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HEPATITIS – B – ASSOCIATED GLOMERULONEPHRITIS IN CHILDREN*

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Three cases with hepatitis B virus (HBV)-related, biopsy-diagnosed glomerulopathies, one of which was membranous glomerulonephritis and the others membranoproliferative glomerulonephritis, are reported, emphasizing the clinical course. Two patients had spontaneous remission after seroconversion to anti-HBe-positivity, while the third patient was lost to follow-up. We reviewed the management of HBV-associated glomerulonephritis and concluded that immunosuppressive drugs should be avoided since spontaneous remission can be expected in these types of glomerulopathies. *Key words: hepatitis-B-associated glomerulopathies, membranous glomerulonephritis, membranoproliferative glomerulonephritis, spontaneous remission.*

The association between hepatitis B virus (HBV) infection and glomerulonephritis (GN) was first described by Combes et al.[1] in 1971, and since that time many other examples of the association have been documented[2-6]. Although the most common presentation of GN associated with HBV infection is membranous glomerulonephritis (MGN), membranoproliferative glomerulonephritis (MPGN) has also been reported[7-13].

The aim of this report was to present three children having hepatitis B surface antigenemia (HBs Ag) associated with glomerulonephritis (two cases with MPGN and one case with MGN), and to emphasize the occurrence of spontaneous remission in these disorders without any immunosuppressive therapy.

Case Reports

Case 1

A three-year-old girl was admitted to the hospital with the chief complaints of swelling of the legs, oliguria and darkness of the urine, which had lasted for a month.

Physical examination on admission revealed edema and hepatomegaly two cm below the right costal margin. Laboratory data revealed a hemoglobin (Hb) level of 11 g/dl and a white blood cell count (WBC) of 12,400/mm^3. Serum

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transaminases, creatinine, total protein and albumin levels were within normal limits. The patient had microscopic hematuria. Daily urinary protein loss was not in the nephrotic range (265 mg/m^2). Third component of complement (C3) (90 mg/dl) and C4 (37 mg/dl) were normal. Abdominal ultrasonography showed diffuse hepatomegaly. Excretory urography was normal. She was followed up for acute GN.

Two months after the initial hematuria, she developed nephrotic syndrome with a serum albumin level of 2.5 g/dl and a daily urinary protein loss of 2.8 g/m^2. Macroscopic hematuria was present. Her liver was enlarged to three cm below the costal margin, and slight splenomegaly was noticed. Liver enzymes were significantly elevated: alanine aminotransferase (SGPT) 1450 IU, aspartate aminotransferase (SGOT) 800 IU. Results of serologic studies for HBV were as follows: HBs Ag (+), antibody to HBs Ag (anti HBs) (-), antibody to hepatitis B core antigen (anti HBc) (-), hepatitis B e antigen (HBe Ag) (+), antibody to HBe Ag (anti HBe) (-). The patient was followed up for HBV-related GN with supportive therapy.

Six months after the development of nephrotic syndrome, her liver enzymes decreased, while anti HBe and anti HBc appeared in the serum. The proteinuria reached 6 g/m^2/day.

Percutaneous renal needle biopsy was performed 10 months after the initial hematuria. Light microscopy showed thickening of the glomerular capillary wall with demonstrable spikes related to the presence of subepithelial and intramembraneous deposits without increased cellularity (Figs. 1, 2). Immunofluorescence studies confirmed rather diffuse granular depositions of C3 (++), C1q (+), IgG (++), IgM (+) and fibrinogen (++) along the glomerular basement membrane zone (BMZ). The patient was diagnosed with MGN, stage III.

