

## **Membranous glomerulonephropathy associated with hepatitis B in childhood. A case report.**

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### **ABSTRACT**

A 8-year-old boy developed nephrotic syndrome with steroid dependent for 3 months. He was a chronic carrier of hepatitis B virus surface antigen (HBs Ag) and hepatitis B virus e antigen (HBe Ag). Raised liver enzymes were also noted. Renal biopsy showed membranous glomerulonephropathy (MGN) stage 2. A short course of high dosage prednisolone was given to patient initially and discontinued slowly after diagnosis of hepatitis B virus (HBV) associated with MGN was established. The patient showed complete remission of nephrotic syndrome but his serum remained positive for HBs Ag, HBe Ag during a 3-year follow up period. A conservative approach should be considered, since the majority of HBV-associated MGN remits spontaneously.

**Key words:** membranous glomerulonephropathy, hepatitis B virus

The association between chronic hepatitis B virus (HBV) infection, characterized by persistent hepatitis B surface antigenemia, and renal disease was first reported in 1971<sup>1</sup>. Since then various morphological patterns of HBV-related renal disease, including membranous glomerulonephropathy (MGN), mesangiocapillary glomerulonephritis, and mesangial proliferative glomerulonephritis, have been described<sup>2,3</sup>. Among them, MGN is the most distinct histopathologic features. The largest series of

patients have come from Southeast Asia<sup>4,5</sup>, consistent with the higher prevalence of hepatitis B surface antigen (HBs Ag) carrier state. The exact pathogenesis of HBV associated MGN is unknown and the clinical course is variable<sup>6</sup>. At present there is no optimal and accepted treatment for HBV-associated MGN in children.

We described here the characteristics and clinical course of a 8-year-old boy who had persistent hepatitis B surface antigenemia and HBV-related MGN.

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## Case report

A 8-year-old boy was referred to Thammasat Hospital on July 15, 1997 due to nephrotic syndrome with steroid dependent. His medical history revealed that he developed generalized edema 3 months prior to admission. He was diagnosed as nephrotic syndrome by the physician at Rayong Hospital and was treated with prednisolone 6 tablets in the morning for 2 weeks. The edema subsided but proteinuria still persisted. A prolonged course of prednisolone had been given without any improvement.

He was the first-born of two children. His previous medical history was not remarkable and there was no history of renal disease in his family.

The physical examination on admission revealed a young boy with a cushingoid facial appearance, no puffy eyelids. His body weight was 41 kg (> 95<sup>th</sup> percentile), height 130 cm (95<sup>th</sup> percentile). His vital signs were body temperature 37°C, respiratory rate 24/min, pulse rate 84/min and blood pressure 130/100 mmHg (> 95<sup>th</sup> percentile). He was not icteric and no hepatosplenomegaly. The abdomen showed no ascites but mild pitting edema was noted at pretibial area.

## Investigations

A complete blood count revealed a hematocrit of 44%, a WBC of 19,400/mm<sup>3</sup> with PMN 68%, lymphocytes 21%, monocytes 11%, and a platelet count of 107,000/mm<sup>3</sup>. A dipstick urinalysis showed 2+ of protein. The urine specific gravity was 1.022, pH 5.0,

WBC 0-1/HPF and RBC 5-10/HPF were detected on microscopic examination. Blood urea nitrogen was 16.4 mg/dL, serum creatinine 0.6 mg/dL, Na 140 mEq/L, K 4.1 mEq/L, CO<sub>2</sub> 27 mEq/L, Cl 106 mEq/L. Total serum protein was 7.1 g/dL, serum albumin 4.2 g/dL, serum cholesterol 355 mg/dL and triglyceride 657 mg/dL.

The 24-hour urine volume was 1,400 ml (1.4 ml/kg/hr), urinary protein 99 mg/m<sup>2</sup>/hr, and creatinine clearance 103 ml/min/1.73 m<sup>2</sup>, FENa 0.4% (normal < 1%), FE Ca 0.2% (normal < 0.5%), FE PO<sub>4</sub> 17.9% (normal < 10%). An ultrasound examination of the urinary tract was normal.

