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Pathology

Favourable Outcome in a Case of Fibrillary Glomerulonephritis: Case Report and Brief Review of Literature

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Abstract **Case Report**

Fibrillary glomerulonephritis (FGN) is a rare pseudoamyloid glomerulopathy characterized by an extracellular deposit of DNAJB9 positive fibrils. Diagnosis of FGN is challenging, since there is no clinical specificity, and pathologically there are others glomerulopathies with organized deposits. Diagnosis of FGN is even more problematic in developing countries, where the necessary diagnostic tools aren't available. Diagnosis of FGN requires DNAJB9 immunostaining or electron microscopy examination. Until today, there is no standard therapeutic regimen for FGN. The prognosis is still unclear and it is unpredictable. More than half of cases progress to the end-stage kidney disease. We report, in this paper, a case of FGN diagnosed in Moroccan woman. She was treated by steroids and rituximab induction therapy. She didn't receive rituximab maintenance therapy due to a sustained CD19 depletion. We suspect here an association with an immunodeficiency condition. The clinical course was favourable. Nephrologists and pathologists, especially in developing countries, should be aware about this entity.

Keywords: Fibrillary glomerulonephritis, Chronic kidney disease, Pseudoamyloid glomerulonephritis, DNAJB9, Rituximab therapy.

INTRODUCTION

Fibrillary glomerulonephritis (FGN) is a proliferative, immunomediated glomerulopathy characterized by an extracellular deposits of an organized, randomly oriented, non-branching fibrils with diameter between 15 to 25µm [1, 2]. FGN is identified by DNAJB9, a heat-shock protein, as the main molecular component of these deposits [3-5]. FGN is rare, occurring approximately in 1% or less of native renal biopsies. It was described the first time by Rosenmann *et al*., in an Arabic patient in 1977 and was recognized as a distinct entity by Duffy *et al*., in 1983 [1, 2]. FGN has long been considered an idiopathic disease but recently an association between FGN and a various of malignant, autoimmune, metabolic, inflammatory and infectious diseases has been reported [1, 2].

Diagnosis of FGN is challenging, especially in developing countries in which electron microscope (EM) and techniques to assess DNAJB9 are unavailable, since there are others glomerulopathies characterized by organized deposits that must be differentiated from FGN [3, 4]. Management of this disease is also delicate and there is still no standard therapeutic regimen. The prognosis is unpredictable and the major risk is the progression to the end-stage kidney disease [1, 2]. Most reported cases were treated by rituximab and steroids with variable outcomes [1, 2].

We report here one case of FGN in a Moroccan woman treated by corticosteroids and rituximab induction therapy alone without maintenance therapy and the evolution was favourable. By reporting this case, we aim to highlight FGN for nephrologists and pathologists and to emphasize various clinicopathological features that can potentially impact

the prognosis. Finally, we would like to mention that we suspect here an association between FGN and an immunodeficiency condition.

CASE REPORT

Clinical and Biological Findings:

Our patient was a Moroccan 52-year-old woman with no relevant past medical or family history. She presented, at the time of diagnosis, a generalized oedema notably in the lower limbs evolving over six months. She had also an arterial hypertension (150/100 mmhg). She didn't present any extra kidney manifestations.

Initial laboratory workup showed high proteinuria (7g/24h) but normal protidogram (protidemia and albuminemia were at 70 and 34g/l respectively). Renal function was altered (creatininemia at 21mg/l). No haematuria or leukocyturia were noted. Inflammatory syndrome was absent. Renal biopsy was performed.

Pathological findings (Figure 1)

Twenty glomeruli were evaluated in which there were two glomerulosclerosis. Mesangial expansion with amyloid like deposits were seen. Crescents formations were absent. Interstitial fibrosis was estimated at 10% with scarce atrophic tubules. Congo-red staining was negative. Immunofluorescence showed polyclonal IgG without C3 in these deposits and immunohistochemistry showed expression of lambda and kappa light chains.

