Clinical Vignettes

Pulmonary Alveolar Proteinosis in a 67-Year-Old Woman with Wegener's Granulomatosis

Shiwan K. Shah, DO¹, Nghi B. Phan, MD¹, Geetinder Goyal, MBBS²,
and Gulshan Sharma, MBBS, MPH³

¹Departments of Internal Medicine and Pediatrics, University of Texas Medical Branch, Galveston, TX, USA; ²Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA; ³Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA.

Mycophenolate mofetil (MM) is commonly used in patients with autoimmune diseases or who have undergone transplantation. Common side effects of MM include anemia, leukopenia, mucositis and opportunistic infections. We report an unusual case of pulmonary alveolar proteinosis (PAP) in a 67-year-old woman on MM for Wegener's granulomatosis (WG). PAP is a disease characterized by defects in macrophage-mediated processing of surfactants, leading to accumulation of periodic acid-Schiff (PAS)-positive lipoproteinaceous material within the alveolar spaces.

KEY WORDS: Mycophenolate mofetil (MM); Pulmonary alveolar proteinosis (PAP); Wegener's granulomatosis (WG).

Abbreviations

ANCA	anti-neutrophil cytoplasmic antibody
BAL	bronchoalveolar lavage
CT	computed tomography
FIO ₂	fraction of inspired oxygen
GM-CSF	granulocyte macrophage colony-stimulating factor
ILD	interstitial lung disease
LDH	lactate dehydrogenase
MM	mycophenolate mofetil
PAP	pulmonary alveolar proteinosis
PAS	periodic acid Schiff
WG	Wegener's granulomatosis

J Gen Intern Med 25(10):1105-8

DOI: 10.1007/s11606-010-1433-7

© Society of General Internal Medicine 2010

INTRODUCTION

Mycophenolate mofetil (MM) is a commonly used immunosuppressant for patients with autoimmune diseases and for those who have undergone organ transplantation. Anemia, leukopenia, mucositis and opportunistic infections are common side effects of MM. We report a case of mycophenolate associated pulmonary alveolar proteinosis (PAP) in a patient with Wegener's granulo-

matosis (WG). PAP is a disease characterized by defects in macrophage-mediated processing of surfactants, leading to accumulation of periodic acid Schiff (PAS)-positive lipoproteinaceous material within the alveolar spaces¹.

CASE REPORT

A 67-year-old woman with a history of WG-associated interstitial lung disease (ILD) presented to the emergency room with worsening shortness of breath, a non-productive cough and subjective fevers. Her symptoms had progressed over a 6-month period from dyspnea on exertion to shortness of breath at rest. During this time, her dose of mycophenolate mofetil was gradually increased from 500 to 2,000 mg per day for presumed worsening of her ILD. She was also started on sildenafil for secondary pulmonary hypertension from underlying interstitial lung disease. Despite these changes to her medications, her symptoms worsened. Her supplemental oxygen requirement also increased from a fraction of inspired oxygen (FIO₂) of 28% to 50% over the 6-month period. However, her anti-neutrophil cytoplasmic antibody (ANCA) titers steadily decreased and were negative 3 months prior to her presentation at the emergency room.

She had been diagnosed with WG 3 years prior to admission. At that time, she presented with acute renal failure, a creatinine of 2.33 mg/dl and microscopic hematuria. A kidney biopsy revealed focal proliferative and sclerosing glomerulonephritis. She was also noted to have ILD at her initial presentation based on computed tomography (CT) of the lungs. Serum anti-neutrophil cytoplasmic antibody (ANCA) titers were 1:256 (normal, less than 1:20; significant titers, greater than 1:40-1:80). Symptoms did not improve on initial therapy with corticosteroids and cyclophosphamide. The patient was switched to a combination of MM and corticosteroids. She developed severe myopathy and hyperglycemia, and the corticosteroids were gradually tapered and stopped.

On examination, she was afebrile and in moderate respiratory distress. She was unable to speak in complete sentences. Auscultation of the chest revealed diffuse bilateral coarse breath sounds. The cardiac examination was normal. Examination of the extremities revealed clubbing and 1+ bilateral lower extremity edema. The remainder of the physical examination was unremarkable.

