中文題目：個案報告－A 型免疫球蛋白腎病變併發肺外結核和巨細胞病毒感染

英文題目：Case report for disseminated TB associated with IgA nephropathy: a rare but possible cause

作　　者：邱裕桓[1]，趙若雁[2]

服務單位：[1]國立成功大學醫院內科部，[2]國立成功大學醫院內科部腎臟科

Case Presentation:

A 65-year-old female patient presented hematuria, proteinuria and acute renal failure. She had a history of hypertension. Her medication included amlodipine and bisoprolol. At presentation, blood pressure was 143/88 mmHg, heart rate was 70 beats/min and ear temperature was 37.3 degree of Celsus. Physical examination was unremarkable without pulmonary rales or peripheral edema. Laboratory studies showed elevated serum creatinine (2.04 mg/dL) with estimated glomerular filtration rate 25 mL/min. Urinalysis revealed hematuria with 148 RBC per high-power field and proteinuria of 100 mg/dL. Spot urine albumin-creatinine ratio of 1675 mg/g and protein-creatinine ratio of 2202 mg/g were recorded. Renal sonography showed bilateral chronic renal parenchymal disease with grade 1 cortical echogenicity and blurred contour. She underwent a renal biopsy. A diagnosis of IgA nephropathy (IgAN) was made among which segmental glomerulosclerosis, focal crescent formation (26%) and moderate arteriosclerosis were found (Figure 1). Oxford classification was M0E1S1T0. She was prescribed high dose prednisolone and cyclophosphamide afterward. Her renal function and hematuria improved gradually (serum creatinine 1.14 mg/dL and eGFR 48 mL/min). Cyclophosphamide was replaced with azathioprine two months later. However, she reported poor appetite, oral ulcers and general weakness at the meanwhile. Leukopenia and fever developed. She was arranged admission for antibiotics treatment.

The patient reported mild cough and dysuria. Urinalysis showed mild pyuria but no bacteriuria. Abdominal sonography revealed right renal cyst but no abnormal space-occupying lesion in the liver. Chest X-ray revealed only non-specific bilateral infiltrates. Cultures of blood, urine and sputum yielded non-specific pathogens. Echocardiogram revealed adequate left ventricular systolic function without vegetation. Gallium inflammation scan was arranged and showed inflammation in bilateral lung and kidneys. Neutropenia improved soon but she still had intermittent fever despite broad-spectrum antibiotics treatment for more than 2 weeks. Further follow-up of chest radiograph was

notable for miliary nodules in bilateral lung fields. Quantiferon test showed positive report, implying latent tuberculosis infection. Examination of bronchoscopy showed only anthracosis without granuloma or acid-fast stain positive pathogen. Video-Assisted lung wedge biopsy was done from which granulomatous inflammation with caseating necrosis and acid-fast stain positive bacilli were found.

The patient was prescribed standard anti-tuberculosis medications for extra-pulmonary tuberculosis infection. However, she still presented intermittent fever after two weeks of anti-TB medication. In addition, she presented increasing hematuria, proteinuria and deteriorated renal function. Again she received renal biopsy, seven months after previous study, which still revealed IgAN with focal crescents formation (about 30%). Besides, one viral inclusion was noted in tubular lumen but disappeared during cytomegalovirus (CMV) and SV40 immunostain (Figure 2). Viral nucleic acid detection of CMV in urine showed positive result. Viral nucleic acid of CMV was not detected in serum. Her fever subsided gradually after Valganciclovir treatment. No pulse steroid therapy or double filtration plasmapheresis administrated for rapid progression of renal function due to families' decision. The patient received complete course of valganciclovir and anti-tuberculosis medication. Followed renal function test remained stationary.

Discussion:

IgAN is an immune complex-mediated glomerulonephritis defined by the presence of mesangial IgA deposits often associated with mesangial hypercellularity. The pathogenesis involves an abnormal glycosylated immunoglobulin A with deficient galactose residues that induce autoantibodies and immune complexes formation in the renal mesangium.[1] The clinical manifestation, disease natural course and pathology pattern vary. This patient presented with hematuria, proteinuria and rapidly progressive renal failure. Her kidney biopsy revealed IgAN with segmental glomerulosclerosis, focal crescent formation (26%) in accompany with moderate arteriosclerosis. There was no obvious evidence of secondary causes of IgAN such as chronic infection or cirrhosis initially. Thus, she received immunosuppressant that seemed reasonable and did lead to improvement of her renal function.

