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Case Report

Difficult Renal Pathological Classification in a Case of Pediatric Nephrotic Syndrome

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Keywords
C4d · Electron microscopy · Immunofluorescence · Light microscopy · Membranous nephropathy · Minimal change nephrotic syndrome · Steroid-resistant nephrotic syndrome

Abstract
The underlying histopathology is very important in determining patient management, as the histopathology usually has direct repercussions on the treatment response and clinical course. However, the impact of the method used to assess renal biopsies, i.e., light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM), on the occurrence of a difficult biopsy classification in the native kidneys of pediatric nephrotic patients is unknown. A 12-month-old Japanese boy was diagnosed with nephrotic syndrome (NS); he was administered prednisolone (60 mg/m^2/day), and a continuous albumin infusion was started. A renal biopsy using LM revealed minimal change. However, an IF study showed granular staining for immunoglobulin G along the glomerular basement membrane. Therefore, he was diagnosed with membranous nephropathy (MN). As his proteinuria was so severe, we started immunosuppressant therapy and continued the albumin infusion for more than 2 months. However, he did not attain complete remission. A month later, EM examination of his renal biopsy showed extensive foot process fusion without electron-dense deposits. Although the result of the IF study suggested MN, the results of the LM and EM studies indicated minimal

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change. We finally diagnosed the patient with minimal change NS, in consideration of his clinical condition and course. Because of the failure of previous treatments, pulse steroid therapy was started. After five rounds of therapy the patient attained complete remission. A difficult renal biopsy finding classification, dependent on the diagnostic method used, might occur in the native kidneys of pediatric nephrotic patients. Therefore, a diagnosis should be made after considering all renal biopsy findings and the clinical course.

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Introduction

Of all children diagnosed with nephrotic syndrome (NS), 10–20% will progress to steroid-resistant NS [1]. In children, the morphological patterns of NS usually show minimal change, diffuse mesangial hypercellularity, or focal segmental glomerulosclerosis; these patients appear to progress to terminal renal insufficiency within several years if treatment is not intensified to include immunosuppressants or pulse methylprednisolone therapy [2]. Also, in children, membranous nephropathy (MN) is a rare cause of NS [3]. The characteristic pathology of MN includes a thickened glomerular capillary wall, showing spikes when observed using periodic acid-methenamine-silver stain and periodic acid-Schiff stain by light microscopy (LM); granular staining for immunoglobulin G (IgG) along the glomerular basement membrane (GBM) by immunofluorescence (IF); and the presence of electron-dense deposits (EDD) along the subepithelial surface of the glomerular capillary wall, between podocyte foot processes, by electron microscopy (EM) [3]. MN has a better outcome and a better long-term prognosis in children than in adults [4, 5]. Furthermore, certain MN patients show mild, self-resolving disease that does not require steroid treatment [4]. Therefore, the underlying histopathology is particularly important for determining the management, as it usually affects the treatment response and clinical course [6].

Whether difficult renal biopsy finding classifications, dependent on the use of LM, IF, or EM, occur in the native kidneys of pediatric patients remains unknown. Here, we present a pediatric patient with NS who demonstrated these rare renal biopsy finding discrepancies.

Case Report

A 12-month-old Japanese boy without a significant medical history was admitted with severe edema. He showed a rapid weight gain of approximately 1 kg within 1 week. Physical examination did not show any abnormalities, except for severe facial edema and pitting edema. A blood test showed hypoalbuminemia (0.7 g/dL), hyponatremia (124 mEq/L), and hypercholesterolemia (481 mg/dL). His renal functions were normal (blood urea nitrogen 13.6 mg/dL, creatinine 0.18 mg/dL). Serological tests for hepatitis B, hepatitis C, antinuclear antibodies, and anti-DNA antibodies were negative; serum C3 and C4 levels were also within the normal range. Urinalysis revealed severe proteinuria (urinary protein/creatinine 24.9 g/gCr) and no hematuria.