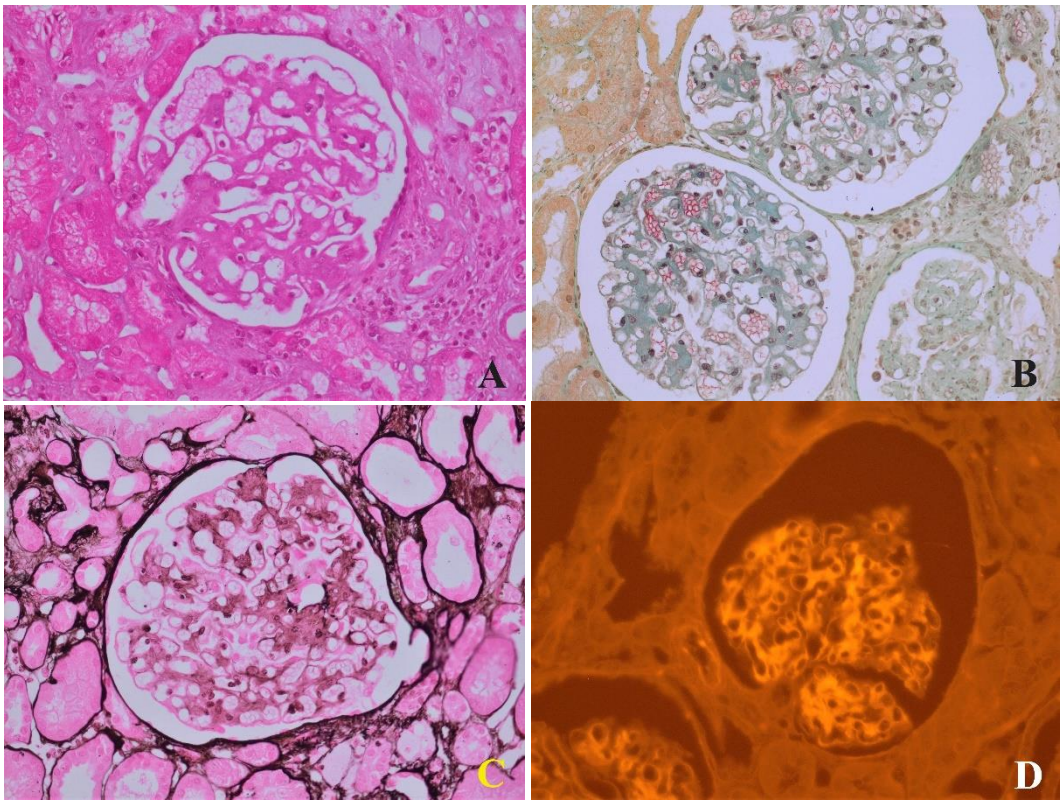

Figure 1: Histopathological findings in our case (photo A: H&E stain, x200; B: Masson's trichrome stain; C: Reticulin stain; D: Immunofluorescence)

Based on all this findings, FGN was suggested. The specimen was sent to another pathological laboratory in France where the diagnosis of FGN was confirmed by DNAJB9 immunohistochemistry.

Etiological check-up:

Overall assessment was negative including:

- Markers of autoimmune diseases (antinuclear antibodies, antiphospholipase A2, soluble anti-antigen antibodies, C3, C4, anti-neutrophil cytoplasmic antibody).
- Viral serologies (VHC, VHB and VIH serologies).
- Whole body CT scan, positron emission tomography (PET), bone marrow biopsy, protein immunofixation electrophoresis in blood and urine and urine light chain assay (to eliminate malignancy).

Treatment:

She received initially rituximab induction therapy (4 weekly infusions of 375 mg/m^2) and steroids (1mg/kg/day) for six weeks followed by gradual decrease over 6 months until 5mg/day. She received also angiotensine enzyme inhibitors.

Follow-up:

The course of the disease was favourable (Table 1): normalization of creatininemia to 12 mg/L, stable proteinuria for 4 years varying between 1.5 and 2.5 g/24h and normal protidogram. Steroids (5mg/day) was maintained.

Table 1: Creatininemia and proteinuria evolution

	Creatininemia (mg/l)	Proteinuria (g/24h)
Avril 2021	12.00	2.29
October 2021	11.97	2.66
January 2022	11.70	2.18
July 2022	12.68	0.91
January 2023	11.68	0.99
October 2023	10.90	0.51

It should be noted that our patient didn't receive rituximab maintenance therapy due to a sustained depletion of CD19+ cells for four years until now (Table 2).

Table 2: Evolution of CD19+ lymphocytes and total lymphocytes count

	jan-21	jui-21	oct-21	nov-21	oct-22	mai-23
CD19+ lymphocytes (/mm3)	6	13	30	30	22	33
Total lymphocytes (/mm3)	2810	3350	3000	3600	2000	2530

Further work-up (carried out in November 2021) showed low levels of IgG levels and normal levels of IgM, IgA, total lymphocytes (3600/mm3), T lymphocytes (3010/mm3), CD4+ T lymphocytes (1920/mm3), CD8+ T lymphocytes (1050/mm3) and NK lymphocytes (520/mm3).

