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Subclass Changes in Fibrillary Glomerulonephritis

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INTRODUCTION

Fibrillary glomerulonephritis (FGN) is a rare glomerular disease diagnosed by renal biopsy and characterized by nonperiodic fibrillar deposits of immunoglobulins in the glomeruli with a mean diameter of 20 nm. Although rarely monotypic, on immunofluorescence the deposits are usually positive for polyclonal IgG and C3. FGN is generally associated with poor outcomes and recurs in transplant allografts.

IgG subclass staining is performed by immunofluorescence and shows dominance for IgG4 with codominant staining for IgG1.[1–5] Long term follow-up of patients with FGN has focused on clinical outcomes, and repeat kidney biopsies are not common. Therefore, little is known about the natural history of IgG subclass distribution in FGN. Herein we report 2 patients with FGN who had a repeat kidney biopsy and an IgG subclass change was observed.

CASE PRESENTATION

The study was approved by the Ohio State University Wexner Medical Center Institutional Review Board. Kidney biopsies with FGN were identified in a renal pathology database at from December 1, 2006 to March 1, 2022. There were 7 patients with a diagnosis of FGN who had both an original and a follow up kidney biopsy. Where available, the medical records were reviewed for patient demographics, history, treatment, and disease progression. Kidney biopsies were reviewed, including light microscopy, immunofluorescence photographs, and electron microscopy. Where necessary, direct immunofluorescence was performed on frozen sections with fluorescein isothiocyanate-conjugated polyclonal rabbit antibodies to IgG1, IgG2, IgG3, and IgG4 (The Binding Site Inc., San Diego, CA).

Two patients with class switching on subsequent kidney biopsy were identified. The first patient presented at age 62 with acute kidney injury, proteinuria, hematuria, and worsening blood pressure. She had an initial biopsy that revealed FGN with focal crescents and mild chronic changes. Immunofluorescence showed strong staining for IgG in the mesangium withIgG4 dominant staining, weak staining for IgG1, and no staining for IgG2 or IgG3. Electron microscopy showed mesangial fibrillary deposits with a mean diameter of 13.9 nm. She was initially treated with cyclophosphamide and corticosteroids with mycophenolate maintenance therapy. Four years later she relapsed clinically with proteinuria and increased serum creatinine. Repeat biopsy revealed glomeruli with mesangial expansion and hypercellularity, no crescents, and moderate chronic changes. Immunofluorescence showed mesangial staining for IgG with only IgG1 staining on subclasses. She progressed to renal failure requiring peritoneal dialysis.

The second patient presented at the age of 53 with proteinuria, hematuria, and mildly elevated serum creatinine. The initial biopsy revealed enlarged glomeruli with diffuse mesangial expansion and mild chronic changes. Immunofluorescence showed strong staining for IgG with IgG4 dominance on subclass staining, slightly weaker staining for IgG1, trace staining for IgG2, and no staining for IgG3. Electron microscopy showed mesangial fibrils with a mean diameter of 17 nm. She was treated conservatively with losartan and Aldactone and went into remission. Her proteinuria recurred, prompting a second biopsy 10 years later which revealed enlarged glomeruli.

