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Case Report

Membranous Nephropathy in a Child with Crescentic Glomerulonephritis: Coincidence or Comorbidity?

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ABSTRACT. Rapidly progressive glomerulonephritis (RPGN) is rare syndrome in children, characterized by clinical features of glomerulonephritis and rapid loss of renal function, and is associated with crescentic glomerulonephritis. Primary membranous nephropathy (MN) is an immune-complex-mediated cause of the adult nephrotic syndrome but occurs less frequently in children. RPGN is rarely observed in adults with primary MN. In this article, we report a case of MN, which developed during long-term follow-up of previously treated RPGN. Our case may be the first to demonstrate primary MN and crescentic glomerulonephritis in a child. We would like to underline the importance of not dropping the long-term follow-up of cases with primary RPGN (not accompanied by other glomerulonephritis and vasculitis symptoms) who had improved with treatment.

Introduction

Rapidly progressive glomerulonephritis (RPGN) is rare syndrome in children with rapid loss of renal function, and is associated with crescentic glomerulonephritis, defined as the presence of ≥50% crescents on pathology.[1,2] RPGN is a medical emergency, which might rapidly progress to irreversible loss of renal function if untreated.[1] This clinical course might be observed in any form of glomerulonephritis, including poststreptococcal glomerulonephritis, renal vasculitis, IgA nephropathy, and membranoproliferative glomerulonephritis (MPGN).[1,2]

Membranous nephropathy (MN) is an immune-complex-mediated entity and is a common cause of nephrotic syndrome in adults but occurs less frequently (1%–2%) in children.[3,4] While systemic disorders [systemic lupus erythematosus (SLE), hepatitis B and C infection, Sjögren syndrome, medications, and neoplasia] may more frequently cause secondary MN in the younger population, primary or "idiopathic" MN has generally been considered as a disease of adults.[5] The phospholipase A2 receptor (PLA2R) is the major target

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antigen in idiopathic MN.[6]

Because of the different pathophysiologies between MN and RPGN, crescent formation is rarely seen in patients with idiopathic MN.[7] RPGN is a rarely observed entity in adults with primary MN.[8-10] In this article, we report a case of MN that developed during long-term follow-up of previously treated RPGN that had healed.

Case Report

Informed consent was obtained from the patient's parents before presenting the report.

A 6-year-old boy was admitted to our hospital with a three-week history of gross hematuria, vomiting, and facial edema. He was admitted in another hospital for these symptoms, wherein evaluation showed hypertension, proteinuria (89 mg/m^2/h), and renal dysfunction (serum creatinine 4.3 mg/dL, serum urea 100 mg/dL). Previous medical and family histories were insignificant.

Physical examination showed the weight of 21.5 kg (25–50 p), height of 118 cm (50 p), a respiratory rate of 28/min, pulse rate 90/min, blood pressure of 155/100 mm Hg, periorbital and pretibial edema. The laboratory results were as follows: hemoglobin 8.4g/dL, hematocrit 25%, white blood cell count 10,540/mm^3, platelet 381000/mm^3, serum urea 106 mg/dL, creatinine 1.85 mg/dL, serum protein 7.8 g/dL, albumin 3.3 g/dL, C-reactive protein 0.25 mg/dL, pro-calcitonin 0.14 ng/dL. The antistreptolysin O was 677 U, complement factors C3 was 85 mg/dL and, C4 was 14 mg/dL, both in the normal range. Serum levels of IgA, IgM, and IgG were normal. Antinuclear antibody (ANA), anti-DNA, antineutrophil cytoplasmic antibody (ANCA), antihepatitis B virus (HBV), anti-hepatitis C virus (HCV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Parvovirus serologies were all negative. Urinalysis revealed macroscopic hematuria and proteinuria with a 24-h urinary protein excretion of 80 mg/m^2/h. Glomerular filtration rate was 35 mL/min/1.73 m^2.

Renal biopsy was performed and a total of 40 glomeruli were obtained and evaluated. Twenty-two glomeruli had cellular and fibrocellular crescents; in additional, increased cellularity and expanded mesangial matrix were observed (Figure 1). Renal interstitium was infiltrated with inflammatory cells. Immunofluorescence staining showed +++ positive ırregular granular deposits of C3.

