

ANCA-Negative Pulmonary-Renal Syndrome with Pathologic Findings Suggesting Thrombotic Thrombocytopenic Purpura

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Abstract

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever and renal dysfunction. The disease classically spares the lung tissue, but recently some cases were reported that presented with respiratory involvement (adult respiratory distress syndrome or pulmonary-renal syndrome). Presentation with pulmonary-renal syndrome has rarely been reported.

Case Presentation: We report a 14-years-old boy admitted to the hospital because of a biochemical evidence of renal failure. Two days after admission he developed a high fever, hemoptysis and respiratory distress. Open kidney biopsy was performed and confirmed the diagnosis and finally the patient expired due to neurologic involvement.

Conclusion: This case is presented to discuss the need to update the criteria for TTP diagnosis and considering TTP in the differential diagnosis of pulmonary renal syndromes.

Key Words: Thrombotic thrombocytopenic purpura, Pulmonary renal syndrome, Anti-neutrophil cytoplasmic antibody (ANCA)

Introduction

The term pulmonary-renal syndrome has been used frequently to describe a great number of diseases in which pulmonary hemorrhage and glomerulonephritis coexist. The classic example of pulmonary-renal syndrome is good pasture's

syndrome which is associated with pulmonary hemorrhage, glomerulonephritis and circulatory anti-glomerular basement membrane antibody (Anti-GBM – Ab). Other systemic vasculitis that can present as pulmonary-renal syndrome are Systemic Lupus Erythematosus (SLE), Henoch-Schonlein Purpura (HSP), mixed cryoglobulin-

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emia, chrug-strauss and more frequently Wegener's granulomatosis and microscopic polyangiitis (MPA) [1].

TTP has rarely has been reported as a cause of pulmonary renal syndrome. TTP and Hemolytic-uremic syndrome (HUS) are two diseases that have always been considered in the differential diagnosis. TTP is characterized by a pentad: microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms, renal involvement and fever [2, 3, 4]. HUS is defined as a triad of microangiopathic-hemolytic anemia, thrombocytopenia and acute renal insufficiency. It is mainly classified as diarrhea associated (typical HUS) and atypical HUS, which has no antecedent diarrhea. In adolescents and adults, TTP, with predominant neurologic features, with minimal or no renal insufficiency, can occur [5-8]. Typically, these syndromes are reported to spare the lungs [9-12]. Pulmonary compromise in HUS/TTP has been reported mainly in the setting of malignancy or its chemotherapeutic treatment [13].

In HUS, the involved organs are mainly the gastrointestinal tract, the kidneys and the central nervous system (CNS). Lung involvement as adult type respiratory distress syndrome may be seen [2, 6]. TTP and HUS are felt to be different spectra of the same disease process consisting of abnormal formation of platelet and microthrombi in small vessels, considered thrombotic microangiopathy [14].

In this report, we presented a patient with pulmonary renal syndrome and negative serologic findings (negative P-ANCA and C-ANCA, Anti GBM-Ab, ANA) in whom kidney biopsy findings suggested TTP.

Case report

A 14-years-old boy presented to the neurology department of Birjand Hospital because of a first attack of convulsion. He complained of decrease appetite and vomiting during the past two-weeks. In the first evaluation, blood pressure, BUN and creatinine levels were high and the patient was referred to the nephrology department of Dr

Sheikh Children Hospital. At the time of admission in our hospital, the temperature was 37°C, the pulse was 80 beats per minute and the respiratory rate was 20 beats per minute. The blood pressure was 140/90 mmHg, Chest and heart examinations were normal. Purple macular lesions were noted on the lower extremities. There was no edema, but urine output was in the oliguric range (<500ml/min/1.73m²). Neurologic examination was normal.

Laboratory examinations revealed a white blood cell count of 9.8×10³/μL with 73% neutrophils, 23% lymphocytes, 1% eosinophils, 2% myelocytes and 1% bandcells. Hemoglobin level was 7.4gr/dl and hematocrite level was 23.7%, platelet count was 149×10³/μL and two days later reached 129×10³/μL. Peripheral blood smear showed anisocytosis and hypochromia, but no schistocyte or burrcell were seen.

