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Case Report

ANCA Negative Pulmonary Renal Syndrome with Pathologic Findings of Thrombotic Microangiopathy

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Abstract

Introduction: Thrombotic microangiopathy (TMA) is characterized by aggregation of platelets in the renal and/or systemic circulation, thrombocytopenia and intravascular hemolysis. The syndrome classically spares the lung. The term pulmonary-renal syndrome describes a number of diseases in which pulmonary hemorrhages and glomerulopathy coexist.

Case Report: We report a 44-year-old man admitted to hospital because of chronic unexplained fever. Six days after admission he developed hemoptysis, respiratory distress and biochemical evidence of acute renal failure. High-resolution computed tomography scan of the chest demonstrated alveolar hemorrhages. The patient developed hypoxia and was shifted to the intensive care unit to be supported by mechanical ventilation. He also received two sessions of continuous veno-venous hemodiafiltration. Kidney biopsy revealed pathological findings of TMA. Serology for anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies and anti-glomerular basement membrane antibodies was negative. The patient was treated with pulse steroids followed by prednisolone with mild improvement. Seven days later, his condition deteriorated with an increase in serum creatinine and pulmonary hemorrhages. His hemoglobin level dropped and he developed features of intravascular hemolysis. A diagnosis of TMA was made and treatment with plasma exchange was initiated. The patient showed dramatic improvement and was discharged in good condition. He remained in remission throughout his subsequent follow up.

Conclusion: TMA should be considered in the differential diagnosis of pulmonary renal syndromes, and can be successfully managed by corticosteriods combined with plasma exchange.

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Introduction

Thrombotic microangiopathy (TMA) is a microvascular occlusive disorder defined by the characteristic histopathological findings of thickening of arterioles and capillaries, endothelial swelling and detachment, subendothelial accumulation of proteins and cell debris, widening of the subendothelial space, platelet thrombi obstructing the lumina of the vessels, and fragmented red blood cells in the vessels or the interstitium [1-4]. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) represent the two most frequently encountered clinical presentations of TMA. There is considerable overlap in the clinical features of HUS and TTP and it is often difficult to distinguish between these entities [5, 6].

The term pulmonary-renal syndrome has been used frequently to describe a number of diseases in which pulmonary hemorrhages and glomerulopathy coexist. The classic example of pulmonary-renal syndrome is Good Pasture's syndrome which is associated with pulmonary hemorrhages, glomerulonephritis and circulatory Anti-GBM antibodies. Other systemic vasculitis that can present as pulmonary-renal syndrome are systemic lupus erythematosus (SLE), Henoch Schonlein Purpura (HSP), mixed cryoglobulinemia, Chrug-Strauss syndrome and more frequently Wegener's granulomatosis and microscopic polyangiitis (MPA) [7]. TTP and HUS have rarely been reported as a cause of pulmonary renal syndrome [8-10]. Typically, these syndromes are reported to spare the lungs [11-14]. Here we report a case of ANCA–negative pulmonary renal syndrome due

to HUS/TTP with the successful use of corticosteriods combined with plasma exchange in patient treatment.

Case Report

A 44-year-old Somalian male patient presented to our hospital with history of fever of three months duration. There was a history of bilateral mild hydronephrosis due to bilateral ureteric strictures of unknown cause for which bilateral double-J stents were inserted. The double-J stents were removed two months prior to presentation because of the fever, with no clinical improvement. Treatment with meropenim, 1500 mg/day, had been initiated four days earlier because of productive cough and hemoptysis. He also complained of anorexia and nausea and reported that his urine output had decreased over the preceding days. His blood pressure was 200/110 mmHg for which nitroglycerin infusion was initiated; heart rate was 90 beats/minute and his temperature was 37.8ºC. He had normal jugular venous pressure and no lymphadenopathy. Chest examination revealed bilateral basal crepitations but heart examination was normal. The abdomen was lax, not tender and there was no organomegaly. He had mild bilateral lower limb pitting edema and no purpura. Neurological examination was normal.

