Letter

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End-stage renal disease due to retroperitoneal fibrosis in neurofibromatosis type I

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SUMMARY Retroperitoneal fibrosis (RF) commonly leads to renal impairment due to compression of ureters, and around 8% of patients eventually progress to end-stage renal disease (ESRD). We present a case of RF in a 61-year-old female patient with neurofibromatosis type 1 (NF1) who developed ESRD. She presented with a postrenal acute kidney injury, being initially treated with an ureteral catheter. A magnetic resonance imaging of the abdomen showed parietal thickening of the right ureter, and she underwent right ureter reimplantation through bladder flap and psoas hitch. There was an extensive area of fibrosis and inflammation over the right ureter. Biopsy disclosed nonspecific fibrosis, which was consistent with RF. Although the procedure was successful, she developed ESRD. We review atypical presentations of RF and causes of renal injury in NF1. RF should be considered a possible cause of chronic kidney disease in patients with NF1, perhaps due to an unknown underlying mechanism.

Keywords end-stage renal disease, neurofibromatosis type 1, retroperitoneal fibrosis.

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is an autosomal dominant disease that affects approximately 1 in 3,000 individuals worldwide. It is characterized by multiple benign peripheral nerve sheath tumors, as well as other nervous system neoplasms. Other common manifestations include multiple flat, light-brown patches of skin pigment (café-au-lait spots), skinfold freckling, visible subcutaneous neurofibromas, and small nodules of the iris (Lisch nodules) (*1*).

Retroperitoneal fibrosis (RF) is a rare disease which causes fibrosis and inflammation in the retroperitoneum, most commonly affecting the abdominal aorta. The ureters are commonly affected by RF as well, leading to postrenal acute kidney injury (AKI) and chronic kidney disease (CKD) (*2*). We present a case of a female NF1 patient with a single kidney who developed end-stage renal disease (ESRD) due to RF. As of April 2023, a literature search on PubMed using the terms "retroperitoneal fibrosis" and "neurofibromatosis" disclosed three results, with none of them describing a case of RF in a person with NF1. This is the first time this association is being reported.

On october 2020, a 61-year old female patient presented to the emergency department with nausea, vomiting, asthenia, decreased appetite, and a 3-month history of recurrent urinary tract infections. She denied fever, dysuria, oliguria, or hematuria. She had a previous history of smoking, weight loss of 6 kg in one week, hypertension, NF1, and a left radical nephrectomy in 2007 because of a renal hematoma from a biopsy-proven chronic pyelonephritis. She was on olmesartan and hydrochlorothiazide.

Laboratory studies revealed leukocytosis, hyperkalemia, uremia, and elevated creatinine levels (6.85 mg/dL). Physical examination was unremarkable, except for multiple neurofibromas and café-au-lait spots in her trunk. Urinalysis revealed microscopic hematuria and proteinuria. A computed tomography scan of the abdomen disclosed right hydronephrosis with proximal dilation of the ureter. There were, however, no signs of obstruction. A diagnosis of AKI was made. She was transferred to the Urology service, with ureteroscopy revealing mild stenosis of the median ureter. An ureteral catheter was placed and treatment with ceftriaxone was started.

On follow-up six-months later, she still had dysuria and suprapubic pain. A magnetic resonance imaging (MRI) of the abdomen disclosed a diffuse parietal thickening of the middle ureter up to the ureterovesical junction (Figure 1). Neurofibroma of the ureter, retroperitoneal fibrosis, and desmoid type fibromatosis

were suspected. An urinary tract X-ray showed correct positioning of the ureteral stent. She then underwent right ureter reimplantation through bladder flap and psoas hitch. There was an intense area of fibrosis and inflammation over the ureteral crossing of the iliac vessels. Biopsy of the ureter revealed nonspecific fibrosis and no signs of malignancy, excluding neurofibroma of the ureter due to a negative S100 staining and desmoid fibromatosis due to negative beta-catenin staining (Figure 2). A diagnosis of RF was made by exclusion. IgG4 titers could not be measured.

