J.S. Szeto, M.D.

MULTIPLE MYELOMA PRESENTING AS PULMONARY RENAL SYNDROME

Jocelyn S. Szeto, M.D.; Jose A. Perez Jr., M.D.
The Methodist Hospital, Houston, Texas

Introduction

Pulmonary renal syndromes are classically associated with systemic vasculitis and autoimmune disorders, such as systemic lupus erythematosus and Goodpasture syndrome. The dramatic presentation of pulmonary hemorrhage in conjunction with new onset renal insufficiency as presented in this case naturally led to the search for primary pulmonary renal syndrome. Interestingly, the patient was found to have a new diagnosis of multiple myeloma presenting with symptoms of hemoptysis and acute renal failure. The constellation of pulmonary renal symptoms seen in this case is extremely rare in association with multiple myeloma; specifically, only one other case has been reported with similar presenting symptoms. This article reviews and discusses a case of pulmonary renal syndrome related to multiple myeloma. A review of the current literature of pulmonary renal syndrome in multiple myeloma is also presented.

Case Presentation

A 67-year-old Caucasian male with past medical history notable only for hypertension and osteoarthritis presented with symptoms of cough and shortness of breath. The patient was in good health overall. Of note, approximately 2 weeks prior to admission, the patient had gone fishing and was accidentally stuck in the hand with a catfish fin. He subsequently developed mild cellulitis around the lesion and was treated with trimethoprim-sulfamethoxazole (TSM) and cephalexin. Approximately 1 week prior to admission, he developed progressive shortness of breath and nonproductive cough, prompting admission to the hospital. He denied any fever, weight changes, or other constitutional symptoms. However, the dyspnea became progressively more debilitating over the course of days, with pronounced malaise. His clinical condition rapidly deteriorated as he developed hypoxia and hemoptysis, requiring intubation and intensive care unit monitoring.

His past medical history was unremarkable except for hypertension, and he denied tobacco, alcohol, or illicit drug use. Home medications included only lisinopril and the recently prescribed antibiotics. On physical examination, the patient was well-nourished (BMI 28.8 kg/m²), intubated, and sedated. Vital signs included a temperature of 98°F, blood pressure of 170/82, pulse of 74 beats per minute, and respiratory rate of 20 breaths per minute with oxygen saturation of 100% on mechanical ventilation. Head examination was normocephalic and atraumatic with pupils equal, round, and sluggish to light and conjunctival pallor. His neck was supple with no jugular venous distension. Lung examination revealed coarse crackles at bilateral bases but no focal consolidation. His cardiac auscultation showed normal S1 and S2 without murmurs, rubs, or gallops, and the abdomen was soft with normoactive bowel sounds and no organomegaly. No skin lesions, rashes, or edema were present. Chest X-ray showed appropriately placed endotracheal tube with extensive diffuse interstitial and alveolar infiltrates bilaterally (see Figure 1).

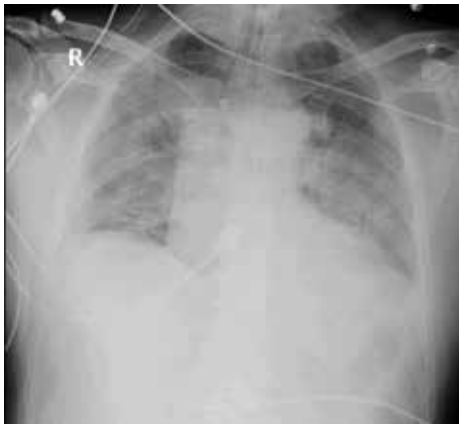

Image 1. Chest X-ray showing appropriately placed endotracheal tube with extensive diffuse interstitial and alveolar infiltrates bilaterally.

