LETTER TO THE EDITOR

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Minimal change nephrotic syndrome showing complete remission after resection of a neurofibroma in a type I neurofibromatosis patient

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To the Editor,

Nephrotic syndrome may occur secondary to conditions such as certain cancers, infections, drugs and inflammations. Secondary glomerulopathies associated with solid tumor mainly present as membranous nephropathy on histological examinations. However, there have been few reports of minimal change disease (MCD) associated with solid tumors. We reported the first case of nephrotic syndrome that showed complete remission following the resection of a plexiform neurofibroma in a patient with neurofibromatosis type 1 (NF1).

On November 2013, a 29-year-old female visited Bucheon St. Mary's Hospital with progressive edema of both lower extremities that had started a week before admission. She was not taking any medication and had no noticeable medical or family history. On initial presentation, there was a café au lait spot on her left upper arm and numerous cutaneous nodules on her chest, abdomen, and back, which she claimed had been present since birth, suggesting the diagnosis of NF1. Her vital signs on admission were as follows: blood pressure of 100/60 mmHg, heart rate of 82 beats per minute, respiratory rate of 14 breaths per minute, and body temperature of 36.8°C. She had a 3+ pitting edema on both lower extremities. Blood tests showed a normal complete blood count, serum creatinine of 0.45 mg/dL (normal range, 0.50 to 1.20), and urea nitrogen 15.0 mg/dL (normal range, 6.0 to 20.0). Urine protein to creatinine ratio was 28.20, 24-hour proteinuria 10.4 g (0.02 to 0.08 g/day), and no red cells or casts were found on the urine sediment examination. Serum albumin was 2.0 g/dL (normal range, 3.4 to 4.8), serum total protein 4.9 g/dL (normal range, 6.6 to 8.7), total cholesterol 346.4 mg/dL (normal range, 120 to 240), triglyceride 161 mg/dL (normal range, 30 to 200), and low-density lipoprotein 230 mg/dL (normal range, 60 to 130). Complement component levels were not decreased, antinuclear antibodies were trace with a speckled pattern and anti-neutrophil cytoplasmic antibodies were negative. Serological tests for hepatitis C virus, hepatitis B virus, and human immunodeficiency virus infection were all negative. Cryoglobulin levels and serum levels of immunoglobulin G, A, M, E were within normal limits; serum electrophoresis showed a marked attenuation of the albumin region, and urine immunofixation was negative for monoclonal immunoglobulin. Light microscopy of the kidney biopsy showed normal size and cellularity of the glomeruli (Fig. 1A); and on

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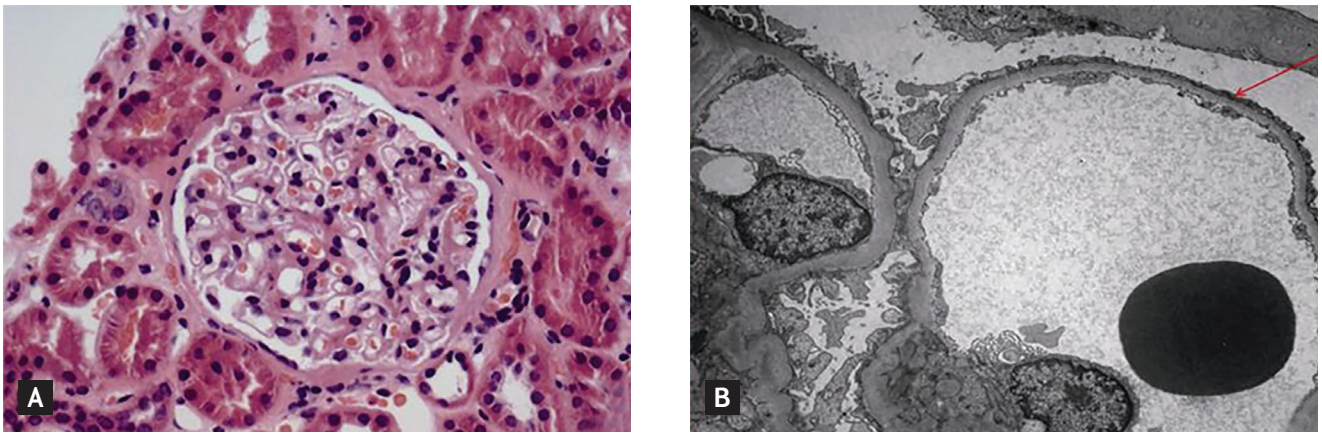

Figure 1. (A) Kidney light microscopy displays no abnormalities (H&E, ×200). (B) Electronic microscopy shows diffuse foot process effacement (arrow) without electron deposits (×4,000).

