Case Report

Pulmonary Hemorrhage with Acute Renal Injury in a Patient with IgA Nephropathy

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IgA nephropathy (IgAN) is a form of glomerular diseases which is usually aggravated by infection in respiratory or gastrointestinal systems. The clinical manifestations in IgAN can be asymptomatic microscopic hematuria, gross hematuria, nephritic syndrome, nephrotic syndrome or acute renal injury from crescentic glomerulonephritis. Acute interstitial nephritis (AIN) has been previously described as an unusual cause of acute renal injury in IgAN. Hemoptysis from diffuse pulmonary hemorrhage is a rare manifestation in IgAN. We reported a patient who presented with fever, hemoptysis from diffuse pulmonary hemorrhage, and acute renal injury. Renal biopsy revealed IgAN concomitant with AIN which was the cause of renal dysfunction. We conclude that pulmonary hemorrhage and acute interstitial nephritis can be found in IgAN. The etiology of pulmonary hemorrhage and acute interstitial nephritis might be from infection. Renal biopsy is a mandatory investigation to make the correct diagnosis.

Keywords: *Acute disease, Glomerulonephritis, IGA, Hemorrhage, Immunoglobulin A, Kidney diseases, Lung diseases, Interstitial*

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IgA nephropathy (IgAN) is a common glomerulopathy which usually has macroscopic hematuria or microscopic hematuria following respiratory tract or gastrointestinal tract infections[1]. The microscopic hematuria with proteinuria is reported in 30-40% of IgAN patients[1]. Acute renal injury is uncommon in IgAN and it can be occurred by two distinct mechanisms. The first mechanism of acute renal injury in IgAN is from immune process with crescent formation and the other mechanism is from tubular occlusion by red blood cells[2]. The definite diagnosis of IgAN is the renal biopsy which demonstrates mesangial cell proliferations, increased mesangial matrix and mesangial deposition of IgA[2]. IgAN can be associated with several diseases such as connective tissue diseases, dermatologic diseases, hematological diseases, or neoplastic diseases[2]. We reported a patient who presented with fever, hemoptysis, azotemia, and nephritis feature then he was diagnosed of IgAN.

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Case Report

A 53-year-old Thai male came to medical department clinic at the HRH Princess Mahachakri Sirindhorn Medical Center because of fever and flu-like symptoms for five days. Two days prior to the hospital, he had diarrhea two to three times per day. He did not have urinary symptoms, skin rash, upper respiratory tract symptoms, or arthralgia. His past medical history was not significant. He was a cigarette smoker and an alcohol drinker. He was admitted to the hospital because of malaise and high grade fever.

Physical examination on admission revealed temperature 38.5°C, pulse rate 120/min, respiratory rate 18 /min, blood pressure 120/70 mmHg and the room air oxygen saturation 92%. Pulmonary examination showed inspiratory crackles at the lower lobes of both lungs and the liver was palpated 2 centimeters below the right costal margin without tenderness. A physical examination in other systems was unremarkable.

Laboratory examination was performed to investigate the cause of fever. His complete blood count (CBC) revealed hemoglobin 12 g/dL, white cell count 6.9 x10^3/mm^3 (85% neutrophils, 5% lymphocytes,

4% monocytes, and 6% eosinophil), platelet count $77x10^3/mm^3$. Urinalysis revealed 2+ protein, 3+ blood with 50-100 red cells per high-power field. The urinary protein excretion was 1.5 g/day. Renal function revealed serum urea (BUN) 65 mg/dL and serum creatinine (s.Cr) 3.8 mg/dL. Other biochemical tests revealed aspartate transferase 76 U/l (normal 15-37 U/l), alanine transferase 50 U/l (normal 30-65 U/l), alkaline phosphatase 185 U/l (normal 50-136 U/l), total bilirubin 3.3 mg/dl, direct bilirubin 2.8 mg/dl, albumin 2.2 g/dl, and globulin 2.9 g/dl. Coagulation tests revealed prothrombin time (PT) 11.70 seconds (normal 10.00-14.00 seconds), international normalized ratio (INR) 0.95, partial thromboplastin time (PTT) 35.00 seconds (normal 29.00-35.00 seconds). Viral hepatitis screening for hepatitis B and hepatitis C and blood cultures for bacteria were negative. Thick and thin film smears for malarial infection were negative. Chest x-ray was normal (Fig. 1).