Laboratory findings included complete blood count, with WBC 10,260 per uL, Hgb 10.3 g/dL, Hct 30.6%, platelets of 167,000 per uL, and MCV 92.4 fL. Complete metabolic panel showed Na 150 mEq/L, K 4.3 mEq/L, Cl 99 mEq/L, CO_2 29 mEq/L, BUN 95 mg/dL, Cr 13.8 mg/dL, glucose 184 mg/dL, calcium 8.9 mg/dL, magnesium 2.1 mg/dL, phosphorus 11.9 mg/dL, total protein 7.8 g/dL, albumin 4.0 g/dL, total bilirubin 0.5 md/dL, direct bilirubin 0.4 mg/dL, ALT 12 units/L, AST 42 units/L, and alkaline phosphatase 71 units/L. Lactic acid was 1.3 mmol/L and urine drug screen was negative. Urinalysis was grossly red and hazy in appearance, with 2+ protein, large blood and leukocyte esterase, 71 WBC/HPF, more than 200 RBC/HPF, gram stain negative, and no culture growth. Urine eosinophils were negative. Additional laboratory studies included negative ANA, DNA antibody, p-ANCA and c-ANCA, anti-GBM, and HIV. Complement levels were normal. IgG was elevated at 1570 mg/dL with low levels of IgA (37 mg/dL) and IgM (27 mg/dL).

Bronchoscopy was performed with BAL cell count of 0.155m/mL, 44% PAMS, 2% lymphocytes, 54% PMNS, and negative

gram stain. Bronchoalveolar lavage was negative for malignancy and GMS stain. However, the lavage aspirate was noted to be progressively bloodier, consistent and characteristic of diffuse alveolar hemorrhage. Renal ultrasound showed relatively normal-sized kidneys with right measuring 10.8 by 6.0 by 5.4 cm and left measuring 10.0 by 5.8 by 4.9 cm. No renal mass, calculi, or hydronephrosis was seen. Subsequent renal biopsy revealed acute tubular injury with intertubular and peritubular neutrophilic inflammation secondary to obstructing tubular casts. Renal sample electron microscopy was unremarkable, specifically without any focal areas of complement deposition. Given the patient's presentation of pulmonary hemorrhage and renal failure, pulmonary renal syndrome was suspected. The patient was therefore started on high-dose steroids and cyclophosphamide and hemodialysis for suspected systemic vasculitis and anticipated start of plasma exchange. However, the patient failed to improve with current treatment. Eventually, a bone marrow biopsy was performed. The bone marrow aspirate showed 90% hypercellular marrow with greater than 50% of marrow cells displaying very immature, undifferentiated plasma cells. Findings were consistent with multiple myeloma. Subsequent therapy was modified to include dexamethasone and bortezomib. The patient's dyspnea and hypoxia improved to allow successful extubation with home oxygen support. Outpatient hemodialysis was continued with improvement in BUN and creatinine, but the patient remained dialysis dependent.

Commentary

This case report highlights pulmonary renal syndrome manifesting as the initial presentation of multiple myeloma. Pulmonary renal syndromes are typically caused by systemic vasculitis and autoimmune disorders such as microscopic polyangiitis, Wegener's granulomatosis, Goodpasture syndrome, and systemic lupus erythematosus. The aforementioned rheumotalogical entities are commonly associated with positive autoantibodies on serologic tests, all of which were negative in this patient. However, antibody negative tests do not definitively rule out a vasculitic or autoimmunie disorder.[1] Futhermore, this patient's clinical presentation of pulmonary hemorrhage and renal failure was strikingly convincing for an antibody negative systemic vasculitis, resulting in his empiric treatment with steroids and cyclophosphamide and strong consideration of plasma exchange. However, failure to respond prompted the search for an alternative diagnosis.

