idiopathic FSGS, especially with the presence of diffuse podocyte effacement on renal biopsy. As his kidney function was abnormal, we could not start angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers as conservative therapy; therefore, his Metoprolol was changed to a calcium channel blocker (CCB) – Diltiazem 90 mg twice daily – to keep blood pressure below or equal to 125/75 mmHg, as some studies showed a benefit of this class in reducing proteinuria [10, 11]. He did not show significant improvement in kidney function, yet his creatinine stabilized around 200 µmol/l and his proteinuria significantly decreased with this treatment, from 8 g to 2.7 g per day.

Six months later, while he was on 5.0 mg of prednisone per day, he returned with severe left hip pain. His creatinine was 350 µmol/l and hemoglobin had fallen to 8.9 gm/dl (from 10.8 gm/dl). His erythrocyte sedimentation rate (ESR) was high, at 125 mm/hr (normal range, 0–20 mm/hr). An MRI was ordered to rule out avascular necrosis of the head of the femur as a possible complication of steroid therapy, but the images showed diffuse bone marrow edema, with no evidence of avascular necrosis or hip infection. His serum calcium level was high, at 2.8 mmol/l (normal range, 2.1–2.55 mmol/l) in comparison to 2.2 mmol/l at presentation, without being on any calcium or vitamin D supplements. MM was suspected. A skeletal survey did not show any significant lesions. Serum

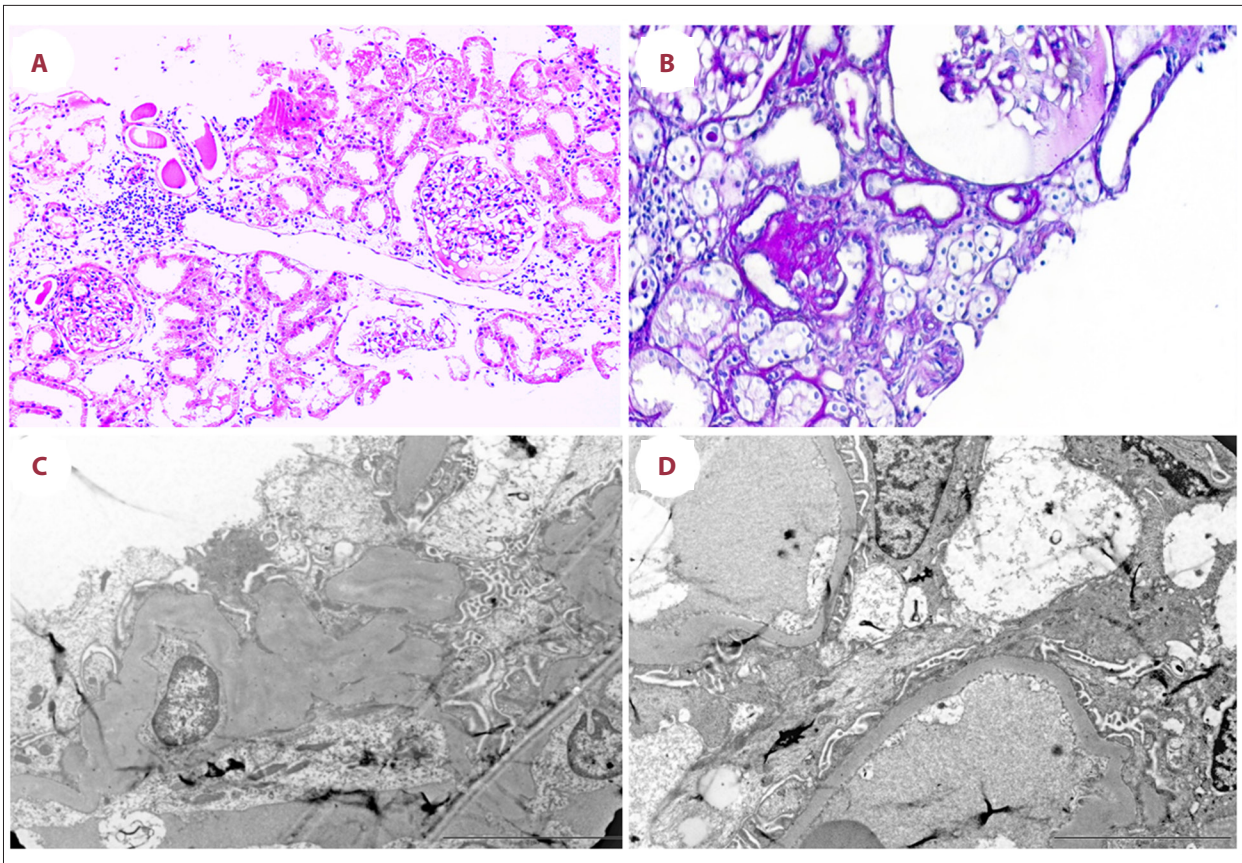


Figure 1. (A) Medium-power magnification of the renal biopsy with normal-looking glomeruli and tubulointerstitium showing mild edema and inflammation (Hematoxylin & eosin 100× magnification). (B) Medium-power magnification showing a glomerulus with a segmental scar and surrounding interstitial fibrosis and tubular atrophy (periodic acid Schiff stain, 100× magnification). (C) Electron micrograph demonstrating marked wrinkling of the glomerular basement membrane with segmental-near occlusion of the glomerular capillary loops. (D) Electron micrograph demonstrating diffuse effacement of the foot processes with focal microvillous transformation.

protein electrophoresis (SPEP) was normal, while urine protein electrophoresis (UPEP) showed a spike of light-chain globulins. He underwent a bone marrow biopsy, which showed hypercellular marrow due to infiltration by sheets and clusters of atypical plasma cells involving about 90% of the biopsy. The atypia was in the form of large cells, high nuclear-cytoplasmic ratio, bi- and tri-nucleation, and prominent nucleoli. The plasma cells were Kappa restricted by immunohistochemical stains. At this point, his creatinine peaked to 710 $\mu\text{mol/l}$ but there was no indication to start hemodialysis.

