

## Case Report

# A case of lupus-like glomerulonephritis in an HIV patient with nephrotic range proteinuria, purpura, and elevated IgA level

Jihyun Yang<sup>1</sup>, Min Young Seo<sup>1</sup>, Ki Tae Kim<sup>1</sup>, Jun Yong Lee<sup>1</sup>, Sun-Chul Kim<sup>1</sup>, Myung-gyu Kim<sup>1</sup>, Sang-Kyung Jo<sup>1</sup>, Won-Yong Cho<sup>1</sup>, Hyoung-Kyu Kim<sup>1</sup>, Nam Hee Won<sup>2</sup>, Ran-Hui Cha<sup>3</sup>, Eunjung Cho<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Division of Nephrology, <sup>2</sup>Department of Pathology, Korea University Anam Hospital, <sup>3</sup>Department of Internal Medicine, Division of Nephrology, National Medical Center, Seoul, Korea

Received March 16, 2014; Accepted June 22, 2014; Epub June 15, 2014; Published July 1, 2014

**Abstract:** Human immunodeficiency virus (HIV) infection is growing medical concern worldwide. There are many types of glomerulonephritis which are associated with HIV infection. We report a case of a 53-year-old Korean man with an HIV infection, who was developed nephritic range proteinuria and purpura with elevated IgA level raising a possibility of Henoch-Schölein Purpura (H-S purpura). However, renal biopsy showed “lupus-like feature” glomerulonephritis without clinical or serologic evidence of systemic lupus erythematosus. Although baseline renal function was maintained without further need for maintenance dialysis following anti-retroviral therapy (ART) and steroid, patient died from uncontrolled gastrointestinal bleeding.

**Keywords:** Human immunodeficiency virus, glomerulonephritis, HIV-associated nephropathy, lupus nephritis, renal biopsy

## Introduction

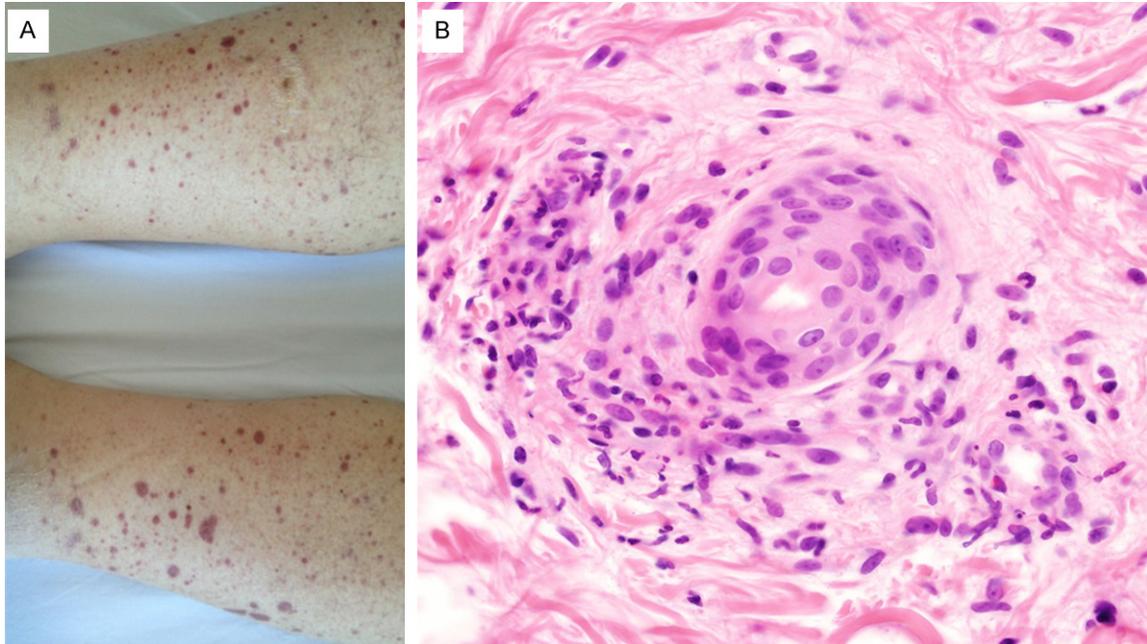
Kidney disease is an important complication of HIV infection and often progresses to end stage renal disease (ESRD) [1-3]. As people live longer with HIV infection, the incidence of kidney disease has increased and glomerulonephritis other than HIV-associated nephropathy (HIVAN) has also been increasingly recognized in the era of anti-retroviral therapy (ART) [1-3]. In Korea, there have been only 2 case reports of non-HIVAN glomerulonephritis, 1 membranous glomerulonephritis and 1 lupus-like glomerulonephritis [4, 5]. Herein, we report a case of HIV-associated immune complex glomerulonephritis with “lupus-like” feature who initially presented with nephrotic range proteinuria and purpura with elevated level of serum IgA.