Intravenous pulse methlyprednisolone was given (30 mg/kg/day) followed by oral prednisolone and cyclophosphamide (2.5 mg/kg/day) for crescentic glomerulonephritis. With this therapy, the serum creatinine normalized to 0.6 mg/dL, proteinuria decreased (5.6 mg/m^2/h), and hematuria disappeared after treatment for one month. The patient was followed up for five years without any problems.

Five years after discharge, during routine evaluation, proteinuria (97 mg/m^2/h) was detected. Physical examination and blood pressure were normal. Hematuria was not detected. Serum urea, creatinine, protein, albumin, and complement factors were normal. Glomerular filtration rate was 170 mL/min/1.73 m^2. ANA, anti-DNA, ANCA, anti-HBV, anti-HCV, CMV, EBV, and Parvovirus serologies were all negative. A repeat kidney biopsy was performed and 60 glomeruli were obtained and evaluated. Global sclerosis was observed in 12 glomeruli.

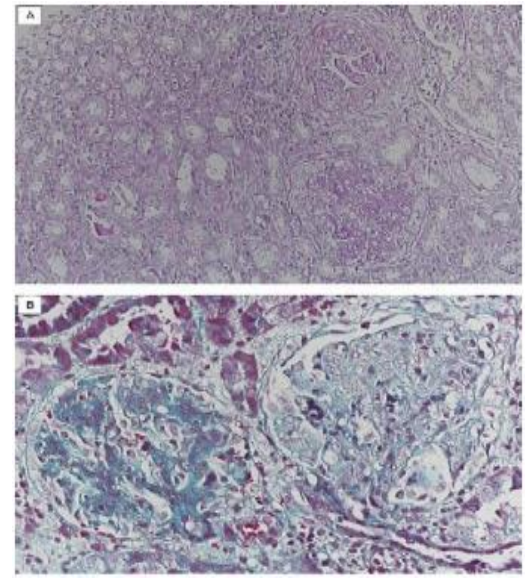

Figure 1. Cellular and fibrocellular crescent formation and expanded mesangial matrix (a: H and E, ×10, b: Masson trichrome, ×20).

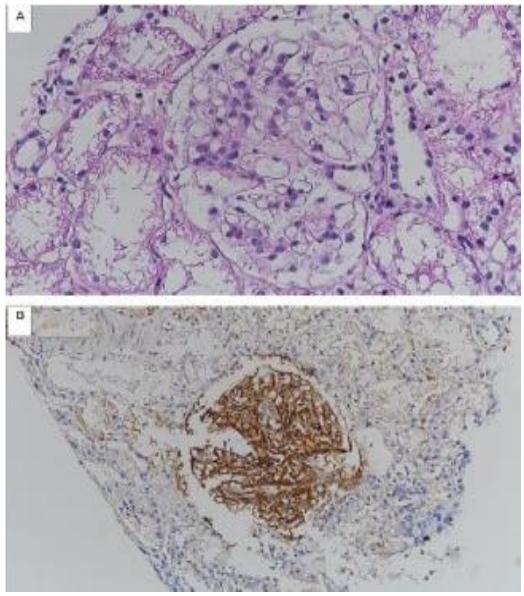

Figure 2. Normal appearing glomerüli and membranous C4d staining (a: H and E, ×40, b: C4d staining, ×20).

Light microscopy showed membranous staining with anti-C4d stain and immunofluorescence microscopy showed membranous granular IgG deposits compatible with MN (Figure 2).

These features were suggestive of MN; he was administered intravenous pulse methylprednisolone followed by oral cyclosporine, after which he went into remission. The patient was in remission for two years and the last glomerular filtration rate was 94.5 mL/min/1.73 m^2 and 24-h urinary protein excretion was 3 mg/m^2/h.

Discussion

RPGN, defined as an acute nephritic syndrome with dramatic loss of renal function within a few months, is associated with crescentic glomerulonephritis, which requires ≥50% crescents on pathology.[1] In our case, due to a sudden impairment in kidney functions, proteinuria, edema, macroscopic hematuria and hypertension, a biopsy was performed on kidney with the pre-diagnosis of RPGN. The case was diagnosed with crescentic, namely, RPGN with 50% crescents in glomerulus during biopsy. RPGN is not a single disease entity. Rather, the crescents are believed to be the result of severe nonspecific glomerular injury, with numerous underlying causes. Immune complex glomerulonephritis is the most common pattern of crescentic glomerulonephritis in children and poststreptococcal glomerulonephritis, Henoch-Schonlein purpura, IgA nephropathy, SLE and MPGN are also classified into this type.[1,2] On the first application, the patient was thought to have primer RPGN, considering the lack of findings of systemic vasculitis, normal values of C3, ANCA, ANA, Anti DNA and ASO, negative markers of other systemic inflammation markers, the lack of other glomerulonephritis findings except for crescents in biopsy.

