


Hepatitis B–Associated Lupus-Like Glomerulonephritis Successfully Treated With Antiretroviral Drugs and Prednisone: A Case Report and Literature Review

Journal of Investigative Medicine High
Impact Case Reports
Volume 10: 1–6
© 2022 American Federation for
Medical Research
DOI: 10.1177/23247096221086451
journals.sagepub.com/home/hic


Sasmit Roy, MD¹ , Rohan Gupta, MD², Sreedhar Adapa, MD³ ,
Subhashish Bose, MD¹, and Amarinder Garcha, MD³

Abstract

Kidney involvement with hepatitis B virus is varied and mostly limited to nephrotic syndrome with membranous nephropathy and nephritic syndrome with membranous proliferative glomerulonephritis. Lupus nephritis is associated with nephritic or nephrotic range proteinuria with most common finding of sub-endothelial electron-dense deposits and immunological stain demonstrating full-house picture with all immunological marker staining. Our case discusses a young male patient presenting with rapidly worsening renal function along with proteinuria, found to be positive for both hepatitis B core antibody along with hepatitis B surface antibody plus positive anti-neutrophilic antibody but negative anti-double-stranded DNA. Kidney biopsy demonstrated hepatitis B–associated lupus-like glomerulonephritis. He responded successfully with antiretroviral therapy and high-dose prednisone. Patient did not need lupus-specific treatment and recovered with antiretroviral therapy only. Hepatitis B–associated lupus-like glomerulonephritis has rarely been reported and possess a diagnostic and therapeutic challenge to all nephrologists.

Keywords

hepatitis B virus nephropathy, hepatitis B–associated lupus-like glomerulonephritis, lupus nephritis, tetralogy of Fallot, high-risk kidney biopsy

Introduction

Kidney involvement with hepatitis B virus (HBV) is varied and mostly limited to nephrotic syndrome with membranous nephropathy (MN) and nephritic syndrome with membranous proliferative glomerulonephritis (MPGN). Hepatitis B Virus nephropathy (HBVN) most commonly presents as MN which usually has subepithelial deposits. The subendothelial glomerulonephritis (GN) condition, although reported to be associated with hepatitis C virus (HCV), is quite uncommon in patients with hepatitis B. Here we have a unique situation of a young male patient presenting with nephrotic range proteinuria and found to have hepatitis B–associated lupus-like GN with subendothelial electron-dense deposits. In this discussion, we would like to elaborate on the pathophysiology of common types of HBVN and approach a case that poses a diagnostic dilemma when the glomerular pathology is suggestive of lupus nephritis with negative lupus serology and lack of clinical features seen in lupus. Our case is unique and broadens the type of kidney disease which can occur with hepatitis B infection.

Case Report

A 46-year-old Caucasian gentleman with a past medical history of tetralogy of Fallot with multiple prior cardiac procedures, essential hypertension, and heart failure with preserved ejection fraction walked into the emergency department (ED) with symptoms of gradual worsening shortness of breath and generalized weakness. This was accompanied by progressive swelling of the ankles along with low-grade fever, petechial rashes of bilateral lower extremities for the last 2 weeks. In the ED, vital signs measured recorded a blood pressure of

¹University of Virginia, Charlottesville, USA

²Community Regional Medical Center, Fresno, CA, USA

³Kaweah Delta Health Care District, Visalia, CA, USA

Received January 7, 2022. Revised February 13, 2022. Accepted February 20, 2022.

Corresponding Author:

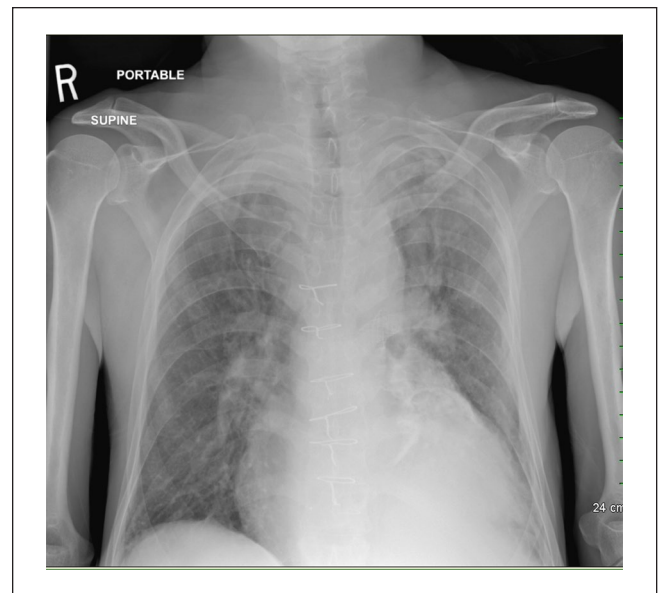
Sasmit Roy, Department of Medicine, UVA Dialysis Unit, University of Virginia, 103 Clifton Street, Lynchburg, VA 24501, USA.
Email: docsasmit@gmail.com



Table 1. Laboratory Values on Admission.

Lab parameters	Value	Reference
Hemoglobin	11.4 gm/dL	12.5-14.5 gm/dL
Hematocrit	31.9%	39%-51%
White blood cells	3.1×10^3 /microliter	$4-11 \times 10^3$ /microliter
Platelet counts	56×10^3 /microliter	$150-450 \times 10^3$ /microliter
Serum sodium	134 mEq/L	135-145 mEq/L
Serum potassium	5 mEq/L	3.5-5.1 mEq/L
Bicarbonate	19 mEq/L	24 mEq/L
Blood urea nitrogen	46 mg/dL	<10 mg/dL
Creatinine	4.2 mg/dL	<1.1 mg/dL
Albumin	2.5 gm/dL	3.5-5 gm/dL
Total bilirubin	0.8 mg/dL	<1.2 mg/dL
Aspartate aminotransferase	25 IU/L	<40 IU/L
Alanine aminotransferase	32 IU/L	<40 IU/L
Alkaline phosphatase	56 IU/L	40-129 IU/L
Brain natriuretic peptide	1153 pg/mL	<300 pg/mL
International normalized ratio	1.2	<1.1

176/86 mm Hg, heart rate of 83 beats/min, temperature 38° Celsius, and pulse oxygen saturation of 97% on 2-liter oxygen. Physical examination revealed grade 4/6 systolic ejection murmur at the neo-aortic area, bilateral nonpitting 1 + pedal edema, and non-blanching petechial rashes in both lower extremities. The rest of the systemic physical examination findings were unremarkable. Laboratory tests are as follows in Table 1. Of note, his creatinine was normal at 1.1 mg/dL at outpatient labs done 3 months ago. Urine analysis revealed large amount of blood with 3 + protein. The urine protein creatinine ratio was elevated at 3.2 gm/g (grams/gram). Brain natriuretic peptide (BNP) was elevated. Chest x-ray did suggest congestion cardiomegaly with diffuse interstitial infiltrates bilaterally (Figure 1). Computed tomography (CT) abdomen pelvis without contrast revealed incidental detection of absent left kidney, mild nonspecific enlargement of right kidney but otherwise no stones or hydronephrosis. The initial working diagnosis was cardiorenal syndrome with possible acute GN. Despite aggressive diuresis with furosemide 80 mg 3 times daily, he did not make much progress with urine output and his creatinine continued to stay elevated and went up to 5.1 mg/dL. An echocardiogram done suggested an ejection fraction of 50% to 55% with normal left ventricular diastolic function. Blood cultures returned negative. Because of low white blood cell count on presentation, recurrent low-grade fever at home, and petechial rash with acute kidney, initially, the diagnosis was thought to be infectious etiology of unknown origin with infective endocarditis in the differential. He was continued on intravenous vancomycin and piperacillin/tazobactam for broad-spectrum coverage. A transesophageal echocardiogram was done as per infectious disease recommendation which returned negative for any vegetations. Serological workup for GN revealed low Complement 4 (C4) level, normal C3 level, positive