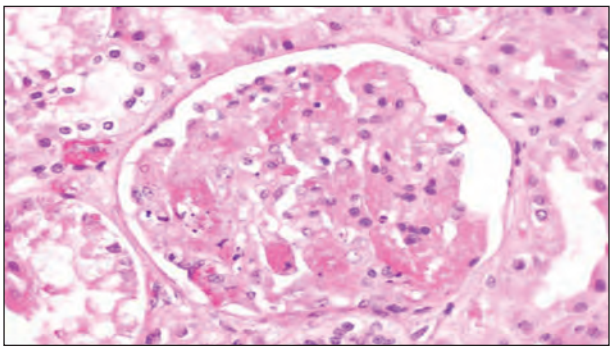
Laboratory tests revealed a creatinine of 5.4 mg/dL and blood urea of 50 mg/dL compared to a baseline value of 0.9 mg/dL and 8.4 mg/dL, respectively. Hemoglobin level was 9.1 g/dL, WBC 11400/µl and platelet count 140,000/µl. Total bilirubin was 1.5 mg/dL, ALT 42 U/L, ALP 109 U/L, total protein 5.3 g/dL and serum albumin 2.8 g/dL. PT, PTT, and INR were normal. Total calcium was 7.8 mg/dL, corrected calcium 8.8 mg/dL, serum phosphorus 7.3 mg/dL, serum sodium 150 mmol/L and serum potassium 3.3 mmol/L. Total cholesterol was 127 mg/dL and triglycerides 219 mg/dL. Lactate dehydrogenase (LDH) and haptoglobin levels were normal and no schistocytes were detected in the peripheral blood film at this point. The direct and indirect anti-globulin Coomb's tests were negative. HCV-Ab, HbsAg, HIV-Ab, Widal test for typhoid and Brucella agglutination tests were all negative. Epstein Bar virus (EBV) was IgG positive, IgM negative. Cytomegalovirus (CMV) was IgG and IgM positive. CRP was elevated at 21 mg/dL. Urinalysis revealed normal urine sediment but he had proteinuria of 1.2 g/day. Urine and blood cultures were negative. Broncoalveolar lavage (BAL) for acid fast bacilli was negative. Purified protein derivative (PPD), Anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin antibodies (ACLP) and anti-glomerular basement membrane antibodies (anti-GBM) were all negative. Complement 3 and 4 (C3 and C4) levels were normal. There were pulmonary infiltrates on chest X-ray. A high-resolution computed tomography scan demonstrated alveolar hemorrhages. Abdominal ultrasound revealed normal-sized kidneys, normal cortico-medullary differentiation with grade-1 echogenicity, coarse liver texture and mild free pelvic collection. Echocardiography revealed mildly dilated right heart side, left ventricular ejection fraction (LVEF) of 66%, normal mitral and aortic valve morphology and function, no pericardial effusion and no intra-cardiac masses or thrombi. Because of persistent nausea and vomiting an upper gastrointestinal endoscopy was performed, revealing grade-2 linear esophagitis and diffuse gastritis. Biopsies were subsequently taken; staining for Helicobacter pylori was negative and therapy with a proton pump inhibitor was initiated.

The patient was hypoxic with an oxygen saturation of 80% on face mask at a flow of 10 L/minute. Upon this, the patient was shifted to the intensive care unit (ICU) and supported by mechanical ventilation. He also received two sessions of continuous veno-venous hemodiafiltration (CVVHDF).

An urgent kidney biopsy was taken. Sections of renal cortex showed 29 glomeruli; one glomerulus was completely sclerosed and two showed partial scarring. All glomeruli showed mesangial prominence and thickened glomerular basement membrane with double contours. One glomerulus showed a cellular crescent. The small blood vessels showed acute thrombosis with luminal occlusion (Fig-1). The large blood vessels showed severe arteriosclerosis. The tubules showed patchy areas of necrosis. There was about 10% interstitial fibrosis and tubular atrophy. Immunoperioxidase staining for IgG, IgA and C3 were negative in the glomeruli. Pathological diagnosis was acute on top of chronic TMA.

Treatment with methylprednisolone 1 g/day for 5 days and then prednisolone 60 mg/day was initiated for suspected pulmonary renal syndrome. CMV infection was suspected for which IV ganciclovir 100 mg/day was initiated with the dose adjusted for renal dysfunction. Ganciclovir was continued for seven days and stopped when CMV-DNA was found negative. Initially, there was a partial response with a decline in pulmonary infiltrates on chest X-ray. The patient was extubated with some improvement of his renal function and urine output, but he didn't reach his basal normal levels. Seven days later, the clinical condition deteriorated and chest X-ray revealed increased opacities of interstitial pattern. Blood tests showed a drop in hemoglobin to 7.9 g/dl and platelet count to 18,000/µl. LDH was elevated at 840 U/l, haptoglobin was severely depressed and schistocytes appeared in the peripheral blood smear. Serum creatinine increased again to 4.5 mg/dL, and the patient developed peripheral edema. A diagnosis of

Figure-1: Histopathological section of kidney biopsy showing glomeruli with capillary thrombosis and some with cellular fragmentation



HUS/TTP was made and treatment with daily plasma exchange was started with 1.5 plasma volumes. After few sessions of plasma exchange, hemoptysis stopped and the patient's urine output and renal function improved. Blood tests revealed gradual increase in platelet count from 18,000 to 135,000/µL and decreased LDH from 840 to 280 U/L. Treatment with plasma exchange continued for 25 sessions and was successfully discontinued after subsequent normalization of hemolytic parameters. The patient was discharged in a good condition. During his follow up, blood test revealed platelet count of 160×103/µL, normal LDH and serum creatinine of 1.5 mg/dL. He was maintained on hydralazine 150 mg/day, prazosin 3 mg/day, omeprazole 40 mg/day, calcium carbonate 1200 mg/day and prednisolone 10 mg/day.