Therefore, the patient was diagnosed with NS, and prednisolone administration (60 mg/m^2/day) and continuous albumin infusion were started. However, as the severe proteinuria continued, the probability of steroid-resistant NS was very high; therefore, we performed a renal biopsy 25 days after admission. As expected, he was finally diagnosed with steroid-resistant NS, and the results of the renal biopsy revealed that 11 of 39 glomeruli had global

sclerosis, and the rest showed minimal change under LM observation (Fig. 1a). The results of periodic acid-Schiff and periodic acid-methenamine-silver stains were unremarkable. A routine IF study (IgG, IgA, IgM, C1q, and C3 staining) showed granular staining for IgG along the GBM in 4 of 4 glomeruli (Fig. 1b), leading to a diagnosis of MN. As his proteinuria was so severe, we started immunosuppressant therapy, including cyclosporine (CyA) and mizoribine (MZB), and continued albumin infusion for more than 2 months. However, he did not attain complete remission. One month after the renal biopsy, his EM study results were returned, indicating that all tissues contained 3 glomeruli with extensive foot process fusion, but without EDD (Fig. 1c). Although the IF study results suggested MN, the LM and EM results indicated minimal change.

Later, to confirm the absence of MN, additional C4d staining was performed on frozen sections. The results showed only mesangial deposition of C4d, without granular positivity along the GBM (Fig. 1d). We finally diagnosed the patient with minimal change NS in consideration of his clinical condition and course. Therefore, in addition to steroids, CyA, and MZB, we performed 5 rounds of intravenous infusion pulses of methyl prednisolone (30 mg/kg/day for 3 consecutive days). After therapy, his proteinuria decreased gradually and he attained complete remission. Currently, he has demonstrated 3 months of complete remission and is being followed as an outpatient; he is continuing to receive oral prednisolone, CyA, MZB, and candesartan.

Discussion

We described a peculiar case involving a difficult method-dependent renal biopsy finding classification in the native kidney of a pediatric patient with NS. In addition, we showed the necessity of EM for determining an accurate diagnosis.

Although the importance of LM, IF, and EM has been reported for achieving an accurate diagnosis of glomerulopathies in children [7, 8], to the best of our knowledge, difficult classifications in renal biopsy findings have not been reported in the native kidneys of pediatric patients with NS. Haas [9] evaluated 233 renal biopsies in adults and showed that in 2 cases, EM resulted in a change from the preliminary diagnosis. One case involved a woman with systemic lupus erythematosus and NS, and the other involved a young adult male. In the latter case, LM showed normocellular glomeruli, and IF showed linear staining of IgG in the glomerular capillaries. The preliminary diagnosis was MN; however, EM failed to showed EDD in the GBM, leading to a final diagnosis of focal segmental glomerulosclerosis. Although there was a difference in the linear versus granular IgG staining, this case was similar to our case. In addition, according to the Ehrenreich-Churg staging of MN in adult transplanted kidneys, “stage 0” or “MN by IF only” has recently been defined as the presence of IgG ± C3 staining in a capillary loop pattern in the absence of EDD visible by EM [10]. Thus, this suggests the possibility of a difficult renal biopsy finding classification.

Recently C4d, in an IF study, was reported as a novel marker for the diagnosis of MN, showing a positive staining rate of nearly 100% along the GBM [11–13]. Thus, we performed an additional IF study for C4d, and the results showed only mesangial deposition of C4d, without granular positivity along the GBM. Therefore, we concluded that the diagnosis was not MN. In our case, although IF indicated granular staining for IgG along the GBM, EM showed only extensive foot process fusion, without EDD. We can hypothesize four reasons for the occurrence of a difficult biopsy classification. First, the amount of EDD was so small that it was not detected by EM. If this was the case, the granular deposition of IgG by IF

would also be expected to be weak. However, our patient's IF findings showed obvious granular staining for IgG along the GBM. Second, the deposits found by IF are absorbed into a damaged GBM. If so, the GBM or endothelial cells might be damaged, demonstrating an accompanying double contour. Our patient did not show such findings. Third, the staining for IgG along the GBM was not actually granular but linear in the IF study. We rechecked these observations carefully and finally confirmed granular staining for IgG along the GBM. Finally, although the IgG staining was actually granular along the GBM, the staining may be like the starry sky pattern seen in infectious nephritis [14]. However, this is unlikely because our patient did not have the symptoms of an infectious disease and there was definite, typical granular staining for IgG along the GBM. Hence, our case did not conform to any of the above hypotheses, leaving the reason for the granular staining of IgG along the GBM still to be identified.