**Figure 1.** Chest x-ray showing enlarged heart and vascular congestion.

antinuclear antibody (ANA), negative anti-double-stranded DNA (dsDNA), and negative anti-neutrophilic cytoplasmic antibody (ANCA) level. Interestingly, his HBV workup came positive for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody negative, hepatitis B core antibody positive. Hepatitis C antibody and HIV were negative. Subsequently, his hepatitis Be antigen was positive, IgM anti-hepatitis B core antibody was negative, and HBV DNA PCR was positive with 42 000 international units/mL. He was not responding with intravenous antibiotics despite the initial thought of infectious etiology being the root cause. He underwent a

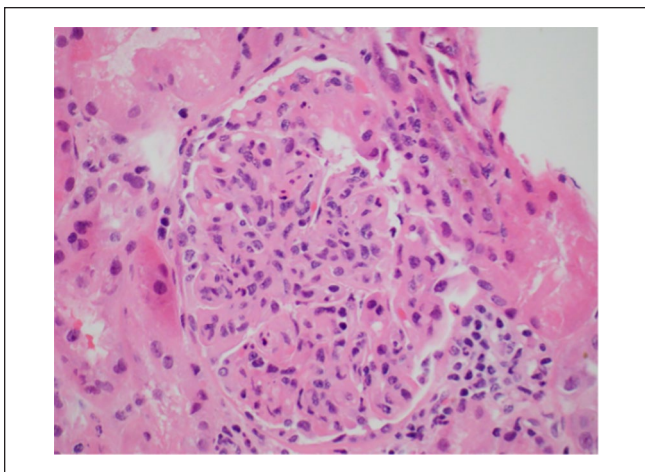


Figure 2. Hematoxylin and eosin-stained light microscopy showing neutrophilic debris in glomeruli.

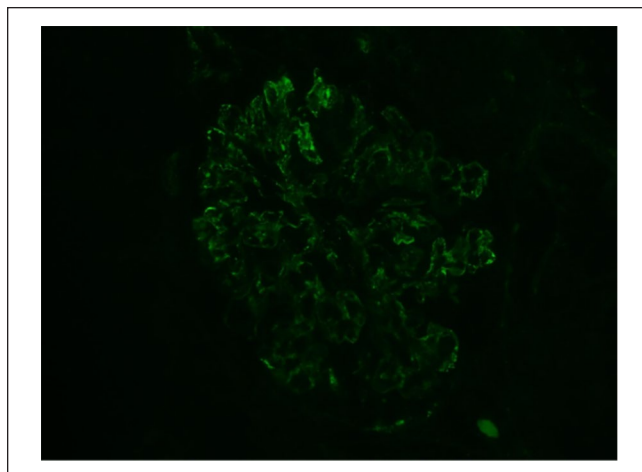


Figure 4. Immune microscopy demonstrating Ig M deposits.

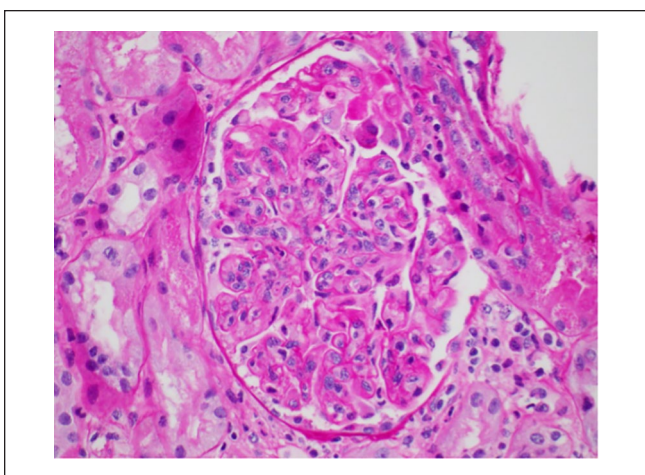


Figure 3. Periodic acid-Schiff-stained light microscopy showing endocapillary hypercellularity.