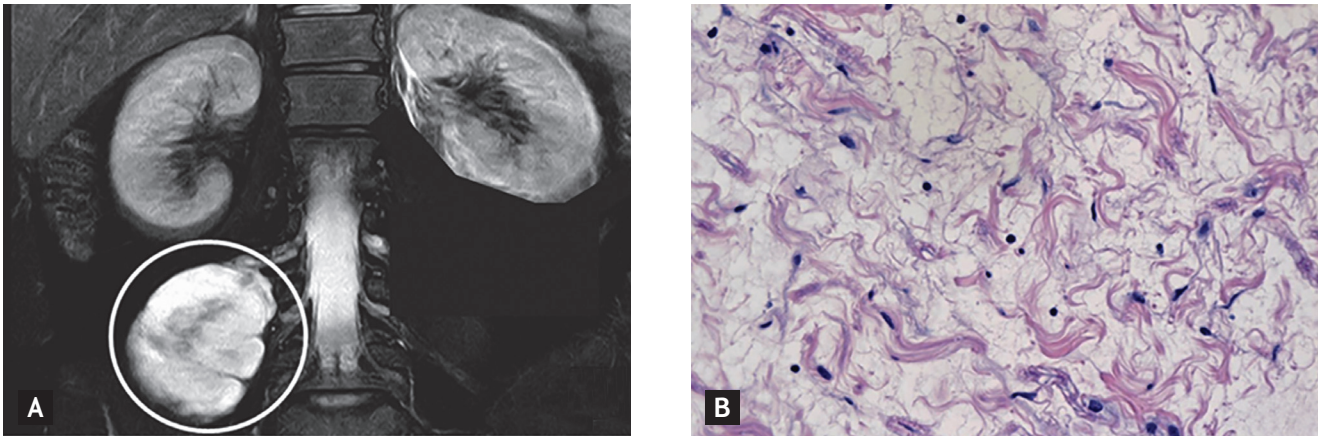

Figure 2. (A) On the L-spine magnetic resonance imaging, a soft tissue mass, consistent with the findings of a neurogenic tumor, such as a neurofibroma arising from right L3 nerve root is seen. (B) Histologic findings of this mass are consistent with neurofibroma, showing low cellularity and spindle cells (H&E, ×400).

electronic microscopy, the glomerular basement membrane showed normal thickness and a generally smooth contour without electron dense deposit, while epithelial foot processes exhibited marked effacement (Fig. 1B). There were no remarkable findings in the tubules and blood vessels. The above changes were consistent with the findings of MCD. An abdominal computed tomography (CT) scan was performed and a 7.2 × 4.8 cm sized soft tissue mass in the right Psoas muscle, probably a neurogenic tumor arising from the right L3 nerve root, was discovered. A magnetic resonance imaging (MRI) of the L-spine was also performed, and the findings were consistent with those of the CT. An excisional biopsy was therefore needed to differentiate malignancy such as malignant peripheral nerve sheath tumor (MPNST), or rhabdomyosarcoma (Fig. 2A). The mass could only be partially excised because of its adherence to the nerve root of L3-4. The histologic finding was consistent with neurofibroma (Fig. 2B). The patient was diagnosed with NF1 and genetic tests were not performed. The urinary protein excretion persistently decreased after the operation without any further treatment with steroids or other immunosuppressive agents, showing a urine protein to creatinine ratio of 0.15 and a serum albumin of 4.2 g/dL (normal range, 3.4 to 4.8) at 6 months.

