


Immunoglobulin A nephropathy in a patient with neurofibromatosis type 1

A case report and literature review

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Abstract

Rationale: Neurofibromatosis type 1 (NF-1) is an autosomal-dominant neurocutaneous disorder that affects the skin, bones, and nervous system. The most common manifestation of kidney involvement is renal artery stenosis; glomerulonephritis is extremely rare. In this case report, we present a patient with NF-1 and immunoglobulin A nephropathy (IgAN).

Patient concerns: A 51-year-old Korean man previously diagnosed with NF-1 presented with persistent proteinuria and hematuria identified during a routine medical check-up. He had no history of hypertension or diabetes, and denied a history of alcohol use or smoking.

Diagnosis: The contrast-enhanced computed tomography scan revealed normal-sized kidneys and no evidence of renal artery stenosis. On the day of the kidney biopsy, laboratory tests showed a serum creatinine level of 1.1 mg/dL, urine protein/creatinine ratio of 1.3 g/g, and urine red blood cell count of >10 to 15/HPF. The kidney biopsy sample revealed IgAN grade III, according to Lee glomerular grading system.

Intervention: The patient was advised to take 4 mg of perindopril.

Outcome: Three months after the treatment, the urine protein/creatinine ratio decreased to 0.6 g/g, with no change in the serum creatinine level (1.03 mg/dL).

Lessons: A genetic link between NF-1 and IgAN or other glomerular diseases is not established. However, activation of the mTOR pathway may explain this association.

Abbreviations: IgAN = immunoglobulin A nephropathy, NF-1 = neurofibromatosis type 1.

Keywords: IgA nephropathy, IgAN, immunoglobulin A nephropathy, neurofibromatosis type 1, NF-1

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1. Introduction

Neurofibromatosis type 1 (NF-1) is a rare genetic disorder that affects 1 out of every 3000 live births.^[1] NF-1 is an autosomal-dominant neurocutaneous disorder that affects the skin, bones, and nervous system.^[1,2] Although kidney involvement is rare, it most commonly presents as renal artery stenosis,^[3,4] which is reported in less than 1% of cases.^[3] Glomerulonephritis is rare in NF-1 patients; only a few cases of membranous nephropathy^[5–7] and focal segmental glomerulosclerosis,^[8–10] and 3 of immunoglobulin A nephropathy (IgAN),^[11,12] have been reported in NF-1 patients. In this case report, we present the case of a 51-year-old Korean man with NF-1 and IgAN.

2. Case presentation

A 51-year-old Korean man presented to the nephrology outpatient clinic with proteinuria and hematuria for more than 9 years. Nine years ago, the patient was diagnosed with NF-1 based on the presence of several café au lait macules and cutaneous neurofibromas. A next-generation sequencing panel test confirmed a NF-1 gene mutation on chromosome 17. At the time of diagnosis, proteinuria (urine protein/creatinine ratio = 0.3 g/g; reference value < 0.15) and hematuria (red blood cell

[RBC] count=10–15/HPF; reference value < 0–2) were present. However, the patient was not evaluated by a nephrologist because he had a normal serum creatinine level (0.64 mg/dL; reference value=0.4–1.2). He had 1 daughter diagnosed with NF-1 during infancy. None of his ancestors were diagnosed with NF-1.

The patient's automated blood pressure in the seated position was 134/99 mmHg and the pulse rate was 71 beats/min. He denied a history of smoking or alcohol consumption. His laboratory tests showed a serum creatinine level of 1.21 (reference value=0.4–1.2) mg/dL, urine protein/creatinine ratio of 1.3 (reference value < 0.15) g/g, and urine RBC count > 100/HPF (reference value < 0–2). A kidney biopsy was planned due to suspicion of glomerulonephritis.

