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Case report

Steroid resistant nephrotic syndrome in a child with chronic hepatitis B infection

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ABSTRACT

Steroid resistant nephrotic syndrome (SRNS) continues to be a challenge for pediatric nephrologists the world over. Secondary causes of nephrotic syndrome need to be searched for in all cases of steroid resistance. Hepatitis B virus (HBV) is associated with several types of glomerulonephritis, most commonly being membranous nephropathy (MN) in children. It is an important cause of secondary nephrotic syndrome in countries with high prevalence of chronic hepatitis B virus (HBV) infection.

We present a case of SRNS in a 5-yr-old boy who had received 3 weeks of daily steroids before referral to our hospital. At presentation the child had urinary tract infection (UTI) which was adequately treated. The child had persistence of proteinuria, even after completing 4 weeks of daily steroids in adequate dose. Secondary causes of nephrotic syndrome were looked for which revealed presence of chronic HBV infection in the patient with a very high viral load. Kidney biopsy was characteristic of MN with predominant IgG, & minor IgM, and C3 deposits in subepithelial region. The child responded to treatment with Lamivudine with reduction in edema and proteinuria.

Introduction

Nephrotic syndrome is an important chronic disease in children, with an annual incidence of 2–7 per 100,000, and prevalence of 12–16 per 100,000 children. The condition is primary (idiopathic) in 95% cases. An underlying disorder might be identified in less than 5% cases, and include Systemic Lupus Erythematosus, Henoch Schonlein purpura, amyloidosis and infection with HIV, parvovirus B19 and hepatitis B and C viruses.

HBV is estimated to have infected about 350 million people worldwide, making it one of the most common human pathogens.[1] Renal involvement is among its most common extra hepatic manifestations and an important cause of secondary nephrotic syndrome in regions with high prevalence of chronic HBV infection. The most commonly described renal pathology is membranous nephropathy (MN).

We report a case of SRNS in a child with HBV infection, with a very high viral load which may be secondary to use of steroids for 4 weeks before HBV infection was identified.

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Case report

Five-year-old boy was referred as a case of nephrotic syndrome who was symptomatic for 4 months prior to admission and had received 3 weeks of daily steroids in a dose of 2 mg/kg/day. At presentation he had anasarca, normal blood pressure, no organomegaly or signs of overt infection. On evaluation, urine protein was 3+, there were no red blood cells in urine, pus cells were 4–6/hpf and urinary protein to creatinine ratio was 17.5. His TLC was 28,200/cmm with 58% polymorphs. Urine culture grew *Pseudomonas aeruginosa* and ultrasonography (USG) of the abdomen revealed ascites with no abnormality detected in the kidneys or urinary tract. He was started on injectable antibiotics for UTI, while steroids were reduced to stress doses.

In spite of adequate treatment of UTI and completing 4 weeks of daily steroids at 2 mg/kg there was no remission; hence secondary causes of nephrotic syndrome were looked for. His ANA, dsDNA, and C3 levels were normal. He was positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). DNA PCR revealed a very high viral load of 8×10^8 copies/ml suggesting active viral multiplication. His transaminases were moderately raised while coagulation profile and other tests of liver function were normal. His father and mother were negative for HBsAg & anti HCV. There was no history of jaundice, blood transfusion or blood component therapy in the past. His immunization for hepatitis B was incomplete. A kidney biopsy was done which showed thickening of capillaries with irregular outer membrane suggesting MN in all of the 22 glomeruli included in the specimen (Figs. 1 and 2). Immunofluorescence was strongly positive for subepithelial IgG, and mildly for IgM and C3 deposits (Fig. 3).

The child was started on Lamivudine (3 mg/kg) and steroids were gradually tapered off. Within 2 weeks of initiation of the antiviral therapy, condition of the patient improved with decrease in the proteinuria to 1+, reduction in edema, and increase in urine output. The patient was discharged on lamivudine, diuretics, and antihypertensive medication and at last visit was in partial remission.

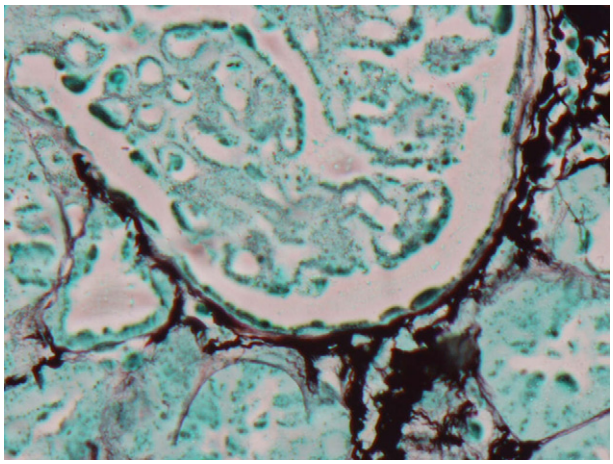

Fig. 2 – Diffuse thickening of glomerular capillary basement membrane with epimembranous argyrophilic spikes (PASM ×400).

Discussion

SRNS is defined as inability to achieve remission after 4 weeks of daily oral steroids in a dose of 2 mg/kg/day and its management continues to pose a therapeutic challenge to all nephrologists. The underlying renal histopathology usually affects the course of the disease as well as the response to treatment. Secondary causes of nephrotic syndrome form up to 5% of total cases and are usually associated with steroid resistance.