A percutaneous kidney biopsy was performed. Light microscopic examination of the renal cortical labyrinth tissue revealed 65 glomeruli. One showed small segmental sclerosis and another showed small cellular crescent. Some glomeruli showed mild segmental widening of the mesangium due to increasing of the cells and matrix. Leucocytic infiltration was noted occasionally. The capillary wall was uniformly thickened (Fig 1,2) with numerous small regular fuchsinophilic deposits in the subepithelium and spike formation (Fig 3). Small foci of atrophic changes of tubules and mild degree of interstitial fibrosis were noted (Fig 4). The immunoperoxidase study showed diffuse global granular staining of Ig G (3+), Ig A (2+), Ig M (4+), C3 (3+) and fibrinogen (4+) mainly along the peripheral loops with lesser amount in the mesangium (Fig 5 A-D). The staining for HBs Ag in renal tissue

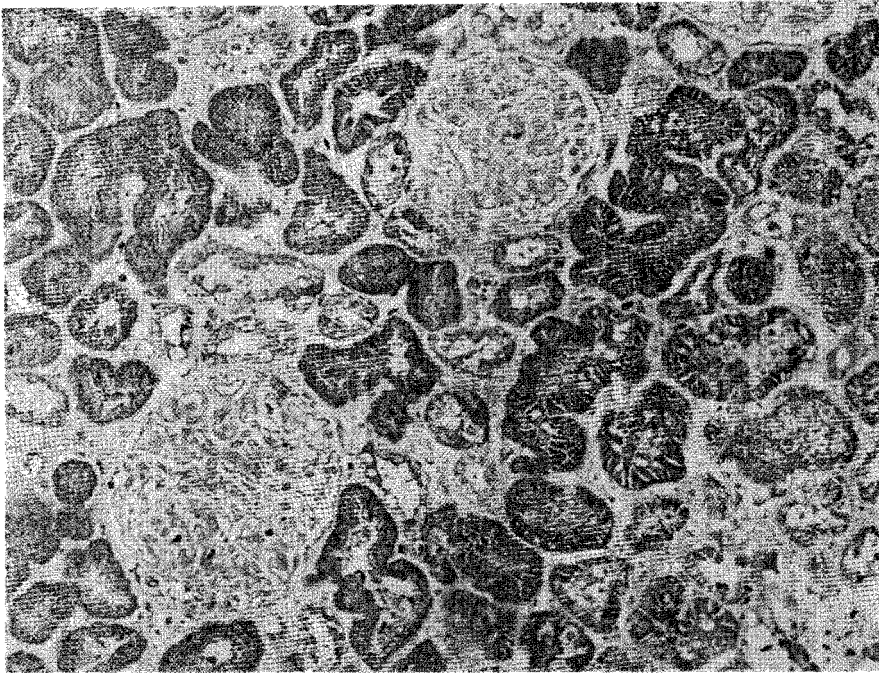


Fig 1 Light microscopic picture of two glomeruli showing uniform thickening of the capillary wall. H&E x 100