## Case report

A 52-year-old man was admitted with 1 month history of fatigue, generalized edema and purpura. He complained about gradual weight gain of 10 kg over 4 weeks and purpura on lower

extremities for 10 days (**Figure 1**). He was a constructor without specific medical history. He was divorced, but was not homosexual and had no history of blood transfusion. The vital signs on arrival were as follows: blood pressure, 129/78 mmHg; pulse rate, 72 beats/min; respiratory rate, 20/min; and body temperature, 36.8°C. He was acutely ill looking, had anemic conjunctiva and palpable purpura on the extensor surface of legs with pitting edema. There were no palpable lymph nodes. The laboratory examination revealed hemoglobin 4.4 g/dL (hematocrit 20%), platelet count 177,000/μL, white blood cell count 3,830/μL, C-reactive protein 8.97 mg/dL, aspartate transaminase 20 IU/L, alanine transaminase 14 IU/L, alkaline phosphatase 91 IU/L, gamma-glutamyltransferase 14 IU/L, total cholesterol 159 mg/dL, blood urea nitrogen (BUN) 51 mg/dL, creatinine 2.49 mg/dL, total protein 5.2 g/dL, albumin 1.5 g/dL. In urinalysis, protein 3+ and red blood cell (RBC) count > 60/high power field were demonstrated. He had nephrotic range proteinuria (protein 4422.6 mg/day, albumin 2525.9 mg/

## Lupus-like glomerulonephritis in an HIV patient



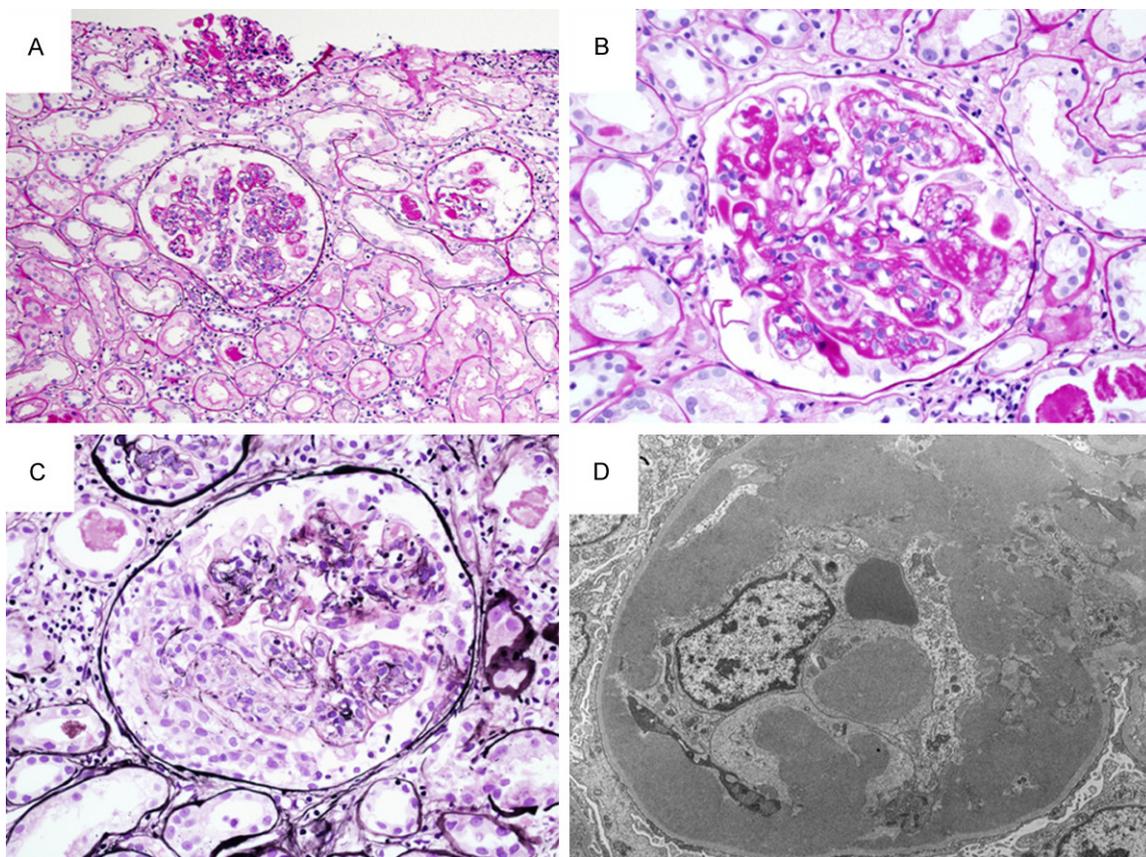
**Figure 1.** A. Palpable purpura on extensor surface of lower legs. B. Skin biopsy shows cutaneous leukocytoclastic vasculitis (H&E, x 400).

