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A 10-Year-Old Boy with Pulmonary-Renal Syndrome and Positive C-ANCA

Mitra Naseri

Department of Pediatrics, Dr. Sheikh Children Hospital, Mashhad University of Medical Sciences and Health Services, MASHHAD-IRAN.

ABSTRACT

The term pulmonary-renal syndrome has been frequently used to describe the clinical manifestations of a great number of diseases in which pulmonary hemorrhage and glomerulonephritis coexist.

Antineutrophil Cryoplasmic Autoantibody (ANCA) associated vasculitides include Wegener's Granulomatosis (WG), microscopic polyangiitis (MPA), renal limited pauci-immune glomerulonephritis and Churg-Strauss syndrome.

Causes of pulmonary-renal syndrome which are more frequently associated with antineutrophil cytoplasmic autoantibodies are included MPA and WG. These diseases involve kidney as pauci-immune rapidly progressive glomerulonephritis.

For MPA the estimated prevalence is 3-37 cases per million; and for WG It is approximately 3 per 100.000 persons that only 0.1 percent of patients are younger than 19 years. Pathologically, the major finding in renal biopsy is necrotizing glomerulonephritis accompanied by crescent formation in MPA and WG.

A 10-year-old boy admitted to our hospital because of respiratory distress, hemoptysis, evidence of renal failure and glomerulonephritis (pulmonary- renal syndrome).

Laboratory findings revealed biochemical evidence of renal failure and positive cytosolic anti-neutrophil cytoplasmic antibody (C-ANCA). Chest x-ray showed multiple round opacities with well defined margins in the right lung. Open renal biopsy showed necrotizing vasculitis with involvement of small and medium sized vessels. ***(Tanaffos 2007; 6(1): 75-79)***

Key words: *Pulmonary renal syndrome, Rapidly progressive glomerulonephritis, Antineutrophil cytoplasmic antibodies, ANCA associated vasculitis*

INTRODUCTION

The term pulmonary-renal syndrome has been frequently used to describe a great number of diseases in which pulmonary hemorrhage and glomerulonephritis coexist. The classic example of pulmonary-renal syndrome is Goodpasture's syndrome, which is associated with pulmonary hemorrhage, glomerulonephritis and circulatory anti-glomerular basement membrane antibody (Anti-GBM). (1). Other systemic vasculitis diseases that can present as pulmonary-renal syndrome include systemic lupus erythematosus (SLE), Henoch-

Correspondence to: Naseri M

Address: Department of Pediatrics, Dr. Sheikh Children Hospital, Mashhad University of Medical Sciences, MASHHAD- IRAN.

Email address: mtr_naseri2006@Yahoo.com

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schonlein purpura (HSP), Behcet's syndrome, mixed cryoglobulinemia, Chrug-Strauss syndrome (CSS) and more frequently Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) (1, 2).

ANCA associated vasculitis (AAV) is a group of similar diseases that includes WG, MPA, renal limited pauci-immune glomerulonephritis (RLPIGN), and CSS; many authorities have proposed that AAVs are phenotypic variants of a single entity (3).

ANCA was originally described on the basis of immunofluorescence patterns, being divided into two groups of cytoplasmic (C-ANCA) and perinuclear (P-ANCA). The antigens responsible for these patterns are proteinase 3 (PR_3) for C-ANCA and myeloperoxidase (MPO) for P-ANCA (4).

CASE PRESENTATION

A 10-year-old boy was admitted to infectious diseases department of Imam-Reza Hospital (Mashhad-Iran) after an episode of hemoptysis and respiratory distress. History revealed dry cough without fever started six months earlier and decreased appetite, weight loss, otalgia and right ear discharge from two weeks ago. He complained about periumbilical crampy abdominal pain starting a few days earlier. He was referred to our hospital for evaluation of the severe increase in serum blood urea nitrogen (BUN) and creatinine levels. At the time of admission, his body temperature was 37°C, pulse rate was 100 beats per minute, respiratory rate was 40/ minute, and blood pressure was 120/80 mm/Hg. Urine output was in oliguric range (<500cc/min/1.73m^2). Physical examinations revealed right tympanic membrane perforation, pallor of mucous membranes, crackles at the bases of the lungs and subcostal retraction. Cardiac examination was normal. The abdomen was tender to palpation in periumbilical region with no rebound tenderness. Severe edema was noted in right lower extremity from inguinal region to toes with mild edema in right part of scorotom. No synovitis was present. Muscle strength and neurologic examinations were normal.

Laboratory examinations were as follows: BUN= 122mg/dl, serum creatinine= 4.9mg/dl, calcium= 8.6mg/dl, sodium= 135mmol/lit, potassium= 6.4 mmol/lit, serum phosphorus= 9.5mg/dl, and uric acid level= 12.6 mg/dl, SGOT= 49 IU/L and SGPT= 30 IU/L. Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) were normal.