The patient was treated as a case of MM with steroids and 4 cycles of Bortezomib. Five months later, there was improvement in kidney function and decrease in his creatinine to 279 $\mu\text{mol/l}$ and proteinuria (falling to 0.6 g/day on last follow-up). ESR was 23 mm/h, and serum protein electrophoresis and urine protein electrophoresis were normal. A follow-up bone marrow biopsy confirmed the absence of plasma cells. Table 1 is a summary of different clinical variables for clinical course and response to therapy.

Discussion

FSGS associated with hematological tumors is infrequent and, when it occurs, it is not clear whether the occurrence of FSGS in these patients is related to the primary hematological disorder or just a coincidence [12]. FSGS has been reported previously in several cases of lymphoproliferative disorders, including T-cell lymphoma [13], Hodgkin's lymphoma [14], and large granular lymphocytosis [15]. Cases of FSGS with MM are even more rare and the pathogenesis of this association is unclear [4,5,16–20].

The presence of renal dysfunction in patients with MM is believed to be due to hypercalcemia, recurrent urinary tract infections, renal stones, urate nephropathy, analgesic nephropathy, cast nephropathy, amyloidosis, and, rarely, infiltration of kidneys by neoplastic plasma cells [21]. A most recent study by Nigro et al. in 2018 showed that in FSGS patients, with or without MM, changes in eGFR and degree of renal impairment may

Table 1. Summary of clinical variables in regard to clinical course and response to therapy.

Variable	At presentation	Renal biopsy	On therapy	Bone marrow biopsy	Last follow-up
SBP, mmHg	123	120	134	120	110
DBP, mmHg	83	80	83	75	70
Scr, $\mu\text{mol/l}$ (53–97 $\mu\text{mol/l}$)	205	275	207	710	279
S. Ca, mmol/l (2.1–2.55 mmol/l)	2.2			2.8	2.3
Albumin, g/l (35–52 g/l)	31	33.9	38.9	30	42
24-h urine protein, g	8.1	8.0	2.7	1.5	0.6
Hb, g/l (11–16 g/l)	11	10.8	10.4	8.9	11.6

SBP – systolic blood pressure; DBP – diastolic blood pressure; Scr – serum creatinine; S.Ca – serum calcium; Hb – hemoglobin.

have a proportional correlation with the tubular density, but this is a fairly new concept that may need further evaluation [22].

The patient in our study presented first with nephrotic syndrome, which was diagnosed as primary FSGS 6 months prior to the diagnosis of MM. The proteinuria and renal impairment did not respond to the usual treatment with steroids and calcium channel blocker, as suggested by some studies [10,11]. Then, the patient developed severe back pain, anemia, and worsening of renal function, so a bone marrow biopsy was performed, rendering a diagnosis of MM. As the diagnosis of MM was convincing, and the management plan would not be affected by another renal biopsy result, we did not repeat the renal biopsy after the making the MM diagnosis.

To the best of our knowledge, only 9 cases of FSGS with MM have been reported in the English language literature [4,5,16,17,19,20]. The average time between diagnosis of MM and FSGS was about 6–18 months [9,20]. Although the relationship between MM and FSGS is hypothetical, the data provided in the literature support an association between these 2 conditions. Dingli et al. [5] reported 4 cases of FSGS with a concomitant or subsequent diagnosis of MM with no other existing cause for FSGS; in all 4 patients, proteinuria and renal function improved after treatment of MM. Similar results were reported by Ashrafi et al. [20]. However, Shah et al. [16] reported partial remission of collapsing FSGS in a patient with MM after treatment of the primary disease. Charney and Wasser [17], demonstrated deteriorated renal function of their patient despite of treatment of MM, but their patient was obese and had sleep apnea, which could have caused the FSGS and the absence of response to treatment.

In our case, the diagnosis based on renal biopsy was FSGS not otherwise specified (NOS). The histological variants of

FSGS that were reported in previous studies are: collapsing in 1 case [16], Tip variant in another case [20], and the remaining were reported as FSGS NOS.

A possible explanation for the association between FSGS and MM is that vascular endothelial growth factor (VEGF) and heparanase have been reported to alter glomerular permeability in patients with FSGS [23]. In addition, VEGF and heparanase are overexpressed in MM patients and play an important role in tumor growth and angiogenesis [24, 25].

Dingli et al. [5] suggested that patients with unexplained FSGS should undergo serum and urine electrophoresis as a part of the work up to rule out plasma cell neoplasms. This is of great importance, as the treatment and prognosis differ between primary and secondary FSGS.

In summary, we present a case of nephrotic syndrome and an initial diagnosis of primary FSGS 6 months prior to the development of multiple myeloma. The patient showed significant improvement in kidney function and proteinuria on MM treatment, with a complete remission of MM.

Conclusions

Our case supports that there may be a direct and causal link between FSGS and MM. However, the exact pathogenesis of this association is unclear, and studies with larger patient sample sizes are needed to produce convincing conclusions.

Conflict of interest

None.

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