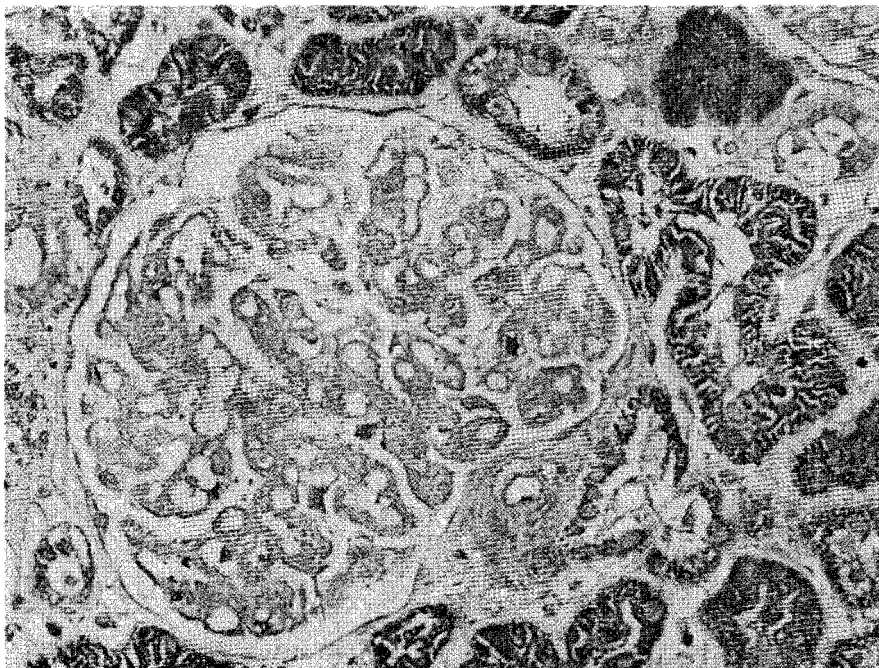
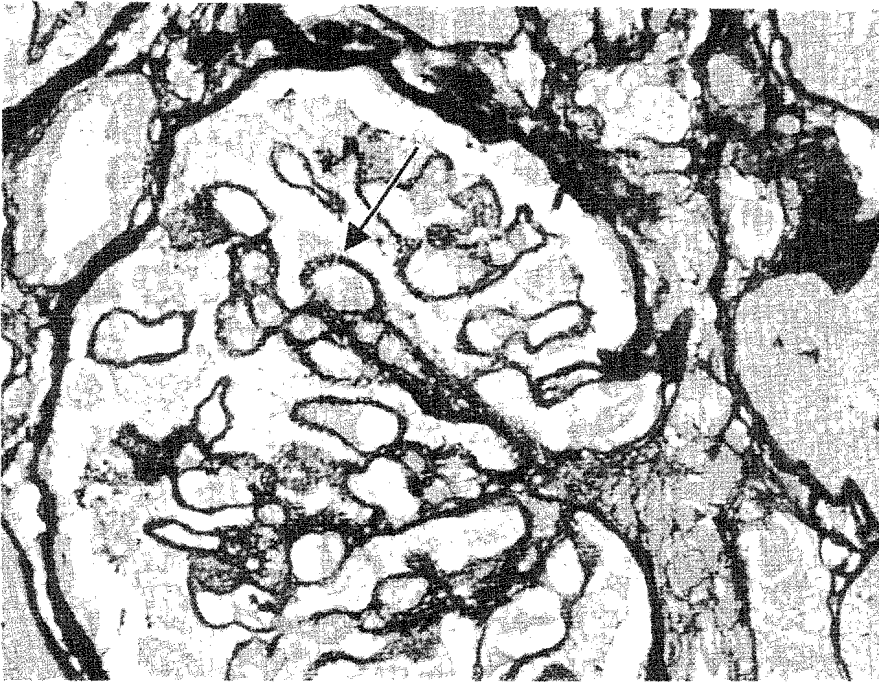
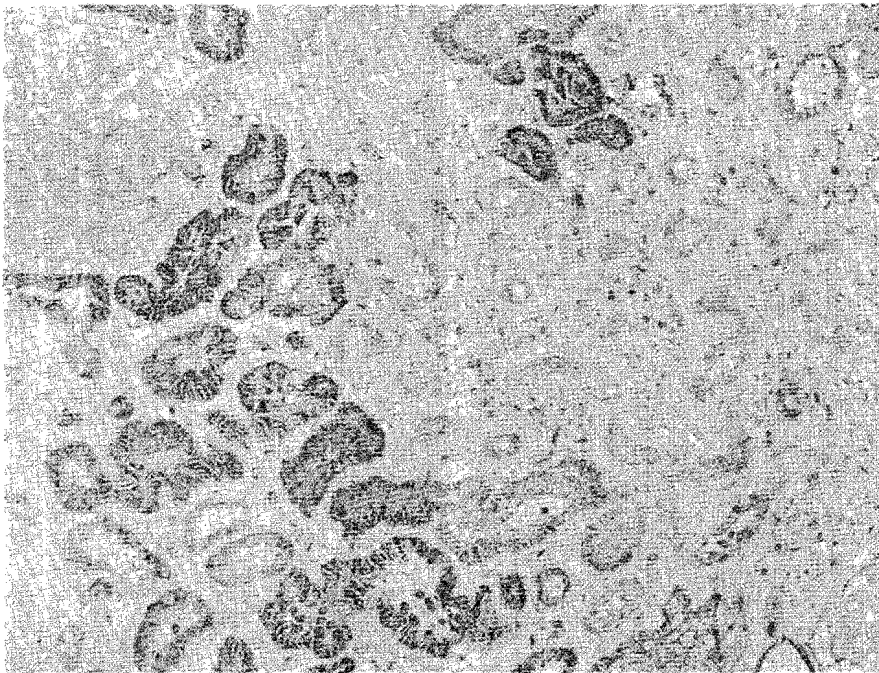


