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Case Report

Presentation antineutrophil cytoplasmic autoantibody negative-associated granulomatosis with polyangiitis with pyuria

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ABSTRACT

Pulmonary renal syndrome is a rare but serious complication of systemic vasculitis. The majority the cases are antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. In this case, a 58 years old female case having aworsening clinical picture of probable urinary infection and acute renal failure was presented. By means of proteinuria, pyuria, hematuria and unexplained acute renal failure, we review the relevant literature on pulmonary renal syndrome associated with granulomatosis with polyangiitis (GPA) with negative serum ANCA serology. This report demonstrates the difficulty of diagnosing granulomatosis with polyangiitis (GPA) until renal biopsy was done while initial diagnostic serological negative ANCA testing.

Keywords: Pyuria, Hemoptysis, Granulomatous polyangiitis

INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is characterized with three clinical manifestations: granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic polyangiitis. GPA is a life threatening and rare small vessel vasculitis associated with ANCA.

Its characteristic pathology is arteritis at small and medium sized vessels and granulomatous inflammation at upper respiratory tract and lungs.[1] Renal involvement is commonly seen in GPA. It is also known as pauci-immune crescentic glomerulonephritis.

Glomerular lesions are characterized with focal necrotizing, cresentic glomerulonephritis or other forms with no or low immunofluorescence staining. Its etiopathogenesis is not known but environmental factors such as infection and drug exposure have been studied as potential risk factors.[2]

In the present case, a female patient presenting with pyuria, treated initially for urinary infection but diagnosed with ANCA negative vasculitis upon history, physical examination, laboratory and imaging findings was reported. And, she was diagnosed as having immune complex glomerulonephritis by renal biopsy.

CASE REPORT

A 58 years old female patient having fever, pyuria and hematuria complaints was hospitalized with a pre-diagnosis of urinary infection. For urinary infection and sepsis, 2x1 piperacillin/tazobactam intravenous treatments were initiated. Upon observing that she developed hemoptysis and epistaxis and had a fever and rapidly deteriorating renal functions, she was referred to our clinic with acute renal injury.

Her physical examination revealed a blood pressure of 150/90mmHg, body temperature of 38.9^{0}C and bilateral basal crackles and bilateral pretibial edema. Her

laboratory examination showed glucose 130mg/dl (70-125), blood urea nitrogen 96mg/dl (6-20), serum creatinine 6.8mg/dl (0.7-1.2), total protein 4.9gr/dl (6.4-8.3), serum albumin 2.9gr/dl (3.5-5.2), aspartate aminotransferase 18 U/L (0-40), alanine aminotransferase 18U/L (0-40), lactate dehydrogenase 261U/L (135-225), normal bilirubin levels, sodium 143mEg/L (135-145), potassium 3.5mEq/L (3.5-5.5), leucocyte count 9500mm^3/L (4000-12000), haemoglobin 8.1gr/dl (12-14), platelet count 166000/mm^3 (150000-450000), international normalized ratio 0.9 (0.8-1.2), negative direct Coombs, sedimentation 9 mm/hr and c-reactive protein 70mg/dl.

Serological examinations showed that ANA, anti-Ds DNA, p-ANCA, c-ANCA, anti-GBM antibodies were negative, complements (C3-C4) were within low levels, and viral markers were negative.

The amount of proteinuria in 24 hr urine was 3.2 gr. High resolution tomography (HRCT) revealed 1.5 cm pleural effusion in both hemithoraxes, several lymph nodes having 1 cm diameter in the precarinal region and many cavitary nodules with irregular margins and 2 cm diameter in both lungs (Figure 1).

Tuberculin skin test of the patient was negative. Thoracentesis was performed from the pleural effusion. Pleural fluid was found to be exudative. In the thoracentesis fluid, adenosine deaminase enzyme was normal, acid-fast bacilli staining were negative and there was no growth in the culture.

Sputum acid-fast bacilli result was negative. Her Otolaryngology examination revealed septal mucosal ulcer. In renal biopsy, light microscopy revealed mesangial cell and matrix increase, segmental sclerosis in both glomeruli, leukocyte infiltration with interstitial polymorphic nuclei, tubular atrophia, IgG (++), IgA (++) and c3 (++) in immunofluorescence (IF) staining. In the treatment of ANCA-negative GPA, plasma exchange was performed 5 times, intravenous 1 gr methylprednizolone was administered for 3 days and then its dose was lowered to 1mg/kg and 500 mg cyclophosphamide was administered for two weeks.

Cyclophosphamid was administered at a total of 10-cycles. After an 8-cycle hemodialysis, the patient did not require any further hemodialysis upon observing that her serum creatinine levels were decreased to normal ranges. After wards, the cyclophosphamide was ceased and azathioprine was started.

In her 5th month follow-up, her laboratory values and complements were within normal limits and she had a proteinuria of <300 mg/day. A high resolution thorax tomography revealed an increase in peribronchial markings in both lung parenchyma, and there were focal frosted glass opacity regions and fibrosis in the lingula of the left lung (Figure 2). The patient is being followed-up with a diagnosis of ANCA-negative GPA and immune complex glomerulonephritis at the clinic.