White blood cell count was 32.8×10^3µl with 84% neutrophils, 7% lymphocytes, 4% myelocytes, 1% metamyelocytes, and 4% band cells. Red blood cell count was 2.07×10^6 µl. Hemoglobin level was 5.3gr/dl. Hematocrit was 15.9%. MCV was 76.8fl and platelet count was 291×10^3/µl.

Peripheral blood smears revealed anisocytosis (+1), hypochromia, schistocyte, eliptocyte, 7% nucleated red blood cells and 2% reticulocyte cells. Direct Coombs' test was negative and lactate dehydrogenase level was 926U/L. Bone marrow aspiration showed hyperplasia of myeloid series with normal erythroid and megakaryocytic series. Urinalysis revealed blood (++) and was negative for protein. The urine sediment contained 30-35 RBCs, and 1-2 WBCs per high power field.

Twenty- four- hour urine protein amount was 120 mg. Blood and urine cultures were negative. Gram-stain, acid fast stain and culture of sputum for usual bacteria were negative.

Serological tests for hepatitis B, hepatitis C and human immunodeficiency virus were negative. ASO titer was 100 Todd units. Antinuclear antibodies (ANA) were negative. Serum C3 and C4 levels were normal. Total protein and albumin levels were normal. Serum triglyceride level was 310mg/dl and serum cholesterol level was 259mg/dl. Arterial blood gases analysis revealed only hypoxemia.

Tests for P-ANCA and Anti-GBM antibody were negative, and C-ANCA titer were positive at 1/80. Kidney ultrasonography showed increased size of both kidneys with increased parenchymal

echogenicity. At the first day of admission, chest x-ray showed multiple small round opacities with well defined margins and a large round opacity in the right lung (Fig 1).

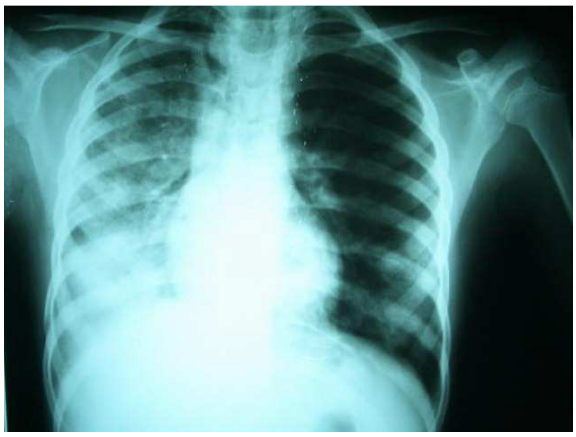

Figure 1. Multiple small round opacities with well-defined margins with a large round opacity in the right lung.

Doppler ultrasonography of lower limbs showed patency of vascular trees in right lower limb and pelvic cavity. Patient received intravenous ceftriaxone daily, hemodialysis urgently and then three times weekly with conservative treatments for renal failure (phosphate binders and human synthetic erythropoietin). Two days later, chest x-ray showed diffuse homogeneous opacities in the right lung with pneumomediastinum (Fig 2).

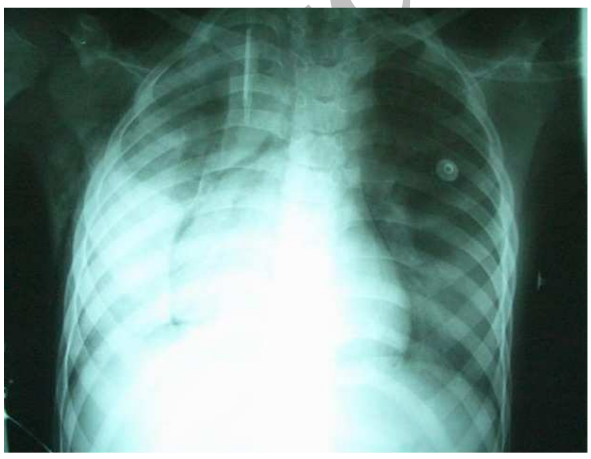

Figure 2. Diffuse homogeneous opacities in the right lung with pneumomediastinum.

Patient received intravenous methyl-prednisolone sodium succinate 30mg/kg for six sequential days and then oral prednisolone 50mg (2 mg/kg) daily for one month with oral cyclophosphamide 1mg/kg/ day for six months, plasmapheresis six times on two weeks and hemodialysis. After one month, prednisolone was tapered very slowly.