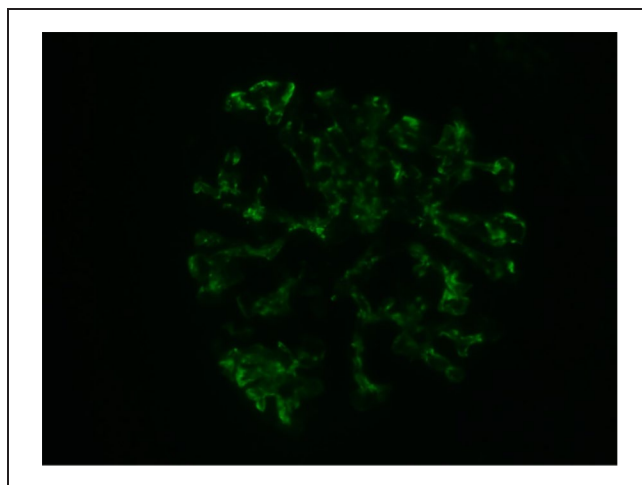


Figure 5. Immune microscopy demonstrating C 3 deposits.

high-risk kidney biopsy through the right internal jugular vein on day 6 of hospitalization. Because of his solitary kidney and thrombocytopenia, kidney biopsy was considered high risk and thus was delayed. Kidney biopsy revealed hepatitis B positive lupus-like GN. Light microscopy revealed severe diffuse endocapillary hypercellularity along with severe interstitial inflammatory infiltrates without any crescents (Figures 2 and 3). Immunofluorescent microscopy revealed granular mesangial and focal subendothelial staining with Immunoglobulin (Ig) G, Ig A, Ig M, C1q, C3 among others suggestive full-house effect as seen in lupus (Figures 4 and 5). Electron microscopy revealed subendothelial glomerular deposits and mesangial plus loop deposits (Figures 6 and 7). He was started on treatment for hepatitis B with tablet entecavir 0.5 mg once daily along with a high dose of oral prednisone 60 mg daily with the tapering plan. He did not need any lupus nephritis-specific immunosuppressants such as

mycophenolate or cyclophosphamide. He responded well to therapy with defervescence of fever in 2 days along with improvement of creatinine down to 2.7 mg/dL in 7 days.

He was subsequently discharged with outpatient follow-up every 2 months. He did well for 8 months thereafter when his outpatient creatinine stayed in the range 2.7 to 3.0 mg/dL with Glomerular Filtration Rate from 22% to 26%. His proteinuria subsided completely too. He finished a tapering course of prednisone in 4 months and was continued on entecavir daily. However, one year later, he succumbed to a massive cerebrovascular accident from uncontrolled hypertension and cardiac complications related to his tetralogy of Fallot.

Discussion

Chronic HBV infection is prevalent in 240 million people in the world which constitutes approximately 5% to 6% of world population. Commonly, it refers to persistent HBsAg

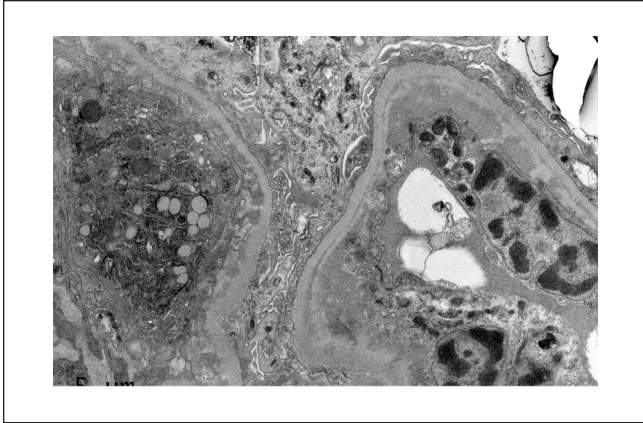


Figure 6. Electron microscopy showing subendothelial deposits.

circulating in the bloodstream. In the United States, nearly 2 million people are chronic HBV carriers and 20 000 to 40 000 new cases of annual exposure to HBV occur. In all, 3% to 5% of chronic HBV carriers develop renal disease.¹

In comparison with renal diseases from Parvovirus B19 virus, Epstein-Barr Virus or Cytomegalovirus which cause nephropathy by acute or subacute viral infection, immune-complex nephropathy caused by HBV usually occurs secondary to a lengthy carrier state. This contrasts with post-infectious GN seen in pharyngeal or cutaneous streptococcal infection which cause GN after a period of latency following resolved active infection. Demonstration of HBV antigen-antibody complexes in renal lesions via immunofluorescence microscopy has shown to document the pathogenesis of HBVN.² The histopathological manifestations of HBVN can be classified as either immune-complex-related vasculitis, for example, polyarteritis nodosa (PAN) or as immune-complex-mediated GN like membranoproliferative GN (MPGN), membranous GN, and IgA nephropathy. HBVN is commonly seen in children than in adults and more in men than in women.³ The most common type of GN in humans is MN and is frequently seen in children. By contrast, MPGN is commonly seen in adults.⁴

