Focal Segmental Glomerulosclerosis Caused by Hepatitis B Infection Comorbid with Human Immunodeficiency Virus (HIV) Infection

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ABSTRACT

Glomerulonephritis is an inflammatory condition on renal glomerulus. These entities can manifest as nephrotic syndrome. One of causes of secondary glomerulonephritis is hepatitis B infection. Glomerulonephritis due to hepatitis B only happens in 0.1 – 25% cases, with the focal segmental glomerulosclerosis (FSGS) is rarely reported. We reported 20 years old male with nephrotic syndrome. He was homosexual with history of unprotected sex and multiple partners. From kidney biopsy, we found focal segmental glomerulosclerosis lesion. Blood examination showed he had both hepatitis B (HBV-DNA > 1.7x10^8 IU/mL) and human immunodeficiency virus (HIV) infection (HIV-RNA 820 copies/mL, cluster of differentiation 4 (CD4) 839 cell/uL). We treated this patient with combination of anti-viral drugs which consist of tenofovir, lamivudine and efavirenz. After three weeks of treatment, he showed improvement in the clinical symptoms and urinalysis.

Keywords: *focal segmental glomerulosclerosis (FSGS), glomerulonephritis, hepatitis B, human immunodeficiency virus (HIV)*

ABSTRAK

Glomerulonephritis adalah kondisi dimana adanya peradangan pada glomerulus ginjal. Kondisi ini dapat bermanifestasi sebagai sindrom nefrotik. Salah satu penyebab dari glomerulonephritis sekunder adalah infeksi hepatitis B. Glomerulonephritis yang diakibatkan oleh infeksi hepatitis b ditemukan hanya 0.1-25% kasus, dimana jenis focal segmental glomerulosclerosis (FSGS) sangat jarang ditemukan. Kami melaporkan kasus laki-laki berusia 20 tahun dengan klinis sindrom nefrotik. Pasien merupakan seorang homoseksual dengan riwayat melakukan hubungan seks yang tidak terproteksi dan memiliki banyak partner seksual. Dari pemeriksaan biopsi ginjal, kami menemukan lesi focal segmental glomerulosclerosis. Dari pemeriksaan darah, kami temukan pasien memiliki infeksi hepatitis B dengan kadar HBV-DNA > 1.7x10^8 IU/mL dan infeksi HIV dengan kadar

HIV-RNA 820 kopi/mL, CD4 839 sel/uL. Kami melakukan tatalaksana pasien ini dengan kombinasi obat anti virus yang terdiri dari tenofovir, lamivudine, dan efavirenz. Setelah pemberian terapi selama tiga minggu, pasien menunjukkan perbaikan dari segi klinis dan urinalisis.

Kata kunci: *focal segmental glomerulosclerosis (FSGS), glomerulonephritis, hepatitis B, human immunodeficiency virus (HIV)*

INTRODUCTION

Glomerulonephritis is an inflammatory condition of the renal glomeruli. These entities can manifest as nephrotic syndrome. Glomerulonephritis could be primary or secondary. Secondary glomerulonephritis caused by systemic lupus erythematosus (SLE), human immunodeficiency virus (HIV) infection, hepatitis C infection and hepatitis B infection.[1]

Hepatitis B virus is normally found in hepatocyte and cause liver inflammation through immune-mediated mechanism. Persistent liver inflammation will cause liver cirrhosis. Hepatitis B virus can manifest in extrahepatic organs such as skin, muscle, joints and kidney. Glomerulonephritis due to Hepatitis B infection occured in 0.1 – 25% of glomerulonephritis cases. In kidney, hepatitis B virus commonly causes membranous nephropathy. Focal segmental glomerulosclerosis (FSGS) due to hepatitis B infection is rarely reported.[2]

Human Immunodeficiency Virus is another virus that can cause kidney disorder. Kidney disorder due to HIV is called HIV-associated nephropathy (HIVAN). HIV-associated nephropathy manifest as collapse of glomerulus with histopathological examination shows FSGS, minimal lesion, thrombotic microangiopathy and lupus-like HIV-immune complex kidney disease (HIVICK).[3] The purpose of this case report is to present a rare case of FSGS due to hepatitis B infection comorbid with HIV infection.