Blood urea nitrogen level was 75mg/dl, creatinine level was 5.8mg/dl, calcium level was 6.7mg/dl and phosphorous level was 7.5mg/dl and other electrolyte levels were normal. Arterial blood gases analysis showed metabolic acidosis. PH was 7.24, bicarbonate level was 9.7mmol/L and PaCo₂ was 22.3mmHg. Total protein and albumin levels were normal, triglyceride level was 515mg/dl and cholesterol level was 278mg/dl. ASO titer was 100 Todd units and antinuclear antibody was negative. C₃ level was normal and C₄ level was 14mg/dl (15-55mg/dl). Prothrombin time and partial thromboplastin time were normal. Urine analysis revealed 1⁺ protein with moderate blood and sediment contained 12-15 red cells per high power field and 1-2 white cells per high power field. 24 hours urine protein level was 1.3gr.

Serologic tests for Hepatitis B, Hepatitis C and human immuno-deficiency virus were negative. Tests for perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA), cytosolic anti-neutrophil cytoplasmic antibody (C-ANCA) and Anti-GBM Ab were negative.

At the time of admission, the chest X-Ray was normal and the kidney ultrasonogram showed increased parenchymal ecogenecity with increased

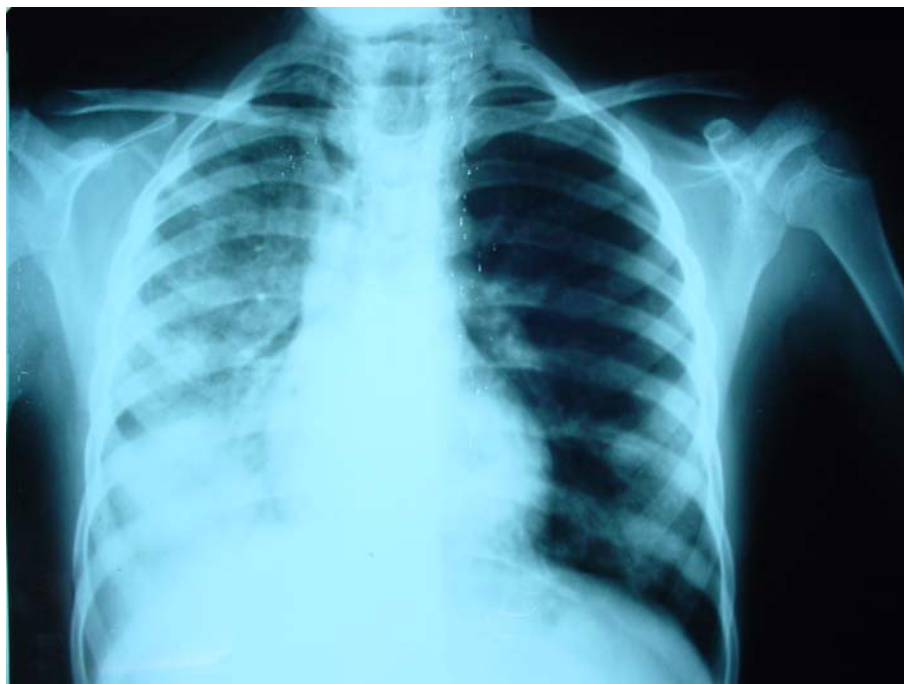


Fig 1- Multiple round opacities in right lung

cortico-medullary differentiation. 2 days later, he developed fever, hemoptysis and respiratory distress. At this time, the chest X-Ray revealed multiple round opacities in the right lung (Fig 1). Blood culture was performed and it was negative.