On electron microscopy, the appearance of HBV membranous nephropathy (HBVMN) is indistinguishable from idiopathic MN with both demonstrating immune-complex deposits in subepithelial space.⁵ All 3 potential viral components, namely, HBeAg, HBcAg, and HBsAg, can act like antigens within the immune deposits found with HBVMN.⁵ The HBeAg is the most likely responsible antigen for the immunologic injury in HBVMN.⁶ De novo deposit formation characterized by deposition of circulating antigen in basement membrane concluded that deposition of antibody on it can occur or an immune mediated complex between IgG with any of the stated types of antigens can lead to deposits.⁷ The HBeAg is detected from the glomerulus of nearly 90% of patients with biopsy proven HBVMN and measurable circulating HBeAg is found in >95% of these patients.

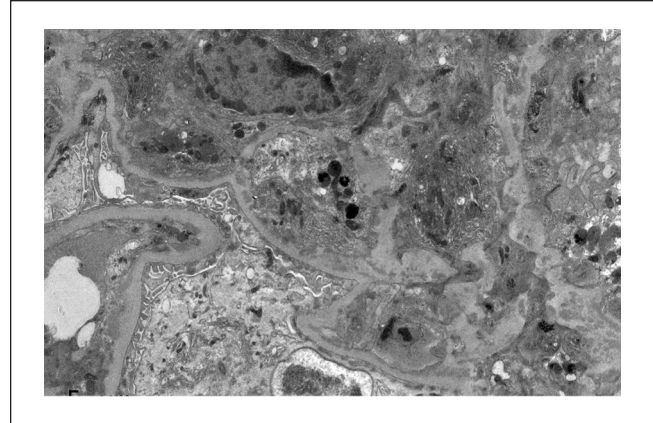


Figure 7. Electron microscopy showing mesangial deposits.

The MPGN is the second most common type of nephropathy in HBV carriers and is characterized by splitting of the basement membrane and typical lobular pattern of the glomerulus with mesangial and subendothelial deposits. These glomerular deposits consist mainly of IgG and C3.⁸ The most common glomerular antigen deposited in the subendothelial space is HBsAg.⁹ Chronic HBV carriers can have both type 1 and type 3 MPGN. Their clinical presentation matches idiopathic MPGN with characteristic nephritic syndrome accompanied with or without nephrotic range proteinuria along with drop in levels of classic complement pathway C3 and C4.¹⁰

In the 1980s, commonest etiology of PAN was HBV in more than 80% of the cases. With time, due to the global HBV vaccination, the prevalence of HBVN has reduced significantly along with the cases of PAN from HBV, which now contribute to <20% of total cases. PAN occurs in medium-size blood vessels as a result of HBsAg antibody immune complexes causing vasculitis leading to renal infarction and ischemia causing Acute Kidney Injury (AKI).¹¹

In patients with IgA nephropathy and renal mesangial cells of patients with FSGS, HBV viral transcripts have been noted suggesting HBV as a possible etiology in anecdotal cases substantiating the possible causative role of HBV in a select group of Focal Segmental Glomerulosclerosis (FSGS) and IgA patients.¹² Case report of minimal change disease with HBV has also been documented.¹³

Biopsy findings of tubulo reticular inclusions (TRIs) on electron microscopy, along with immunofluorescent microscopy demonstrating polytypic and polyclonal complement immune complexes “full-house” findings, appear to be highly suggestive of Lupus nephritis.^{14,15} In some cases of HBVN, immune depositions of polyclonal immuno-globulins associated with polytypic complements in glomeruli have been noted.¹⁵⁻¹⁷ The TRIs are commonly seen in systemic lupus erythematosus and HIV-associated renal disease and now also been seen in HCV- and

HBV-related glomerular lesions.¹⁸ TRIs are seen with upregulation of endogenous interferons associated with viral illness and their presence makes the diagnosis of idiopathic etiology of MN less likely and more likely due to infectious or autoimmune in origin.

