and polymerization at 72°C for 50 s for a total of 35 cycles. PCR products were checked on 2% agarose gel to confirm single product in order to perform direct sequencing. PCR products were purified by Montage-PCR column (Millipore) to remove excess primers and salts. The purified products were then directly sequenced with dGTP BigDye Terminator Cycle Sequencing Chemistry (Applied Biosystems) using the same PCR primers. Sequencing was performed by 3730 DNA Analyzer by Applied Biosystems.

References


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Thrombotic thrombocytopenic purpura associated with anti-glomerular basement membrane disease

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Abstract

Goodpasture’s disease is associated with circulating anti-glomerular basement membrane (anti-GBM) antibodies. Thrombotic thrombocytopenic purpura (TTP) is a disease related to platelet clumping and microthrombosis in the circulation. We report an unusual case where both entities coexist in the same patient. The patient was a 43-year-old Caucasian male, with a recent history of inhalational hydrocarbon exposure for ~10 weeks. He initially presented with confusion, persistent fever and acute oliguric renal failure. In addition, he was found to be thrombocytopenic and had concurrent microangiopathic haemolytic anaemia. All presenting signs, symptoms and laboratory findings had a temporal relationship within 3 weeks. In addition, he was also found to have active pulmonary hemorrhage and positive anti-GBM antibody. During his stay, the patient underwent treatment with plasmapheresis, and an open lung biopsy, which confirmed the diagnosis of anti-GBM disease. This case report confirms previously reported findings which were noted in a few sporadic case reports about the possible association between Goodpasture’s disease and TTP. In addition, it adds to our current understanding of the pathophysiology of autoimmune diseases in general and supports the theory of an autoimmune disease.
mosaic, which has also been noted in various other autoimmune diseases.

**Keywords:** anti-glomerular basement membrane; Goodpasture's disease; hydrocarbon exposure; microangiopathic hemolytic anemia; thrombotic thrombocytopenic purpura (TTP)

**Introduction**

Goodpasture's disease is currently attributed to circulating anti-glomerular basement membrane (anti-GBM) antibody. It is characterized by a rapidly progressive glomerulonephritis and pulmonary hemorrhage. At the other end of this disease spectrum is the anti-GBM disease which affects only the kidneys. The incidence of Goodpasture’s disease overall is one per million per year [1]. Similarly, thrombotic thrombocytopenic purpura (TTP) is an uncommon disease, with an incidence of only 11 per million per year [2]. The combination of these two uncommon diseases is, as expected, exceedingly rare.

We conducted a computerized search of the PubMed database using combinations of the following terms: ‘Goodpasture’s’, ‘thrombotic thrombocytopenic purpura’, ‘microangiopathic haemolytic anaemia’ and ‘anti-glomerular basement membrane disease’. The references of retrieved articles were also searched for any relevant articles. Case reports of TTP, anti-GBM disease and microangiopathic haemolytic anaemia were then reviewed [3–5].

**Case presentation**

A 43-year-old Caucasian man presented with gradual onset of weakness, fevers and hemoptysis. His past medical history is significant for a history of a repair of coarctation of the aorta with aortic grafts, an aortic prosthetic valve (St. Jude’s) replacement, and repair of a left subclavian artery aneurysm in his late teens. This patient also had a recent history of significant inhalational exposure to hydrocarbons via oral siphoning of kerosene twice weekly at least, for the previous 3 months, in addition to exposure to naphtha, an insecticide, just 3 days prior to his current illness.

An initial examination revealed a lethargic man with the following presenting vital signs and physical findings: BP 150/80 mmHg, pulse 65 beats/min, respiratory rate 24 breaths/min and temperature 101°F (38.3°C).

Bilateral crackles were heard in the middle and lower lung fields; a mechanical second heart sound was noted without any associated murmurs. Additional findings were a distended abdomen with shifting dullness, an elevated jugular venous pressure at 10 cm above the sternal angle and bilateral lower extremity pitting oedema. Radiologically, a chest X-ray showed a diffuse alveolar infiltrate.

Initial laboratory test results are shown in Table 1. At this point, the patient underwent a bronchoscopy which showed blood in all bronchial segments, and bronchoalveolar lavage results showed an RBC count of >500 × 10³/mL.