CASE ILLUSTRATION

A 20 years-old male came to internal medicine clinic with complaint of swelling all over his body in the last two weeks. Swelling first appeared on his face, especially in eyelids, around the nose, cheeks, and neck when he woke up in the morning. He had intermittent fever with subfebrile temperature (around 37º C). Fever decreased when patient took paracetamol. This was the first time he felt this complaint. Patient had history of gonorrhea two times, which was about three years and one year prior. Patient was homosexual and had a history of unprotected sex and multiple partners.

From physical examination, we found blood pressure of 120/70 mmHg, pulse of 86 times/minute, temperature of 36.8º C, respiratory rate of 18 times/minute and weight of 50 kg. Examination of extremities revealed enlargement of both calves and insteps. There was pitting edema in both extremities.

Abdominal ultrasound examination showed bilateral nephritis, minimum ascites with normal liver, gall bladder, spleen, bladder, prostate. Fibroscan examination was 5.7 KPa which corresponded to Metavir F0-1 which mean there was no fibrosis or fibrosis was limited to the widened portal zone.

Table 1. Laboratory results

Parameter	Results	Parameter	Results
Hemoglobin	14.37 g/dL	Albumin	1,90 g/dL
White blood count (WBC)	6,570 /uL	Cholesterol	455 mg/dL
Neutrophil	2.46 10^3/uL	Low density lipoprotein (LDL)	340 mg/dL
Lymphocyte	3.50 10^3/uL	High density lipoprotein (HDL)	58 mg/dL
Monocyte	0.44 10^3/uL	Triglycerides	242 mg/dL
Eosinophil	0.11 10^3/uL	Anti human immunodeficiency virus (Anti-HIV)	Reactive
Basophil	0.06 10^3/uL	human immunodeficiency virus - deoxyribonucleic acid (HIV-RNA)	820 copies/mL
Platelet (PLT)	369,000 /uL	Cluster of differentiation 4 (CD4)	839 sel/uL
Aspartate aminotransferase (AST)	32.3 U/L	Cluster of differentiation 8 (CD8)	1,246 sel/uL
Alanine aminotransferase (ALT)	22.7 U/L	Hepatitis B surface antigen (HBsAg)	Reactive
Blood urea nitrogen (BUN)	8.40 mg/dL	Hepatitis B virus deoxyribonucleic acid (HBV-DNA)	>1.70 x 10^8 IU/mL
Creatinine	0.91 mg/dL	Hepatitis B e antigen (HBeAg)	Reactive
Natrium	141 mmol/L	Anti hepatitis C virus (Anti-HCV)	Non-reactive
Kalium	4.42 mmol/L	Random blood sugar	111 mg/dL

Table 2. Urinalysis results

Parameter	Results
Proteinuria	4+
Glucose	1+
Blood	2+
Sediment Leucocyte	2
Sediment Erythrocyte	17
Specific Gravity	1,039
pH	7.00
Protein Creatinine Ratio	11.668
Esbach Protein	5.10 gram/24 hours