One week after admission, the patient had good general condition with no respiratory distress and chest x-ray two weeks after the admission was normal. Due to some difficulties and limitations, open kidney biopsy was performed after 45 days. It demonstrated complete obliteration of the normal architecture of 90% out of 40 glomeruli by hyalinized and sclerotic crescents or mesangial hyalinosis. The remaining parts showed either mesangial proliferation or no significant change. Vessels showed fibrinoid necrosis. Immunofluorescence microscopy demonstrated focal fine granular staining for IgM in interstitium, 1-2 positive granular diffuse staining for IgA in glomerular capillary wall and trace focal staining for C4 in tubular wall and interstitium.

Now it has been about 9 months from initiation of treatment and the patient is receiving oral prednisolone 20mg on alternate days with hemodialysis three times weekly.

DISCUSSION

Pulmonary renal syndrome can be divided into three groups: (1, 5)

1) Little or no immune deposits in the vascular wall (pauci-immue) which is frequently associated with ANCA: WG, MPA, and CSS.

2) Immune complex deposits: HSP, mixed cryoglobulinemia and other types of small vessels vasculitis diseases such as SLE and serum sickness.

3) Anti GBM deposits: Good pasture's syndrome.

ANCA plays an important role in differential diagnosis of pulmonary-renal syndromes. According

to ANCA results, this complex group of vasculitis is practically restricted to three entities: WG, MPA and CSS. ANCAs are highly sensitive and specific serological markers for those diseases (6). In MPA, 50-80% of patients has positive findings for ANCA and are mostly positive for PANCA. A negative test result for ANCA excludes MPA. ANCA type and specificity is not pathognomonic, because some patients with MPA are C-ANCA positive (1, 6). The sensitivity and specificity of PR_3 ANCA (C-ANCA) in active WG are about 90 percent (7).

WG is a granulomatous necrotizing vasculitis characterized by its predilection to affect the upper and lower respiratory tracts and in most cases the kidney. It affects both sexes equally; and occurs in patients of all ages (mean age, 41 years). Only 0.1 percent of patients are younger than 19 years old. Its prevalence was estimated to approximate 3 per 100.000 persons. Ocular, cutaneous, musculoskeletal, and neurologic involvements have often been reported (8).

MPA is a rare disease, with an estimated prevalence of 3-37 per million (3, 5). The age range is 2- 92 years (mean age, 50 years) (2, 6, 9). Its etiology is unknown, and it is very rare in children (2, 5).

MPA is characterized by pulmonary infiltrates and RPGN, often coupled with musculoskeletal, skin and ocular lesions, peripheral neuropathy, CNS and gastrointestinal involvement. Ear, nose and throat involvements occur less frequently than renal involvement (2- 6).

At the Chapel Hill consensus conference, MPA was defined as necrotizing vasculitis of small vessels, with few or no immune deposits, but involvement of medium-sized arteries may also be observed (5). Kandeel et al. reported a case of microscopic polyangiitis in a 17-year-old male that presented with respiratory distress, arthralgia, skin rashes, and normal renal function (2). Blanco Filho et al. reported a case of ANCA positive pulmonary renal syndrome in a 10-year-old girl. She died before institution of glucocorticosteroids and immunosuppressive therapy and before definitive diagnosis by kidney biopsy (1).

This case presented with upper and lower respiratory tract involvement (right ear discharge and otalgia, hemoptysis and lung infiltrates) and renal involvement (evidence of acute renal failure and glomerulonephritis). We did not find any explanation for severe unilateral edema of lower extremity. Clinical presentations were similar to a case who was reported by Blanco Filho, et al., but in this patient C-ANCA titer was positive, instead of P-ANCA. This is similar to the case reported by Kandeel in whom C-ANCA titers were positive at 1/100. Renal biopsy showed evidence of necrotizing vasculitis with involvement of small and medium-sized vessels. There was no evidence of immunofluorescence on renal biopsy suggestive of SLE or Goodpasture's syndrome.

The standard treatment for ANCA-positive glomerulonephritis is high dose corticosteroids (intravenous methylprednisolone 1gr each day for 3 days), and cytotoxic immunosuppressive drugs (6, 10, 11). This is followed by oral prednisone 1-2 mg/kg/day for 2 to 4 weeks , then reduced to a maintenance level for up to 6 months or until the underlying disease process has been controlled and disease is in remission (10). In ANCA glomerulonephritis, cyclophosphamide is the drug of choice for induction of remission (11).

The combination of cyclophosphamide and high dose glucocorticoids is generally agreed to be the standard of care for the induction of remission in severe small vessel vasculitis (3).

A study performed by Frasca et al. showed that the acute phase of disease was better controlled by the combination of plasmapheresis and drug therapy (12). The prognosis and outcome depend on the

extent and severity of organ involvement (2). Mortality due to pulmonary hemorrhage can occur in acute phase of disease. In ANCA-glomerulonephritis, a higher proportion of histologically unaffected glomeruli correlate with increased renal survival.

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