DISCUSSION

Few reports of FGN have been documented in literature. This can be explained by its extreme rarity and probably also to undiagnosed cases [6, 7]. We haven't found any Moroccan report of FGN. We have presented here a Moroccan case of FGN. The clinicopathological features of our patient are globally consistent with what was described in literature. What are remarkable here: firstly, the favourable course of the disease for four years without rituximab maintenance therapy and secondly the persistence of an undetectable CD19 in addition to a low level of IgG. These latest findings have led us to suspect the co-occurrence of fibrillary glomerulonephritis and an immunodeficiency condition.

FGN occurs mostly among patients of middle age (49 to 61 years old), females and Caucasians [1, 2]. Various clinical and pathological aspects can be observed in this disease. Majority of patients have already kidney failure at the time of diagnosis [1, 2]. Common clinical presentations include also proteinuria (average 4.1–7.3 g/day) and haematuria. Few patients show frank nephrotic syndrome [1, 2].

Pathologically, there is no pathognomonic histopathological presentation for FGN. Variable morphological patterns can be observed: mesangial proliferative pattern, membranoproliferative pattern (MPGN), diffuse proliferative pattern, membranous pattern and diffuse sclerosing pattern [1, 2, 8]. Crescents formations may be seen. Whatever, an amyloid-like glomerular extracellular deposits, typically negative for Congo-red stain, is noted [1, 2, 8]. Rare congophilic FGN were also reported [9, 10]. Immunofluorescence demonstrates intensely IgG and usually C3, K and λ chains in deposits [1, 2, 8].

Based on morphological and immunofluorescence findings, the diagnosis of FGN can only be suggested since there are other forms of glomerulopathies with organized deposits that have distinct treatments and outcomes especially amyloidosis. Immunotactoid glomerulopathy, cryoglobulinemic glomerulonephritis, fibronectin glomerulopathy and collagenofibrotic glomerulopathy are also a differential diagnoses [4, 7].

EM or DNAJB9 immunohistochemistry are necessary for confirmation. EM is no longer mandatory to diagnose FGN given to the recent techniques used for detecting DNAJB9 [6]. DNAJB9 immunohistochemistry is a rapid, inexpensive tool with sensitivity at 98% and specificity highest than 99% [3, 6, 7]. DNAJB9 immunohistochemistry can also be used to diagnose congophilic forms of FGN [6, 9].

There is no standard therapeutic regimen for FGN. Diverse immunosuppressive drugs are used like steroids, rituximab, cyclophosphamide and mycophenolate mofetil. Inhibitors of renin-angiotensin system are used systematically [1, 2, 6]. Rituximab has demonstrated significant results in many studies. Renal transplantation is a viable option in fibrillary glomerulonephritis but recurrences are possible. Outcomes remain unpredictable. Up to 50% cases progress to the end-stage kidney disease [1, 11, 12].

Risk factors known to be related to the progression of FGN are numerous and include: initial

creatininemia and proteinuria, male sex, older age, histopathological patterns, crescents formations and rate of glomerulosclerosis and interstitial fibrosis [6, 10]. Mesangial proliferative pattern is associated with better prognosis and diffuse sclerosing pattern with the worst [2, 11]. We believe also that the management of an underlying disease of FGN may improve prognosis [11, 13].

Number of cases of FGN have been reported as idiopathic. Recently, an association was found with other diseases including malignancy, autoimmune, dysproteinemia, infectious and inflammatory diseases [1, 2, 6]. Significant association between FGN and viral hepatitis C especially in black patients have been observed. Familial forms of FGN are rare (<1%) [14]. HLA-DR7 and HLA-B35 seem also to be related to FGN and have an impact on outcome and therapy [1, 15]. No co-occurrence of FGN with immunodeficiency has been described in literature, except with HIV infection [16]. The discovery of DNAJB9, as the main molecule involved in the physiopathology of this disease, is revolutionary and suggests the possibility of a future target therapy in FGN [1, 2]. Finally, nephrologists and nephropathologists in developing countries, should be aware about this entity and shouldn't hesitate to send the sample to another laboratory that have the necessary diagnostic tools to confirm the diagnosis.

CONCLUSION

FGN is an underrated and heterogeneous disease with unpredictable outcomes. Nephrologists and nephropathologists should be aware about this pathology and shouldn't hesitate to assess DNAJB9 immunohistochemistry in all cases of glomerulopathy with amyloid-like deposits. Future studies evaluating therapeutic response to different treatment options according to clinical, pathological and immunological aspects would be relevant. More complete understanding of physiopathology of FGN will surely solve a number of questions relating to both diagnosis and treatment. In our case, we suspected an underlying immunodeficiency but investigations have not been performed given the lack of resources.