Gram stain, acid-fast staining of the sputum and culture of the sputum for usual bacteria were negative. Treatment with intravenous ceftriaxone was started. Renal function dropped progressively, and four-days after admission, creatinine level

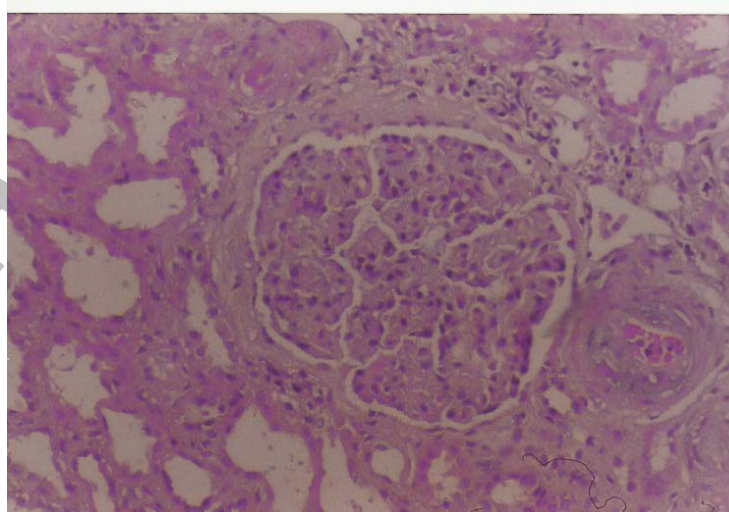


Fig 2- Diffuse thickening of glomerular capillary wall accompanied by an increase in mesangial matrix ($\times 20$ - H&E)

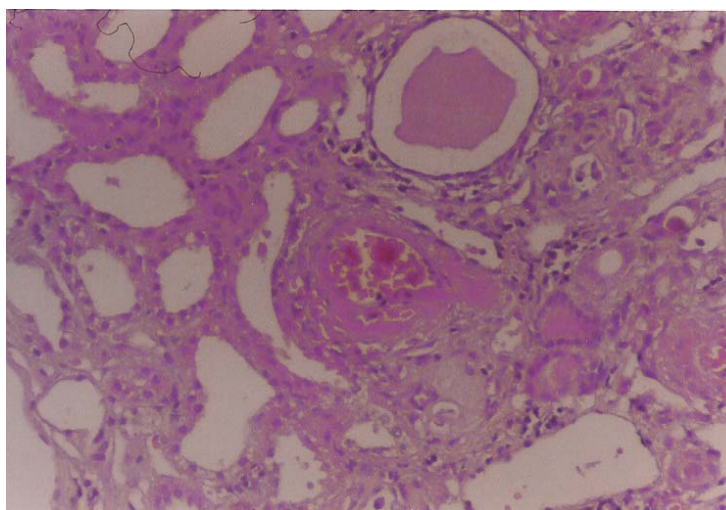


Fig 3- The wall of an arteriole infiltrated by fibrin (fibrinoid necrosis) and fragmented red blood cells ($\times 20$ - H&E)

was 7.8mg/dl. The patient received intravenous methylprednisolone one-gram daily for 5-consecutive days, a plasma exchange six-times in 2 weeks and hemodialysis three times weekly.

One week after admission, kidney needle biopsy was performed and the specimen showed diffuse increased capillary wall thickness and increased mesangial matrix with fibrillar appearance, and mildly increased mesangial cellularity (Fig 2). In some glomeruli, there were aggregations of fragmented red blood cells in the capillary wall and mesangium. There was no extra capillary proliferation. Arteriolar sections showed subintimal edema, obstruction of glomerular lumen and fibrinoid necrosis, and few neutrophils with glomeruloid structure formation (Fig 3). There were severe tubular atrophy and thyroidization with diffuse lymphoplasmacytic infiltration and mild interstitial fibrosis with periglomerular and perivascular distribution. There was no evidence of granulomatous inflammation. Unfortunately the specimen was not examined by florescent microscopy (because it was not available). Pathologic findings suggested HUS-TTP or vasculitis with small and medium-sized vessels involvement. One week after starting treatment, chest X-Ray showed clear lungs with no infiltration or opacity.