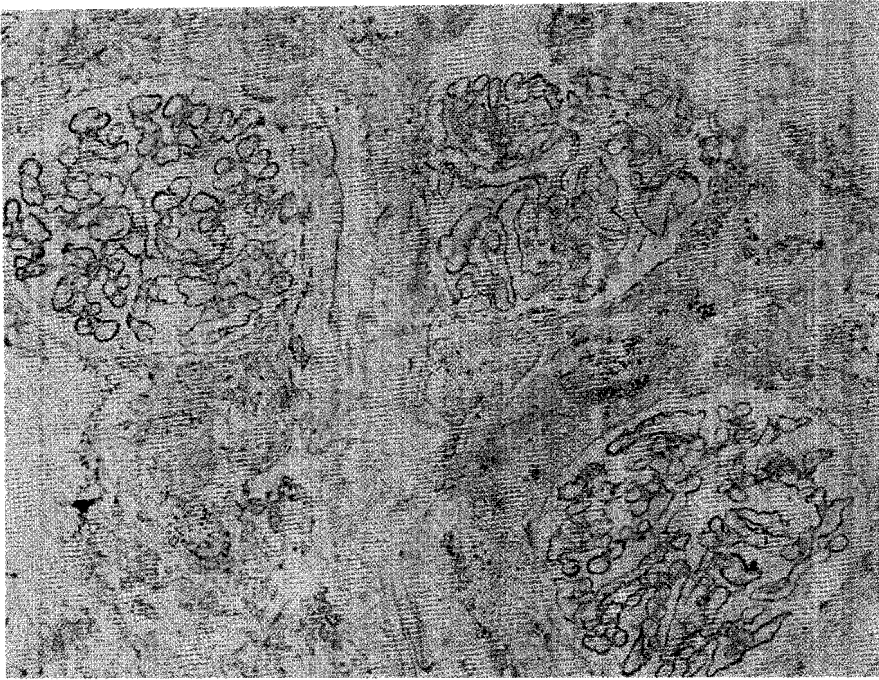
Fig 2 Higher power of Fig 1. Showing marked thickening of the capillary wall regularly. H&E x 200



**Fig 3** High magnification of one glomerulus showing diffuse spike formation along the thickened capillary wall (arrow). PASM x 400