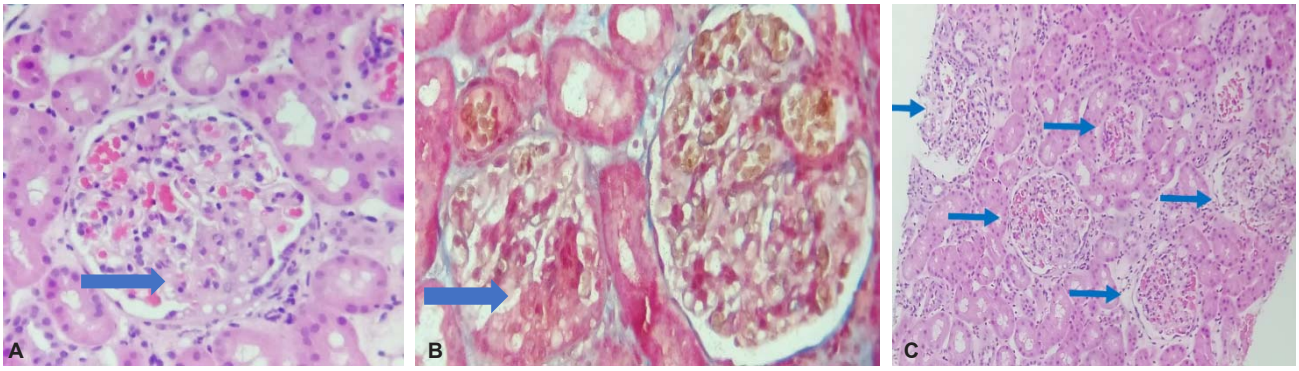

Figure 1. Image A used Hematoxyline Eosine staining with 400x magnification. It showed hyalinosis on one glomerular segment (blue arrow). Image B used Masson Trichrome staining with 400x magnification. It showed segmental hyalinosis of the glomerulus (blue arrow) with normal glomerulus on its right. Image C used Hematoxyline Eosine staining with 100x magnification. It showed multiple sclerosis glomeruli (blue arrows).

Patient was diagnosed with secondary nephrotic syndrome caused by hepatitis B infection comorbid with HIV infection, chronic hepatitis B with HBeAg positive in immunotolerant phase. Secondary nephrotic syndrome in this patient was suspected to be caused by hepatitis B infection. Patient was treated with captopril 25 mg twice daily, simvastatin 20 mg once daily and anti-viral drugs fixed dose combination (FDC) which consist of tenofovir, lamivudine and efavirenz one tablet once daily. These anti-viral drugs were chosen because they contain tenofovir and lamivudine, which belong to anti-viral treatment of chronic hepatitis B infection. After three weeks of treatment, there were improvements on patient's clinical condition and urinalysis results. From clinical condition, edema in patient's extremities decreased. From urinalysis results, there were decrease in proteinuria and glucosuria.

DISCUSSION

Nephrotic syndrome is pathognomonic sign of glomerular disease characterized by anasarca edema, massive proteinuria of more than 3.5 grams per day, hypoalbuminemia (serum albumin < 2.5 g/dL), hypercholesterolemia and lipiduria. According to Kidney Disease Improving Global Outcome (KDIGO) 2012, nephrotic syndrome can be diagnosed with findings of proteinuria > 3.5 grams per day, serum albumin < 2.5 g/dL, and presence of edema.[1,4] In our case, we found all of criteria for diagnosing nephrotic syndrome, which are edema, hypoalbuminemia < 2.5 g/dL, proteinuria > 3.5 g/day, and hypercholesterolemia.

Focal segmental glomerulosclerosis is the most common lesion seen in idiopathic adult nephrotic syndrome. In United States of America, it accounts as many as 35% of nephrotic syndrome cases and 50% of them are African-American race. Histological examination may show abnormalities on some but not on all glomeruli (called focal) and only few mesangial collapse and sclerosis (called segmental). Focal segmental glomerulosclerosis can appear as an idiopathic syndrome, or be associated with HIV infection, reflux nephropathy, idiosyncratic reactions to non-steroidal anti-inflammatory drugs (NSAIDs), severe obesity and, quite rarely, hepatitis B infection. According to the Columbia classification, FSGS disorders are divided into five types, which are perihilar variant, cellular variant, tip variant, collapsing variant and not otherwise specified (NOS) variant.[5]

In this case, patient was diagnosed with FSGS NOS variant, where the abnormality was not suitable to be classified into other variants. Not Otherwise Specified variant is the most common type of FSGS. In order to diagnose patient as FSGS NOS variant, other variants must be excluded.

Another cause of FSGS is HIVAN. Human immunodeficiency virus-associated nephropathy is one of causes of end-stage renal disease in the HIV-infected population. Several risk factors such as African-American race, Apolipoprotein-1 (APOL-1) gene polymorphism, comorbidities, high level of human immunodeficiency virus – ribonucleic acid (HIV-RNA) viral load, low CD4 cell counts and nephrotic syndrome have been associated with progressive progression of HIVAN to end-stage renal disease. In one study, it was found that in patients with proven HIVAN from their biopsies have average HIV-RNA viral load of > 30,000 copies/mL and average CD4 cell counts of 127 cells/mm^3.[3,6,7]

In this case, there was focal segmental glomerulosclerosis which was typical abnormality in HIV patients. However, patient's high CD4 cell counts of > 800 cells/L and low level of HIV-RNA viral load, made us difficult to consider if this kidney disorder was caused by HIV infection and more confident that hepatitis B virus infection was causing it, due to high level of Hepatitis B virus deoxyribonucleic acid (HBV-DNA). Hepatitis B infection usually shows histopathological lesions of membranous nephropathy due to the deposition of immune complexes in the glomerulus. However, several studies reported that FSGS abnormality can also be caused by hepatitis B infection with the same mechanism as HIV infection, which is supposed to be direct viral damage.[3,7]