In demographics where HBV infection is endemic, “full house” immuno-reactant glomerular pattern can also suggest HBVMN is an alternative possibility in addition to lupus nephritis.^{9,15,16} Such a pattern in HBVN has also been reported in non-endemic areas.² The diagnosis of lupus membranous nephritis (LMN) is clear when this “full-house” pattern is accompanied by diffuse proliferative GN, because such a lesion is rarely, if ever, a form of HBVN.^{2,15,16} However, it is challenging to differentiate between HBVN and LMN at the time of biopsy when clinical features of SLE are not present.^{2,17} SLE and lupus nephritis have a female predominance and attributed to hormonal and genetic factors, although no specific genetic markers have been recognized so far.^{17,19,20} In contrast to lupus nephritis, HBVMN has a strong predilection in men as was noted in our case. Just a positive serum HBsAg does not always link HBV with the underlying glomerulopathy, as close to >50% with primary glomerulopathy with positive serological evidence of the virus do not always demonstrate glomerular viral antigens.²¹

As for treatment choices, Kidney Disease Improving Global Outcomes (KDIGO) recommends Interferon-alpha (IFN) or oral antiviral agents representing either nucleoside (entecavir, telbivudine, lamivudine) or nucleotide reverse transcription inhibitors (adefovir, tenofovir) for HBVMN.²² The most used agent associated with complete resolution of the MN lesion and initial remission of viremia in 75% to 80% of patients are lamivudine. However, because of a somatic mutation of the HBV reverse transcription gene, this drug is meeting with a resistance rate of 20% yearly.²³ Therefore, either tenofovir or entecavir have become the first-line therapy due to absence of clinical resistance so far.²⁴ As a therapeutic trial, corticosteroids can be given for a period of <6 months for symptomatic relief of proteinuria without much significant effect on HBV viremia, liver disease, or overall morbidity or mortality if used concomitant with antiviral therapy.²⁵

Lastly, our discussion would be incomplete without mentioning transjugular renal biopsy briefly. This is mainly performed in situations where percutaneous kidney biopsy might be risky such as cases of coagulopathy, solitary kidney, too small kidneys bilaterally, or where very high body mass index precludes patients’ lying down in prone position. With the patient lying in a supine position, transjugular renal biopsy is approached mainly with a guidewire running through the right internal jugular vein into the inferior vena cava and then to the right renal vein. Thereafter, sample is obtained through one of the subcortical veins through a tru-cut needle in a flexible sheath.²⁶

Conclusion

The HBVMN and HBV MPGN are the commonly reported renal pathologies. Incidence of lupus-like HBV-related nephropathy has rarely been reported. The treatments for lupus-like nephropathy and lupus nephropathy are different and physicians should be aware of this rare association to facilitate timely recovery from this glomerular pathology with appropriate antiretroviral therapy.

Data Availability

PubMed, Goggle Scholar databases. The authors declare that data supporting the findings of this article are available within the article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval


Our institution does not require ethics approval for reporting individual cases

Patient Consent

Written informed consent was obtained from the patient for her anonymous information to be published in this article.

ORCID iDs

Sasmit Roy  <https://orcid.org/0000-0002-2509-3915>

Sreedhar Adapa  <https://orcid.org/0000-0001-5608-5654>

References

1. Gupta A, Quigg RJ. Glomerular diseases associated with hepatitis B and C. *Adv Chronic Kidney Dis*. 2015;22:343-351.
2. Lai KN, Li PKT, Lui SF, et al. Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med*. 1991;324:1457-1463.
3. Chan TM. Hepatitis B and renal disease. *Curr Hepatol Rep*. 2010;9:99-105.
4. Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. *Kidney Int*. 1990;37:663-676.
5. Li P, Wei RB, Tang L, Wu J, Zhang XG, Chen XM. Clinical and pathological analysis of hepatitis B virus-related membranous nephropathy and idiopathic membranous nephropathy. *Clin Nephrol*. 2012;78(6):456-464
6. Hsu HC, Wu CY, Lin CY, Lin GJ, Chen CH, Huang FY. Membranous nephropathy in 52 hepatitis B surface antigen (HBsAg) carrier children in Taiwan. *Kidney Int*. 1989;36(6):1103-1107