Initial laboratory findings are shown in Table 1. Of note, the lactate dehydrogenase (LDH) level was 1,375 U/l (normal, 300-

Received June 20, 2009

Revised November 12, 2009

Accepted May 25, 2010

Published online July 10, 2010

Table 1. Initial Laboratory Findings

	Laboratory results on presentation	Reference range
WBC (10^3 cells/mm ³)	5.5	4.0–10.0
RBC (10^6 cells/mm ³)	3.64	3.90–5.30
Hemoglobin (g/dl)	11.0	11.5–15.5
Hematocrit (%)	36.5	34.0–45.0%
Platelet (10^3 cells/mm ³)	248	150–400
Sodium (meq/l)	142	135–145
Potassium (meq/l)	3.4	3.5–5.0
Chloride (meq/l)	96	98–108
Bicarbonate (meq/l)	38	23–31
Anion gap	8	2–16
Blood urea nitrogen (mg/dl)	36	23
Glucose (mg/dl)	113	70–110
Creatinine (mg/dl)	1.83	0.70–1.70
Alk Phos (IU/l)	69	34–122
ALT (IU/l)	22	9–51
AST (IU/l)	26	13–40
LDH (IU/l)	1,375	300–600
ANCA	<1:20	<1:20

600 U/l). ANCA titers were less than 1:20, supporting remission of the underlying WG. Echocardiography revealed normal left ventricular systolic function and estimated right ventricular systolic pressures of 30–40 mmHg (normal, less than 35 mmHg), which suggested improved pulmonary hypertension on sildenafil therapy (Table 2).

The chest radiograph showed diffuse bilateral reticulonodular interstitial opacities. High-resolution CT scan revealed subpleural cysts/honeycombing with evidence of traction bronchiectasis (Fig. 1). In addition, there were diffuse ground-glass and alveolar opacities. These opacities were new since the patient's prior chest CT 3 years ago, which revealed only subpleural cysts/honeycombing (Fig. 2). While not typical, honeycombing and interstitial fibrosis have been reported in patients with WG².

The presence of new ground-glass and alveolar opacities, as well as the subjective fevers, in an immunocompromised host raised suspicion for superimposed infection. Bronchoscopy with a bronchoalveolar lavage (BAL) was performed. The BAL returns were opaque and milky. Cytopathology revealed abundant inspissated lipoproteinaceous material. The material was periodic acid Schiff (PAS) positive, which was evidence of the glycosylated phospholipids present in the surfactant (Fig. 3). No inflammatory cells were noted in the BAL. Stains for pneumocystis, fungi and acid-fast bacilli were negative, and no

Figure 1. High-resolution CT scan at presentation: Note the ground-glass and alveolar opacities as well as the thickening of the interlobular and intralobular septum.

viral changes were identified. BAL cultures for bacteria, fungi, acid-fast bacilli and viruses were negative. Because of worsening respiratory status, presence of ground-glass opacities on the high-resolution CT, the milky return on the bronchoalveolar lavage and the PAS-positive extracellular material on BAL, the patient was diagnosed with pulmonary alveolar proteinosis. This was thought to be secondary to MM as her symptoms developed after starting the drug and worsened with dose escalation.

An attempt to discontinue MM was unsuccessful. The patient's renal function worsened with reduction in mycophenolate from 2 g to 1.5 g. Because of a history of previous intolerance to cyclophosphamide and prednisone, a change in the immunosuppressant was not an option. Instead, the patient was started on granulocyte macrophage colony-stimulating factor (GM-CSF). Her symptoms improved in the ensuing 4 months. However, due to worsening renal function, GM-CSF therapy had to be discontinued. Subsequently, she became more dyspneic and hypoxemic, requiring increased oxygen supplementation. A whole lung lavage resulted in improvement

Table 2. Differential Diagnoses

Differential diagnoses	
Worsening WG-associated lung disease	Unlikely given negative ANCA titers and lack of response to increasing doses of mycophenolate mofetil
Superimposed infection	Ruled out by negative bronchoalveolar lavage findings
Diffuse alveolar hemorrhage	Ruled out by bronchoalveolar lavage findings
Pulmonary edema/heart failure	Echocardiogram showed normal left ventricular function
Worsening pulmonary hypertension	Echocardiogram revealed improvement in estimated right ventricular pressures

Figure 2. CT scan about 2 years prior to presentation. Note the significant cystic lung disease.

Figure 3. (a) Low power, Papanicolaou staining: Note the presence of extracellular material interspersed among the cells. (b) High power, PAS staining. The amorphous extracellular material stains well with PAS.

of her symptoms. At 1-month follow-up, she required a FiO_2 of 0.28% and was able to perform her activities of daily living without assistance.