In conclusion, we presented a pediatric patient demonstrating the rare occurrence of a difficult classification in the renal biopsy findings from his native kidney. In our case, LM, IF, and EM studies were necessary for arriving at an accurate diagnosis. Therefore, a diagnosis should only be made after considering all of the patient's renal biopsy findings and the clinical course.

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Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from the patient's parents.

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. They received no financial support.

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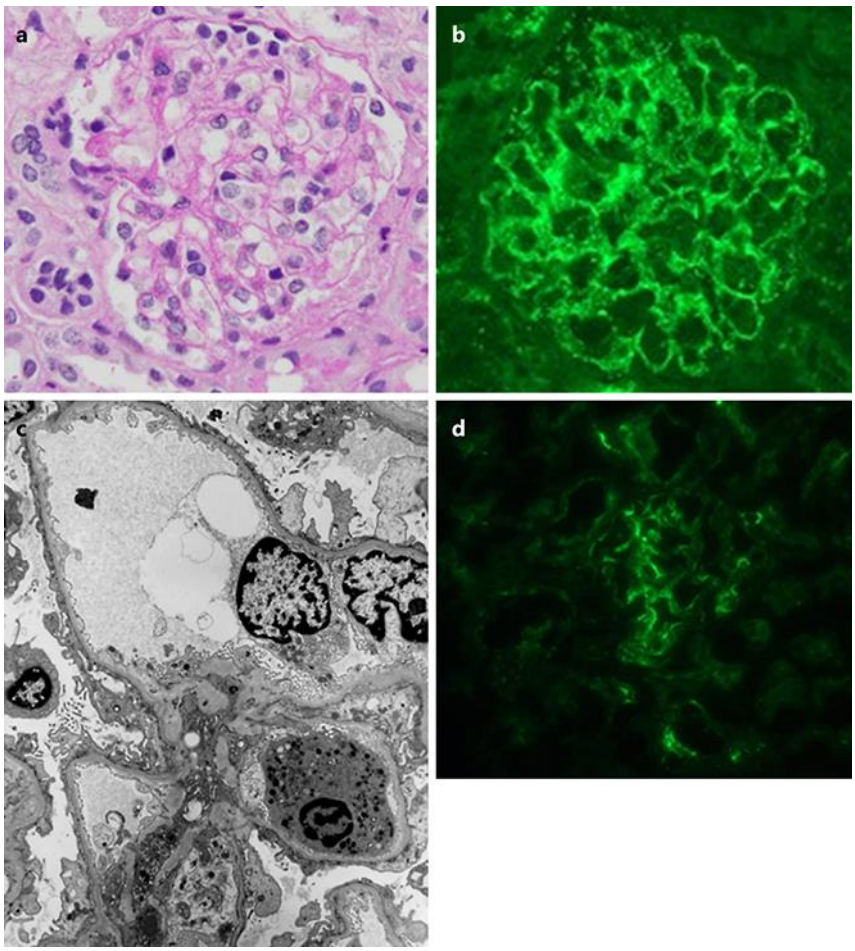

Fig. 1. Renal biopsy findings. **a** Light microscopy showed minimal changes (periodic acid-Schiff stain; original magnification, ×400). **b** Immunofluorescence for immunoglobulin G showed granular staining along the glomerular basement membrane. **c** Electron microscopy showed foot podocyte fusion, without electron-dense deposits (original magnification, ×2,500). **d** Immunofluorescence for C4d showed a mesangial staining pattern.