A follow-up renal ultrasound (US) in December 2021 showed a normal renal parenchyma. Due to her continuously rising creatinine levels, she was referred to the Nephrology service, ultimately being diagnosed with ESRD, with a glomerular filtration rate (GFR) of 11.9 mL/min/1.73 m² at the first consult. ESRD was attributed to a probable long-standing RF, which was diagnosed after an AKI. In August 2022, with a GFR of 11.15 mL/min/1.73 m², another follow-up renal US revealed hydronephrosis. As of her last follow-up visit, on January 2023, she has not started kidney replacement therapy and has no urgent indications for it, since her GFR has remained stable. Her creatinine levels and timeline are summarized in Figure S1 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=147*). Written informed consent was obtained from the patient prior to publication.

This is the first described case of NF1 with concurrent RF. Renal function impairment in NF1 is usually related

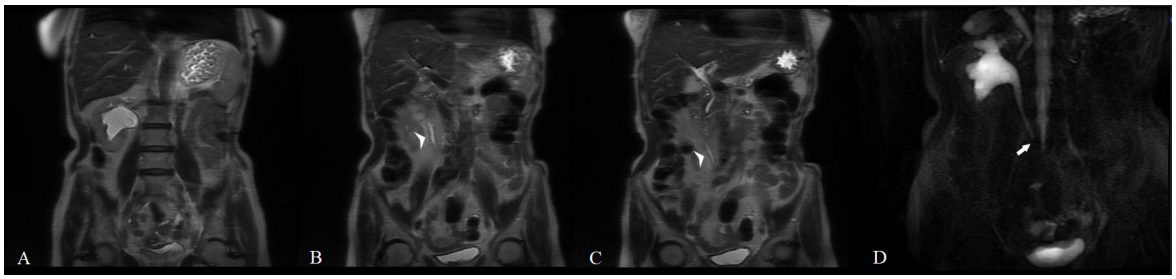

Figure 1. T2-weighted abdominal MRI scan showing right hydronephrosis (A) and progressive thickening of the right ureter (B,C) (arrowheads). Magnetic resonance urography showing the classic triad of retroperitoneal fibrosis: medial deviation of the ureter, tapering of the ureteral lumen (arrow), and hydronephrosis (D).