DISCUSSION

Pulmonary alveolar proteinosis (PAP) is a non-inflammatory lung disorder, with an annual incidence of 0.36 cases per million. It is characterized by the accumulation of lipoproteinaceous material due to impairment in macrophage clearance of the alveolar surfactant. These patients typically present with progressive dyspnea, cough, low-grade fevers and fatigue. Laboratory testing often reveals an elevated LDH, as was seen in our patient. Radiographic findings include bilateral alveolar and interstitial disease on chest x-ray and a crazy paving pattern on high-resolution CT. Crazy paving is the combination of ground-glass opacification and septal thickening. BAL characteristically reveals milky-appearing fluid. Microscopic examination of the fluid may show large foamy alveolar macrophages as well as extracellular debris derived from surfactant. This debris, especially if present in small amounts, may not be seen on standard staining such as May-Grunwald-Giemsa and Papanicolaou staining, but is seen well with PAS staining. While BAL findings are usually sufficient, the gold standard for diagnosis is open lung biopsy^{1,3}.

PAP may be classified as congenital, acquired and secondary. Congenital PAP is thought to result from mutations in surfactant protein B and C or a mutation in the beta-C chain of the GM-CSF receptor on pulmonary macrophages. Acquired PAP is usually a result of GM-CSF antibodies causing macrophage dysfunction.

Secondary PAP is due to qualitative or quantitative macrophage dysfunction as a result of environmental exposures (i.e., silica, cement dust, cellulose fibers, aluminum dust and titanium dioxide¹), autoimmune diseases or immunosuppression. The latter may be from underlying hematological malignancies or immunosuppressive medications^{1,3}. Macrophage dysfunction in secondary PAP is a result of the underlying immunodeficient state and not anti-GM-CSF antibodies.

Malignancies, especially hematological malignancies, are associated with both quantitative and qualitative macrophage

impairment⁴⁻⁷. Chronic myeloid leukemia is most commonly associated with PAP⁸. However, the role of malignancy is complicated by the fact that the treatment for malignancies often involves the use of immunosuppressive medications.

Immunosuppressive medications reported to be associated with PAP include corticosteroids, leflunomide, sirolimus, tacrolimus, cyclosporine, azathioprine and busulfan^{4-7,9-12}. To our knowledge, this case is the first to report an association of mycophenolate mofetil with PAP.

Mycophenolate interrupts *de novo* purine synthesis by inhibiting inosine monophosphate dehydrogenase. Because lymphocytes do not have a salvage pathway by which to recycle purine nucleotides, they depend on the *de novo* pathway for the supply of these nucleotides. Thus, inhibition of the *de novo* pathway results in depletion of these nucleotides, impairing DNA synthesis. This results in impairment of cell-mediated immunity, which may lead to macrophage dysfunction. Another consequence of depletion of guanosine nucleotides is reduced mannosylation of membrane glycoproteins (guanosine nucleotides form complexes with mannose in the mannosylation process). This results in altered adhesion molecules on the surface of monocytes, preventing them from interacting with and migrating across the alveolar endothelium. This may lead to a decrease in the alveolar macrophage pool and reduced surfactant clearance^{13,14}.

PAP has been associated with autoimmune disorders such as rheumatoid arthritis, IgA nephropathy, multiple sclerosis and dermatomyositis, as well as in a patient with smooth muscle antibodies^{3,11,15,16}. There is one prior case report of WG-associated PAP¹². Most of these patients are also on immunosuppressive medications; the reported patient with WG was on cyclophosphamide and prednisone at the time of diagnosis of PAP. Thus, it is difficult to assess the contribution of autoimmune disease in the development of PAP. It is feasible that anti-GM-CSF antibodies may occur with WG-associated hypergammaglobulinemia. However, as in the previous reported case, ANCA titers in our patient were negative at presentation, indicating good control of the underlying WG. Therefore, mycophenolate mofetil is more likely responsible for the development of PAP.

Acquired PAP resolves spontaneously in 10% to 30% of patients^{1,3}. The remaining patients have either stable symptoms or progressive worsening. The standard of care for treatment is whole lung lavage, which removes the lipoproteinaceous material

in the alveoli, allowing for improved gas exchange. Whole lung lavage improved symptoms in 84% of reported cases³. The median duration of response is about 15 months, and whole lung lavage may be repeated as necessary¹. Other options include therapy with subcutaneous GM-CSF, which, at a dose of 5-9 µg/kg/day, results in improved symptoms in about 50% of patients³. GM-CSF works by stimulating alveolar macrophages to clear the surfactant³. Treatment of secondary PAP consists of treating the underlying disease or withdrawing immunosuppression if possible⁸. If unsuccessful, whole lung lavage should be performed. GM-CSF has not been studied in secondary PAP, and therapy with GM-CSF in patients with autoimmune disease should be undertaken with caution so as not to worsen the underlying medical condition.