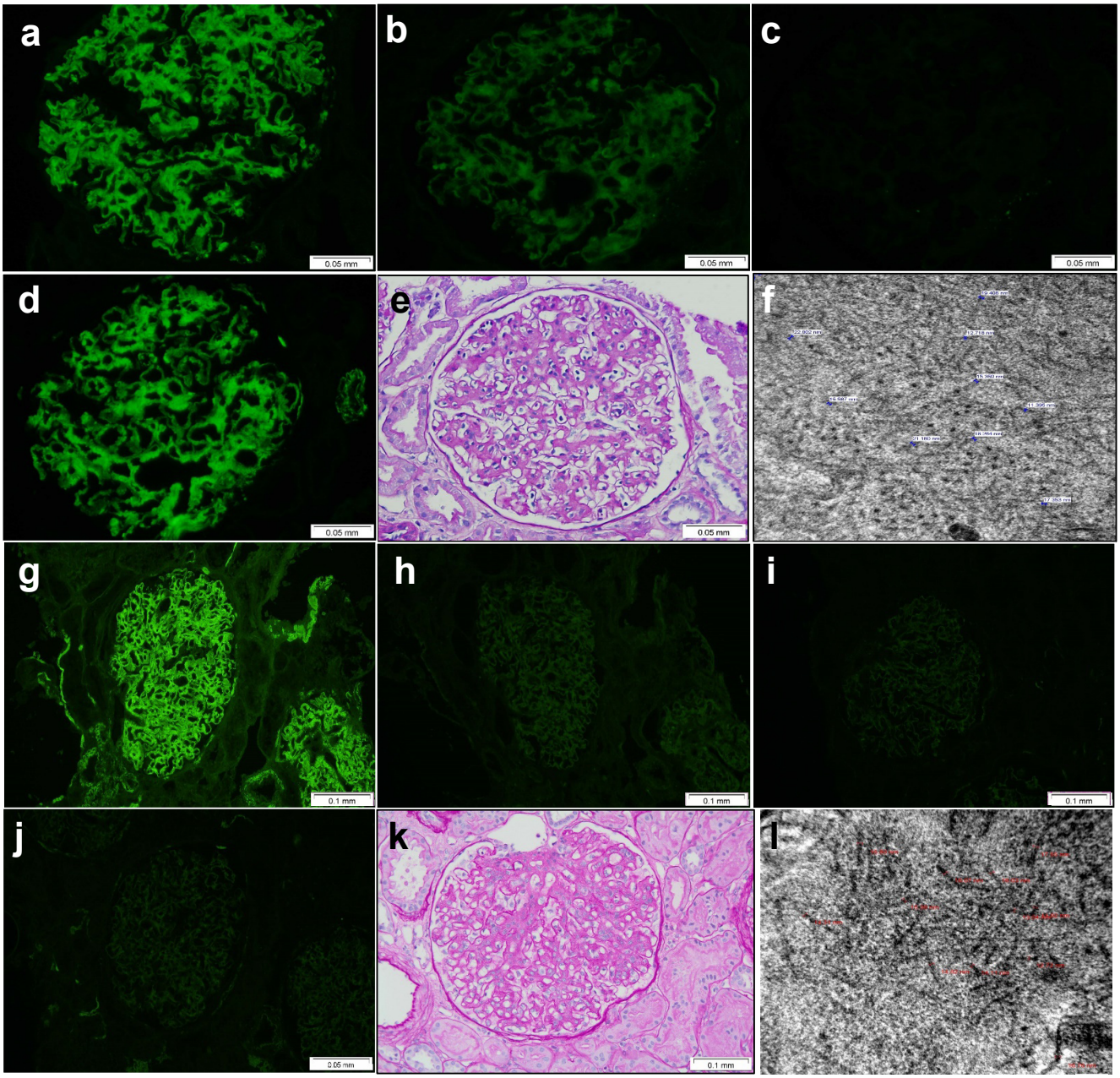

Figure 1. Patient 2- Initial biopsy in 2012 with strong staining for IgG1 (a), weak staining for IgG2 (b), negative IgG3 (c), and strong staining for IgG4 (d) on immunofluorescence. Glomeruli are enlarged with an expanded mesangium on PAS stain (e). Electron microscopy shows classic fibrils (f). Subsequent biopsy in 2022 with strong staining for IgG1 (g), no significant staining for IgG2, IgG3, and IgG4 (h, i, and j, respectively). Glomeruli show further enlargement with increased mesangial expansion of PAS stain (k). Electron microscopy shows classic fibrils (l).

Immunofluorescence showed confluent staining for IgG with IgG1 dominance and trace staining for IgG4 and the other IgG subclasses (Figure 1 and Supplementary Figure S1).

After these cases were identified, a deeper inquiry into FGN cases at our institution was performed. A total of 164 cases of FGN were identified since December 2006 with IgG subclass staining. Of these patients, 48% were male and 52% were female. Of those, 39 (24%) were dominant for IgG1, 67 (41%) were dominant for IgG4, and 58 (35%) had codominant staining for IgG1 and IgG4 (Supplementary Table S1). There was no change in the ratio of subclass dominance over time. Among these, a total of 7 patients, including the 2 previously discussed had a repeat biopsy.

Therapies received by these patients were diverse and ranged from conservative treatment and monitoring to immunosuppression. Two of the patients had hepatitis C and 1 had psoriatic arthritis. The remaining patients had no active malignancy or autoimmune conditions.

