

Inflammatory demyelinating neuropathies with focal segmental glomerulosclerosis

Two case reports

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Abstract

Rationale: Inflammatory demyelinating neuropathies such as Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and focal segmental glomerulosclerosis (FSGS) are autoimmune disorders that may have a common pathogenesis. Here, we describe 2 unique cases of FSGS, 1 with GBS and the other with CIDP. We believe that reviewing these multisystemic diseases will help in better understanding of FSGS pathogenesis.

Patient concerns: The 1st patient, a 66-year-old woman, complained of tingling and numbness in the limbs and within 2 days, she developed progressive muscle weakness. The 2nd patient was a 63-year-old man with a complaint of lower-limb edema, lower-limb weakness, and numbness.

Diagnosis: In the 1st patient, a diagnosis of GBS was confirmed with the nerve conduction velocity test as well as CSF studies. A renal biopsy revealed FSGS. The 2nd patient was diagnosed with CIDP and a subsequent renal biopsy revealed FSGS.

Interventions: Large dose of steroid with calcineurin inhibitor, intravenous immunoglobulin, and supportive treatment.

Outcomes: Neurologic symptoms disappeared, urine protein was maintained at low levels, and no further recurrences were noted in 2 cases. INF2 gene mutation was not found in either case.

Lessons: Co-occurrence of inflammatory demyelinating polyneuropathy, GBS, CIDP, and FSGS suggests synergistic cellular and humoral autoimmune mechanisms related to either cross-reactivity within antigenic targets or mimicry epitopes. Further follow-up and intensive study for the pathogenesis are necessary.

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy, CSF = cerebrospinal fluid, FSGS = focal segmental glomerulosclerosis, GBS = Guillain–Barré syndrome, NOS = not otherwise specified.

Keywords: chronic inflammatory demyelinating polyneuropathy, focal segmental glomerulosclerosis, Guillain–Barré syndrome, nephrotic syndrome

1. Introduction

Inflammatory demyelinating neuropathies such as Guillain–Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) and focal segmental glomerulosclerosis (FSGS) are autoimmune disorders that may have common pathogenesis. INF2 encodes a formin protein that interacts with the Rho-GTPase CDC42, and myelin and lymphocyte protein (MAL) that are implicated in essential steps of myelination and

myelin maintenance. It was reported that INF2 mutations appear to cause many cases of FSGS-associated Charcot–Marie–Tooth neuropathy,^[1] a group of inherited disorders of the peripheral nerves. Thereafter, the INF2 might be a link between kidney podocytes and peripheral nerve cells. Previous literature reported inflammatory demyelinating neuropathies associated with nephritic syndrome.^[2–5] Fewer cases of FSGS have been associated with GBS than with CIDP. Here, we describe 2 unique cases of FSGS, 1 with GBS and the other with CIDP. We believe that reviewing these multisystemic will help in better understanding of FSGS pathogenesis.

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2. Case presentation

2.1. Case 1: a case of Guillain–Barré syndrome and focal segmental glomerulosclerosis

A 66-year-old woman was found to have hyperlipidemia during a health checkup. She was prescribed fluvastatin by a local hospital; after taking fluvastatin for 5 days, the patient felt tingling and numbness in the limbs. Within 2 days, she developed progressive weakness, and the muscle weakness worsened between day 4 and day 10. She became bed-ridden and was admitted to our neurology ward. Urinalysis showed hematuria (dysmorphic erythrocytes, 181.7/μL), 4+ protein, and her 24-hour protein excretion was 3.31 g. Laboratory tests showed serum creatinine

to be $47\ \mu\text{mol/L}$ and a low serum albumin level of $20\ \text{g/L}$. Immunologic tests showed normal complement levels and negative antinuclear antibody, cryoprotein, and rheumatoid factor. Serum protein immunofixation was also negative. Bence-Jones protein was not detected in the urine. Serologic testing showed normal titers for hepatitis B and C and cytomegalovirus. Cerebrospinal fluid (CSF) studies showed normal white blood cell counts and higher albumin levels of $561\ \text{mg/L}$. Nerve conduction studies showed multiple peripheral nerve injuries with predominant axonal injury and partial sensory nerve involvement. These findings were consistent with a primary demyelinating polyneuropathy. Accordingly, the diagnosis of GBS was verified with the nerve conduction velocity test as well as CSF studies.

The patient received intravenous immunoglobulin (IVIG) $0.4\ \text{g/kg/d}$ for 2 days and methylprednisolone $500\ \text{mg/d}$ for 3 days that was continued at a dose of $40\ \text{mg/d}$. Despite receiving plasmapheresis, the patient developed respiratory failure on day 19, and hence needed temporary artificial ventilation. After continued plasma exchange, corticosteroid treatment, IVIG, and anti-infections treatment, the patient was weaned from the ventilator after more than a month. There was residual weakness in her legs at the time of discharge.