CONCLUSION

We present evidence that mycophenolate mofetil, like most other immunosuppressants, may be associated with the development of PAP. Presentation of PAP can be subtle and often confused with worsening of underlying lung disease. This case demonstrates the importance of including PAP in the differential diagnosis in patients with WG who have worsening of their lung disease while on mycophenolate. Accurate diagnosis of this condition can allow for appropriate treatment, including withdrawal of immunosuppression, GM-CSF therapy and whole lung lavage. The latter is indicated for patients with worsening symptoms despite reduction in immunosuppressive therapy, especially those with significant arterial hypoxemia or significant symptoms, either at rest or with exertion¹⁷.

Acknowledgements: The authors presented this case in oral and poster format at the Texas Association of Internal Medicine Associate's Day on April 4, 2009 in Houston, Texas. The authors acknowledge Sarah Toombs Smith, PhD, for assistance in preparation of the manuscript and Vicki Schnadig, MD, for assistance with the pathology images.

Conflict of Interest: None disclosed.

Corresponding Author: Shiwan K. Shah, DO; Departments of Internal Medicine and Pediatrics, University of Texas Medical Branch, 301 University Blvd, Route 0561, Galveston, TX 77555, USA (e-mail: skshah@utmb.edu).

REFERENCES

1. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med*. 2003;349(26):2527-39.
2. Bicknell SG, Mason AC. Wegener's granulomatosis presenting as cryptogenic fibrosing alveolitis on CT. *Clin Radiol*. 2000;55(11):890-1.
3. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med*. 2002;166(2):215-35.
4. Aymard JP, Gyger M, Lavalley R, Legresley LP, Desy M. A case of pulmonary alveolar proteinosis complicating chronic myelogenous leukemia. A peculiar pathologic aspect of busulfan lung? *Cancer*. 1984;53(4):954-6.
5. Miyake S, Ohdama S, Kumagai T, Ishikawa M, Umino T, Takano S, et al. A case of pulmonary alveolar proteinosis and disseminated atypical mycobacteriosis complicating chronic myelogenous leukemia. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1992;30(9):1770-6.
6. Watanabe K, Sueishi K, Tanaka K, Nagata N, Hirose N, Shigematsu N, et al. Pulmonary alveolar proteinosis and disseminated atypical mycobacteriosis in a patient with busulfan lung. *Acta Pathol Jpn*. 1990;40(1):63-6.
7. Du EZ, Yung GL, Le DT, Masliah E, Yi ES, Friedman PJ. Severe alveolar proteinosis following chemotherapy for acute myeloid leukemia in a lung allograft recipient. *J Thorac Imaging*. 2001;16(4):307-9.
8. Ladeb S, Fleury-Feith J, Escudier E, Tran Van Nhieu J, Bernaudin JF, Cordonnier C. Secondary alveolar proteinosis in cancer patients. *Support Care Cancer*. 1996;4(6):420-6.
9. Yousem SA. Alveolar lipoproteinosis in lung allograft recipients. *Hum Pathol*. 1997;28(12):1383-6.
10. Pedroso SL, Martins LS, Sousa S, Reis A, Dias L, Henriques AC, et al. Pulmonary alveolar proteinosis: a rare pulmonary toxicity of sirolimus. *Transpl Int*. 2007;20(3):291-6.
11. Wardwell NR Jr, Miller R, Ware LB. Pulmonary alveolar proteinosis associated with a disease-modifying antirheumatoid arthritis drug. *Respirology*. 2006;11(5):663-5.
12. Compa DR, Beegle SH. Wegener granulomatosis and alveolar proteinosis in a 32-year-old female. *Chest*. 2007;132(4 (Supplement)):687 S.
13. Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus*. 2005;14(Suppl 1):s2-8.
14. Laurent AF, Dumont S, Poindron P, Muller CD. Mycophenolic acid suppresses protein N-linked glycosylation in human monocytes and their adhesion to endothelial cells and to some substrates. *Exp Hematol*. 1996;24(1):59-67.
15. Samuels MP, Warner JO. Pulmonary alveolar lipoproteinosis complicating juvenile dermatomyositis. *Thorax*. 1988;43(11):939-40.
16. Gray ES. Letter: Autoimmunity in childhood pulmonary alveolar proteinosis. *Br Med J*. 1973;4(5887):296-7.
17. Olade RB. Pulmonary alveolar proteinosis. *Emedicine* 2008.