The etiology of IgAN might be secondarily caused in some patients. Literature

reviews showed some patients present renal mesangial IgA deposits secondary to tuberculosis infection.[2-8] Many have noted elevations of serum levels of IgA with circulating immune complexes in patients with active tuberculosis. Deposition of these IgA-containing immune complexes in the kidney leads to activation of alternate complement pathway and consequent local injury and IgA nephropathy.[9]

Cytomegalovirus (CMV) is worldwide distributed. Immunocompromised adult are more likely to undergo reactivation disease.[10-12] CMV persists indefinitely in host tissue. On the other hand, findings from several case series had identified CMV antigens in renal biopsy specimen in patients with IgAN with varying degree of serum antigenemia.[13, 14] It is still controversial that the presence of CMV antigen might be pathognomonic or merely a co-incidence. Studies had shown two separate pathologic mechanisms involved in CMV glomerulopathy in renal transplant patients.[15] One is through direct infection of glomerular cells by CMV, while additional mechanisms may include antibody or cytokine-mediated injury which may come from monocytes carrying CMV virus. In our patient, the most probable explanation of viral inclusion which is typical of CMV disease may imply the reactivation of CMV in immunosuppressed status.

The use of immunosuppressant therapy increases risk of infection or cause reactivation of occult infections. It is possible that the patient's IgAN was caused by TB infection though was not clinically detected or diagnosed at that time. According to current consensus, patients with cresentic IgAN should receive high-dose steroids and cyclophosphamide therapy.[1, 16, 17] The prescription of immunosuppressant did lead to improvement of our patient's renal function, hematuria and proteinuria. However, her TB infection became full-blown afterward. Her prolonged fever did not subside until the prescription of anti-CMV agents. Therefore, closely clinical monitor for any infection signs during immunosuppressant treatment for these patients is needed. Repeated renal biopsy for other etiology surveillance is necessary. Otherwise, plasma exchange as an adjunctive therapy for crescentic IgA nephropathy could be considered in severe crescentic IgAN instead of intensive immunosuppressive therapy alone.[18]

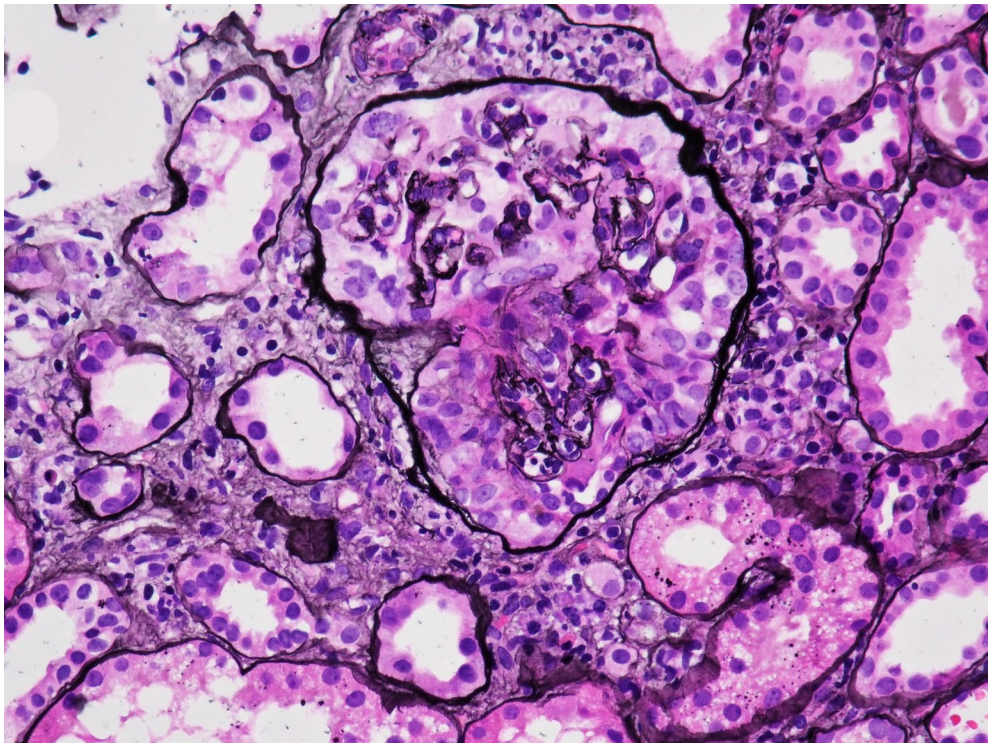

Figure 1. The glomerulus shows cellular crescent formation.

