Combined Primary IgA nephropathy and Membranous Glomerulonephritis in a Child

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Introduction

IgA nephropathy and membranous glomerulonephritis are common primary glomerular diseases, characterized by circulating IgA immune deposits in the mesangium and in situ immune complex deposits in the subepithelial basement membrane, respectively. It is rare that two distinct primary glomerular diseases with different phathogenesis occur in one person at the same time. We report a case of coexistent primary IgA nephropathy and membranous glomerulonephritis developed in a child with nephrotic syndrome.

Case

The patient was a 7-year-old boy who developed generalized edema in the middle of October, 1997. Proteinuria and gross hematuria were detected at another clinic. He visited our hospital for further evaluation on November 11, 1997 because symptoms persisted. Physical examination revealed BW 26kg, a blood pressure of 122/64 mmHg, periorbital swelling, distended abdomen, and pretibial pitting edema at both lower extremities.

On admission, laboratory studies were hematocrit 41.4%, hemoglobin 14.1 g/dL, red cell count 4,960,000/mm^3, whitecell count 19,800/mm^3, platelet count 397,000/mm^3, BUN 10 mg/dL, creatinine 0.4 mg/dL, total serum protein 4.43 g/dL, albumin 2.73 g/dL, cholesterol 429 mg/dL, triglyceride 728 mg/dL, serum IgA 85 mg/dL, C3 68.8 mg/dL, C4 13.4 mg/dL, antinuclear antibody determination(-), antineutrophil-cytoplasm antibody(-), RF(-), HBsAg/HBsAb(-/-), anti HCV(-). Urinalysis showed 3+ protein, many red blood cells/HPF and negative test for glucose. In 24-hour urine study, protein was 9.18 g/day and creatinine 5,100 mg/day. The creatinine clearence was 66.67 ml/min. Abdominal sonogram findings were within normal limit.

Pathologic findings

On the light microscopy, there were nine glomeruli, which had variable expansion of mesangial regions with mild to severe increase in cellulrarity. On Massion-Trichrome stain, small fuchsinophilic deposits were in subepithelial locations as well as in mesangial regions.

Most of capillary walls and basement membranes were thin and single contoured but some were double countoured(Fig 1).

On the immunofluorescence microscopy, IgA(3+),

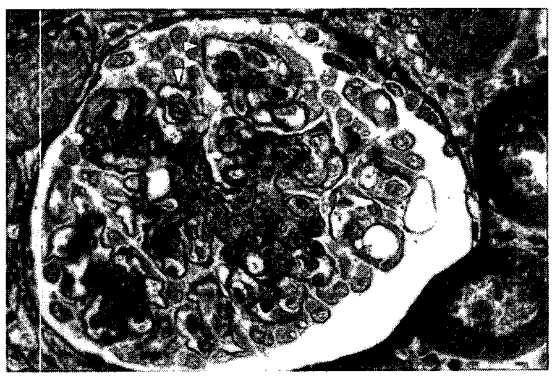

Fig 1. The glomerulus shows an increase in cellularity of mesangial regions with thin and single contoured basement membranes. There are small granular deposits along the basement membranes(white arrowhead). Masson-Trichrome stain × 400

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C3(1+), kappa immunoglobulin light chain(2+) were in mesangial regions as well as in capillary walls, in a coarsely granular pattern and diffusely distributed. IgG(+) were in capillary walls, in a finely granular and pseudolinear pattern(Fig 2, A&B).

On the electron microscopy, there were 4 glomeruli, which had small electron dense deposits in the subepithelial side of basement membrane in some capillary loops. Mesangial electron dense deposits were found in a small amount. The basement membranes were irregulary thickened and thinned in focal. In the thickened area electron lucency or fluffy materials were present(Fig 3).

Clinical course and treatment

This child was treated with oral prednisolone(40mg/day) for 2 weeks. But proteinuria and hematuria were persistent. So solumedrol pulse therapy(390mg/day for 5days) with captopril(15mg/day) was attempted. And oral prednisolone and cyclophophamide(50mg/day) were medicated in out-patient-department. After this treatment, general condition was improved gradually. Proteinuria was reduced to nonnephrotic range(487.5mg/day) and hematuria(RBC 0-1/HPF) was disappeared also.

Discussion

IgA nephropathy and membranous glomerulonephritis are relatively common in primary glomerular lesions but, their frequency in the general population is low. So it is rare that both of these glomerular diseases develop simultaneously in a person. Since Doi *et al* [1] reported 3 cases of combined IgA nephropathy and membranous glomerulonephritis, about 20 cases in adult were reported and only one case was reported in children[2]. Some of these cases may be linked pathogenetically to hepatitis B infection[3], autoimmune disease[4], psoriasis[5], or renal transplantation[6] but, most appear to be idiopathic[7-10].