He was treated with ceftriaxone and doxycycline as the empirical treatment for systemic infections, suspected leptospirosis and enteric fever. One day after admission, the patient developed shortness of breath, pleuritic chest pain, and hemoptysis. He had 1+ pitting edema in both legs but no orthopnea or paroxysmal nocturnal dyspnea. CBC, serum creatinine and chest x-ray were repeated. CBC revealed hemoglobin 12 g/dL, white cell count $13.4 \times 10^3/mm^3$ (90% neutrophils, 6% lymphocytes, and 4% monocytes), platelet count $43 \times 10^3/mm^3$. Serum creatinine level was 4.1 mg/dl. Chest x-ray showed bilateral alveolar and interstitial infiltrations (Fig. 2). Intravenous furosemide was prescribed for treatment of hypervolemia, but the patient's condition and pulmonary infiltrations were not improved. Sputum gram stain, acid-fast bacilli stain, cultures, and cytology were negative. Serological tests for leptospirosis, scrub typhus, and human immunodeficiency virus were negative. Other tests for immunological-related diseases such as ANA, ANCA, and lupus anticoagulant were negative. Complement levels (C3 and C4) and cogulation profiles (PT, INR and PTT) were in normal ranges. The patient rejected to be performed bronchoscopic investigation.

The patient's fever subsided after the fifth day of antibiotic treatment. The course of antibiotics was fourteen days. His hemoptysis spontaneously stopped, complete blood count returned to normal, and creatinine level decreased to 1.6 mg/dl before he was discharged. He was followed-up one week later and serum creatinine level was 1.7 mg/dl. Serum albumin was 3.0 g/dl. A renal biopsy was performed because of a prolonged duration of acute renal injury. Conventional light microscopic examination revealed total 12 glomeruli with 4 global sclerotic glomeruli and one segmental sclerotic glomerulus (Fig. 3A). Eight glomeruli showed mesangial cell proliferations

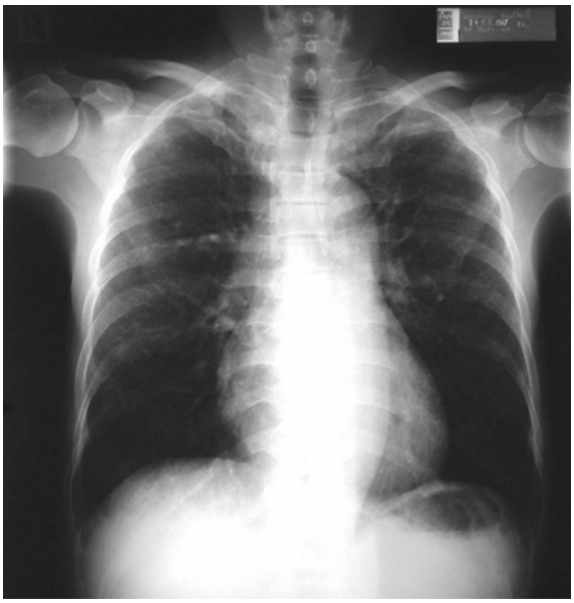

Fig. 1 Chest x-ray on admission date; showing normal study

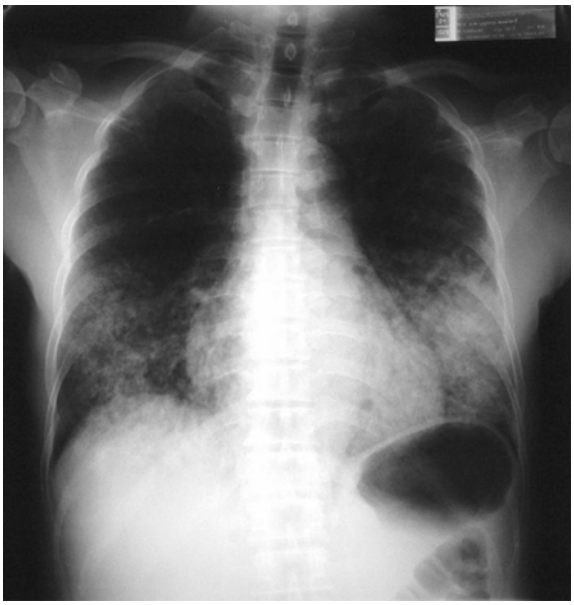

Fig. 2 Chest x-ray one day after admission; showing extensive bilateral alveolointerstitial infiltrations, predominantly in the lower lobes