Pulmonary hemorrhage and acute renal failure as the initial presentation of multiple myeloma has been reported in only one other case report in 2010. In the initial case report, the patient was treated with plasma exchange, steroids, and melphalan, resulting in improvement of symptoms.[2] Our patient did not receive plasma exchange. The use of plasmapheresis to improve renal function is controversial, and multiple studies have failed to establish general consensus. The largest systematic review in 2010 showed no significant improvement in renal failure or morbidity and mortality with plasmapheresis, although smaller studies showing restoration of normal renal function have been reported.[3, 4, 5] Thus, it is unclear if plasmapheresis was the cause for improvement in renal function or if function was related to severity of underlying multiple myeloma or other still unknown variables. Although the antibiotic therapy with TSM could be implicated in the development of renal failure, the failure of the creatinine to return to baseline after discontinuation and the presence of casts suggest myeloma kidney since, in a recent study, these features were not associated with cases of TSM-induced renal injury.[6]

Multiple myeloma involves bone marrow invasion by plasma cell tumor. It is associated with monoclonal gammopathy and classic findings of bone pain from the infiltrating tumor, pathological fractures, fatigue, and weight loss. Renal failure is commonly seen in association with multiple myeloma. Increased production and excretion of free immunoglobulin light chains results in the formation of obstructive tubular casts that are classically seen on renal biopsy, as was in this reported case.[7] Pulmonary hemorrhage, however, is much less commonly encountered in the setting of multiple myeloma. Possible hypotheses for the association with pulmonary hemorrhage and multiple myeloma have been proposed, including secondary amyloidosis or concurrent infection, but the exact pathophysiology remains unclear.[2] Pulmonary hemorrhage without renal failure has been reported in two other case reports of multiple myeloma. Although congestive heart failure and fluid overload could be implicated in the development of pulmonary hemorrhage, the absence of jugular venous distension, gallop rhythm, edema in addition to the finding of diffuse alveolar hemorrhage makes this less likely. This patient's acute deterioration was likely hypoxic in nature given the presence of diffuse pulmonary hemorrhage and the absence of signs of fluid overload. His pulmonary condition improved with treatment of multiple myeloma, implicating this condition as the source of pulmonary hemorrhage.

This case is the second published report of multiple myeloma presenting as pulmonary hemorrhage and acute renal failure. Clinical symptoms of pulmonary renal syndrome are commonly seen as a rheumatological manifestation, with subsequent therapy directed towards controlling the autoimmune response. However, multiple myeloma should be considered as a cause of pulmonary renal syndrome as redirected therapy will impact clinical outcome.

Conflict of Interest Disclosure: All authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Funding/Support: The authors have no funding disclosures.

Keywords: multiple myeloma, pulmonary hemorrhage, acute renal failure

References

1. Perez-Suarez G, Marrero D, Rodriguez R, Delgado P, Cobo M, Gonzalez-Posada JM, et al. [Goodpasture's syndrome with neurologic involvement and negative ANCA]. Nefrologia. 2010;30(5):584-7.
2. Morita Y, Yasuda M, Nakao M, Tsujimura Y, Isono M. Pulmonary hemorrhage and acute renal failure as an initial presentation of multiple myeloma. Intern Med. 2010;49(14):1401-3.
3. Clark WF, Stewart AK, Rock GA, Sternbach M, Sutton DM, Barrett BJ, et al. Plasma exchange when myeloma presents as acute renal failure: A randomized, controlled trial. Ann Intern Med. 2005 Dec 6;143(11):777-84.
4. Zucchelli P, Pasquali S, Cagnoli L, Ferrari G. Controlled plasma exchange trial in acute renal failure due to multiple myeloma. Kidney Int. 1988 Jun;33(6):1175-80.
5. Gupta D, Bachegowda L, Phadke G, Boren S, Johnson D, Misra M. Role of plasmapheresis in the management of myeloma kidney: A systematic review. Hemodial Int. 2010 Oct;14(4): 355-63.
6. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012;67:1271-77.
7. Hutchison CA, Cockwell P, Stringer S, Bradwell A, Cook M, Gertz MA, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol. 2011 Jun;22(6):1129-36.