7. Bhimma R, Coovadia HM. Hepatitis B virus-associated nephropathy. *Am J Nephrol*. 2004;24:198-211.
8. Lu Y, Shen P, Li X, et al. Re-evaluation of the classification system for membranoproliferative glomerulonephritis. *Contrib Nephrol*. 2013;181:175-184.
9. Venkateshan VS, Lieberman K, Kim DU, et al. Hepatitis-B-associated glomerulonephritis: pathology, pathogenesis, and clinical course. *Medicine (Baltimore)*. 1990;69(4):200-216.
10. Li P, Wei RB, Tang L, Wu J, Zhang XG, Chen XM. Clinical and pathological analysis of hepatitis B virus-related membranous nephropathy and idiopathic membranous nephropathy. *Clin Nephrol*. 2012;78(6):456-464
11. Sharma A, Sharma K. Hepatotropic viral infection associated systemic vasculitides-hepatitis B virus associated polyarteritis nodosa and hepatitis C virus associated cryoglobulinemic vasculitis. *J Clin Exp Hepatol*. 2013;3(3):204-212
12. Sun IO, Hong YA, Park HS, et al. Clinical characteristics and treatment of patients with IgA nephropathy and hepatitis B surface antigen. *Ren Fail*. 2013;35(4):446-451
13. Zhou TB, Jiang ZP. Is there an association of hepatitis B virus infection with minimal change disease of nephrotic syndrome? A clinical observational report. *Ren Fail*. 2015;37(3):459-461
14. Baskin E, Agras PI, MenekÅYe N, Ozdemir H, Cengiz N. Full-house nephropathy in a patient with negative serology for lupus. *Rheumatol Int*. 2007;27(3):281-284
15. Churg J, Bernstein J, Glassock RJ. *Renal Disease: Classification and Atlas of Glomerular Diseases*. 2nd ed. New York, NY, USA: Igaky-Shoin, 1995.
16. Mac-Moune Lai F, Lai KN, Tam JS, et al. Primary glomerulonephritis with detectable glomerular hepatitis B virus antigen. *Am J Surg Pathol*. 1994;18:175-186.
17. Tan EM, Cohen AS, Fries JF, et al. The revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271-1277.
18. Lee CJ, Suh KS, Kim KH, Chang YK, Na KR, Lee KW. The clinicopathologic significance of endothelial tubuloreticular inclusions in glomerular diseases. *Ultrastruct Pathol*. 2013;37(6):386-394
19. Steinberg AD. Systemic lupus erythematosus: theories of pathogenesis and approach to therapy. *Clin Immunol Immunopathol*. 1994;72(2):171-176.
20. Sequeira JF, Keser G, Greenstein B, et al. Systemic lupus erythematosus: sex hormones in male patients. *Lupus*. 1993;2:315-317.
21. Lai KN, Lai FM, Tam JS. Comparison of polyclonal and monoclonal antibodies in determination of glomerular deposits of hepatitis B virus antigens in hepatitis B virus-associated glomerulonephritides. *Am J Clin Pathol*. 1989;92(2):159-165.
22. KDIGO Glomerulonephritis Work Group: Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:200-208.
23. Tipples GA, Ma MM, Fischer KP, Bain VG, Kneteman NM, Tyrrell DL. Mutation in HBV RNA-dependent DNA polymerase confers resistance to lamivudine in vivo. *Hepatology*. 1996;24(3):714-717
24. Elewa U, Sandri AM, Kim WR, et al. Treatment of hepatitis B virus-associated nephropathy. *Nephron Clin Pract*. 2011;119:c41-c49, discussion c49.
25. Zheng XY, Wei RB, Tang L, Li P, et al. Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis. *World J Gastroenterol*. 2012;18:821-832.
26. See TC, Thompson BC, Howie AJ, et al. Transjugular renal biopsy: our experience and technical considerations. *Cardiovasc Intervent Radiol*. 2008;31:906-918.