After 20 days, the patient was discharged on prednisone 2mg/kg daily and preparation of hemodialysis twice a week. At the time of discharge, the patient had no fever and respiratory condition was good.

One week after discharge, the patient was admitted to the hospital because of a high fever, fatigue and hemoptysis. At the time of admission, the temperature was 39°C, the pulse was 100 beats per minute and respiratory rate was 22 beats per minute. Blood pressure was 100/70mmHg. Heart and lung examinations were normal. The patient was alert and oriented. Sensory and motor neurologic examinations were normal. But we found expressive aphasia and bilateral horizontal nystagmus. Laboratory examinations revealed a white cell count of $15.8 \times 10^3/\mu\text{L}$. Hemoglobin level was 14.5gr/dl and hematocrite level was 44.4%, platelet count was $67 \times 10^3/\mu\text{L}$. Chest X-Ray showed a round opacity in the apex of the right lung. Computed tomographic scan of the brain was normal. Thirty-six hours after admission, cardiopulmonary arrest suddenly occurred and cardiopulmonary resuscitation was unsuccessful and unfortunately the patient expired.

Discussion

TTP, first described by Moschowitz in 1925, consists of the following pentad: fever, thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities and renal involvement. The exact pathologic processes remains unknown, but it is thought to cause endothelial cell damage with subsequent occlusion of arterioles and capillaries by hyaline thrombus composed primarily of platelets and fibrin immune complex. Infection and genetic predisposition have been proposed as activators of these pathologic processes, however, none of these conditions have been consistently present in TTP cases [4]. A variety of pulmonary infections have been associated with TTP. Influenza [9], legionella [10], and streptococcus pneumonia [11] have all been implicated as pathogenic factors in this disease. In a recent study from the Italian registry of recurrent and familial HUS/TTP, Remuzzi et al confirmed that most TTP adult patients have VWF-cleaving protease deficiency due to the presence of an inhibitor, whereas some have a constitutional and familial deficiency [15].

Before the introduction of plasmapheresis in the 1970's, TTP was fatal. The introduction of plasmapheresis has provided substantial benefit in term of survival and mortality of HUS/TTP. Mortality has been reduced from over 90% to 15-20% [16], however; despite the rapid initiation of up-to-date therapy, it remains a potentially life threatening disorder. Recently some cases of atypical TTP and cases with severe pulmonary involvement has been reported. Panoskaltsis et al described a case of TTP which presented as pulmonary-renal syndrome, and suggested TTP in the differential diagnosis of pulmonary-renal syndrome [17]. Bone et al reported respiratory impairments in six patients with TTP that were characterized by tachypnea, hypoxemia and infiltration on chest roentgenogram. Information from outpatients with TTP revealed respiratory dysfunction as a component of the disease [2]. Wajima and Johnson described an atypical form of TTP that presented by severe

thrombocytopenia, striking renal and CNS symptoms, but fever and anemia were not present [3]. D'Andrea and Chan reported a subtle form of TTP, presenting as expressive aphasia [4].

Our patient presented by severe renal and pulmonary involvement, mild thrombocytopenia, anemia, CNS involvement (expressive aphasia and bilateral horizontal nystagmus) and fever, on first admission the main presentation was as pulmonary-renal syndrome and renal biopsy showed findings suggestive of HUS/TTP.

Conclusion

In TTP the presentation is usually of an acute nature with neurologic or hemorrhagic complications. It usually spares the lungs, but recently some cases of disease have been reported with lung involvement as adult respiratory distress syndrome or pulmonary renal syndrome.

We presented a patient with pulmonary renal syndrome and negative serologic findings (negative P-ANCA and C-ANCA, Anti GBM-Ab, ANA) in whom kidney biopsy findings suggested TTP. So, we suggest the need to update the criteria for TTP diagnosis and suggest considering TTP in the differential diagnosis of ANCA-negative pulmonary-renal syndromes, so that appropriate treatment can be promptly instituted.

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