day) and serum/urine protein electrophoresis and immunofixation electrophoresis showed non-specific findings. Enzyme immunoassay test for HIV antigen and antibody was positive, but other viral markers including hepatitis B and C were negative. Serum IgA was elevated to 612.6 (70~400) mg/dL and C3 was slightly decreased to 83.2 (90~180) mg/dL, but IgG, IgM, and C4 were within normal range. Other serologic tests including rheumatoid factor, antinuclear antibody (ANA), double-stranded DNA, anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, and cryoglobulin were all negative. Low mean corpuscular volume 65.3 (80-96) fL, mean corpuscular hemoglobin concentration 20.6 (26-34) pg, low transferrin saturation [iron:  $\leq 10$  (70-180)  $\mu\text{g/dL}$ , total iron binding capacity 178 (250-450)  $\mu\text{g/dL}$ ], low ferritin concentration 105 (17-390) ng/mL and history of recent bleeding from external hemorrhoid indicated iron deficiency anemia. No specific abnormalities except chronic proctitis were found in gastro- and colono-fiberscopy and 5 pints of packed RBC were administered. Chest roentgenogram showed bilateral pleural effusion with inactive pulmonary tuberculosis. Continuous intravenous furosemide administration (640 mg/day) was immediately started to con-

trol peripheral edema. However, despite the high dose of furosemide administration, the patient's urine output and edema were not improved and the level of BUN and creatinine showed a gradual increase. Several sessions of ultrafiltration were then performed to control edema before kidney biopsy.

The skin biopsy from purpura revealed leukocytoclastic vasculitis, but unfortunately the presence of IgA deposition could not be determined (**Figure 1**). Light microscopic examination of kidney tissue showed diffuse endocapillary and mesangial proliferation along with segments of active epithelial crescents and "wire-loop" appearance (**Figure 2A-C**). Direct immunofluorescence revealed diffuse, fine or coarse granular deposition of IgG, IgA, IgM, C3, kappa and lambda light chain with  $\geq 2+$  intensity (0-4+ scale), but the intensity of C1q deposition was 0 to trace (**Figure 3**). On electron microscopy, there was massive subendothelial deposits along with subepithelial and mesangial deposits, and endothelial tubuloreticular inclusions were also found (**Figure 2D**). Despite nearly absence of C1q deposition, all these features were more compatible with HIV-associated immune complex glomerulonephritis with "lupus-like" features rather than IgA nephropathy found in H-S purpura.

## Lupus-like glomerulonephritis in an HIV patient



**Figure 2.** A. Renal biopsy shows increased cellularity of mesangial cells and endocapillary proliferation with some neutrophils. Capillary walls and basement membranes are thickened with “wire-loop” appearance. (PAS stain, x 400). B. Epithelial crescent (Silver stain, x 400). C. Massive subendothelial fuchsinophilic deposits and some subepithelial as well as mesangial deposits are noted. (MT stain, x 400). D. Massive subendothelial, subepithelial and mesangial deposits are observed (Electron microscopy, x 3000).

Because absolute CD4 T cell count was only 135/ $\mu$ L with very high viral load (74,500 copies/mL), ART was immediately started and followed by high dose steroid (1 mg/kg) for treatment of glomerulonephritis.

After 3 months of ART and high dose steroid therapy, HIV-1 RNA was not detected anymore. However, CD4 T cell count still remained low (90/ $\mu$ L), proteinuria persisted (7200 mg/day), and steroid was gradually tapered to 10 mg/day. While renal function was maintained stable (BUN/creatinine 68/2.4 mg/dL) without need for maintenance dialysis, he readmitted to hospital due to massive upper gastrointestinal bleeding from gastric ulcer. He died from hypovolemic shock despite gastrofiberscopic and angiographic interventions.

