CASE REPORT
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Membranous Nephropathy in a 13-Year-Old Boy with Common Variable Immunodeficiency

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Various forms of hypogammaglobulinemia can occur in patients with autoimmune diseases and vice versa. We report a 13-yr-old boy with membranous nephropathy and common variable immunodeficiency. He presented with the nephrotic syndrome, pneumonia with bronchiectasis, and profound hypogammaglobulinemia. Renal biopsy showed diffusely thickened glomerular capillary walls with 'spikes' suggesting a membranous nephropathy. Secondary causes were ruled out by laboratory studies; however, heavy proteinuria persisted with steroid therapy. Cyclosporine and intravenous immunoglobulin were added, and the patient was discharged with decreased proteinuria. Hypogammaglobulinemia may have a deleterious impact on the immune dysregulation in some patients with membranous nephropathy.

Key Words: Autoimmunity; Common Variable Immunodeficiency; Immunoglobulins; Membranous Glomerulonephritis

INTRODUCTION

It is becoming widely accepted that membranous nephropathy (MN) is an organ-specific autoimmune glomerular disease (1). Various forms of hypogammaglobulinemia including common variable immunodeficiency (CVID) can occur in patients with autoimmune diseases whereas persistent antigen stimulation due to defective immune system is the leading cause of the development of autoimmunity in patients with primary immunodeficiency states (2). Here, we describe a rare case of CVID and MN presenting as nephrotic syndrome, pneumonia with bronchiectasis, and hypogammaglobulinemia.

CASE DESCRIPTION

A 13-yr old boy was admitted with generalized edema over the past two months on July 24, 2009. During infancy, he had been treated intermittently for bronchiolitis and otitis media. On presentation, he had mild respiratory symptoms, and had taken no medication. The physical examination revealed abdominal distension and pretibial pitting edema. The chest radiographs showed an ill-defined opacity in the right middle and lower lobes suggesting pneumonia. The results of the laboratory tests revealed: a leukocyte count, $13.8 \times 10^3/\mu L$; hemoglobin, 12.0 mg/dL; platelets, $297 \times 10^3/\mu L$; c-reactive protein, 5.54 mg/L; blood urea nitrogen, 14.5 mg/dL; creatinine, 0.39 mg/dL; serum total protein, 3.6 g/dL; serum albumin, 1.8 g/dL; total cholesterol, 396 mg/dL; 24-hr urine protein, 7,700 mg/day; and the urinalysis showed no abnormal findings except proteinuria. The C3, C4, CH50, C1q, rheumatoid factor, anti-neutrophil antibody, anti-dsDNA antibody, anti-glomerular basement membrane antibody, and anti-neutrophil cytoplasmic antibody were all normal. Hepatitis B and C virus antigens were negative, and the antibody titer for mycoplasma was not increased. Immunological studies showed: IgG, 138 mg/dL; IgA, < 5 mg/dL; IgM, 100 mg/dL; IgD, < 0.41 mg/dL; IgE, 2.4×10^{-4} mg/dL. The IgG subclasses were markedly decreased (IgG1 238 mg/dL, IgG2 19.2 mg/dL, IgG3 14.3 mg/dL, IgG4 1.12 mg/dL). The CD3-, CD4- and CD8-positive T cell counts showed no specific findings. The abdominal ultrasound was non-specific. A diagnosis of nephrotic syndrome and CVID was made and oral deflazacort was started. The renal biopsy showed diffusely thickened glomerular capillary walls with short 'spikes' on silver staining suggesting MN. IgG, IgM, C3, C4, C1q, Kappa and Lambda deposits were stained on immunofluorescence. On electron microscopy, the glomerular basement membranes were diffusely thickened with subepithelial electron dense deposits and perpendicular extension of a basement membrane substance to form short "spikes" (Stage II). Mesangial dense deposits were occasionally observed (Fig. 1). Methylprednisolone pulse therapy was administered from the 15th hospital day. Cyclosporine was added after seven steroid pulses because the hypoalbuminemia and heavy proteinuria persisted (5,600 mg/day). The chest CT showed bronchiectasis, pneumonia and atelectasis in right middle lobe and left lower