Within a couple of days of his admission, he was intubated due to an acute deterioration of his condition. An open lung biopsy was done at that time, which showed evidence for recent intra-alveolar hemorrhage, as well as pig-

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**Table 1. Initial laboratory test results**

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Patient’s lab results</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>6</td>
<td>13.9–16.3</td>
</tr>
<tr>
<td>WBC count (cells/L)</td>
<td>14 × 10⁹</td>
<td>4.0–10.0 × 10⁹</td>
</tr>
<tr>
<td>Platelet count (cells/L)</td>
<td>35 × 10⁹</td>
<td>150–450 × 10⁹</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Occasional schistocytes</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>&lt;6</td>
<td>24–160</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>360</td>
<td>98–192</td>
</tr>
<tr>
<td>Direct Coomb’s test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-C3 antibodies</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-IgG antibodies</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>5.5 (419)</td>
<td>0.64–1.24</td>
</tr>
<tr>
<td>(μmol/L)</td>
<td></td>
<td>(53–105)¹</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL) (μmol/L)</td>
<td>2.5 (42.5)</td>
<td>0.2–1.2</td>
</tr>
<tr>
<td>Corrected reticulocyte count (%)</td>
<td>4</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>ADAMTS13 Level (%)</td>
<td>17</td>
<td>60–130</td>
</tr>
<tr>
<td>Anti-GBM titer (%)</td>
<td>1:160</td>
<td>Negative</td>
</tr>
</tbody>
</table>

¹Values in international system of units (SI).

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**Fig. 1.** Lung biopsy showing alveolar hemorrhage (black arrow) and hyperplasia of type 2 pneumocytes (white arrows) (×40 magnification).

**Fig. 2.** Focal areas of IgG immunoflorescence in a linear pattern on the alveolar septal wall consistent with anti-GBM disease.
ment-laden macrophages, in the absence of vasculitis or capillaritis. In addition, hyperplastic type 2 pneumocytes were seen (Figure 1), and immunofluorescence showed an IgG linear stain along the alveolar septa (Figure 2). Electron microscopy was done which showed focal electron densities on the capillary basement membranes, consistent with anti-GBM disease.

The decision was taken to initiate plasmapheresis which then resulted in an improvement of his platelet count. However, he continued to have hemolysis, with a resultant requirement for multiple blood transfusions.

Pertinent normal or negative laboratory tests at that time included vitamin B12, folate, anti-neutrophil antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), anti-double-stranded DNA (anti-dsDNA), anti-phospholipid antibodies, Escherichia coli 0157, blood cultures and complement levels. In addition, both transthoracic and transesophageal echocardiograms effectively excluded vegetations, thrombi and, in particular, a paravalvular leak.

Plasmapheresis was retried but with the addition of a pulse dose of methylprednisolone 1 g daily for 3 days, followed by 1 mg/kg orally, and finally cyclophosphamide 750 mg/m². This resulted in an immediate improvement in the kidney function, but the hemolysis and thrombocytopenia responses lagged behind for a further 10 weeks after his platelet count, hemoglobin and peripheral blood smear normalized.

Discussion

The story of Goodpasture’s disease dates back to 1919, when Goodpasture described a patient with pulmonary hemorrhage and hematuria. In 1950, Stanton and Tange [6] described a series of patients with pulmonary–renal syndrome. It is not known whether these cases, or indeed if Goodpasture’s original case, had anti-GBM antibodies because the techniques for detecting these antibodies were not yet available at that time.

Our patient presented with rapidly progressive renal failure and alveolar hemorrhage coupled with a positive anti-GBM antibody, and a lung biopsy showed a linear pattern of IgG deposition on the basement membrane making the diagnosis of anti-GBM disease definite. However, the patient also had other features not typically associated with anti-GBM disease, which included confusion, thrombocytopenia and haemolytic anaemia. These features, along with renal failure, represent the classic pentad for the diagnosis of TTP. This is further supported by low levels of ADAMTS13. The combination of all these, including his clinical profile and supportive laboratory evidence, indicates an exceedingly high likelihood that our patient has both anti-GBM disease and TTP. It must be conceded that the patient does have a prosthetic aortic valve, and it can be argued that prosthetic valves are associated with haemolytic anaemia, low haptoglobin levels and fragmentation of the red blood cells during any of the remission periods. Malignant hypertension is another differential to consider in this case, as it can cause fragmented red blood cells as well as confusion and renal failure. In our patient, the blood pressure was persistently in the normal range.