HBV is globally distributed and is estimated to have infected about 2 billion people, of which about 350 million are chronically infected, making it one of the most common human pathogens.[1] A variety of extra hepatic manifestations, one of the commonest being HBV associated nephropathy, may appear in persons chronically infected with HBV. Several morphological forms of renal disease including MN, membrano-proliferative glomerulonephritis (MPGN), mesangial-proliferative glomerulonephritis (MesPGN),

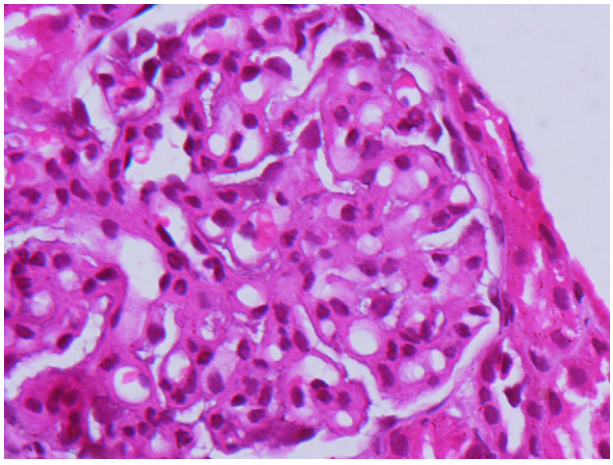

Fig. 1 – Stiff and thickened glomerular capillary loops (H&E ×400).

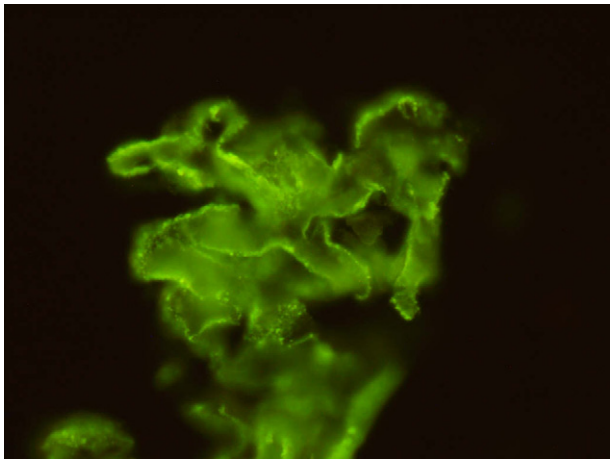

Fig. 3 – Discrete granular subepithelial deposits, 4+ intensity (FITC IgG ×400).

minimal change disease (MCD), IgA nephropathy and rarely focal segmental glomerulosclerosis (FSGS), have been described in association with HBV infection. The prevalence of HBV associated with SRNS varies from 6% in Jamaica[2] to 30% in Hong Kong,[3] while Indian data is unavailable.

HBV associated nephropathy affects both children and adults with different clinical manifestations. Most pediatric patients suffer from transient asymptomatic proteinuria with preservation of renal function. MN was first described by Brzosko et al, and subsequent reports from other countries showed that the strongest association of chronic HBV carriage, particularly in children, is with MN.[4] The pathological diagnosis of MN is based on immunofluorescence and ultra structural findings of IgG containing subepithelial deposits of antigen–antibody complexes. In the present case the renal histology was classical of MN with deposits of IgG, IgM, and C3.

Various therapeutic approaches have been used for HBV associated MN including corticosteroids, adenine arabinoside, thymic extracts, acyclovir, interferon (IFN), and lamivudine. Only antiviral therapy (IFN or lamivudine) proved to be effective in clearing HBV antigens and abrogating proteinuria. Lamivudine is a nucleoside analog, which has been proven to be safe and effective against hepatitis B in both adults and children, producing similar rates of HBeAg clearance as IFN therapy.[1] While there is no consensus on duration of therapy with lamivudine in HBV associated nephropathy, the current strategy is to administer lamivudine for 12 months.[5] IFN alfa has been shown to induce the proliferation of natural killer cells, which are helpful in clearing the virally infected cells.[6] IFN therapy has a beneficial effect in 30–40% of patients with chronic hepatitis B who respond by clearing HBeAg from serum.

In general, patients with raised serum aminotransferases between two and five times the upper limits of normal respond best to antiviral treatments for HBV. However, in HBV MN, antiviral treatment may be associated with resolution of proteinuria and HBeAg seroconversion, even when serum transaminases are normal.[7] Our patient had moderately increased transaminases when treatment was introduced and we chose lamivudine in preference to IFN because of its oral route of administration and fewer side effects.

Monotherapy with either lamivudine or interferon leads to sustained viral suppression in less than half of the patients treated for chronic HBV infection, hence the recent trials of combination therapy using lamivudine with IFN which have shown increased rates of seroconversion with minimal occurrence of drug resistant strains.[8,9]

The present case highlights the possibility of hepatitis B associated MN in children presenting with nephrotic syndrome and the possible harm by initiating steroids without confirming HBsAg status. It is recommended that hepatitis B serology should be part of the initial screen in all children presenting with nephrotic syndrome, especially those from endemic areas where hepatitis B is prevalent. Furthermore, these patients should be referred for immediate renal biopsy to elucidate the underlying pathology. Antiviral therapy should be started at the earliest which leads to remission in majority of patients.

Conflicts of interest

All authors have none to declare.

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