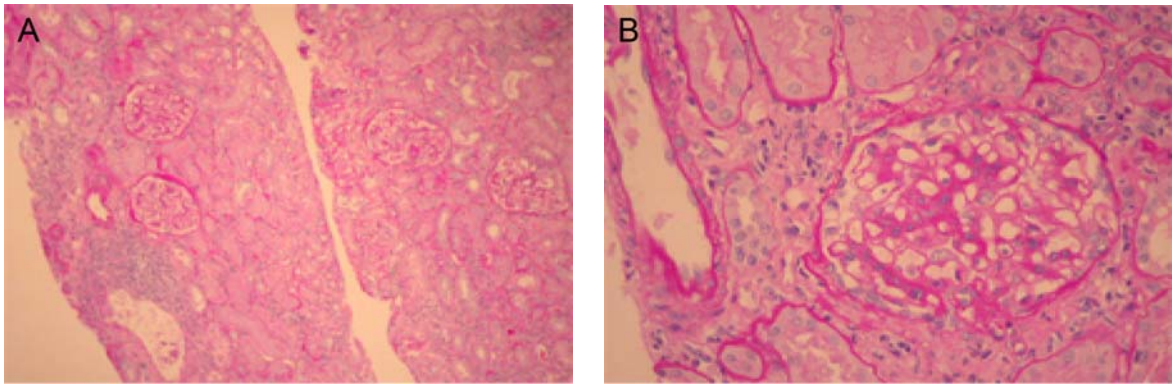

Fig. 3 Renal biopsy with periodic-acid Schiff stain demonstrated glomeruli with mesangial cell proliferations and increased mesangial matrix and area of interstitial infiltration (A; magnification x 100 and B; magnification x 250)

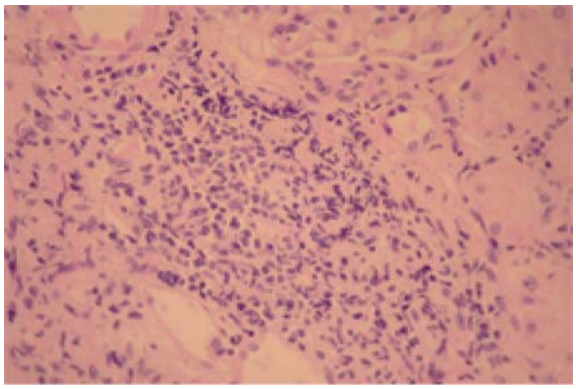

Fig. 4 Interstitial areas showed lymphocyte and plasma cells infiltration with mild interstitial edema (hematoxylin-eosin stain; magnification x 250)

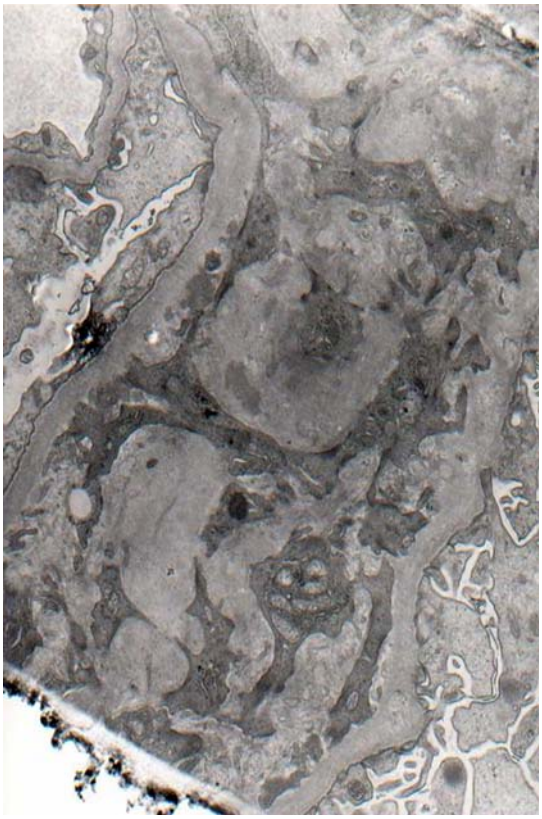

Fig. 5 Electron microscopic examination of a glomerulus showed electron-dense deposits in the paramesangial basement membrane and mesangial area

and increased mesangial matrix but normal glomerular capillary thickening (Fig.3B). Crescent formation in Bowman's space was not found. There were lymphocyte and plasma cells infiltration with mild interstitial edema and fibrosis in interstitial areas (Fig. 4). There were mild tubular atrophy, focal tubular necrosis, tubular cells regeneration and tubulitis. Blood vessels demonstrated arteriolar hyalinosis and intimal sclerosis. Immunofluorescent examination showed 2+ of IgA, and 2+ of C3 depositions in granular pattern at mesangial areas in all glomeruli. No immune complex deposition was seen in the tubulointerstitial areas. Electron microscopic examination showed electrondense deposits in mesangial areas (Fig. 5). The results of renal biopsy were compatible with IgAN and acute interstitial nephritis.