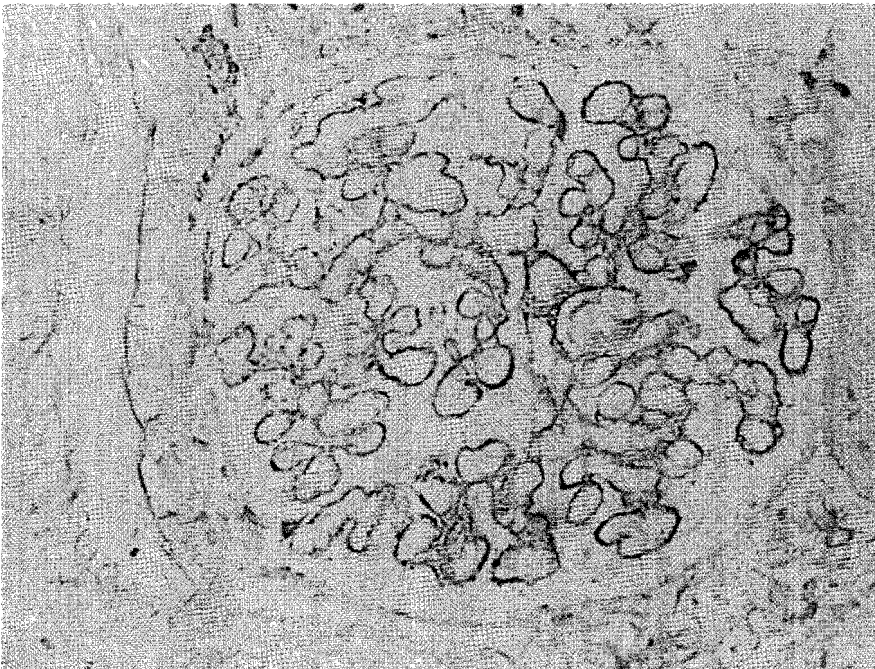


**Fig 4** Some area of the cortical labyrinth show tubular atrophy and interstitial fibrosis. H&E x 100



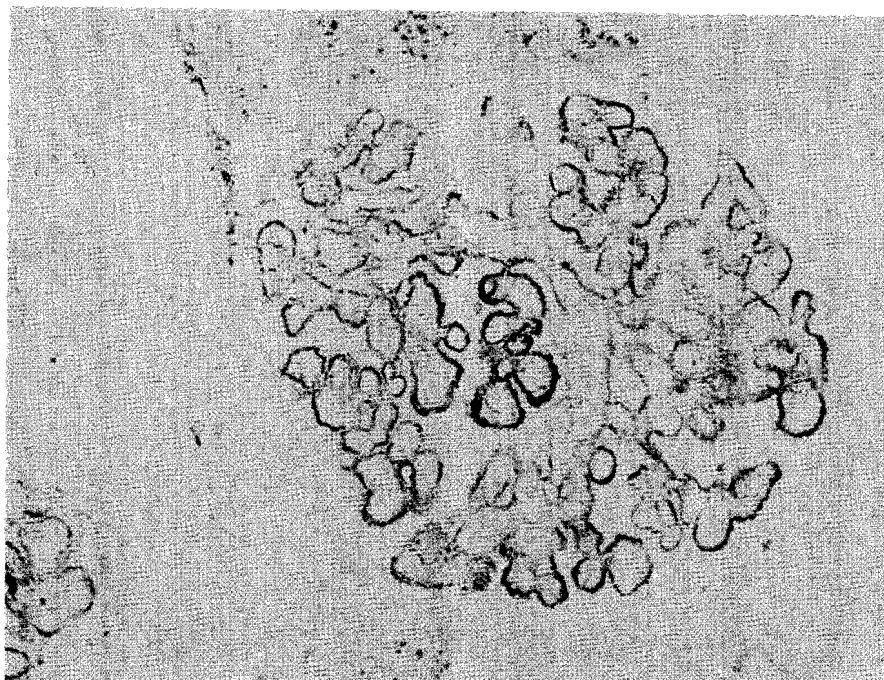
**Fig 5 Immunoperoxidase staining showing diffuse global granular immunopositivity mainly along the capillary wall.**