She was discharged with corticosteroids and still has proteinuria but with normal renal function. Renal biopsy was carried out in other hospital 7 months after continued proteinuria. The diagnosis was FSGS, and she was prescribed tacrolimus $1\ \text{mg}$ (every 12 hours). Proteinuria was minimal after 15 months ($0.38\ \text{g/d}$). However, in the 16th month, the patient developed a cold and her proteinuria increased to $4.77\ \text{g/24h}$; thus, she was admitted to our inpatient department. Laboratory tests showed her serum creatinine and albumin levels to be $56\ \mu\text{mol/L}$ and $3.1\ \text{mg/L}$, respectively. The needle electromyogram examination was normal, but CSF studies still showed a higher than normal albumin level ($517\ \text{mg/L}$) with normal white blood

cell count. The patient underwent another renal biopsy, the results of which were consistent with the 1st pathologic diagnosis, FSGS. Light microscopy showed glomerular segmental sclerosis, mesangial cell hyperplasia, and arterial hyalinosis. Under light microscopic examination, 2 glomeruli with segmental sclerosis were seen in different sections, 1 with a tip lesion and the other with a not-otherwise-specified (NOS) variant (Fig. 1A, B). Glomerular immunofluorescence was negative for IgA, IgG, IgM, C3, and C1q. Electron microscopy showed diffuse podocyte foot process effacement (Fig. 1D). Oral methylprednisolone ($1\ \text{mg/kg/d}$) and cyclosporin A ($75\ \text{mg}$ [q12 hours]) were prescribed. Seven months after our treatment, there was improvement of proteinuria to $0.85\ \text{g/d}$ without neurologic symptoms. No further recurrences were noted. After more than a year's follow-up, the patient still takes small doses of prednisone ($7.5\ \text{mg/d}$) and cyclosporin A ($150\ \text{mg/d}$) with a small amount of proteinuria, $<1\ \text{g/d}$. The INF2 gene sequence did not show any mutation.

2.2. Case 2: a case of chronic inflammatory demyelinating polyneuropathy and focal segmental glomerulosclerosis

A 63-year-old man complained of lower-limb edema. The local hospital diagnosed his case as nephrotic syndrome because of hypoproteinemia and hyperalbuminuria. He was prescribed intravenous methylprednisolone ($1\ \text{g}$ daily for 5 days). At the same time, he also complained of lower-limb weakness and numbness, especially on the right side, for 2 months. The muscle weakness got progressively worse in 3 days. Then, he was admitted to our nephrology ward. His serum creatinine was $61\ \mu\text{mol/L}$ and albumin was $36\ \text{g/L}$. The complement levels were normal and hepatitis panel was negative. The 24-hour protein excretion was $0.87\ \text{g}$. Results of laboratory tests including antinuclear antibody, antineutrophil cytoplasmic antibodies, virologic screenings, and serum protein immunofixation were