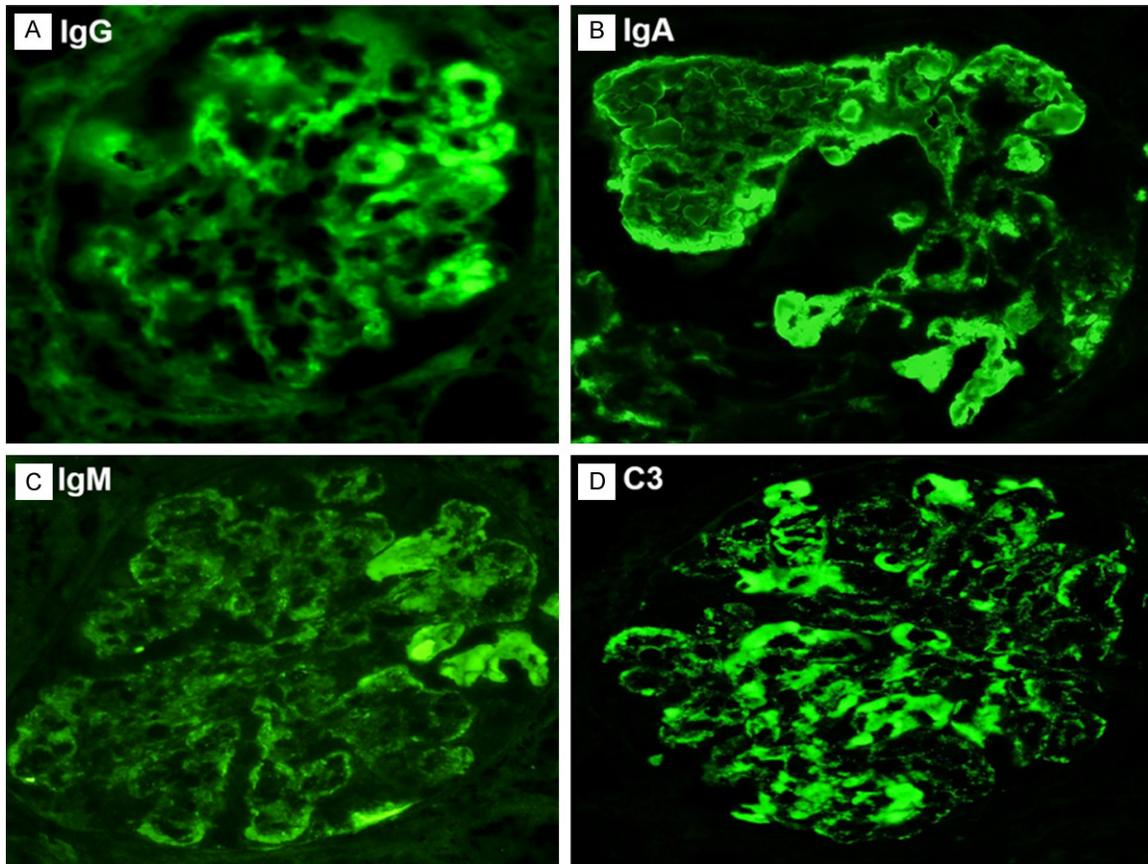
### Discussion

The prevalence of HIV infection is increasing and was estimated to be 34 million (31.4~35.9

million) at the end of 2011 [6, 7]. With increased life expectancy of HIV infected patients in the era of ART, complications and morbidities associated with HIV infection have become emerging problems [8-11]. Kidney dysfunction is one of major comorbid conditions and develops in up to 30% of HIV infected patients [11]. Both acute kidney injury or chronic kidney disease (CKD) can develop either directly linked to HIV infection or related to coexisting conditions such as hypertension, diabetes or nephrotoxic medications such as antiretroviral therapy. HIV infection is one of the leading causes of CKD especially in African-Americans. Progression to ESRD was reported as 35% in HIV-related CKD patients [12] and the prevalence of HIV-related ESRD continues to increase even in the antiretroviral era [13, 14].

