

An Unusual Case Of Double Antibody Positive Goodpasture's Syndrome With Immune Mediated Thrombocytopenia

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Citation

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Abstract

Our case report is about a 52-year-old female who developed renal impairment, alveolar hemorrhage and thrombocytopenia. She was diagnosed to have Goodpasture's syndrome by the demonstration of anti-GBM antibodies and MPO-ANCA. The diagnosis was confirmed by a kidney biopsy. The evaluation of the thrombocytopenia ruled out TTP due to the absence of a microangiopathic hemolytic anemia and ruled out heparin-induced thrombocytopenia based on negative tests for PF4 antibodies and a negative serotonin release assay. While it was difficult to rule out a drug-induced thrombocytopenia, the most likely cause was an immune thrombocytopenia. This case portrays an unusual development of immune mediated thrombocytopenia in a patient with Goodpasture's syndrome.

INTRODUCTION

Goodpasture's syndrome (anti glomerular basement membrane disease) is a pulmonary renal syndrome caused by circulating auto antibodies against alpha 3 chain of type IV basement membrane collagen. Simultaneous renal and pulmonary involvement occur in 60-80% of the patients, isolated glomerulonephritis occurs in 10-30% of patients, and isolated diffuse alveolar hemorrhage occurs in 5-10% of patients.¹ The patient in the case report was a 52-year-old female initially presenting with rapidly progressing glomerulonephritis (RPGN). She was diagnosed with Goodpasture's syndrome by the presence of anti-glomerular basement membrane antibodies (anti-GBM antibodies) and myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA). The unusual aspect of this case is that the patient also developed a concomitant immune mediated thrombocytopenia.

CASE REPORT

A 52-year-old female who presented with nausea and vomiting for two weeks. There was a past medical history of hypertension and one episode of urinary tract infection five months ago. She also complained of fever, chills, reduced urinary output and pink colored urine during that period. Review of systems was positive for fatigue, heartburn, nausea and chills. Physical examination was unremarkable. Initial biochemical workup revealed a blood Urea Nitrogen

of 91 mg/dl, creatinine of 9.4 mg/dl, hemoglobin of 7.7 g/dl, and a WBC count of $12.1 \times 10^9/l$ and platelet count of $373 \times 10^9/l$. Prior studies 8 months ago revealed a serum creatinine of 1.4 mg/dl. Urinalysis showed mild proteinuria and hematuria with 50 RBC per high power field but no erythrocyte casts. An autoimmune panel was sent and it was positive for anti Glomerular Basement Membrane antibodies (54.8 EU) and MPO-ANCA (22 U/ml).

Empirical treatment was started with methylprednisolone intravenously along with renal replacement therapy. A kidney biopsy was planned. CT scan of chest did not show any evidence of focal consolidation, infiltrates or pleural effusion. Subsequently, plasmapheresis was started and patient received 5 sessions of plasmapheresis. Anti GBM antibody titers progressively decreased through the course of plasmapheresis from 54.8 to 2.8 EU. In the interim, kidney biopsy revealed cellular crescents in fifty percent of glomeruli. Two plus linear IgG and C3 deposition in glomerular capillary walls on immunofluorescence microscopy was documented. These studies confirmed the diagnosis of anti-GBM glomerulonephritis (Figure 1, 2 and 3). Red blood cell casts were seen on light microscopy. Approximately five days after the fifth session of plasmapheresis (day 23 of hospital stay), she started having shortness of breath with desaturation. Chest radiograph at this point showed worsening bilateral airspace opacities

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predominantly at lung bases and small bilateral pleural effusions. Troponin was also elevated along with EKG changes. She was subsequently transferred to intensive care unit. She required respiratory support, non-invasive Bipap, and endotracheal intubation with mechanical ventilation. In the ICU, bronchoscopy was done and bronchoalveolar lavage showed bloody fluid bilaterally consistent with diffuse alveolar hemorrhage. Plasmapheresis was restarted at this point to complete 14 consecutive daily treatments.

She started developing thrombocytopenia on day 17 of her hospital stay after she received additional four sessions of plasmapheresis. Her platelet count on day 17 was $126 \times 10^9/l$ and progressively decreased to $26 \times 10^9/l$ by day 27. Workup for heparin induced thrombocytopenia including an assay for heparin-induced antibody and a serotonin release assay and these studies were negative. There was no evidence of thrombosis.