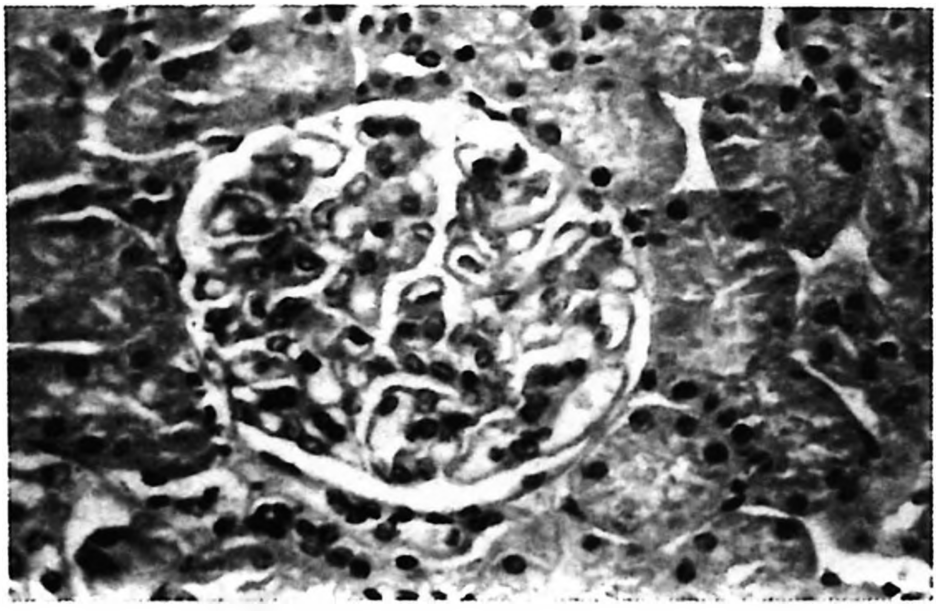

Fig. 1: A glomerulus of a case of MGN showing thickening of the basement membrane without hypercellularity, open capillary luminae (H+E stain X 200, Case 1).

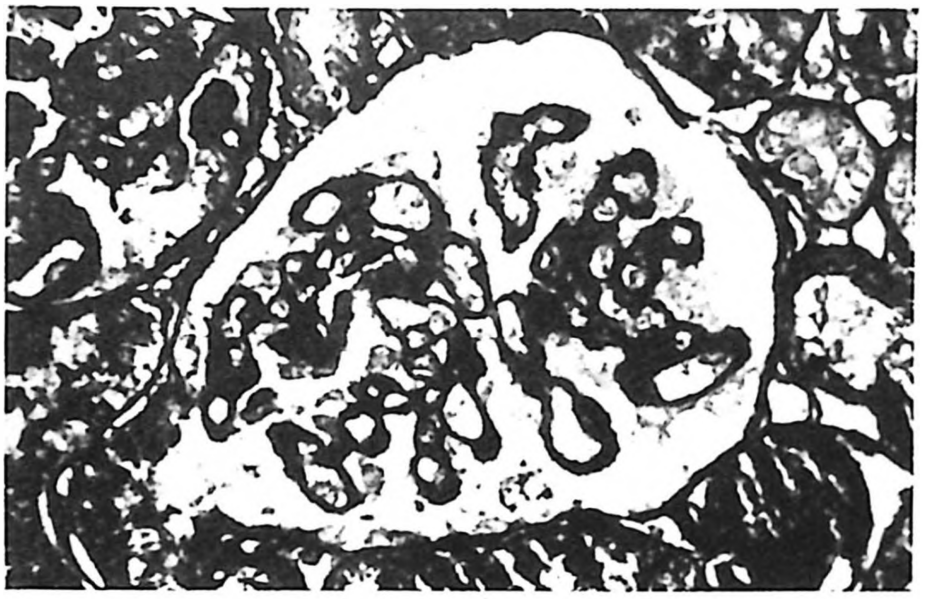

Fig. 2: A glomerulus with subepithelial and intramembranous humps in stage III membranous glomerulonephritis (X 225 Johnes Silver Stain, Case 1).

The patient received albumin infusions and low-dose diuretic therapy for seven months. A year after the renal biopsy, spontaneous remission occurred. She has not developed any relapse for 24 months.

Case 2

A 12-year-old girl was admitted to the hospital because of edema and darkness of the urine.

Physical examination revealed a well-developed child with elevated blood pressure (140/90 mm Hg) and periorbital edema. The laboratory data showed normal complete blood count, total protein and albumin levels, and elevated blood urea nitrogen and creatinine levels (30 mg/dl and 2.5 mg/dl, respectively). Liver enzymes were slightly increased. The levels of C3 (16 mg/dl) and C4 (10 mg/dl) were decreased. Antinuclear antibody (ANA) was found to be negative, while anti DNA was within normal limits (4.5 IU/ml). Serological studies for hepatitis B virus were as follows: HBs Ag (+), anti HBc IgM (-), anti HBc IgG (+), HBe Ag (+), anti-HBe (-). The mother and one sibling of the patient were HBs Ag carriers no hepatic or renal disease. The urinalysis showed hematuria and proteinuria (++). The daily urinary protein loss was 900 mg/m^2. Abdominal ultrasonography demonstrated normal echogenicity of the kidneys and the liver.