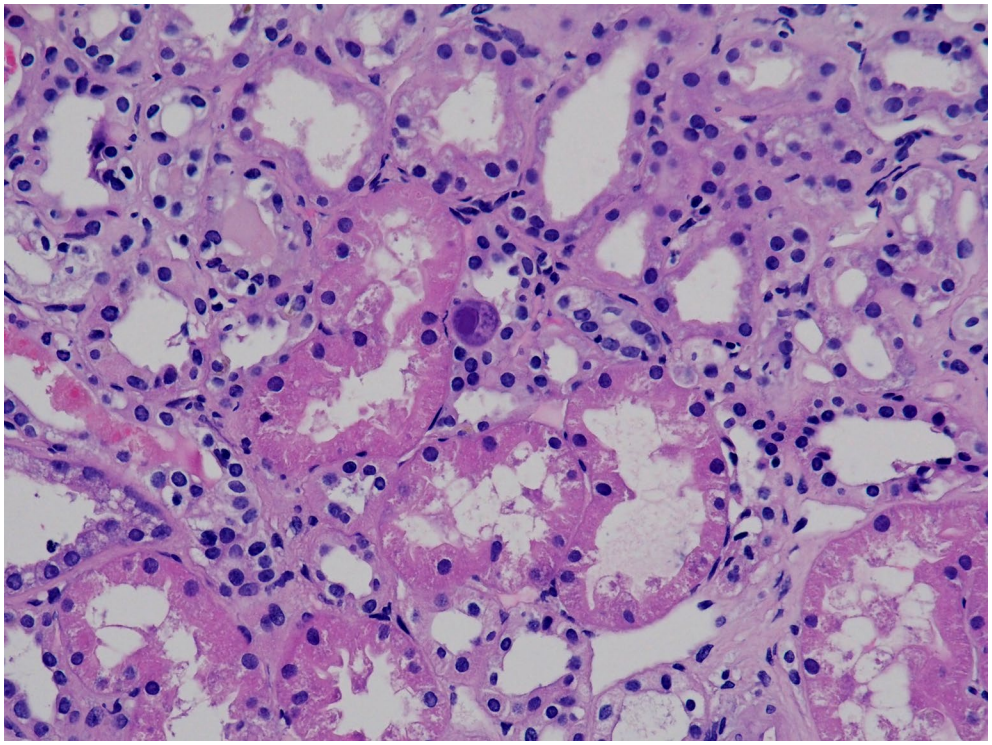

Figure 2. One viral inclusion in tubular epithelium.

Reference:

1. Lewis JB, Neilson EG. Glomerular Diseases. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine, 19e*. New York, NY: McGraw-Hill Education; 2015.

2. Cohen AJ, Rosenstein ED. IgA nephropathy associated with disseminated tuberculosis. *Archives of internal medicine.* 1985;145(3): 554-556.

3. De Siati L, Paroli M, Ferri C, Muda AO, Bruno G, Barnaba V. Immunoglobulin A nephropathy complicating pulmonary tuberculosis. *Annals of diagnostic pathology.* 1999;3(5): 300-303.

4. Keven K. A case of pulmonary tuberculosis associated with IgA nephropathy. *Int J Tuberc Lung Dis.* 2004;8(10): 1274-1276.

5. Matsuzawa N, Nakabayashi K, Nagasawa T, Nakamoto Y. Nephrotic IgA nephropathy associated with disseminated tuberculosis. *Clinical nephrology.* 2002;57(1): 63-68.

6. Ortmann J, Schiffl H, Lang S. Partial clinical remission of chronic IgA nephropathy with therapy of tuberculosis. *Deutsche medizinische Wochenschrift (1946).* 2010;135(24): 1228-1231.

7. Singh P, Khaira A, Sharma A, Dinda A, Tiwari S. IgA nephropathy associated with pleuropulmonary tuberculosis. *Singapore Med J.* 2009;50(7): e268-269.

8. Kanodia KV, Vanikar AV, Patel RD, Suthar KS, Trivedi HL. Crescentic Glomerulonephritis Associated with Pulmonary Tuberculosis. *J. Clin. Diagn. Res.* 2016;10(1): ED1-ED2.

9. Wang Y, Tao Y. Tuberculosis-associated IgA nephropathy. *Journal of International Medical Research.* 2018: 0300060518774127.

10. Hung K-Y, Chen W-Y, Yan T-S, Yang C-S, Ferng S-H, Kao C-L. Adult primary IgA nephropathy and common viral infections. *Journal of Infection.* 1996;32(3): 227-230.

11. Lim CC, Tung YT, Tan BH, et al. Epidemiology and risk factors for cytomegalovirus infection in glomerular diseases treated with immunosuppressive therapy. *Nephrology (Carlton).* 2018;23(7): 676-681.

12. Numata A. The Nephritis Associated with Viral Infections. *Journal of Nephrology & Therapeutics.* 2012;01(S4).

13. Gregory M, Hammond ME, Brewer E. Renal deposition of cytomegalovirus antigen in immunoglobulin-A nephropathy. *The Lancet.* 1988;331(8575-8576): 11-14.

14. Telenti A, Donadio J, Smith T. Failure to detect cytomegalovirus DNA in IgA nephropathy by polymerase chain reaction. *Journal of the American Society of*

Nephrology. 1990;1(5): 841-841.

15. Vichot AA, Formica RN, Moeckel GW. Cytomegalovirus Glomerulopathy and Cytomegalovirus Interstitial Nephritis on Sequential Transplant Kidney Biopsies. *Am. J. Kidney Dis.* 2014;63(3): 536-539.

16. Floege J, Eitner F. Current therapy for IgA nephropathy. *J Am Soc Nephrol.* 2011;22(10): 1785-1794.

17. Floege J, Rauen T. Immunosuppression in IgA nephropathy: how certain are we? *Kidney Int.* 2016;89(1): 9-11.

18. Xie X, Lv J, Shi S, et al. Plasma exchange as an adjunctive therapy for crescentic IgA nephropathy. *American journal of nephrology.* 2016;44(2): 141-149.