PT and APTT was normal, LDH was high at 497 u/l, haptoglobin level was normal, reticulocyte count was 5.66% and when corrected was normal. Peripheral blood smear revealed anisopoikilocytosis, 1-2 schistocytes per HPF, increased white cells mostly mature neutrophils and decreased platelets with occasional large platelets (Figure 4). An ADAMTS 13 activity was slightly low at 66% (normal activity 68% to 163%). A subsequent ADAMTS13 was 73%. TTP was unlikely as there was no evidence of a microangiopathic hemolytic anemia based on the dearth of schistocytes and a normal corrected reticulocyte count.

A drug-induced thrombocytopenia could not be ruled out as patient since had been on Esomeprazole. Our impression was that she had an immune-mediated thrombocytopenia. She was started on dexamethasone for 3 days followed by re-initiation of methylprednisone. She was continued on daily plasmapheresis to manage the diffuse alveolar hemorrhage. Intravenous immunoglobulin was started at this time, as the underlying etiology was considered immune-mediated. After treatment with 4 doses of dexamethasone and 2 sessions of intravenous immunoglobulin, her platelet count improved to $100 \times 10^9/cc$. Thereafter, the platelet count fluctuated between $80-100 \times 10^9/l$ until day 41 of hospital stay when it decreased to $40 \times 10^9/l$, requiring platelet transfusions to control bleeding and to keep the count about above $50 \times 10^9/l$. Esomeprazole was also discontinued around this time and final session of plasmapheresis was administered on day 42. The patient subsequently got extubated with partial resolution of lung

infiltrates. Oral steroids were continued and cyclophosphamide was started to prevent relapse of Goodpasture's syndrome. The platelet count stabilized between $60-80 \times 10^9/ml$ a week after starting cyclophosphamide. Her WBC count was $6 \times 10^9/l$ and her RBC count of $3.45 \times 10^{12}/l$. Her cell counts improved slowly as cyclophosphamide was tapered. At the time of discharge to rehabilitation unit (Day 70 of hospital stay), her WBC count improved to $10.3 \times 10^9/l$, RBC count was $3.61 \times 10^{12}/l$ and platelet count was $139 \times 10^9/l$.

Her pulmonary hemorrhage resolved after 2 weeks of plasmapheresis and anti-GBM antibodies became undetectable in serum. She had minimal evidence of hemolysis during the hospital course and her coagulation panels were normal. She continued to be dependant on hemodialysis for renal failure secondary to rapidly progressive glomerulonephritis. At follow up after two weeks of being transferred to rehabilitation unit for deconditioning, her platelet count was $182 \times 10^9/l$.

Figure 1

Figure 1: Renal biopsy on light microscope showing cellular crescents and hypercellularity; H&E.

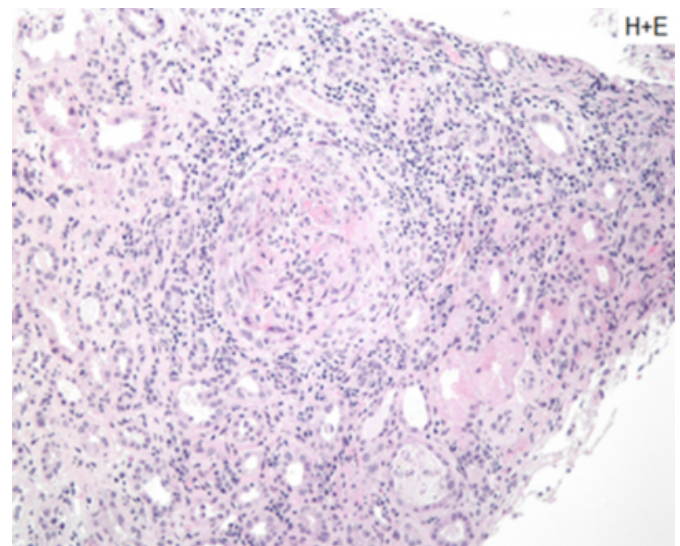


Figure 2

Figure 2: Fluorescent anti-IgG staining of renal biopsy revealing linear deposits of autoantibody along the basement membrane.