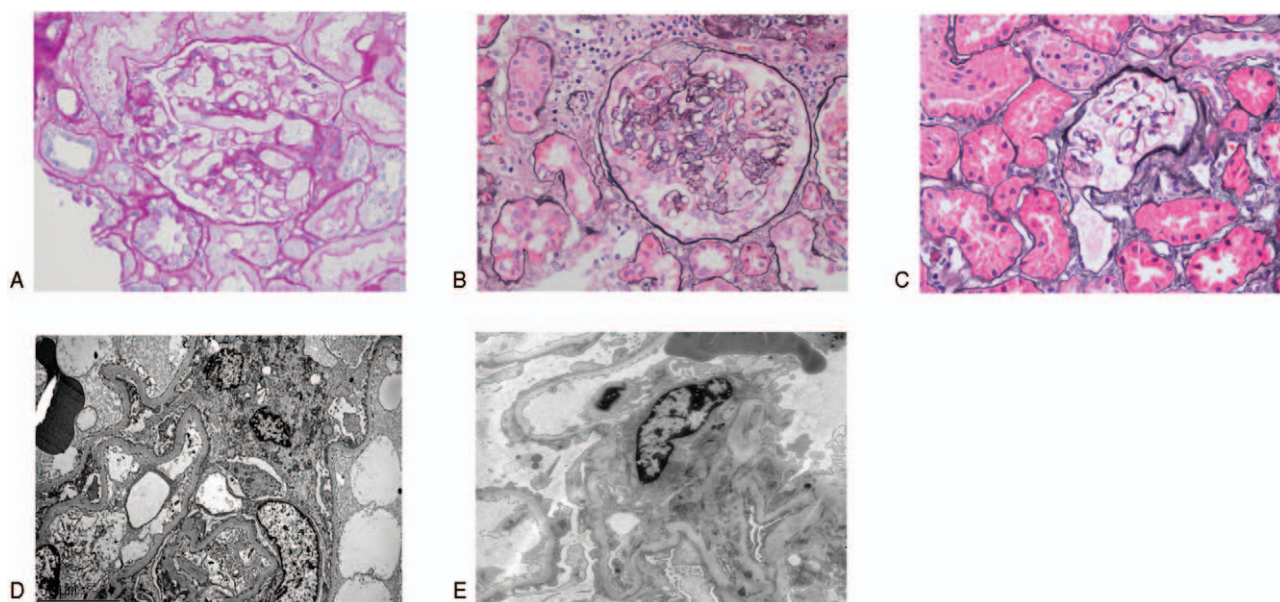


Figure 1. The renal biopsy showed segmental sclerosis. (A) Light microscopy of the renal biopsy of patient with Guillain-Barré syndrome (GBS). A glomerulus with tip lesion. Periodic acid-Schiff stain, original magnification: $\times 400$. (B) The GBS patient. A glomerulus with not otherwise specified lesion. Periodic Schiff-methenamine stain, original magnification: $\times 400$. (C) The light microscopy of the renal biopsy of patient with CIDP. A glomerulus with tip lesion. Periodic Schiff-methenamine stain: original magnification, $\times 400$. (D) Electron microscopy of the renal biopsy of patient with GBS. The glomerular capillary loops with podocyte foot process effacement. No electron dense deposits are present. (E) The electron microscopy of the renal biopsy of patient with chronic inflammatory demyelinating polyneuropathy. The glomerular capillary loops with podocyte foot process effacement. No electron dense deposits are present.

all negative. CSF studies showed normal white blood cell count and high albumin levels (846 mg/L). Nerve conduction studies showed multiple peripheral nerve injuries, which mainly involved distal predominant axonal injury with predominant axonal injury and partial sensory nerve involvement. At first, he refused renal biopsy. As his clinical evolution was consistent with CIDP, he received prednisolone (60 mg/d) treatment.

One month later, limb weakness increased and was accompanied by edema, limb numbness, and difficult defecation. Proteinuria increased to 3.95 g/24 h, and albumin was 32 g/L. Repeat nerve conduction studies showed similar results to the previous study. Repeat CSF evaluation revealed normal white blood cell counts and protein level of 950 mg/L. However, sural biopsy revealed endoneurial edema and absence of inflammatory infiltrates. The renal biopsy showed 4 glomeruli (a total of 23) with segmental sclerosis (tip lesion), and no glomerular inflammatory cellular infiltrates or foci of capillary thrombosis or necrosis were present (Fig. 1C). Glomerular immunofluorescence was uniformly negative for immunoglobulins IgG, IgA, complement C3, C1q, and light chains. Electron microscopy showed diffuse podocyte foot process effacement (Fig. 1E). The diagnosis was FSGS with CIDP. The patient received IVIG 10 g/d for 5 days and methylprednisolone 500 mg/d for 3 days that was continued with prednisone 60 mg/d. The patient showed transient improvement. Two weeks later, weakness progressed to involve all 4 limbs, and the muscle strength was graded as 0 (i.e., no contraction or muscle movement). Deep tendon reflexes were diffusely absent. Nerve conduction studies showed that the amplitudes of motor and sensory nerves were lower than before. Because of dysphagia and urinary retention, the patient was fitted with an indwelling gastric tube and urinary catheter. High-dose methylprednisolone was given (500 mg/d for 7 days and continued at a dose of 120 mg/d, and gradually reduce to 80 mg/d). His limb strength gradually recovered from the distal end. Considering the recurrence of CIDP, he was prescribed cyclophosphamide 0.6 g (0.2 g first, and 0.4 g 12 days later). After 6 months of corticosterone and cyclophosphamide treatment, his muscle strength was almost back to normal, and the proteinuria decreased to 1.3 g/d. Corticosterone and cyclophosphamide were continuously used for 1 year and the cumulative dose of cyclophosphamide was 8 g. Then low dose corticosterone with tacrolimus 2 mg/d. In recent half year, methylprednisolone 8 mg/d and tacrolimus 1.5 mg/d was prescribed. After 2 years follow-up, till now, the patient proteinuria maintained at 0.6 to 0.8 g/24 h. The INF2 gene sequence of this patient too did not show any mutation.

This study was approved by the ethics committee of Huashan Hospital, Fudan University, China. Both patients provided written consent for the use of their medical data and subsequent publication of the case report.