One month after the performed kidney biopsy, the patient came to follow-up with normal physical examination. He returned back to work and had normal renal function. He did not visit the hospital again. We interviewed him by phone recently and found that he was in good condition.

Discussion

IgAN in association with pulmonary hemorrhage is uncommon. A total eight cases of IgAN and pulmonary hemorrhage have been previously reported[3-6]. In these reports[3-6], four patients died (two patients died from respiratory failure, one patient died from cardiac arrest, and one patient died from overwhelming sepsis), two patients developed dialysis-dependent renal impairment, and two patients had normal renal function. Some patients in these reports were treated with corticosteroid and cyclophosphamide. The pathogenesis of pulmonary hemorrhage in IgAN has not been definitely known. There was a case report suggested that pulmonary hemorrhage was related to immune-complex capillaritis. This patient had pulmonary IgA deposition[3]. Some patients with IgAN had IgA and C3 depositions in skin which were distant to the kidney[7]. One patient with IgAN was reported of having recurrent bloody peritoneal dialysate during respiratory tract infection[8]. These reports demonstrate that non-renal hemorrhage can occur in IgAN patients.

Renal impairment can occur in patients with IgAN[9]. It can be resulted from crescentic glomerulonephritis, acute tubular necrosis (ATN), or acute interstitial nephritis (AIN)[10-15]. Crescentic glomerulonephritis presented at the initial course of IgAN is uncommon but it usually occurs as the course of IgAN lengthens[1]. The pathogenesis of ATN in patients with IgAN may be associated with blockage of tubular lumens by red blood cell casts and subsequently tubular epithelial cell damage[11,13]. The causes of AIN in the reported patients of IgAN are probably related to infection or drug exposure[15,16]. It has been postulated that the superimposed infection or drug exposure might trigger an autoimmune response to tubular antigen in patients with IgAN resulting in AIN[15]. Some cases of IgAN with AIN in these reports received corticosteroids and they had the recovery of renal function[15].

Our patient presented with fever, renal impairment, hemoptysis, and abnormal chest x-ray which were similar manifestations in previous reported cases of IgAN with pulmonary involvement. The treatment in our patient was different from previous cases[4] because we did not prescribe prednisolone and cyclophosphamide treatment. Renal tissue biopsy in our patient was also different from previous reported cases of IgAN with hemoptysis as it revealed pathological evidence of IgAN together with acute interstitial nephritis. The cause of renal impairment in our patient was from acute interstitial nephritis. We believed that the cause of pulmonary hemorrhage and acute interstitial nephritis in our IgAN patient was from systemic infection because the patient had fever and multi-organ dysfunction such as thrombocytopenia and hyperbilirubinemia. Unfortunately, we could not identify the specific infected organism. We could not conclude that infection aggravated manifestation of IgAN or it was only coincident with IgAN in this case because the patient refused to repeat urine examination as he was fine.

In summary, we reported a case of IgAN who presented with hemoptysis from pulmonary hemorrhage and reversible acute renal injury from AIN. The diagnosis of IgAN and the cause of acute renal injury in this case resulted from renal biopsy tissue interpretation. Therefore, the renal biopsy is a mandatory investigation to make a correct diagnosis in patients with nephritic features and acute renal injury.

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รายงานผู้ป่วยไตอักเสบชนิด IgA ที่มีภาวะเลือดออกในปอดและไตวายเฉียบพลัน

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ไตอักเสบชนิด IgA (IgA nephropathy) มักเกิดตามหลังการติดเชื้อทางเดินหายใจหรือทางเดินอาหาร อาการทางคลินิกในผู้ป่วยไตอักเสบชนิด IgA อาจจะพบเม็ดเลือดแดงในปัสสาวะโดยไม่มีอาการ, ปัสสาวะเป็นเลือด, บวมชนิด nephritis หรือ nephrosis, ไตวายเฉียบพลันชนิด crescentic glomerulonephritis รายงานนี้นำเสนอผู้ป่วยที่มีอาการไข้, ไอเป็นเลือด, และไตวายเฉียบพลัน ผู้ป่วยได้รับการตรวจเนื้อไตทางพยาธิวิทยาพบว่ามีไตอักเสบชนิด IgA ร่วมกับมีการอักเสบของไตชนิด acute interstitial nephritis ซึ่งเป็นสาเหตุไตวายเฉียบพลัน ดังนั้น acute interstitial nephritis ทำให้เกิดไตวายเฉียบพลันได้ในผู้ป่วยไตอักเสบชนิด IgA และการตรวจเนื้อไตทางพยาธิวิทยาเป็นการตรวจที่จำเป็นในการวินิจฉัยสาเหตุไตวายเฉียบพลันได้อย่างถูกต้อง