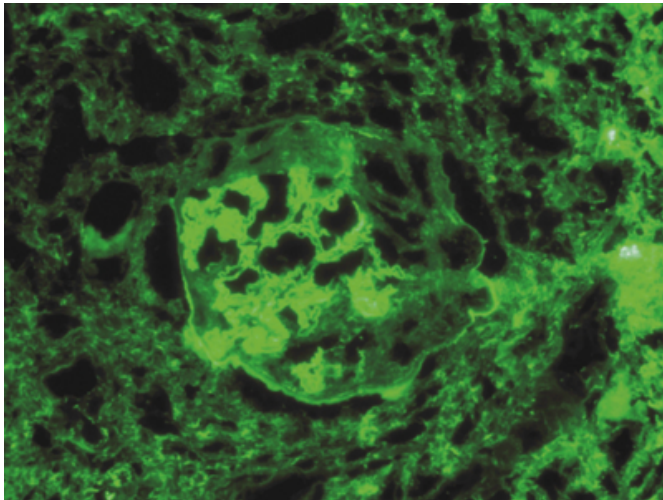


Figure 3

Figure 3: Immunofluorescence microscopy showing linear C3 deposition in glomerular capillary wall.

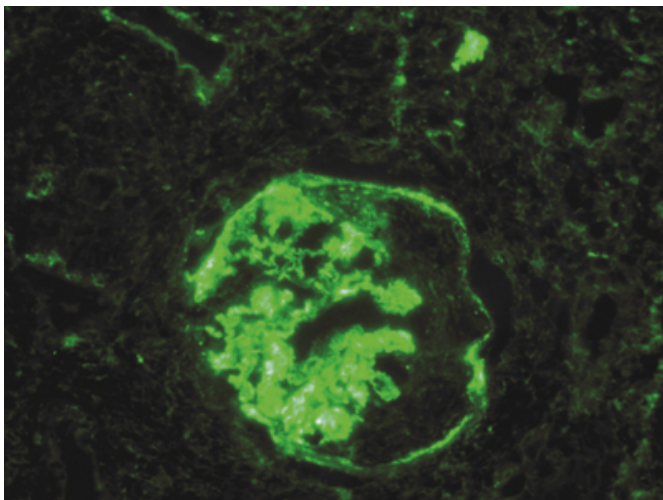
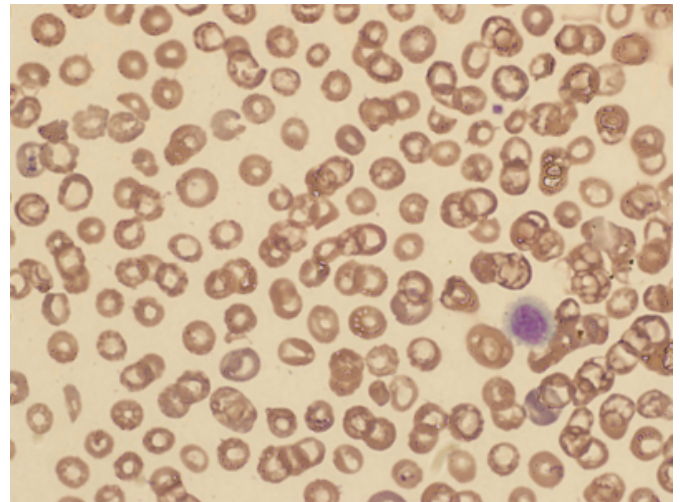


Figure 4

Figure 4: Peripheral blood smear showing rare schistocytes and a giant platelet.



DISCUSSION

During the 1918-1919 influenza pandemic, the pathologist Ernest Goodpasture (1866-1960) reported about two patients with rapidly progressive and ultimately fatal syndrome characterized by hemoptysis, anemia and renal failure. Today the term Goodpasture's syndrome is used to describe the combination of glomerulonephritis and lung hemorrhage in the absence of another specific cause (e.g. Wegener's granulomatosis), whether or not there are circulating anti-glomerular basement membrane antibodies². Goodpasture's syndrome is associated by auto antibodies to the noncollagenous-1 domain of alpha 3 chain of type IV collagen in the basement membrane of glomerular and alveolar tissue.

Goodpasture's syndrome was diagnosed by positive anti-GBM antibodies and MPO ANCA. Between 5% to 14% of patients with MPO ANCA also will have anti-GBM antibodies and between 30% and 38% of patients with anti-GBM antibodies will have MPO ANCA³⁻⁶.