Percutaneous renal needle biopsy was performed. Light microscopic examination revealed hypercellular enlarged glomeruli with increment of the mesangial matrix and double countering of the basement membrane in a few places (Fig. 3). Fluorescent microscopic study showed depositions of C3 in the BMZ, without

demonstrable depositions of immunoglobulins. Membranoproliferative glomerulonephritis was diagnosed, and the patient was followed up with supportive therapy. Six months after the initial symptoms, anti-HBe positivity was noted and spontaneous remission occurred within eight months. All the clinical and laboratory findings returned to normal except the HBs Ag positivity which persisted for 18 months.

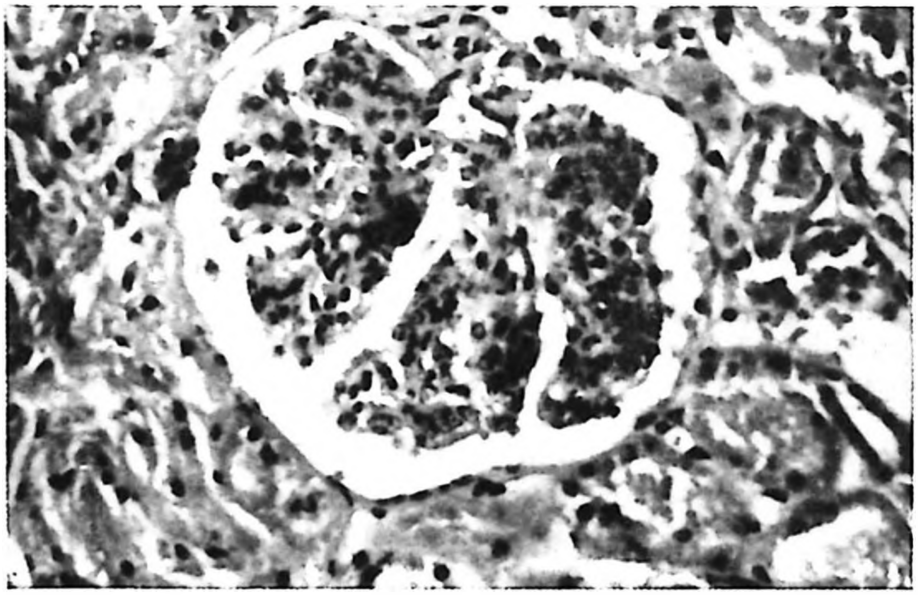

Fig. 3: A glomerulus of a case of MPGN showing hypercellularity with increment of mesangial matrix forming lobulation and obstruction of the majority of the capillary luminae (X 200, H+E, Case 2).

Case 3

A nine-year-old boy was admitted to the hospital with the complaint of edema of the face and legs for the previous month. Similar symptoms had appeared six months prior to admission and his symptoms had disappeared in one month following corticosteroid treatment.

Physical examination revealed marked orbital, scrotal and ankle edema with ascites in the abdomen. The laboratory examination showed normal Hb, WBC, blood urea nitrogen and creatinine levels. Serum albumin was 2.3 g/dl, SGOT: 426 IU, SGPT: 241 IU, the serum electrolytes, C3 and C4 levels were within normal limits. HBs Ag was (+), HBe Ag (+), anti HBe (-), and anti HBc IgM (+). Urinalysis revealed heavy proteinuria (++++) and hematuria. Daily protein loss was 10.6 g/m^2/day. Abdominal ultrasonography showed slightly enlarged kidneys.

Percutaneous renal needle biopsy was performed. Light microscopic study revealed characteristic findings consistent with MPGN. On fluorescent microscopic study, there was a frame-like pattern of glomeruli imitating lobulations with fine granular sticky deposits of C3 (++), C1q (+), IgG (++), IgM (+) and fibrinogen (+) in the BMZ. The patient was diagnosed with MPGN.

The patient was discharged from the hospital after his edema disappeared on diuretic therapy and albumin infusion. Five months after the biopsy the nephrotic syndrome was persisting with proteinuria of 5.78 g/m^2/day, while his liver enzymes were normal (SGOT: 25 IU, SGPT: 15 IU) and HBsAg was (+). The patient was unfortunately lost to follow-up after that time.

The pertinent clinical data of these patients are summarized in Table I.