**A lg G x 100**

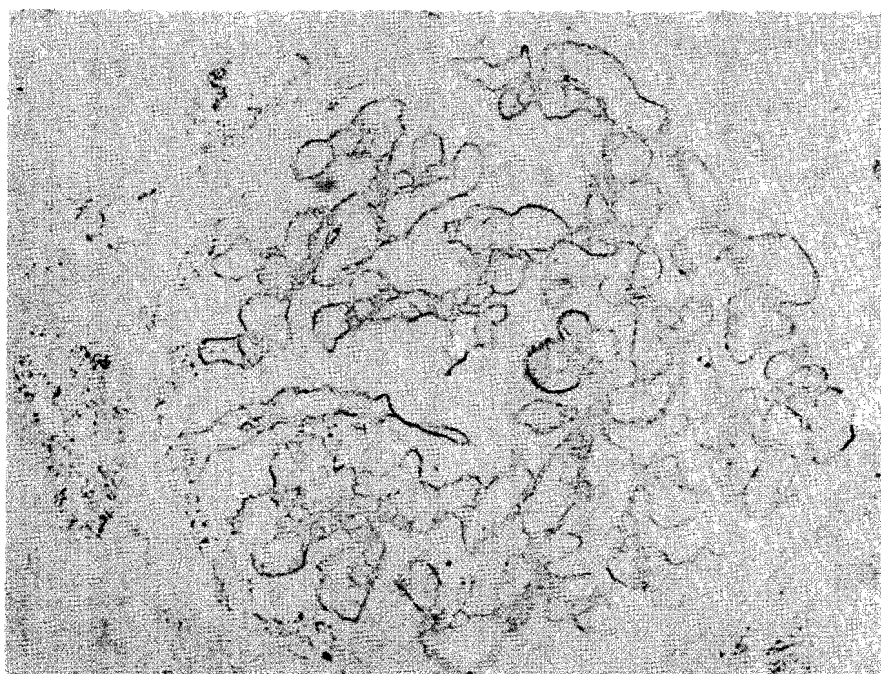


**B lg G x 200**





C Ig M x 200

D C<sub>3</sub> x 200

yielded negative result.

The patient was diagnosed as membranous glomerulonephropathy (MGN) stage 2. Further investigations had been performed in order to detect the etiology of MGN. VDRL, LE-cell, antinuclear antibodies anti-DNA and Coomb's test were all negative results. Serum  $C_3$  level was 2,200 ug/ml (normal 1,200-1,500 ug/ml). HBs Ag, hepatitis Be antigen (HBe Ag) and hepatitis B surface antibody (anti-HBs) were measured by enzyme linked immunosorbant assay (ELISA). The results showed HBs Ag-positive, HBe Ag-positive and anti-HBs-negative but HBs Ag and anti-HBs in his mother showed negative results. The liver function test revealed a total bilirubin of 0.26 mg/dL, direct bilirubin 0.04 mg/dL, alanine aminotransferase (ALT) 105 units/L (normal 5-45 units/L), aspartate aminotransferase (AST) 71 units/L (normal 15-55 units/L), alkaline phosphatase 130 units/L (normal 145-420 units/L).

He was given a high dosage of prednisolone (60 mg/m<sup>2</sup>/day) for induction of remission. Proteinuria resolved after starting the steroid therapy for 10 days. The prednisolone was gradually reduced and discontinued after a 4-month course of treatment. Hypertension was controlled with ACE-inhibitor (Enalapril).

During the follow up for 3 years, the patient had a complete remission of the nephrotic syndrome. The most recent investigations revealed a BUN of 8.4 mg/dL, serum creatinine 0.6 mg/dL, serum albumin 4.2 g/dL, serum cholesterol 168 mg/dL.

Test for HBV antigens and antibodies were performed each year during follow up. The patient was persistently seropositive for HBs Ag and HBe Ag, but no seroconversion to anti HBs. Liver function test was also done on repeated testing. The results showed slightly decreased level of ALT and AST (47 and 45 units/L, respectively).

## Discussion

The pathology of MGN associated with HBV is similar to that of idiopathic MGN. The two conditions may be differentiated on the basis of demonstration of HBe Ag in the glomerular immune deposits by immunofluorescence microscopy<sup>4-12</sup> However, in our patient, the renal tissues had not been tested for HBe Ag, but the direct causal relationship between HBV infection and MGN was highly probable according to the following features<sup>13</sup> : young child, presence of positive HBe Ag, raised liver enzymes, renal histologic MGN stage II with small numerous regular fuchsinophilic deposits in the subepithelium on light microscopy and a benign clinical course. Other causes of membranous glomerulonephropathy such as SLE, syphilis had been excluded.