The patient had a normal platelet count upon admission but developed thrombocytopenia during her hospitalization. Thrombocytopenia is a rare manifestation of Goodpasture's syndrome. There are only three previous case reports of thrombocytopenia associated with Goodpasture's syndrome, all of them reported as thrombotic thrombocytopenic purpura (TTP)⁶⁻⁸. There is evidence that helper T (Th) cell-associated cytokine, interleukin (IL)-12 is involved in the pathogenesis of thrombotic thrombocytopenic purpura^{9,10}.

Furthermore, Kalluri et al. developed a new mouse model of human anti-GBM disease, in which crescentic glomerulonephritis and lung hemorrhage were associated with emergence of IL-12/Th1-like T-cell phenotype¹¹.

There was no evidence that our patient had TTP since her corrected reticulocyte count was normal and she did not have a microangiopathic hemolytic anemia (absence of and elevated reticulocyte count and the absence of a significant number of schistocytes on the peripheral smear). In addition, the pentad that characterized TTP was not present. The ADAMTS 13 activity was initially borderline low at 66% but was subsequently 73%.

Heparin-induced thrombocytopenia needs to be considered since she developed thrombocytopenia during hospitalization. However, there was no evidence of thrombosis. Furthermore, PF4 antibodies were not detected and a serotonin release assay was negative. It is generally difficult to distinguish immune thrombocytopenia and drug induced thrombocytopenia, but we believe that the patient developed an immune thrombocytopenia.

This case further supports the theory of a "mosaic of autoimmunity" as it incorporated emergence of multiple autoimmune pathologies in the same individual¹². Immune mediated thrombocytopenia has also been observed in association with idiopathic pulmonary hemosiderosis in a case reported by Buchanan et al. with good response to corticosteroid and splenectomy¹³.

References

1. Cosgrove GP, Schwarz MI. Vasculitis & the diffuse alveolar hemorrhage syndromes; Current diagnosis and treatment in pulmonary medicine.
2. Golberger ZD, Weinberger SE, Nicosia RF, Saint S, Young BA. Variations on a theme. *N Engl J Med* 2008; 359:1502-1507.
3. Jayne DR, Marshall PD, Jones SJ, Lockwood CM. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int.* 1990; 37:965-70.
4. Hellmark T, Niles JL, Collins AB, McCluskey RT, Brunmark C. Comparison of anti-GBM antibodies in sera with or without ANCA. *J Am. Soc. Nephrol.* 1997; 8: 376-85.
5. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CT. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int.* 2004; 66: 1535-40.
6. Watanabe H, Kitagawa W, Suzuki K, Yoshino M, Aoyama R, Miura N, Nishikawa K, Imai H. Thrombotic thrombocytopenic purpura in a patient with rapidly progressive glomerulonephritis with both anti-glomerular basement membrane antibodies and myeloperoxidase anti-neutrophil cytoplasmic antibodies. *Clin Exp Nephrol.* 2010 Dec; 14(6):598-601.
7. Torok N, Niazi M, Al Ahwel Y, Taleb M, Taji J, Assaly R. Thrombotic thrombocytopenic purpura associated with anti-glomerular basement membrane disease. *Nephrol. Dial. Transplant.* 2010; 25(10): 3446-3449.
8. Terryn W, Benoit D, Van Loo A, Peeters P, Schepkens H, Cokelaere K, Vanholder R. Goodpasture's syndrome associated with autoimmune thrombotic thrombocytopenic purpura an unusual case. *Nephrol Dial Transplant.* 2007 Dec; 22(12):3672-3.
9. Takatsuka H, Takemoto Y, Okamoto T, et al. Thrombotic microangiopathy following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1999; 24:303-306.
10. Kakishita E. Pathophysiology and treatment of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). *Int J Hematol* 2000; 71:320-327.
11. Kalluri R, Danoff TM, Okada H, et al. Susceptibility to anti-glomerular basement membrane disease and Goodpasture syndrome is linked to MHC class II genes and the emergence of T cell-mediated immunity in mice. *J Clin Invest* 1997; 100:2263-2275.
12. Brickman CM, Shoenfeld Y. The mosaic of autoimmunity. *Scan. J Clin. Lab. Invest. Suppl.* 2001; 235:3-15.
13. Buchanan GR, Moore GC. Pulmonary hemosiderosis and immune thrombocytopenia. Initial manifestations of collagen-vascular disease. *JAMA* 1981; 246:861-864

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