Three days later, the patient was admitted to the hospital. At admission, his blood pressure was 110/70 mmHg in the supine position, the heart rate was 74 beats per minute, and the body temperature was 36.2°C. Physical examination revealed café au lait spots and multiple neurofibromas on the abdomen, back, and arms. Serologic tests were negative for anti-neutrophilic cytoplasmic antibody, antinuclear antibody, anti-phospholipid 2 receptor antibody, anti-glomerular basement membrane antibody, rheumatoid factor, serum/urine protein electrophoresis, and hepatitis B and C. Complement 3 and 4 levels were normal. His biochemical tests showed a hemoglobin level of 12.4 (reference value=13.5–17.5) g/dL, platelet count of $230 \times 10^3/\mu\text{L}$ (reference value=140–420), albumin level of 4.1 (reference value=3.3–5.2) g/dL, creatinine level of 1.1 (reference value=0.4–1.2) mg/dL, cystatin C level of 1.28 (reference value=0.61–0.95) mg/dL, CysC-Cr-based eGFR (as determined by the CKD-EPI equation) of 66.3 (reference value > 60) mL/min/1.73 m², sodium level of 134.5 (reference value=138–148) mmol/L, and potassium level of 4.52 (reference value=3.5–5.3) mmol/L. Urinalysis showed a protein/creatinine ratio of 0.9 (reference value < 0.15) g/g and an RBC count of 15 to 20/HPF (reference value < 0–2). Contrast-enhanced abdominal computed tomography showed no evidence of renal artery stenosis. In the reconstructed view, the right and left kidneys were estimated to be 10.5 and 11.2 cm long, respectively.

A kidney biopsy was performed and 3 cores of kidney tissue were obtained. Each core was evaluated by light and electron microscopy and immunofluorescence analysis. On light microscopy, 20 glomeruli were observed and 5 (25%) of them showed global sclerosis. The glomeruli were slightly increased in size and moderately hypercellular, with an increase in mesangial cells and the mesangial matrix also seen (Fig. 1A). Four glomeruli (20%) exhibited segmental sclerosis. Tubules had moderate to severe focal atrophy and loss, with interstitial infiltration of mononuclear cells and fibrosis. Mild arteriosclerosis was also noted. On electron microscopy, localized tiny mesangial deposits were observed (Fig. 1B). The glomerular basement membrane exhibited normal thickness with widening due to severe focal subendothelial edema. Epithelial cell foot processes showed focal marked effacement. The sections for immunofluorescent microscopy contained 3 glomeruli. The mesangium diffusely stained for immunoglobulin A (+3; IgA) (Fig. 1C), C3 (+1) (Fig. 1D), and lambda (+2–3). Tests for IgG, IgM, C1q, C4, fibrinogen, and kappa were negative. The aforementioned findings were consistent with a diagnosis of IgAN grade III, according to Lee glomerular grading system. At discharge, the patient was prescribed 4 mg/day of perindopril.