IgA nephropathy was first described by Berger and Hinglais in 1968. The occurrence rate of IgA nephropathy is different geographically, and it is known that this rate is high in east Asia, such as Korea or Japan[11]. Clinical symptoms are episodic gross hematuria

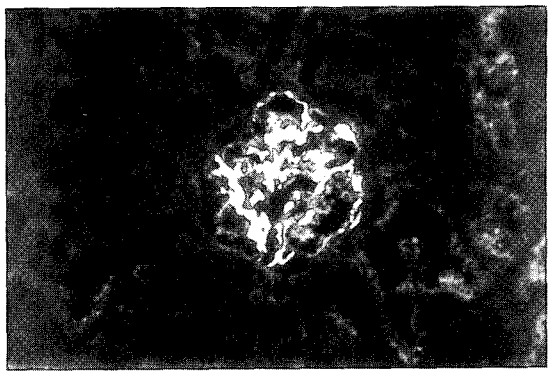

Fig 2(A). Immunofluorescence study shows IgA deposits in mesangial regions and capillary walls in a coarsely granular pattern, and diffuse segmental distribution, respectively. ×100

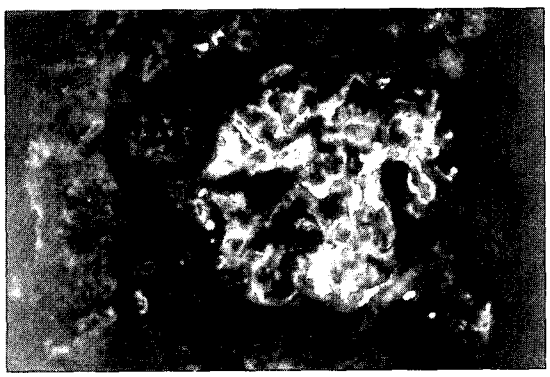

Fig 2(B). IgG is stained along capillary walls in granular pattern as well as in mesangial regions of a small amount. ×200

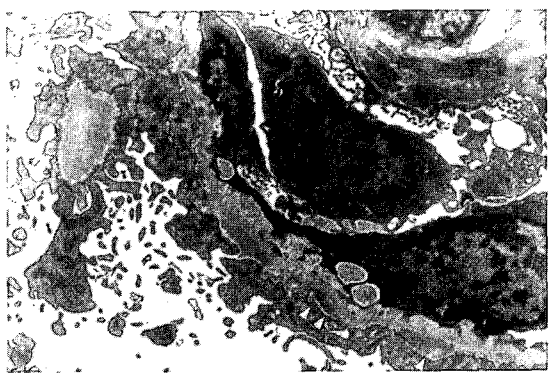

Fig 3. Electron microscopy reveals small electron dense deposits in the subepithelial side of basement membrane(white arrowhead). ×6,000

or persistent microscopic hematuria with variable proteinuria. It is pathologically charactersized by IgA deposits predominantly in glomerular mesangium. IgG and C3 deposits are also found, but the location of these deposits are identical with IgA deposits. Membranous glomerulonephritis is a common cause of nephrotic syndrome in adults but, rare in children. It is characterized by generalized IgG immune deposits on the epithelial side of the glomerular basement membrane.

The pathological process of two glomerular diseases is still unclear but, current theories propose that IgA nephropathy is caused by immune complex deposition from the circulation, whereas membranous glomerulonephritis is produced by capillary wall *in situ* immune complex formation.

The clear understanding of the mechanisms that morphologically and histologically different glomerulopathies developed in one person is not attained. But reporting of low frequency in general population of these two diseases and the occurrence in a single kindred of this overlap, Jennette *et al* [8] assumed that it could be the result of interrelated pathogenic mechanism. That is, first of all, if a single person is exposed to a complex disassociating antigen, it is possible that different types of immune complexes could be produced simultaneously and result in different patterns of glomerular immune complex localization. Or it could be that either IgA nephropathy or membranous glomerulonephritis is a primary event and subsequently induces the other form of glomerular disease, rather than occuring simultaneously.

In hepatitis B-induced glomerulonephritis, it was recognized that IgG-dominant subepithelial deposits contained HBeAg, whereas IgM-dominant mesangial deposits contained HBsAg[3].