Discussion

TMA is characterized by aggregation of platelets in the renal and/or systemic circulation, thrombocytopenia and intravascular hemolysis [5, 6]. TTP is characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms, renal involvement and fever. HUS is defined as a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency [8-10].

In this patient, there was acute renal failure and pulmonary involvement with fever, thrombocytopenia, anemia and markers of intravascular hemolysis but there was no neurological involvement. The main presentation was pulmonary-renal syndrome due to HUS/TTP proven by kidney biopsy which showed features of TMA.

The pathogenesis of TMA involves increased expression of unusually large von Willebrand factor (ULvWF) multimers on endothelial cells, decreased breakdown of these multimers and/or increased secretion of these multimers into the circulation [15]. In TTP, this situation arises either as a result of an inherited deficiency of the metalloprotease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) that normally cleaves the ULvWF multimers, or as a result of circulating IgG-directed against ADAMTS13 [15]. These mechanisms explain the reduced ADAMTS13 activity in the familial and acquired idiopathic variants of TTP, respectively. In both cases, ULvWF multimers can persist on the surface of endothelial cells and in the systemic circulation and cause platelet aggregation by binding to the platelet glycoprotein Ib/IX/V receptor much more efficiently than 'normal-sized' multimers. This results in systemic platelet thrombi.

In contrast, ADAMTS13 activity is normal in HUS, another variant of TMA, and the mechanism of TMA in this setting is thought to be due to locally increased expression and/or release of ULvWF multimers by endothelial cells in response to endothelial cell injury [15]. Shiga toxin may cause endothelial cell injury in diarrhoea-associated HUS, in which case endothelial cells expressing the receptor for this toxin, primarily in the renal and cerebral circulations, are the sites of injury. Endothelial cell injury in this case may also cause local activation of the coagulation cascade and initiate a local inflammatory reaction involving tissue invasion by neutrophils and monocytes. Consequently this mechanism results in platelet-fibrin thrombi and an inflammatory reaction that is usually localized to the renal circulation. A similar clinical picture may be seen in the familial variants of HUS in which the endothelial cell injury may be due to a deficiency in factor H. Factor H regulates the activity of the alternative complement pathway, and deficiency may lead to increased C3 convertase activity that potentiates auto-antibody- and/or immune complex-mediated glomerular injury [15]. In the autosomal recessive form of HUS, factor H levels and serum C3 levels are both reduced. The autosomal dominant form of HUS is due to a defective factor H protein, and the levels of both factor H and serum C3 are typically normal.

Before the introduction of plasmapharesis in the 1970's, TTP was fatal. The introduction of plasmapharesis has provided substantial benefit in terms of morbidity 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.

In our patient, after few sessions of plasma exchange, hemoptysis stopped and renal function improved with good improvement in pulmonary infiltrate and hemolytic parameters. Plasma exchange continued for 25 sessions within four weeks and after subsequent normalization of

hemolytic parameters plasma exchange was successfully discontinued with sustained hematological remission.

TTP and HUS have rarely been reported as a cause of pulmonary renal syndrome [8-10] and both syndromes typically spare the lungs [11-14]. Nevertheless, here we report a patient with pulmonary renal syndrome due to HUS/TTP.

Recently, some cases of atypical TTP and cases with severe pulmonary involvement have been reported. Panoskaltsis *et al* described a case of TTP which presented as pulmonary-renal syndrome, and suggested TTP to be included in the differential diagnosis of pulmonary-renal syndromes [17]. Nasseri and Zabolinejad also reported a patient with pulmonary renal syndrome and negative serologic findings in whom kidney biopsy findings suggested TTP [18]. Bone *et al* reported signs of respiratory impairments in six patients with TTP; these were tachypnea, hypoxemia and infiltration on chest roentgenograms [19].

In the case presented here, the lack of a family history, lack of a history of exposure to infectious agents or drugs known to be associated with TMA, normal C3 and C4 levels and negative ANA, p-ANCA, c-ANCA, ACLP and anti-GBM antibodies are all consistent with the clinical diagnosis of acquired idiopathic HUS/TTP. We did not formally measure the ADAMTS13 level as this assay is not available locally and would not have altered the patient's management. In our patient, treatment with pulse methylprednisolone resulted in a partial response with a decline in pulmonary infiltrate on chest X-ray and some improvement in kidney function. These findings tend to suggest that the likely underlying pathogenesis of TMA in this case is the presence of antibodies against ADAMTS13 (immune-based TMA).