Table 1. Teaching points

FGN is a uncommon but progressive glomerular disease that usually shows IgG4 dominance on subclass staining
IgG subclass changes can be observed in FGN in both native and transplant biopsies
FGN can show a change from IgG4 dominance or IgG1 and IgG4 dominance to IgG1 only
A subclass change is more likely to be seen in long standing disease
Cases which show a subclass change show classic diagnostic features of FGN, and a change in subclass staining on subsequent biopsy should not preclude a diagnosis of FGN

FGN, fibrillary glomerulonephritis.

At initial biopsy, 5 showed dominant subclass staining for IgG4, with 2 showing dominant staining for IgG1 alone or IgG1 and IgG2 (Supplementary Table S2). Repeat kidney biopsy was initiated for a variety of reasons, including worsening clinical status and disease monitoring. Of the 5 patients with repeat biopsies who did not show subclass switching, 2 had repeat biopsies at 1 year or less, 2 had repeat biopsies between 1 year and 5 years after initial diagnosis, and 1 had a repeat biopsy at 9 years or more. The patient biopsied at more than 9 years showed IgG1 dominance on both the initial and subsequent biopsies. No patient with dominance for a subclass other than IgG4 showed subclass changes on the second biopsy. Patients who had FGN recurrent in the transplant were also reviewed, and 4 patients were identified. Of these, 3 did not have definitive data available on their pretransplant subclass staining, and 1 of those 3 did not have glomeruli on immunofluorescence on the transplant biopsy. Of the 2 patients with no pretransplant subclass information, 1 biopsied 8 years after transplantation showed IgG1 dominance with weaker staining for IgG2. The other showed codominant staining for IgG1 and IgG4 6 years post-transplant. The patient for which there was both pretransplant and post-transplant subclass information showed IgG4 dominant staining for 2 pretransplant biopsies, but biopsies performed at 2 years and 3 years post-transplant showed IgG1 dominance with weaker staining for IgG4 (Supplementary Table S3).

DISCUSSION

FGN is an uncommon glomerular disease with a poor prognosis. Despite recent advances in understanding the pathogenesis of this disease, including the discovery of DNAJB9, the progression and natural history of FGN remain poorly understood. We present a series of patients who had follow-up biopsies at variable intervals. Although most of these patients had retained IgG subclass distribution on subsequent biopsies, 2 patients showed a switch in subclass distribution from IgG4 to IgG1 dominance. This has not been reported elsewhere and may be part of the progression of the disease in some patients. It is unlikely that subclass switching occurs in response to therapy because one of the patients that showed a subclass change was treated conservatively, and the other was treated with immunosuppression. Interestingly, the longer duration between biopsies, the more likely a subclass switch was to occur. Although the information for allografts is incomplete, the data do support this because all were biopsied many years after initial diagnosis and 2 show IgG1 dominance. For the native kidney biopsies, of the 3 patients rebiopsied at >3 years, 2 of them showed subclass switching.

CONCLUSION

Although this is not sufficient data to draw definitive conclusions, it may be that patients with IgG1 dominance on biopsy may simply be biopsied later in the course of their disease. It could be hypothesized that patients with slow accumulation may present later in the course of their disease and be more likely to show IgG1 dominance as a result of class switching (Table 1). Changes in immunofluorescence patterns on subsequent biopsies are known to occur in a variety of diseases, perhaps most notoriously in C3 but is seen in other diseases as well, including both in serum and in tissues.[6-9]

Regardless, all patients showed typical features of FGN. Therefore, a change subclass staining pattern should not preclude a diagnosis of FGN in patients, especially those with longstanding disease.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1. Initial biopsy in 2012 with immunofluorescence staining for albumin (A), IgG (B), C3 (C), kappa light chain (D), and lambda light chain (E) showing bright, smudgy staining for IgG, C3, and kappa and lambda light chains. Subsequent biopsy in 2022 with immunofluorescence staining for albumin (F), IgG (G), C3 (H), kappa light chain (I), and lambda light chain (J) with a similar staining pattern.

Table S1. IgG subclass distribution in all FGN cases.

Table S2. IgG subclass distribution on native initial and repeat biopsies.

Table S3. IgG subclass distribution on pre and post transplant biopsies.

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