REFERENCES

1. Andeen, N. K., Kung, V. L., Robertson, J., Gurley, S. B., Avasare, R. S., & Sitaraman, S. (2022). Fibrillary glomerulonephritis, DNAJB9, and the unfolded protein response. *Glomerular Diseases*, *2*(4), 164-175.
2. Rosenstock, J. L., & Markowitz, G. S. (2019). Fibrillary Glomerulonephritis: An Update. *Kidney Int Rep*, *4*(7), 917-922.
3. Mubarak, M. (2022). Deciphering the autoimmune pathogenesis in fibrillary glomerulonephritis: The story is not yet complete. *Indian J Nephrol*, *32*(3), 195-196.
4. Gambella, A., Pitino, C., Barreca, A., Nocifora, A., Giarin, M. M., Bertero, L., ... & Cassoni, P. (2022). DNAJB9 Is a Reliable Immunohistochemical Marker of Fibrillary Glomerulonephritis: Evaluation of Diagnostic Efficacy in a Large Series of Kidney Biopsies. *Biomedicines*, *10*(9), 2102.
5. Andeen, N. K., Yang, H. Y., Dai, D. F., MacCoss, M. J., & Smith, K. D. (2018). DnaJ homolog subfamily B member 9 is a putative autoantigen in fibrillary GN. *Journal of the American Society of Nephrology*, *29*(1), 231-239.
6. Nasr, S. H., & Fogo, A. B. (2019). New developments in the diagnosis of fibrillary glomerulonephritis. *Kidney Int*, *96*(3), 581-592.
7. Nasr, S. H., Vrana, J. A., Dasari, S., Bridoux, F., Fidler, M. E., Kaaki, S., ... & Alexander, M. P. (2018). DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. *Kidney international reports*, *3*(1), 56-64.
8. Lusco, M. A., Fogo, A. B., Najafian, B., & Alpers, C. E. (2015). AJKD atlas of renal pathology: fibrillary glomerulonephritis. *American Journal of Kidney Diseases*, *66*(4), e27-e28.
9. Alexander, M. P., Dasari, S., Vrana, J. A., Riopel, J., Valeri, A. M., Markowitz, G. S., ... & Nasr, S. H. (2018). Congophilic fibrillary glomerulonephritis: a case series. *American Journal of Kidney Diseases*, *72*(3), 325-336.
10. Andeen, N. K., Troxell, M. L., Riazy, M., Avasare, R. S., Lapasia, J., Jefferson, J. A., ... & Smith, K. D. (2019). Fibrillary glomerulonephritis: clinicopathologic features and atypical cases from a multi-institutional cohort. *Clinical Journal of the American Society of Nephrology*, *14*(12), 1741-1750.
11. Marinaki, S., Tsiakas, S., Liapis, G., Skalioti, C., Kapsia, E., Lionaki, S., & Boletis, J. (2021). Clinicopathologic features and treatment outcomes of patients with fibrillary glomerulonephritis: A case series. *Medicine*, *100*(20), e26022.
12. Raikar, M., & Shafiq, A. (2022). Fibrillary Glomerulonephritis: A Great Mimicker of Rapidly Progressive Glomerulonephritis. *Cureus*, *14*(6), e26001.
13. Payan Schober, F., Jobson, M. A., Poulton, C. J., Singh, H. K., Nickeleit, V., Falk, R. J., ... & Pendergraft III, W. F. (2017). Clinical features and outcomes of a racially diverse population with fibrillary glomerulonephritis. *American journal of nephrology*, *45*(3), 248-256.
14. Jeyabalan, A., Batal, I., Piras, D., Morris, H. K., & Appel, G. B. (2021). Familial fibrillary glomerulonephritis in living related kidney transplantation. *Kidney International Reports*, *6*(1), 239-242.
15. Andeen, N. K., Smith, K. D., Vasilescu, E. R., & Batal, I. (2020). Fibrillary glomerulonephritis is associated with HLA-DR7 and HLA-B35 antigens. *Kidney International Reports*, *5*(8), 1325-1327.

16. Matthai, S. M., Valson, A. T., Duhli, N., Rupali, P., Pulimood, A. B., & Varughese, S. (2018). Fibrillary glomerulonephritis in a human immunodeficiency virus-positive, hepatitis C-negative Indian patient: Expanding the profile of renal involvement in human immunodeficiency virus infection. *Indian Journal of Pathology and Microbiology*, *61*(4), 610-613.