3. Discussion

In this report, we present two cases of GBS and CIDP each, both presented with FSGS. CIDP is closely related to GBS and it is considered the chronic counterpart of the latter. Both conditions have an autoimmune etiology and, in our patients, both conditions improved with high-dose steroids or immunosuppressant agents. Previous literature reported inflammatory demyelinating neuropathies associated with FSGS, membranous glomerulonephritis, and minimal change disease.^[2-5] Fewer cases of FSGS associated with GBS have been reported than with CIDP.

Both patients presented symptoms of inflammatory neuropathies. By reviewing the cases reported in literature, Quek et al classified the clinical diagnoses as follows: GBS was time to nadir within 4 weeks, whereas CIDP followed a chronic course lasting beyond 2 months.^[6] The patient in case 1 showed rapidly deteriorating muscle weakness within 19 days, while the 1 in case 2 presented as the same in a more progressive, recurrent, and chronic (more than 6 months) manner. Based on the CSF and nerve conduction studies, they were diagnosed as having GBS and CIDP. Both were inflammatory demyelinating neuropathies synchronously accompanied with proteinuria, and renal pathology showed tip lesion FSGS. Plasma exchange was an effective way to treat GBS.^[7] IVIG, large dose of steroids, and immunosuppressant therapy were beneficial to both cases. At the same time, the effective treatment for FSGS is also steroid and even immunosuppressant therapy, especially calcineurin inhibitor.^[8]

Five mutually exclusive variants of FSGS may be distinguished by the pathologic findings seen on renal biopsy: collapsing variant, glomerular tip lesion variant, cellular variant, perihilar variant, and not otherwise specified (NOS) variant.^[9] Both these cases were inflammatory demyelinating neuropathies with tip-lesion FSGS; the patient with GBS additionally presented with another NOS lesion. Tip lesions affect the portion of the glomerular tuft juxtaposed to the tubular pole. Abnormalities include adhesion to the Bowman capsule at the tip, hypercellularity, presence of foam cells, and/or sclerosis. Several reports in nephrotic patients with glomerular tip lesion suggest an excellent response to steroids and favorable course similar to that of minimal change disease rather than FSGS.^[10-12] In the 1st case, the patient was not sensitive to the steroid for nephrotic syndrome but underwent remission after taking calcineurin inhibitor with steroid. In the 2nd case, the proteinuria was decreased after methylprednisolone treatment. Both patients had tip-lesion FSGS but with different response to steroid treatment. The patient with GBS had both tip- and NOS-lesion FSGS, which is likely why she was not sensitive to steroids.

Therefore, there might be a common underlying immunopathogenic mechanism of inflammatory neuropathy associated with FSGS. CIDP is closely related to GBS and is considered the “chronic counterpart” of GBS. They are thought to be autoimmune diseases.^[13] In GBS or CIDP, autoreactive-activated T-cells crossing the damaged blood-nerve barrier enhance cytokine upregulation, macrophage activation, and phagocytic attack on the myelin either directly or by proinflammatory mediators.^[14] This might increase glomerular permeability to albumin by T-cell clones secreting vascular circulating factor in FSGS. Our patients improved with corticosteroid and immunosuppressive therapy, which may suggest that inflammatory neuropathy and FSGS share a common immune target antigen.

The FSGS is a diverse syndrome that arises after podocyte injury from diverse causes, some known and some unknown. The sources of podocyte injury are varied (circulating factors especially primary FSGS, genetic abnormalities, viral infection, and medication), although the effect on podocytes is similar. Boyer et al^[11] described that 75% of patients with Charcot-Marie-Tooth neuropathy and FSGS had mutations involving INF2, and the INF2 expressed in Schwann cell cytoplasm and podocytes might be a common link between kidney podocytes and peripheral nerve cells. This probably implies similarities in the mechanism between inflammatory demyelinating disease and FSGS. Therefore, the specific relationship and mechanism

between inflammatory demyelinating neuropathies and FSGS need further study.

There are 2 main limitations of these cases: 1 is the duration of follow-up is not long enough to get the end point such as renal fail; the other is that we did not find the pathology relationship between FSGS and inflammatory demyelinating neuropathies. We did not do the advanced study to detect the level of soluble urokinase-type plasminogen activator receptor, a potential circulating factor which is identified as the pathogenesis of primary FSGS, in these GBS, CIPD accompanied FSGS patients and compared the difference with primary FSGS. Further follow-up and intensive study for the pathogenesis are necessary.

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Author contributions

LYL and YHM participated in revising the manuscript. LYL, MZ, JX and CMH followed up the patients. YHM obtained blood samples and recorded clinical data. SJL is the renal pathologist. YYX did genetic sequence test of INF2 gene. All authors read and approved of the final manuscript.

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