Minimal Change Disease in a Patient with Neurofibromatosis Type I

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Abstract

Neurofibromatosis type I (NF-1), the most common neurocutaneous disorder, can be an inherent or spontaneous mutation of the NF-1 gene on chromosome 17q11.2 and encodes neurofibromin proteins. There have only been a few cases reported of NF-1 associated with nephrotic syndrome and the relation rests unclear. Herein, we present a case of NF-1 combined with minimal change disease (MCD).

KEY WORDS: glomerulonephritis, minimal change disease, neurofibromatosis

Introduction

Neurofibromatosis type I (NF-1) is the most common neurocutaneous disorder and occurring in approximately 1 in 3,000 people. This occurs at any age and is hereditary disease with autosomal dominant fashion, but about half of NF-1 cases are sporadic. NF-1 is caused by a mutation in the NF1 gene, which is located at chromosome 17q11.2. This gene codes for a protein known as neurofibromin, which is involved in inhibiting cell proliferation and other unclear functions (1). Clinically, this disease presents with cafe-au-lait spots, freckles near the axilla and groin, and benign tumors of the peripheral nerve sheath called neurofibromas. Patients may also get small hamartomas of the iris, known as Lisch nodules. Kidney can be also involved and most common presented with renal artery stenosis (2). Coexistence of NF-1 and glomerulopathy has rarely been reported (3-8).

Case Report

A 32-year-old woman presented to the nephrology outpatient clinic with bilateral leg edema and foamy urine for one week. Upon physical examination, she weighed 50 kg and had a blood pressure of 122/78 mmHg, a heart rate of 78 beats/min, and a respiratory rate of 16 breaths per minute. There were several café-au-lait spots with sizes over 1.5 cm on the area of the trunk with the greatest diameter, wide spreading freckles over the whole skin including the axilla and inguinal areas and more than two small skin tumors scattered across the arms, face, and trunk. The skin lesions were noted since her childhood and progressed with age. Her mother’s and sister’s skin lesions were similar to hers, but they did not have the same presentation in the kidney and lacked definite diagnosis. She had no history of medication or surgery. She denied using alcohol, cigarettes, or other drugs. She reported no history of abdominal pain, hematuria, or arthralgia. The urine protein level was three plus. Serological workup noticed normal complement levels, negative results for antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies and hepatitis B and C. Other laboratory data depicted the albumin level of 2.1 g/dL, total protein of 4.7 g/dL, blood urea nitrogen of 17 mg/dL, creatinine of 0.96 mg/dL, total cholesterol of 393 mg/dL, triglyceride of 147 mg/dL,
and normal complete blood count. The 24 hours creatinine clearance was 29.3 mL/min and total urine protein was 11.6 g/day. Renal ultrasound showed normal sized kidneys with normal cortical echogenicity and without hydronephrosis or stones. Renal biopsy and skin tumor biopsy were performed. The skin tumor pathologic report was neurofibroma. Neurofibromatosis type I was diagnosed according to the criteria developed by the National Institute of Health. In the kidney pathologic findings, light microscopy revealed that 5 of 17 glomeruli have slight focal segmental mesangial expansion and hypercellularity, minimal interstitial inflammatory infiltration with mild tubular atrophy and mild interstitial fibrosis. Immunofluorescence revealed non-specific linear immunoglobulin G staining along the glomerular capillary walls in one of 10 glomeruli and negative staining for IgA, IgM, C3, C4 and Clq. An electron microscope revealed extensive foot process effacement with moderate microvillus transformation with no electron dense deposits in the glomeruli. The diagnosis of kidney pathology was minimal change disease (MCD). She had remission of proteinuria after 3 weeks of prednisolone 1 mg/kg/day and no relapse or recurrence developed even after incomplete self-treatment.

Discussion

Notwithstanding NF-1, the most common nephrotic syndrome occurs in approximately 1 in 3,000 people of any age. It is a hereditary disease in an autosomal dominant fashion and about half of the cases are sporadic (1). Its outstanding feature is development of neurofibromas in various organs (9). The other classical presentations include café-au-lait spots, freckles, Lisch nodules, bone deformities, learning disabilities, short stature, macrocephaly and predisposition to develop neoplasia (1). According to the National Institute of Health (NIH) diagnostic criteria for NF-1, our patient fulfilled the criteria of café-au-lait spots, neurofibroma and freckles in the axillary region. NF1 caused by mutations of the NF1 gene at chromosome 17q11.2 has highly variable expression which is supposed from modifying genes, allelic heterogeneity, a mutation in the second allele, somatic mosaicism, contiguous gene deletion, and environmental factors (10, 11). The NF1 gene encodes neurofibromin, a cytoplasmic GTPase, activating protein predominantly expressed in neurons. This gene is also found in other organs like the lung, kidney, liver, pancreas and skeletal muscles (12). The neurofibromin has a complex function which is well known to downregulate the p21-ras oncogene. This involves many signaling pathways which effect cell mitosis, proliferation, differentiation, survival and apoptosis. It also interacts with different proteins like focal adhesion kinase which involves cell motility, and syndecan, a transmembrane heparan sulfate proteoglycan (HSPG), which involves cell migration and cell-matrix interaction (13-15).

The neurofibromin absence stimulates cell proliferation and induces high tumor incidence in NF-1.

The most common renal involvement in NF-1 is renal artery stenosis (2).

Only a few cases of glomerulopathy associated with NF-1 have been reported. The most common among them is membranous glomerulopathy (MGN). The rest include IgA nephropathy, MCD, Alport syndrome and focal segmental glomerular sclerosis (3-8).

MCD is a common cause of nephrotic syndrome in children, but is less prevalent in adults. Light microscopy of the glomeruli usually appears normal in MCD, whereas electron microscopy manifests podocyte foot process effacement with no electron dense deposits in the glomeruli. The pathogenesis of MCD is ill-defined; loss of glomerular charge selectivity is thought to be the main mechanism of proteinuria in MCD. HSPGs have been reported to be associated with podocyte modulation and glomerular inflammation (13, 16). The interaction with HSPGs and neurofibromin might be related to the pathogenesis of glomerulopathy in NF-1. Paraneoplastic glomerulonephritis is a rare complication from tumor cell products, typically including solid tumor-pertinent membranous nephropathy and Hodgkin lymphoma-relevant MCD. Ras gene-related inflammation or growth factor production may share the common pathogenesis of glomerulonephropathy in NF-1 and in paraneoplastic glomerulonephritis (17).

Despite the above possible mechanism for the combination of NF-1 and glomerulopathy, whether or not they occurred independently could not be determined. Further studies are needed to prove the hypothesis.

References