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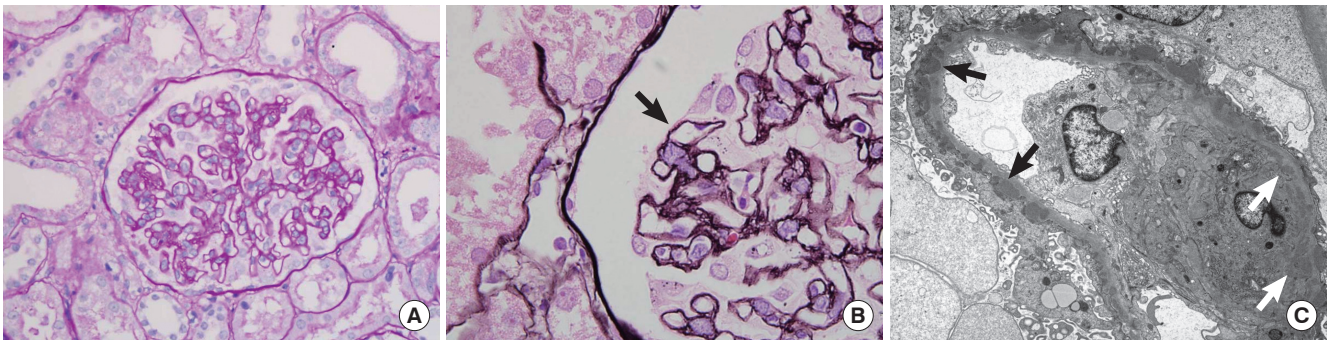

Fig. 1. Renal biopsy findings. (**A**) Capillary walls are diffusely thickened in the absence of significant glomerular hypercellularity (periodic acid-Schiff, original magnification × 100). (**B**) Short spikes along the outer aspect of the glomerular basement membrane (arrow) (Jones' silver stain, original magnification × 400). (**C**) Electron micrograph showing multiple electron-dense deposits along the subepithelal side of the glomerular basement membrane (black arrows) and mesangial area (white arrows) (orginal magnification × 3,500).

lobe. The cultures for fungus, tuberculosis and pneumocystis carinii were all negative. On the 29th hospital day, intravenous immunoglobulin (IVIG) was administered due to the persistent hypogammaglobulinemia, pneumonia and severe proteinuria. The IgG increased to low normal values. The IgM was normal. The IgA deficiency was unchanged. On the 39th hospital day, the patient was discharged with decreased proteinuria (825 mg/day) with normal renal function.

DISCUSSION

The patient reported here initially had profound hypogammaglobulinemia as a form of CVID and MN presenting as nephrotic syndrome. The serum IgG increased after IVIG therapy; however, the IgA deficiency persisted. Heavy proteinuria also decreased after adding cyclosporine with IVIG followed by steroid treatment.

CVID is characterized by low serum levels of IgG, IgA and/or IgM, and normal or decreased B cell numbers, which results in recurrent infections mostly of the respiratory and gastrointestinal tracts. CVID may develop from IgA deficiency and vice versa (3, 4). IgA deficiency is occasionally connected with IgG subclass deficiency that may cause bacterial infections and could signal the onset of CVID. Interestingly, there have been several case reports on MN combined with selective IgA deficiency (5).

Recent studies have substantially strengthened the idea that MN is an autoimmune disease of the kidney. Since MN has been reported as an IgG4 mediated disease, autoantibodies of the IgG4 subclass to at least three podocyte membrane proteins including phospholipase A_2 receptor, aldose reductase, and manganese superoxide dismutase have been detected (6). Autoimmune diseases affect about 20% of CVID patients and are frequently the first manifestation of immune deficiency. Renal involvement is rare in CVID, despite common involvement of other organ systems. Interstitial nephritis, granulomas, immune complex glomerulonephritis or membranoproliferative glomerulonephritis have been described in patients with CVID (7, 8). To our knowledge, this is the first case report of a child who had combined findings of MN and CVID.