Conclusion

TMA due to HUS/TTP should be considered in the differential diagnosis of pulmonary renal syndromes. Corticosteroids combined with plasma exchange can be successfully used in the treatment of this condition.

References

1. Ponticelli C, Banfi G Thrombotic microangiopathy after kidney transplantation. Transpl Int. 2006 Oct;19(10):789-94.

2. Le Quintrec M, Lionet A, Kamar N, Karras A, Barbier S, Buchler M, Fakhouri F, Provost F, Fridman WH, Thervet E, Legendre C, Zuber J, Frémeaux-Bacchi V. Complement mutation-associated de novo thrombotic microangiopathy following kidney transplantation. Am J Transplant. 2008 Aug;8(8):1694-701.

3. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009 Oct 22;361(17):1676-8.

4. Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. Am J Transplant. 2010 Jul;10(7):1517-23.

5. Chiurchiu C, Ruggenenti P, Remuzzi G Thrombotic microangiopathy in renal transplantation. Ann Transplant. 2002;7(1):28-33.

6. Matsuda J, Sanaka T, Gohchi K, Matsui K, Uchida S, Matsumoto M, Fujimura Y. Occurrence of thrombotic thrombocytopenic purpura in a systemic lupus erythematosus patient with antiphospholipid antibodies in association with a decreased activity of von Willebrand factor-cleaving protease. Lupus. 2002;11(7):463-4.

7. Blanco Filho F, Ernesto LC, Rosa MA, Stuginski LA, Zlochevsky ER, Blanco F. Rapidly progressive antineutrophil cytoplasm antibodies associated with pulmonary-renal syndrome in a 10-year-old girl. Sao Paulo Med J. 2001 Jan 4;119(1):29-32.

8. Bone RC, Henry JE, Petterson J, Amare M. Respiratory dysfunction in thrombotic thrombocytopenic purpura. Am J Med. 1978 Aug;65(2):262-70.

9. Wajima T, Johnson EH. Sudden cardiac death from thrombotic thrombocytopenic purpura. Clin Appl Thromb Hemost. 2000 Apr;6(2):108-10.

10. D'Andrea CC, Chan L. Acute thrombotic thrombocytopenic purpura presenting as expressive aphasia. Am J Emerg Med. 1998 May;16(3):270-1.

11. Wasserstein A, Hill G, Goldfarb S, Goldberg M. Recurrent thrombotic thrombocytopenic purpura after viral infection. Clinical and histologic simulation of chronic glomerulonephritis. Arch Intern Med. 1981 Apr;141(5):685-7.

12. Riggs SA, Wray NP, Waddell CC, Rossen RD, Gyorkey F. Thrombotic thrombocytopenic purpura complicating Legionnaires' disease. Arch Intern Med. 1982 Dec;142(13):2275-80.

13. Myers KA, Marrie TJ. Thrombotic microangiopathy associated with Streptococcus pneumoniae bacteremia: case report and review. Clin Infect Dis. 1993 Dec;17(6):1037-40.

14. Neau D, Bonnet F, Viallard JF, Longy-Boursier M, Le Bras M. Thrombotic thrombocytopenic purpura and cytomegalovirus infection in an immunocompetent adult. Clin Infect Dis. 1997 Dec;25(6):1495-6.

15._ Moake JL. Thrombotic microangiopathies. N Engl J Med. 2002 Aug 22;347(8):589-600.

16. Brandenburg VM, Gaertner S, Lindemann-Docter K, Ortlepp JR, Westerhuis R, Ketteler M,

Westenfeld R, Floege J. Underestimated complications in thrombotic thrombocytopenic purpura--haemolytic uraemic syndrome. Nephrol Dial Transplant. 2004 Aug;19(8):2142-6.

17. Panoskaltsis N, Derman MP, Perillo I, Brennan JK. Thrombotic thrombocytopenic purpura in pulmonary-renal syndromes. Am J Hematol. 2000 Sep;65(1):50-5.

18. Naseri M, Zabolinejad N. ANCA-Negative Pulmonary-Renal Syndrome with Pathologic Findings Suggesting Thrombotic Thrombocytopenic Purpura. Iranian Journal of Pediatrics. 2007 March;17(1):63-8.

19. Bone RC, Henry JE, Petterson J, Amare M. Respiratory dysfunction in thrombotic thrombocytopenic purpura. Am J Med. 1978 Aug;65(2):262-70.