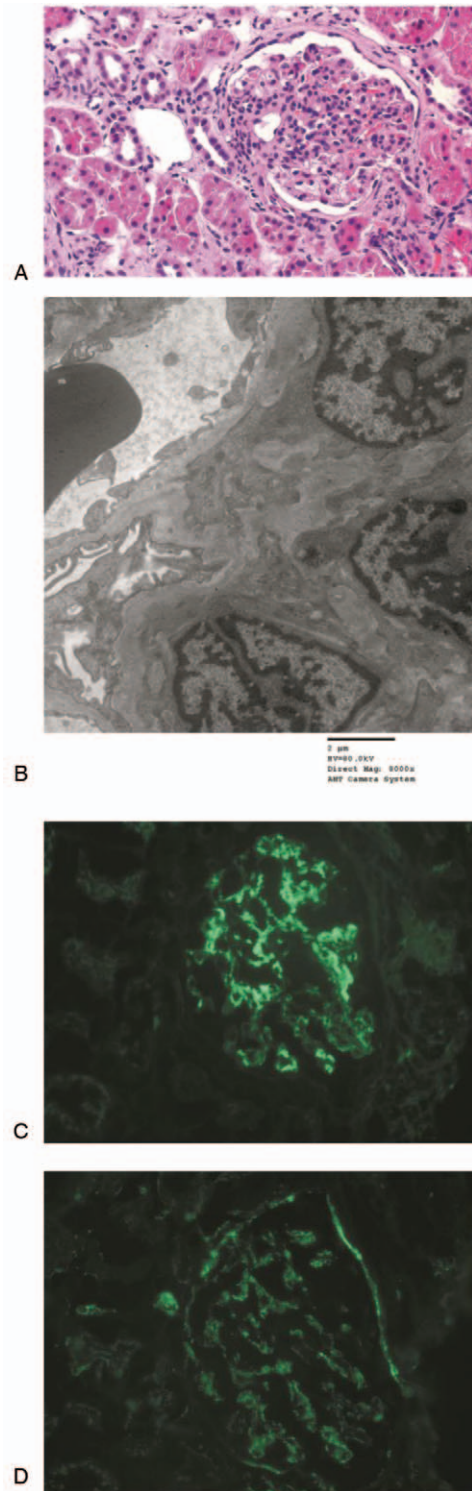


Figure 1. Hematoxylin and eosin-stained light microscopy image showing mesangial hypercellularity (magnification: $\times 400$) (A); Electron microscopy image showing localized mesangial deposits (magnification: $\times 8000$) (B); Immunofluorescent microscopy image showing +3 diffuse mesangial staining for immunoglobulin A (C); and +1 diffuse mesangial staining for C3 (D).

Three months after hospital discharge, the patient was followed up in the outpatient clinic. The urine protein/creatinine ratio decreased to 0.6 (reference value < 0.15) g/g, and the serum creatinine level remained stable at 1.03 (reference value=0.4–

1.2) mg/dL. The patient was advised to attend long-term follow-up visits to monitor his renal function.

3. Discussion and conclusions

The first cases of IgAN in NF-1 patients were reported in 1997 from Japan, in a 41-year-old female and her 24-year-old son.^[11] The mother presented with proteinuria and occult hematuria for 1 year before the diagnosis of NF-1. Renal biopsy revealed moderate IgAN. Her renal function gradually deteriorated, and repeat biopsy revealed marked sclerosis of the glomeruli, tubules, and interstitium. Her son underwent a kidney biopsy for proteinuria and occult hematuria 5 years after the NF-1 diagnosis. At that time, his serum creatinine was 1.25 mg/dL, and he had proteinuria (3.3 g/d). The kidney biopsy specimen confirmed a diagnosis of IgAN with fibrocellular crescents. The authors of this report did not suggest a genetic relationship between IgAN and NF-1.

Another case of IgAN was reported in 2020,^[12] in a 56-year-old Japanese woman with NF-1. She presented with new-onset microscopic hematuria and arthralgia. She also had palpable purpura on the lower parts of her legs. Her kidney and skin biopsy samples revealed IgA vasculitis. A genetic relationship between NF-1 and IgA vasculitis was not suggested by the authors.

In our patient, IgAN was diagnosed 9 years after genetic confirmation of NF-1. However, hematuria and proteinuria had been present since the diagnosis of NF-1, so IgAN may have been present before the pathologic confirmation. We excluded all possible causes of secondary IgAN,^[13] including liver cirrhosis, inflammatory bowel disease, hepatitis B and C, autoimmune diseases, malignancies, psoriasis, sarcoidosis, cystic fibrosis, and pulmonary fibrosis. At the time of kidney biopsy, his serum creatinine level was 1.1 mg/dL and the urine protein/creatinine ratio was 0.9 g/g; this had worsened over the previous 9 years.

Among the 4 reported cases of IgAN with NF-1, 2 had progressive renal dysfunction, and 1 exhibited accelerated inflammation at the time of kidney biopsy. Compared to the natural course of IgAN in the general population,^[14] NF-1 patients seemed to have a worse clinical condition.