The outcome for patients with RPGN largely depends on the factors such as the severity of renal failure at presentation and the promptness of intervention, renal histology, and underlying diagnosis.[1] Some studies in literature have reported that the interval between disease onset and the start of treatment, ratio of crescents, ratio of fibrous crescent than fibrocellular crescent, tubular atrophy, interstitial fibrosis, and need for acute dialysis were considered to be independent risk factors for the development of end-stage renal disease.[11]

Our case was found to have acute renal failure, acute nephritic syndrome, proteinuria, 50% crescents on biopsy, which were of fibrocellular and cellular type. Clinical and laboratory symptoms completely regressed after pulse methlyprednisolone, prednisolone and cyclophosphamide. During the five-year-follow-up period, renal functions remained normal, and hematuria and proteinuria were absent in urine.

MN is a pathologic condition associated with an immune complex deposition within the glomerulus, resulting in glomerular dysfunction. Primary MN accounts for only 1%–2% of children with NS. Whereas systemic disorders such as hepatitis B infection, SLE, sickle hemoglobinopathies, drugs, malignancy may more often result in secondary MN in the younger population, primary or idiopathic MN has been regarded as disease of adults.[3,4] Clinical manifestations of pediatric MN are

NS (40%–75%), microscopic hematuria (70–90%), hypertension (<%10), and in some cases renal dysfunction (<25%).[12] Understanding of the pathogenesis of MN has largely come from decades of work in the Heymann nephritis experimental rat model of MN, first described more than 50 years ago.[13] In rats, megalin is present on the podocyte foot process, a location that provided a rational explanation for the mechanism underlying the formation of the subepithelial deposits.[14] However megalin is not expressed on human podocytes, and the pathogenesis of MGN in humans is unknown, but it is believed to be an autoimmune disorder mediated by immune complexes formed *in situ*. The antibody responsible for this lesion is probably directed against an antigen within the kidney, resulting in the formation of subepithelial deposits.[2] In 2002, podocyte neutral endopeptidase was identified as an antigenic target of circulating antibodies in alloimmune neonatal nephropathy, and in 2009, podocyte PLA2R was reported as an antigenic target in autoimmune adult MN.[15] Anti-PLA2R antibody titers have been shown to be an excellent marker of disease activity and correlated with proteinuria being elevated in a relapsed state and absent in a state of remission.[16] Anti-PLA2R antibody titers could not be measured and PLA2R antigen staining in biopsy could not be performed in our patient during morbidity. Immunsuppressive therapy is often necessary for primary disease. Alkylating agents in combination with corticosteroids, as well as calcineurin inhibitors are the first-line agents for primary MN.

Because of the different pathophysiologies between MN and RPGN, crescent formation is rarely seen in patients with idiopathic MN. Rapid deterioration in renal function is a rare complication of MN, except when accompanied by renal vein thrombosis, malignant hypertension or other underlying disease, including lupus nephritis, ANCA associated GN and, anti-glomerular basement membrane antibody-mediated glomerulonephritis.[7] RPGN is a rare case encountered in primary MN in adults.[8-10]

In conclusion, we have reported a case of MN which developed during long-term follow-up of previously treated RPGN. Our case may be the first to demonstrate primary MN and crescentic glomerulonephritis in children. When the first pathology sample was re-examined retrospectively, no findings indicating membranous or other glomerulonephritises except for crescents were detected. In the 5th year of remission, the patient developed proteinuria and underwent a second renal biopsy which suggested subepitelial IgG deposits and MN. Therefore, we emphasize that patients who have been diagnosed with primer RPGN and have improved and do not have an illness in etiology should not be dropped out of follow-up. We thought that co-occurrence of these two diseases may also be a coincidence.

Conflict of interest: None declared.

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