Most cases of MN are idiopathic; however, a number of secondary processes can also cause MN that is clinically and histologically similar to idiopathic MN. Generally, characteristics of secondary forms of MN include mesangial proliferative features, full-house pattern of immunoglobulin staining including staining for C1q, glomerular deposits predominantly containing immunoglobulin other than IgG4, and electron-dense deposits at the subendothelial location of the capillary walls and mesangium. In our case, the findings of staining for C1q and mesangial electron-dense deposits showed the inability to exclude secondary MN completely. Although secondary causes of MN were ruled out by laboratory studies in our case, inflammatory activation associated with immune dysregulation might contribute to the development and progression of MN primarily or secondarily. Similar to our patient, the case of a 23-yr-old man with X-linked agammaglobulinemia who developed MN has been reported recently (9).

There are no specific treatment guidelines for MN. Although several immunosuppressive drugs often are employed to manage individual patients, the treatment of idiopathic MN remains empiric. Our patient had persistent heavy proteinuria despite steroid pulse therapy. Cyclosporine therapy with IVIG appeared to be effective during the clinical course. Cyclosporine treatment has been achieved remission in MN patients with steroid-resistant nephrotic proteinuria (10). IVIG has also been utilized in several types of glomerulonephritis in the case of being resistant to conventional therapy, but there is no controlled study supporting its use in MN. However, remission of nephrotic syndrome has been reported in some patients (11). In our patient, IVIG contributed to control the clinical course of MN as well as CVID and pneumonia. Long term follow-up for the progression of MN and re-appearance of severe hypogammaglobulinemia should be done.

In conclusion, the association between CVID and MN was suggested by several findings. A failure to eliminate microbial

antigens in our patient with hypogammaglobulinemia may lead to chronic immunological activation and the development of autoimmunity with MN. Because various forms of hypogammaglobulinemia can also occur in patients with autoimmune diseases, the question of which came first, the chicken or the egg remains unclear. Hypogammaglobulinemia may be an important, but largely unrecognized factor, in the pathogenesis and progression of MN in some patients.

REFERENCES

1. Beck LH Jr, Salant DJ. *Membranous nephropathy: recent travels and new roads ahead. Kidney Int 2010; 77: 765-70.*
2. Fernández-Castro M, Mellor-Pita S, Citores MJ, Muñoz P, Tutor-Ureta P, Silva L, Vargas JA, Yebra-Bango M, Andreu JL. *Common variable immunodeficiency in systemic lupus erythematosus. Semin Arthritis Rheum 2007; 36: 238-45.*
3. Seligmann M, Aucouturier P, Danon F, Preud'Homme JL. *Changes in serum immunoglobulin patterns in adults with common variable immunodeficiency. Clin Exp Immunol 1991; 84: 23-7.*
4. Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, Hammarstrom L. *Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol 2008; 147: 87-92.*
5. Vanacker A, Van Dorpe J, Maes B. *Membranous glomerulopathy in a patient with selective IgA deficiency: is there a link? Acta Clin Belg 2011; 66: 228-30.*
6. Makker SP, Tramontano A. *Idiopathic membranous nephropathy: an autoimmune disease. Semin Nephrol 2011; 31: 333-40.*
7. Ohkubo H, Nagai M, Hojo S, Daikuhara H, Takahara J, Itoh T, Harada A. *Membranoproliferative glomerulonephritis in a patient with common variable hypogammaglobulinemia. J Rheumatol 1993; 20: 918-9.*
8. Hermaszewski RA, Webster AD. *Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med 1993; 86: 31-42.*
9. Endo LM, Giannobile JV, Dobbs AK, Foote JB, Szymanska E, Warnock DG, Cook WJ, Conley ME, Schroeder HW. *Membranous glomerulopathy in an adult patient with X-linked agammaglobulinemia receiving intravenous gammaglobulin. J Investig Allergol Clin Immunol 2011; 21: 405-9.*
10. Frassinetti Castelo Branco Camurça Fernandes P, Bezerra Da Silva G Jr, De Sousa Barros FA, Costa Oliveira CM, Kubrusly M, Evangelista JB Jr. *Treatment of steroid-resistant nephrotic syndrome with cyclosporine: study of 17 cases and a literature review. J Nephrol 2005; 18: 711-20.*
11. Quaglia M, Stratta P. *Idiopathic membranous nephropathy: management strategies. Drugs 2009; 69: 1303-17.*

http://dx.doi.org/10.3346/jkms.2012.27.11.1436