Although there is no conclusive evidence of a genetic link between IgAN and NF-1, we suspect that NF-1 affects the development and progression of IgAN. NF-1 is caused by a mutation in the *NF-1* gene, located on the long arm of chromosome 17.^[15] *NF1* gene encodes neurofibromin, which negatively regulates the Ras/PI3K signaling pathway that in turn regulates the mTOR pathway.^[16–19] Therefore, alteration of neurofibromin in NF-1 patients can cause aberrant activation of the mTOR pathway.^[16–19]

Activation of the mTOR pathway has been reported in an experimental model of IgAN. In the experiment by Nagai et al,^[20] mesangial cell mTOR 1 activation induced mesangium expansion and increased the production of collagen IV, collagen I, and smooth muscle actin in glomeruli. Additionally, treatment with rapamycin, an mTOR inhibitor, suppressed mesangial expansion. In another experiment with an IgAN rat model, rapamycin attenuated IgA deposition in glomeruli and preserved the renal function.^[21]

The multihit hypothesis is the most widely accepted with respect to IgAN pathogenesis.^[13,22] This framework involves aberrant glycosylation of IgA1, synthesis of antiglycan autoantibodies that target galactose-deficient IgA1 (Gd-IgA1), formation of circulating Gd-IgA1-antiglycan IgG immune complexes, and accumulation of nephritogenic complexes in the mesangium, which activate the inflammatory response that contributes to mesangial matrix production and mesangial cell proliferation. Even though the genetic link between IgAN and NF-1 is not established, we speculate that the inflammatory response to nephritogenic Gd-IgA1-antiglycan IgG immune complexes in mesangium is enhanced in NF-1 patients due to aberrant mTOR activation. Glomerulonephritis other than IgAN have also been reported in NF-1 patients, including membranous nephropathy,^[5,7,23] focal segmental glomerulosclerosis,^[8–10] immunoglobulin M nephropathy,^[24] C1q nephropathy,^[25] minimal change disease,^[26] and renal amyloidosis^[26] (Table 1). Activation of the mTOR pathway in NF-1 patients may increase susceptibility to diverse nephritogenic antigens.

In this article, we report the case of a patient with NF-1 and IgAN. It is unclear whether the co-occurrence of NF-1 and IgAN was due to a genetic association or coincidence. However,

Table 1
Reported cases of glomerular disease in patient with neurofibromatosis type 1.

Reference	Year	Country	Race	Sex	Age	Type of GN
Kokubo et al ^[5]	1993	Japan	Asian	F	68	MN
Toth et al ^[7]	1996	Hungary	Unknown	NA	NA	MN
Taniguchi et al ^[11]	1997	Japan	Asian	F	41	IgAN
Taniguchi et al ^[11]	1997	Japan	Asian	M	24	IgAN
Wani et al ^[23]	2006	India	Unknown	F	70	MN
Gersch et al ^[8]	2006	USA	White	M	22	FSGS
Tarrass ^[9]	2008	Morocco	Unknown	M	58	FSGS
Afshinnia et al ^[10]	2013	USA	White	F	42	FSGS
Chang et al ^[24]	2015	S. Korea	Asian	F	44	IgM nephropathy
Varyani et al ^[25]	2019	India	Unknown	M	51	C1q nephropathy
Orera et al ^[26]	2019	Spain	Unknown	F	41	MCD
Orera et al ^[26]	2019	Spain	Unknown	F	71	Renal amyloidosis
Shimamura et al ^[12]	2020	Japan	Asian	F	56	IgAN
Rhee et al	2021	S. Korea	Asian	M	51	IgAN

FSGS = focal segmental glomerulosclerosis, IgAN = immunoglobulin A nephropathy, IgMN = immunoglobulin M nephropathy, MCD = minimal change disease, MN = membranous nephropathy, NA = not available.

activation of the mTOR pathway may reflect a possible genetic association. Further experimental and clinical studies are required to evaluate the potential genetic association between NF-1 and IgAN.

Author contributions

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