Table I: Selected Patient Data

	Case 1	Case 2	Case 3
Age at presentation	3 yrs	12 yrs	9 yrs
Sex	female	female	male
Clinical presentation of glomerular disease	Nephrotic + nephritic syndrome	Nephritic syndrome	Nephrotic + nephritic syndrome
Histological diagnosis	MGN (Stage III)	MPGN	MPGN
Treatment	supportive	supportive	steroid + supportive
Outcome	remission	remission	unknown

Discussion

The pathogenesis of HBV-associated GN is not completely understood. Immune complex mechanism including HBs Ag and HBe Ag, are thought to play an important role in the development of glomerular capillary wall damage[4, 5, 8]. The finding of immunoglobulins, complement components and viral antigens (HBs Ag, HBe Ag) within glomerular deposits also supports an immune complex pathogenesis[4, 5, 8]. Takehoshi et al.[14] demonstrated the presence of HBe Ag within glomerular deposits that were not stained with fluorescent anti-HBs and anti-HBc antisera. Ito et al.[15] reported glomerular deposits containing HBe-Ag in four children, and within one of them both HBe-Ag and HBs-Ag were demonstrated. From follow-up studies they concluded that larger HBs Ag immune complexes could be deposited secondarily along glomerular basement membrane damaged by smaller HBe Ag immune complexes, which may act as planted antigens. This hypothesis is compatible with the experimental findings of Adler et al.[16], who demonstrated that the endogenous antigen placed in rat glomerular capillary membranes produced MGN with complement-dependent, neutrophil-independent proteinuria. Spontaneous remission in patients with HBV-associated GN after seroconversion of HBe Ag to anti HBe is another example of the role of immune complex mechanism in the pathogenesis[10]. We also observed spontaneous remission in two of our patients with the appearance of anti HBe. On the other hand, we cannot explain why only Case 2 developed glomerulopathy, while the other two members of her family have no signs of GN although they are also seropositive for HBs Ag.

In most reports, HBV antigens have been detected within subepithelial deposits by immunofluorescence studies[4, 5, 8]. However, Kleinknecht et al.[3] were unable to detect HBs Ag in the kidneys of eight patients studied. We could not perform immunofluorescence studies to demonstrate HBV antigens in the glomerular lesions. Whether our cases represent a true association or a coincidental finding is uncertain. However, in all cases, HBs Ag was associated with elevated levels of transaminase and enlarged liver without jaundice at the onset of the GN. The disappearance of proteinuria was simultaneous with the occurrence of anti-HBe and anti HBc in Case 1 and anti HBe in Case 2, and with the normalization of transaminase levels. These results provide indirect evidence that the immune complex nephritis in these patients may involve the deposition or formation of immune-complex-containing HBV antigens.

Reports on hypocomplementemia and HBV-associated GN have previously been contradictory, but recently the tendency for low C3 and C4 levels in HBV-associated GN has been reported, suggesting the activation of the classical complement pathway[10]. Only one of our patients (Case 2) had low serum C3 and C4 levels during the acute phase of the disease, reaching normal values after remission. On the other hand, the type of MPGN in this case could not be demonstrated since only light microscopic examination was available.

HBV infection is the most frequent cause of MGN in children; however, MPGN and mesengial proliferative GN have been reported[4]. One of our patients had MGN while the other two had MPGN, which is a rare nephrological disease in children.

The optimal treatment for HBV-associated GN remains undefined. Corticosteroid therapy in patients with MGN and persistent HBs antigenemia was concluded to be harmful, as activation of viral replication could occur[17]. There are also several reports showing that different immunosuppressive therapies have been given to patients with MPGN with consistent efficacies[6, 10]. However, Wyszynska et al.[2] found that immunosuppressive treatment did not affect the course and outcome of the disease. The relapse of the symptoms of Case 3 five months after steroid therapy may also suggest that steroid therapy had no advantage in the course of the disease. Recently there have been several reports demonstrating the beneficial effect of recombinant human interferon-alpha treatment in HBV-associated GN[6, 18-21]. On the other hand, improvement of proteinuria in HBV-associated GN after spontaneous seroconversion of serum HBV markers has also been reported[15, 18]. We were not able to follow up Case 3, but the glomerulopathies of Cases 1 and 2 achieved spontaneous remission during the course of the disease after the seroconversion of HBe Ag to anti-HBe positivity, although the MGN of Case 1 was at stage III.

Although we do not have an adequate number of cases, we emphasize that spontaneous remission in HBV-related glomerulopathies can occur. Since

treatment with immunosuppressive drugs such as steroids or azathioprine may prolong the persistence of liver and/or renal disease, besides their other adverse effects, the use of such drugs should be avoided in HBV-associated GN, and patients should be given a chance for spontaneous remission. For patients with persistent infection, recombinant human interferon-alpha may be the treatment of choice.

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