Identically, an immune response to a single or complex antigenic stimulus could produce both IgA and IgG that respectively form mesangial and subepithelial deposits in combined IgA nephropathy and membranous glomerulonephritis

In a different way, glomerular inflammation caused by IgA deposits could lead to exposure or alteration of glomerular antigens stimulating IgG antibody production leading to *in situ* formation of subepithelial immune complexes. The fact that membranous glomerulonephritis frequently superimposed on a variety of other glomerular diseases[12] explains that preexisting glomerular disease may form subepithelial immune complex by a mechanism involving *in situ* production of immune complexes containing glomerular epithelial antigens released by glomerular injury.

The clinical presentation of combined IgA nephropathy and membranous glomerulonephritis are not reported systemically, but mostly, there is one of nephrotic proteinuria and microscopic hematuria. Edema and hypertension are also found in some patients but gross hematuria is rare. And most patients have normal renal function or mild renal insufficiency at presentation.

Although follow-up information is limitied, renal function is preserved in the few individuals[10]. In this case, patient had nephrotic proteinuria and gross hematuria. His renal function was within normal range.

Treatment of combined IgA nephropathy and membranous glomerulonephritis has not been presented apparently, but there was the result of reduction in edema and proteinuria after treated with prednisolone, ACE inhibitor, and diuretics in adults[9,10]. In this present case, the child was prescribed oral prednisolone every day. But proteinuria and hematuria persisted. So solumedrol pulse therapy, furosemide, and captopril were attempted. After this treatment, proteinuria was decreased to nonnephrotic range. It was not certain that the decrease of proteinuria was due to prednisolone or ACE inhibitor.

Although proteinuria was persistent in our patient, the level was less than the nephrotic range and creatinine clearance was maintained normally. Therefore, it seems that the combination of these two patterns of glomerular injury may not have a poor impact on renal outcome in this patient.

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< 한 글 요 약 >

소아에서 IgA 신병증과 막성 사구체신염이 병발한 사구체신염 1례

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IgA 신병증은 사구체 중맥에 IgA가 침착하는 것이 특징적인 질환이며 막성 사구체 신염은 IgG가 사구체 기저막의 상피하에 미만성으로 침착하는 질환이다. 원발성 사구체 질환중 IgA 신병증과 막성 사구체신염은 비교적 흔한 질환이나 전체적인 빈도는 낮은 편으로, 한 환자의 사구체에서 두 질환이 동시에 발생하는 경우는 매우 드물다. IgA 신병증과 막성 사구체신염의 중복 신염은 Doi 등이 1983년 원발성 신질환으로서 처음 보고한 이래, 성인에서 20여례가 보고되었다. 저자들은 신증후군이 발생한 환아에서 신생검을 시행한 결과 원발성 신질환으로서 IgA 신병증과 막성 사구체신염의 소견이 동시에 보이는 중복신염의 드문 예를 경험하였기에 보고하는 바이다.

환아는 7세된 남아로 내원 한달 전부터 발생한 전신부종을 주소로 내원하였다. 가족력과 과거력상 특이 소견 없었으며, 내원시 이학적 소견상 전신적인 허약감과 안와부종, 복부팽만, 하지의 함요부종이 관찰되었고, 검사소견에서는 WBC 19,800/mm^3, Hb 14.1g/dL, Platelet 397,000/mm^3, BUN/Cr 10/0.4mg/dL, protein/albumin 4.43/2.73g/dL, cholesterol 429mg/dL, IgA 85mg/dL, C_3 68.8mg/dL, C_4 13.4mg/dL, ANA(-), ANCA(-), RF(-), HBsAg/Ab(-/-)이었다. 뇨검사에서는 RBC many/HPF, WBC 2-3/HPF, protein ≥ 300mg/dL 였으며, 24시간 소변 검사상 protein 9.18g/day, Ccr 66.67ml/min의 소견을 보였다. 신생검을 시행한 결과 광학현미경상에서 띄띄 사구체의 분절성 경화와 중맥역의 증식이 관찰되었고, 면역형광현미경검사에서는 IgA(3+)가 과립상으로 미만성 분포를 보이며 중맥역에 침착되어 있고, 미세한 과립상과 위선의 양상으로 IgG(1+)가 모세혈관벽에 침착되어 있었으며, 전자현미경 소견상 중맥역과 모세혈관 기저막 상피하에 소량의 전자 고밀도 침착이 함께 관찰되었다. 환아는 prednisolone을 경구 투여 받았으나 단백뇨와 혈뇨가 지속되어 solumedrol pulse therapy, captopril과 cyclophophamide로 치료 받은 후, 전신 상태 호전되고, 혈뇨가 사라졌으며, 24시간 소변 검사상 단백뇨가 487.5mg/day로 감소하여 외래에서 추적 관찰 중이다.