Three major types of nephropathies pathogenetically linked to HIV infection have been reported before the antiretroviral era: throm-

## Lupus-like glomerulonephritis in an HIV patient



**Figure 3.** Immunofluorescence study shows (A) IgG (3+), (B) IgA (3+ to 4+), (C) IgM (2+), and (D) C3 (4+) deposits in capillary walls with finely or coarsely granular pattern and diffuse distribution.

botic microangiopathies, immune complex renal diseases, and HIVAN [15]. While HIVAN, a collapsing variant of focal segmental glomerulosclerosis (FSGS) which is frequently observed in patients with African heritage, was known to be the most common subtype, recent studies have demonstrated that classical FSGS or immune complex glomerulonephritis is more frequent especially among Caucasians and Asians [16, 17]. The prevalence of HIV-associated immune complex glomerulonephritis has been estimated as 37-76% in Europe and Asia [18].

In 2005, Haas first advocated a new entity of immune complex nephropathy called HIV-associated immune complex glomerulonephritis with “lupus-like” features by performing clinicopathologic study of 77 specimens. He noted that 14 patients who belonged to this new entity showed full house fluorescence staining of IgG, IgA, IgM, C3, C1q with negative serologic test for anti-nuclear antibody or dou-

ble-stranded DNA. He also showed that most of the patients presented with nephrotic syndrome, microscopic hematuria, and impaired renal function progressing to ESRD and concluded that immune complex glomerulonephritis with “lupus-like” feature is not an uncommon disease entity.

Our first clinical impression of this patient was H-S purpura among HIV-associated glomerulonephritis because the patient initially presented with palpable purpura, increased serum level of IgA and nephrotic range proteinuria with positive HIV antibody. However, presence of strong positive granular deposition of “full-house” immunoglobulin and C3 in immunofluorescence microscopy along with typical “wire-loop” appearance in light microscopy and massive subendothelial, subepithelial and mesangial deposits with tubuloreticular inclusion in electron microscopy led us to conclude that “HIV-associated glomerulonephritis with lupus-like feature” rather than H-S purpura

might be more suitable for pathological diagnosis despite the nearly absence of C1q.

However, the nearly absence of C1q in our patient's kidney biopsy specimen still can raise the possibility of IgA nephropathy/H-S purpura. In fact, IgA nephropathy was found to be the second most common subtype in non-lupus "full-house" nephropathies in one study (21%, 5/24) [19]. On the other hand, glomerular deposition of C1q is not always present even in lupus nephritis and small vessel vasculitis with purpura can also be seen in patients with lupus [20].

After considering all, renal pathology and clinical presentation in our case seem to be overlapping between IgA nephropathy/H-S purpura and lupus-like feature, suggesting that these two are not completely different entities but lie in a same spectrum of immune complex mediated glomerulonephritis where either passive trapping of immune complexes or in-situ immune complex formation occurs in HIV patients.

Despite ART and high dose steroid, CD4 T cell count remained low and our patient's outcome was poor. Haas et al. also demonstrated poor renal outcome by identifying that 9 out of 10 patients, who initially presented with heavy proteinuria with nephrotic syndrome (> 5.0 g/day), progressed to ESRD. In contrast to HIVAN, less is known about risk factors, presence of racial predilection or outcome in HIV-associated immune complex glomerulonephritis due to the paucity of data. United State multicenter cohort study showed ART did not retard the progression of kidney disease [21]. Also, they mentioned that patients with HIV-associated immune complex glomerulonephritis had lower HIV viral load, higher CD4 T cell count, higher estimated glomerular filtration rate, and lower ESRD incidence compared to those with HIVAN. However, the risk factors, clinical manifestation, treatment response to ART or steroid and outcome in HIV-associated immune complex glomerulonephritis need to be determined in larger clinical studies.

In conclusion, we report a case of HIV-associated nephropathy with lupus-like feature who presented with purpura, nephrotic range proteinuria with elevated IgA level.

### Acknowledgements

There was no special acknowledgment issue.

### Disclosure of conflict of interest

There are no conflicts of interest.