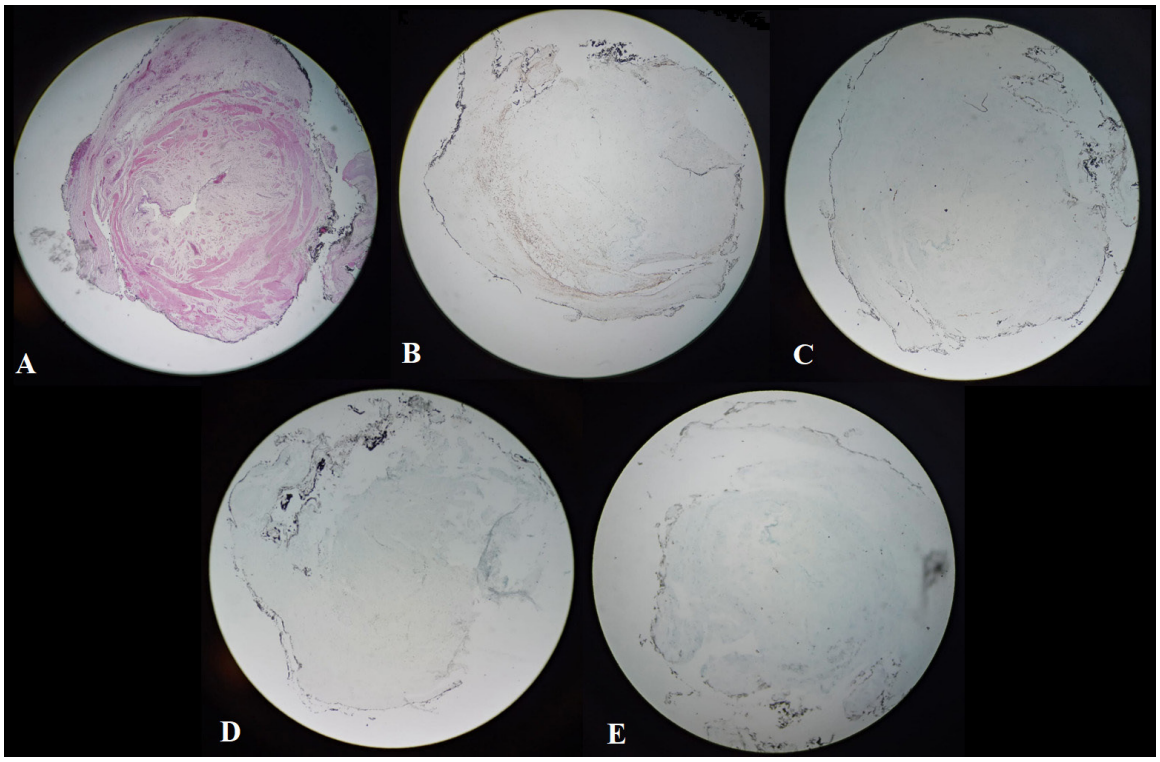

Figure 2. Ureter biopsy showing fibrous thickening of the lamina propria and serosal fibrosis (A). Immunohistochemistry panel revealed a slightly positive CD34 staining (B) and negativity for S100 (C), beta-catenin (D), and collagen type IV (E).

to vessel disease, such as renal artery stenosis, which is the most common cause of death after malignancies in NF1 (*3*). RF most commonly presents as a fibrous retroperitoneal plaque surrounding the abdominal aorta and some of its branches, the inferior vena cava, and the ureters. However, atypical locations have been described, such as purely periureteral (as in our case), around the renal hilum, periduodenal, and peripancreatic. In these cases, a biopsy is warranted for diagnostic confirmation. There were no signs of chronic inflammation in our patient biopsy, a hallmark of RF (*4*). Other cases of RF without evidence of chronic inflammation have been published (*5-7*).

Hydroureteronephrosis is the most common complication of RF, affecting 60-70% of patients, which occurs due to the extrinsic compression of the ureters (*8*). Bilateral disease may be found in 40% of cases (*4*), and a similar proportion may suffer from unilateral disease. The latter may be asymptomatic for years but may lead to kidney atrophy, a finding which is present in up to 30% of patients at time of diagnosis (*8*). Accordingly, around 40% of cases develop CKD and 8% progress to end-stage renal disease (*9,10*).

We presented for the first time a case of RF with atypical location and histopathological findings in a patient with NF1 who developed ESRD. Although rare, RF should be considered a differential diagnosis when evaluating an NF1 patient with CKD. Finally, further studies are needed to elucidate whether NF1 predisposes to RF.

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References

1. Tamura R. Current understanding of neurofibromatosis type 1, 2, and schwannomatosis. Int J Mol Sci. 2021; 22:5850.
2. Raglianti V, Rossi GM, Vaglio A. Idiopathic retroperitoneal fibrosis: An update for nephrologists. Nephrol Dial Transplant. 2021; 36:1773-1781.
3. Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, Macedo TA, Stanson A. Vascular abnormalities in patients with neurofibromatosis syndrome type I: Clinical spectrum, management, and results. J Vasc Surg. 2007; 46:475-484.
4. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. Lancet. 2006; 367:241-251.
5. Dişel U, Alpay NR, Paydas S. Retroperitoneal fibrosis secondary to different etiologies (hemilaminectomy and hypothyroidism): Reports of two cases. Ren Fail. 2007; 29:639-646.
6. Pérez-Sanz MT, Cervilla-Muñoz E, Alonso-Muñoz J, Marcelo-Ayala A, Pulfer MD, Galeano-Valle F. Retroperitoneal fibrosis associated with orbital pseudotumor without evidence of IgG4: A case report with review of literature. Intractable Rare Dis Res. 2019; 8:29-35.
7. Keerthivasagam S, Roy Moulik N, Pandey A, Gala K, Patil V, Dhamne C, Chatterjee G, Patkar N, Narula G, Banavali S. Imatinib-induced retroperitoneal fibrosis in a child with chronic myeloid leukemia: A case report. Am J Blood Res. 2021; 11:600-604.
8. Fenaroli P, Maritati F, Vaglio A. Into clinical practice: Diagnosis and therapy of retroperitoneal fibrosis. Curr Rheumatol Rep. 2021; 23:18.
9. Raffiotta F, Escoli RS, Quaglini S, Rognoni C, Sacchi L, Binda V, Messa P, Moroni G. Idiopathic retroperitoneal fibrosis: Long-term risk and predictors of relapse. Am J Kidney Dis. 2019; 74:742-750.
10. Moriconi D, Giannese D, Capecchi R, Cupisti A, Barsotti S, Morganti R, Orsitto E, Tavoni AG, Egidi MF. Risk factors for relapse and long-term outcome of idiopathic retroperitoneal fibrosis. Clin Exp Nephrol. 2019; 23:1147-1153.

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