In order to diagnose nephropathy due to hepatitis B infection, we must find HBsAg serology in the patient's serum, evidence of glomerulonephritis from kidney biopsy, and hepatitis B antigen from immunohistochemical examination of kidney biopsy. We could not perform immunohistochemical examination because of limitation of the biopsy tissue samples and also limitation of immunohistochemical examination in Sanglah Hospital. Patient was not diagnosed with HIVAN because HIVAN usually occurs at an advanced stage of HIV infection, accompanied by low CD4 cell counts and high level of HIV-RNA viral load, while in this case, the patient was still in the early stages of HIV infection accompanied by high CD4 cell counts and low level of HIV-RNA viral load.[8] With high level of HBV-DNA and incompatibility of the course of this disease with HIVAN, we diagnosed patient with nephropathy due to hepatitis B infection. In one study, it was proved that high level of HBV-DNA increases glomerular damage and proteinuria. This study showed that level of HBV-DNA is an indicator of viral replication. High level of HBV-DNA represents high viral replication and high release of virus into the blood circulation.[2,8]

Based on the 2012 KDIGO guidelines, treatment of FSGS due to hepatitis B is interferon or nucleoside analogues. Several drugs are already available such as lamivudine, adefovir, entecavir, telbivudine and tenofovir. Patient's therapy should be based on hepatitis B guidelines and nephrotoxic effect of some nucleoside analogues are considered.[9]

According to European Association for the Study of the Liver (EASL) 2017 guidelines, patient with extrahepatic manifestation of hepatitis B infection and replicative active should receive antiviral treatment with nucleoside analogue and PegIFN should not be administered in patient with immune-related extrahepatic manifestations because can worsen some immune mediated extrahepatic manifestation. Guideline from Perhimpunan Peneliti Hati Indonesia (PPHI) also said that PegIFN only use when patient had normal CD4, positive HBeAg, low level of HBV-DNA, increase ALT without decompensated cirrhosis. EASL 2017 also recommend in all HIV-positive patients with Hepatitis B co-infection should start the initiation of antiretroviral-therapy (ART) irrespective of CD4 cell count due to increased risk of fibrosis progression, cirrhosis and hepatocellular carcinoma (HCC). HIV-HBV co-infected patients should be treated with a TDF of TAF-based ART regimen. PPHI also recommend the use of Tenofovir and lamivudine in HBV-HIV co infected but should not be used as monotherapy. EASL guideline said that Tenofovir is the first choice of Nucleoside analogue especially in patient with normal kidney function. Entecavir represent as alternative but without strong evidence against HIV. Indonesian HIV consensus recommend the use of Tenofovir, lamivudine and emtricitabine because these drugs have higher affinity against HIV infection.[10–12]

In this case, we decided to give anti-viral hepatitis B drug, which include tenofovir, because patient had extrahepatic manifestations and also had HIV comorbid. Even though we don't do immunohistochemical examination to confirm exactly cause of glomerulonephritis, as EASL guideline, patient with HIV comorbid and extrahepatic manifestation should be treated as soon as possible. We decided to give fixed dose combination (FDC) highly active ant retro-viral therapy (HAART) drugs which contain tenofovir, lamivudine and entecavir. These drugs can both targeted hepatitis B virus and HIV at the same time. Captopril was given as anti-proteinuria therapy and simvastatin as hypercholesterolemia therapy.

Within three weeks of therapy, there was a decrease in proteinuria from proteinuria +4 to proteinuria +3. From several case reports, remission of proteinuria usually occurred after two months of taking either lamivudine or tenofovir.

CONCLUSION

A 20-years old male with nephrotic syndrome was reported. From histopathological examination of kidney biopsy, we found focal segmental glomerulosclerosis. From laboratory examination, we found high level of HBV-DNA. It was concluded that patient had focal segmental glomerulosclerosis due to hepatitis B infection with HIV infection comorbid. After treatment with hepatitis B anti-viral, there was improvement in symptoms of nephrotic syndrome.

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