**Address correspondence to:** Dr. Eunjung Cho, Department of Internal Medicine, Korea University Anam Hospital, 73 Incheon-ro, Seongbuk-gu, Seoul 136-705 Korea. Tel: +82 2 920 5475; Fax: +82 2 927 5344; E-mail: icdej@naver.com

### References

- [1] Chandran S, Jen KY and Laszik ZG. Recurrent HIV-Associated immune complex glomerulonephritis with lupus-like features after kidney transplantation. *Am J Kidney Dis* 2013; 62: 335-338.
- [2] Haas M, Kaul S and Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005; 67: 1381-1390.
- [3] Szczech LA. Renal disease: the effects of HIV and antiretroviral therapy and the implications for early antiretroviral therapy initiation. *Curr Opin HIV AIDS* 2009; 4: 167-170.
- [4] Kim JS, Yang JW, Kim MS, Han ST, Kim BR, Han BG and Choi SO. A case of membranous glomerulonephritis in a patient with HIV infection. *Korean Journal of Nephrology* 2007; 26: 740-743.
- [5] Yoon JH, Chun SH, Shin JY, Lim BJ, Kim YS, Na KR, Suh KS, Lee KW and Shin YT. A case of lupus-like glomerulonephritis in an HIV-infected patient. *Infection and Chemotherapy* 2009; 41: 362-365.
- [6] Anglaret X. Global AIDS epidemic: from epidemiology to universal treatment. *La Revue de médecine interne/fondée. Par La Société Nationale Française De Médecine Interne* 2008; 29: S269.
- [7] Demberg T and Robert-Guroff M. Controlling the HIV/AIDS epidemic: current status and global challenges. *Front Immunol* 2012; 3: 250.
- [8] Wali RK, Drachenberg CI, Papadimitriou JC, Keay S and Ramos E. HIV-1-associated nephropathy and response to highly-active antiretroviral therapy. *Lancet* 1998; 352: 783-784.
- [9] Jackson S, Dawson LM and Kotler DP. IgA1 is the maunoglobulin component of immune complexed in the acquired immune deficiency syndrome. *J Clin Immunol* 1988; 8: 64-68.

## Lupus-like glomerulonephritis in an HIV patient

- [10] Aydin S, Mete B, Yilmaz M, Yenidunya G, Zaras R, Tunckale A and Tabak F. A patient with HIV infection presenting with diffuse membranous glomerulonephritis in a country with a low HIV prevalence-remarkable remission with therapy. *J Infect Public Health* 2012; 5: 207-210.
- [11] Gupta SK, Eustace JA, Winston JA, Boydston II, Ahuja TS, Rodriguez RA, Tashima KT, Roland M, Franceschini N, Palella FJ, Lennox JL, Klotman PE, Nachman SA, Hall SD and Szczech LA. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV medicine association of the infectious disease society of America. *Clin Infect Dis* 2005; 40: 1559-1585.
- [12] Lucas GM, Lau B, Atta MG, Fine DM, Keruly J and Moore RD. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis* 2008; 197: 1548-1557.
- [13] Hartle PM, Carlo ME, Dwyer JP and Fogo AB. AKI in an HIV patients. *J Am Soc Nephrol* 2013; 24: 1204-1208.
- [14] Wyatt CM and Klotman PE. HIV-associated nephropathy in the era of antiretroviral therapy. *Am J Med* 2007; 120: 488-492.
- [15] Kimmel PL, Phillips TM, Ferreira-Centeno A, Farkas-Szallasi T, Abraham AA and Garrett CT. HIV-associated immune-mediated renal disease. *Kidney Int* 1993; 44: 1327-1340.
- [16] Casanova S, Mazzucco G, Barbiano di Belgiojoso G, Motta M, Boldorini R, Genderini A and Monga G. Pattern of glomerular involvement in human immunodeficiency virus-infected patients: an Italian study. *Am J Kidney Dis* 1995; 26: 446-453.
- [17] Williams DI, Williams DJ, Williams IG, Unwin RJ, Griffiths MH and Miller RF. Presentation, pathology, and outcome of HIV associated renal disease in a specialist centre for HIV/AIDS. *Sex Transm Infect* 1998; 74: 179-184.
- [18] Praditpornsilpa K, Napathorn S, Yenrudi S, Wankrairo P, Tungsaga K and Sitprija V. Renal pathology and HIV infection in Thailand. *Am J Kidney Dis* 1999; 33: 282-286.
- [19] Wen YK and Chen ML. Clinicopathological study of originally non-lupus "full-house" nephropathy. *Ren Fail* 2010; 32: 1025-1030.
- [20] Tan Y, Song D, Wu LH, Yu F and Zhao MH. Serum levels and renal deposition of C1q complement component and its antibodies reflect disease activity of lupus nephritis. *BMC Nephrol* 2013; 14: 63.
- [21] Foy MC, Estrella MM, Lucas GM, Tahir F, Fine DM, Moore RD and Atta MG. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. *Clin J Am Soc Nephrol* 2013; 8: 1524-1532.