Stallworthy et al. [4] reported a case of microangiopathic haemolytic anaemia and Goodpasture’s disease which showed no response to plasmapheresis. Terryn et al. [3] also reported a case of Goodpasture’s disease limited to the kidneys but coupled with TTP and a concurrent history of hydrocarbon exposure similar to that in our case. Stave et al. [5] described thrombotic angiopathy as a complication of anti-GBM glomerulonephritis in a series of 12 patients with anti-GBM disease, of which six had thrombotic microangiopathy by renal biopsy and fragmentation of red blood cells on peripheral blood films.

Our findings here are consistent with those noted above. However, it is important to mention that the aforementioned series preceded the availability of testing for ANCA, which is found in ~30% of patients with anti-GBM disease. On the other hand, 5–10% of patients presenting with ANCA-positive systemic vasculitis have anti-GBM antibodies [7], with the resultant possibility that some of the cases noted above could have been ANCA-positive anti-GBM disease. We believe, however, that the actual figures may be less than those which were reported.

Anti-GBM antibody disease is a disorder in which circulating antibodies are directed against an antigen intrinsic to the GBM, specifically with the alpha-3 chain of type IV collagen representing the antigenic target [8]. Certain triggering factors have been associated with this disease, such as the hydrocarbon exposure described in our patient, as well as smoking and certain infections. Our patient’s lung biopsy shows diffuse alveolar damage (DAD) with hyperplasia of the type 2 pneumocytes (Figure 2). This specific histopathological finding further supports the theory that the exposure of some type of cryptic epitope(s) within the alveolar basement membrane itself is what triggers an autoimmune response [9].

TTP is a disease with an underlying pathology of thrombosis in different organs, secondary to a deficiency of ADAMTS13 which can be congenital or acquired. The ADAMTS13 is a von Willebrand factor (vWF)-cleaving protease which degrades vWF multimers, thereby decreasing their activity. A deficiency of ADAMTS13 will usually lead to the accumulation of large vWF multimers, platelet clumping and thrombosis. TTP is also associated with an inhibitory IgG autoantibody, especially in patients with very low levels of ADAMTS13, which further supports the autoimmune theory of TTP. Moreover, the production of this antibody is suggested to be part of a larger autoimmune process [10], and the association of TTP and systemic lupus erythematosus (SLE) is an example of this theory. Our case represents yet another intriguing example of multiple autoimmune diseases occurring in the same patient which lends further credence to the unifying theory of a ‘mosaic of autoimmunity’ [11].

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Can mycophenolic acid dose requirement during the first transplant help predict dosing for the second transplant?

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Abstract

We describe the pharmacokinetic profile of mycophenolic acid (MPA) in a patient receiving Mycophenolate mofetil (MMF) during her first and second renal transplantations. The MMF dose required to achieve a therapeutic range of MPA-AUC0–12h early following the second transplantation was 10 times greater than that required late following the first transplantation. Her MMF requirement then declined and continued to decrease even beyond 1 year. Intra-individual variability in MPA profiles precluded the ability to predict MMF dosing for the second transplant based on that during the first. Therapeutic drug monitoring of MMF should be continued beyond 1 year of transplantation.

Keywords: intra-individual variability; mycophenolic acid; pharmacokinetics; renal transplantation; therapeutic drug monitoring

Background

Mycophenolate mofetil (MMF), which is widely prescribed in renal transplantation, is rapidly absorbed and converted to its active moiety, mycophenolic acid (MPA). Therapeutic drug monitoring (TDM) of MPA is advocated because of large inter-individual variability in pharmacokinetic profiles [1]. Individualization of MMF dose based on the maintenance of MPA area under the curve (MPA-AUC0–12h) within 30–60 mg h/L reduces renal allograft rejection [2].

Case report

A 34-year-old woman, who had lost her native kidney function to lupus nephritis, received her first renal allograft from her haplo-matched mother in July, 1994. She