NF1 is a congenital disorder known to occur by autosomal dominant inheritance, while half of all cases occur as spontaneous mutation. The National Institute of Health (NIH) diagnostic criteria requires the presence of 2 or more of the following: six or more café au lait spots, axillary or inguinal freckling, two or more cutaneous neurofibromas, one plexiform neurofibroma,

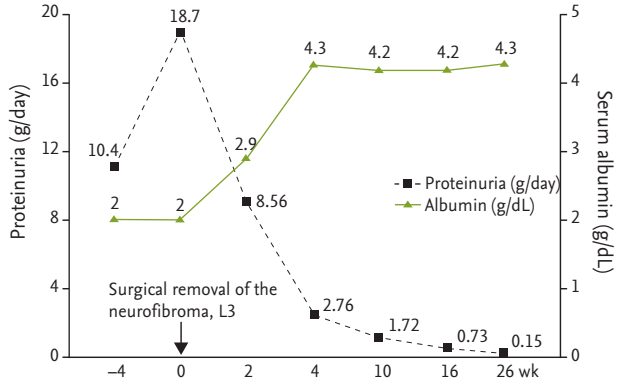

Figure 3. Serial results of proteinuria and serum albumin before and after the removal of the neurofibroma.

characteristic bony lesions, an optic glioma, two or more iris Lisch nodules, or a first-degree relative with NF1. Although our patient had no family history, the diagnostic criteria were fulfilled by the presence of many cutaneous neurofibromas and a plexiform neurofibroma of the L3 spinal root, that had been histologically confirmed. We carefully considered the possibility that the nephrotic syndrome had occurred as a manifestation of the various syndromes associated with NF1. The dominant feature of renal involvement of NF1 is renal artery stenosis; in addition, there have been only a few reports of nephrotic syndrome occurring in NF1 [1].

In the minimal change nephrotic syndrome, the majority of cases occur independently, without associated condition; however, the possibility of secondary cause of nephrotic syndrome should also be ruled out. In this case, we were unable to find the causal relationship between the neurofibromatosis and the presence of MCD. However, evidence supported the possibility of the secondary nephrotic syndrome associated with NF1, although it cannot be fully explained.

In this patient, the plexiform neurofibromas involved large nerves associated with functional impairment and may have transformed into MPNST. Therefore, histologic identification and surgical resection is needed in patients of all ages. We removed as much of the mass as possible, and urinary protein loss decreased to a non-nephrotic range without the use of steroids. In such cases of secondary MCD, histologically indistinguishable from the primary form, the causal link is strongly supported if cure of the extraglomerular disease leads to the resolution of MCD, irrespective of the underlying pathogenetic mechanism [2]. Moreover, previous studies have shown that spontaneous remission without treatment with corticosteroids or other immunomodulators occur in less than10% of adults with idiopathic minimal change nephrotic syndrome. In our patient, following the removal of the neurofibroma, the degree of proteinuria and serum albumin level changed from 10 to 0.15 g/day, and 2.0 to 4.2 g/day (Fig. 3), respectively, which is within the criteria for complete remission of nephrotic syndrome (proteinuria range < 0.20 g/day and serum albumin > 3.5 g/day). Thus, it can be presumed that this response was associated with the resection of the mass.

Also, there are weak molecular mechanisms that might explain the association of *NF1*. NF1 is associated with a mutation in the *NF1* gene that is located on chromosome 17. The *NF1* gene encodes a cytoplasmic protein called neurofibromin, which is a tumor suppressor gene involved in ras GTPase activation in various cells, inactivation of neurofibromin leads to activation of ras protein including p21-ras proto-oncogene and its overactivity [3]. The activation of ras upregulates mammalian target of rapamycin activity that is associated with a balance in podocyte homeostasis [4].

Also, neurofibromin encoded by *NF1* gene interacts with syndecan transmembrane heparan sulfate proteoglycan [5]. Syndecan 2, a transmembrane heparin sulfate proteoglycan (HSPG) has a neurofibromin protein binding site [5]. HSPG is known to critically contribute to the charge selective barrier of the glomerular basement membrane. The pathogenesis of MCD in NF1 has been ill defined, but their interaction might contribute to the development of minimal change nephrotic syndrome. These mechanisms could explain the association with neurofibromatosis, although we cannot exclude the possibility of chance occurrence. When a patient is diagnosed with nephrotic syndrome, glomerulopathy due to secondary causes, although uncommon, should also be considered.

Keywords: Nephrotic syndrome; Neurofibromatosis 1; Neurofibroma, plexiform

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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