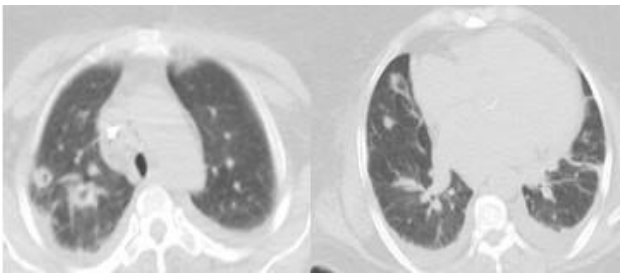

Figure 1: Two nodular cavities lesions (large one with diameter of 13mm) with peripheral frosted glass density (a holo sign) in the lapical segment of the left.

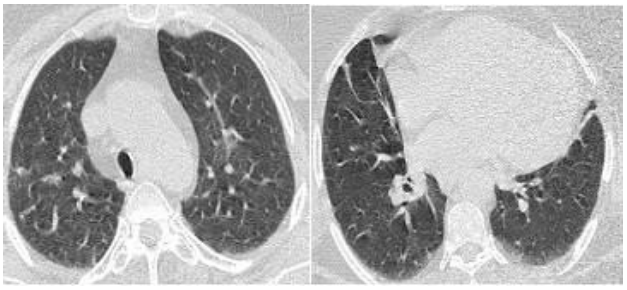

Figure 2: No nodular lesions in the apical segment and middle lobe of the left lung in the follow-up tomography.

DISCUSSION

In present study, there was positive urinary sediment, pulmonary involvement and nasal ulceration as diagnostic criteria. Biopsy could not be taken from the upper respiratory tract of the patient. GPA is diagnosed when at least two of the diagnostic criteria established by the American College of Rheumatology are present.

1) Sinus involvement, 2) nodule, pulmonary infiltrate, cavitation in lung imaging, 3) urinary sediment hematuria or red cell casts, 4) histological granulomatous inflammation.[3] PR-3 ANCA has a high sensitivity and specificity in diagnosing active GPA. However, there may be ANCA-negative and MPO-ANCA positive cases. Symptoms of the upper respiratory tract are epistaxis, sinusitis, otitis media, deafness, hoarseness and stridor. Granulomatous inflammation may cause local injuries such as nasal septal perforation, saddle nose and tracheal stenosis.[4] Present patient had epistaxis and her physical examination revealed septal mucosal ulceration. Her hearing test was normal.

Our patient reported that she had an occasional cough for the last one week. Three days after her hospitalization, she developed dyspnea and hemoptysis. HRCT showed pulmonary nodules, pulmonary cavitation and pleural effusion. In lung involvement, coughing, dyspnea, hemoptysis and chest pain are the most common

symptoms. Alveolar haemorrhage can be located around the nodules and are observed as frosted glass opacity around the consolidated nodule (Halo sign) in HRCT.[5]

Renal involvement is a common feature of GPA and hematuria, proteinuria, hypertension and acute renal injury may be present. Histologically, necrotising and crescentic glomerulonephritis may occur in 75% of the cases at a specific stage of the disease.[6] In ANCA-associated glomerulonephritis, no or a few immunoglobulins and complement components are observed. Presence of IgG and complement C_3 in ANCA-positive glomerulonephritis suggests presence of other associated glomerular pathologies. Our case had renal involvement with hematuria, proteinuria, hypertension and acute renal injury.

In a study on ANCA-associated glomerulonephritis, immune-complex deposits were found in half of the patients in a total of 126 renal biopsies. IgM was the most frequently found immunoglobulin.[7] Detecting IgG(++), IgA (++) and C3(+) staining in IF staining shows that immune-complex glomerulonephritis is present with GPA.

ANCA associated vasculitis is an important mortality and morbidity reason. Diagnosing the disease and initiating a treatment rapidly is essential in terms of mortality and to prevent permanent organ damage. The ratio of remission with treatment has been found to be 85-90%. However, the ratio of relapse is 50% in a 5 years term.[8,9]

ANCA-negative patients with pathology-proven pauciimmune glomerulonephritis with rapid progress are not different than ANCA-positive patients in terms of clinical findings, treatment and prognosis. In the treatment of ANCA associated vasculitis patients, plasmapheresis and haemodialysis support are given together with an immunosuppressive treatment.

In the treatment of our case, 1 g/day methylprednisolone was initially administered for 3 days and then 1 mg/kg/day for 2 months. Afterwards, methylprednisolone was ceased by decreasing the dose. Cyclophosphamide was administered for every two weeks in 10 cycles as 500 mg/day. Then, a maintenance treatment was initiated with 2x1 tablet azathioprine. Moreover, the patient was treated with hemodialysis (8 sessions) and plasmapheresis (5 sessions). We achieved full remission with the mentioned treatment above (proteinuria<300 mg/day).

CONCLUSION

As a conclusion, GPA rarely presents with pyuria. It should be kept in mind that there may be glomerulonephritis in cases having pyuria with proteinuria and hematuria. Our case that was serologically negative for ANCA shows the importance of renal biopsy at early stage. This would allow early diagnosis of patients with pathology-proven immuno-complex glomerulonephritis. We think that this report will increase the awareness about the unusual clinical presentation of GPA and the importance of early aggressive management to avoid further severe complications.

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