Children with MGN associated with HBV usually present with nephrotic syndrome<sup>4,5,14</sup>. Microscopic hematuria is common and even macroscopic hematuria has occasionally been reported<sup>15</sup>. Age at onset has varied from 2-16 years with boys predominate. Our patient had onset of edema in early childhood and the urinalyses revealed

microscopic hematuria and nephrotic range proteinuria. Laboratory tests on serum for a profile of hepatitis B antigen and antibodies show a positive result for HBs in all patient, usually a negative result of HBs antibody, and a positive result for HBe Ag in more than 90% of patients<sup>4,5</sup>. Serum levels of complement components C<sub>3</sub> and C<sub>4</sub> are usually low at onset, but they may return to normal at sometime during the course of disease<sup>5</sup>. Serum levels of liver transaminase enzymes may be elevated on presentation, and in some cases persist chronically<sup>4</sup>. The absence of evidence of HBV infection in the majority of mothers tested supports the conclusion that MGN is primarily a complication of horizontally transmitted HBV infection<sup>5</sup>. Our patient was similar to that described by others.

In several reports<sup>5,16-19</sup> remission of proteinuria had been correlated to seroconversion from HBe Ag to anti HBe carriage. Our patient had persistently positive HBe Ag. However it had no relationship to clinical remission, which is similar to that described by Wong SN, et al<sup>13</sup>. Further studies are needed to assess the effect of HBe Ag on clinical status.

In most reports, the clinical course of HBV-associated MGN is a benign one. Spontaneous remission occurred within 2 years in 64%, 5 years in 83%, and 7 years in 92% of patients in one series<sup>4</sup>. However, chronic renal failure has been reported from other series<sup>14</sup>. Our patient showed complete remission after follow up for 3 years without any medication.

Corticosteroids do not appear to be beneficial<sup>4,14</sup> and probably should not be used because they may enhance viral replication in mononuclear cells<sup>19</sup>. Recently, recombinant human interferon - $\alpha$  has been reported to be beneficial<sup>20,21</sup>. Our patient was given short course of high dosage prednisolone before kidney biopsy and decreasing stepwise after diagnosis of HBV-associated MGN was made.

HBV nephropathy is an important condition in areas of high HBV prevalence. Since the majority of HBV - associated MGN remit spontaneously, it is appropriate to adopt conservative approach initially. Active treatment such as interferon should be preserved for severely symptomatic patients<sup>13,20,21</sup>

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### บทคัดย่อ

**รายงานผู้ป่วยเด็ก Membranous glomerulonephropathy สัมพันธ์กับไวรัสตับอักเสบบี**  
จักรชัย จิ๊งิรพานิช, พ.บ.\*, ไพศาล ปาริชาติกานนท์, พ.บ.\*\*

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ผู้ป่วยเด็กชายไทย อายุ 8 ปี ป่วยด้วยกลุ่มอาการเนโฟรติก ซึ่งตอบสนองต่อการรักษาแบบฟิงพาสติรอยด์ เป็นเวลา 3 เดือน การตรวจเลือดพบแอนติเจนชนิดเปลือกผิวของไวรัสตับอักเสบบี (Hepatitis B virus surface antigen, HBs Ag), แอนติเจนชนิด อี ของไวรัสตับอักเสบบี (Hepatitis B virus e antigen, HBe Ag) และมีเอนไซม์ของเซลล์ตับสูงกว่าปกติ การตรวจชิ้นเนื้อไตพบลักษณะเฉพาะของ Membranous glomerulonephropathy ขั้นที่ 2 ผู้ป่วยได้รับการรักษาด้วยเพร็ดนิโซโลนขนาดสูงในระยะแรกและค่อยลดขนาดยาจนหยุดยาได้หลังจากให้การวินิจฉัยโรค Membranous glomerulonephropathy (MGN) สัมพันธ์กับไวรัสตับอักเสบบี (Hepatitis B virus, HBV) ผู้ป่วยหายจากกลุ่มอาการเนโฟรติก แต่ยังคงตรวจพบ HBs Ag และ HBe Ag ในช่วงที่เฝ้าติดตามผู้ป่วยเป็นเวลา 3 ปี การรักษาเบื้องต้นในผู้ป่วยกลุ่มนี้ ควรเลือกวิธีการรักษาแบบประคับประคองก่อนเนื่องจากผู้ป่วยส่วนใหญ่มักมีอาการดีขึ้นเองได้