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## Mycophenolate Mofetil and Pulmonary Fibrosis After Kidney Transplantation: A Case Report

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Male, 50  
**Final Diagnosis:** Pulmonary fibrosis  
**Symptoms:** Short of breath  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Transplantology

**Objective:** Adverse events of drug therapy

**Background:** Mycophenolate mofetil (MMF) induced lung disease has been described in only a few isolated reports. We report a case of fatal respiratory failure associated with MMF after kidney transplantation.

**Case Report:** A 50-year-old Hispanic male with a history of end-stage renal disease secondary to hypertension underwent deceased donor kidney transplantation. His preoperative evaluations were normal except for a chest x-ray which showed bilateral interstitial opacities. Tacrolimus and MMF were started on the day of surgery. His postoperative course was uneventful and he was discharged on postoperative day 5. One month later, he presented with shortness of breath and a cough with blood-tinged sputum. His respiratory condition deteriorated rapidly, requiring intubation. Chest computer tomography (CT) demonstrated patchy ground-glass opacities with interlobular septal thickening. Comprehensive pulmonary, cardiac, infectious, and immunological evaluations were all negative. Open lung biopsy revealed extensive pulmonary fibrosis with no evidence of infection. He temporarily improved after discontinuation of tacrolimus and MMF, however, on resuming MMF his respiratory status deteriorated again and he subsequently died from hypoxic respiratory failure.

**Conclusions:** An awareness of pulmonary lung disease due to MMF is important to prevent adverse outcomes after organ transplantation. MMF must be used with utmost care in recipients with underlying lung disease as their pulmonary condition might make them more susceptible to any harmful effects of MMF.

**MeSH Keywords:** Abnormalities, Drug-Induced • Immunosuppressive Agents • Pulmonary Fibrosis • Tacrolimus

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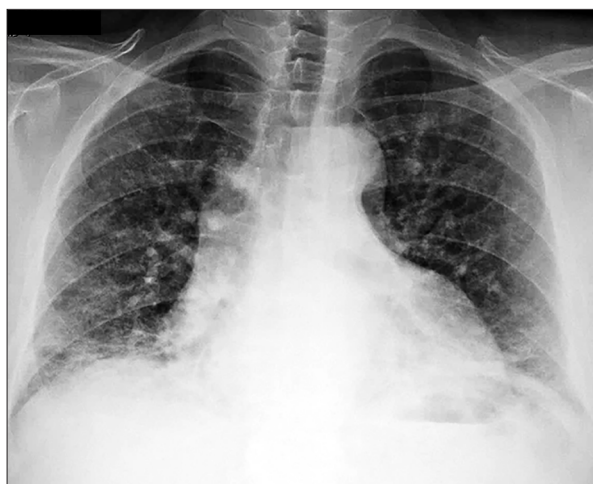
## Background

Pulmonary complications are one of the major causes of death in kidney transplant recipients [1,2]. Their frequency varies from 3.1% to 37% with a mortality rate of 22.5% to 32% [3–5]. They have also been known to be associated with a 20% incidence of graft failure [3]. The most common complication observed is bacterial pulmonary infection followed by cardiogenic pulmonary edema and acute lung injury or acute respiratory distress syndrome (ARDS) related to extrapulmonary bacterial sepsis [3,6]. Pulmonary toxicity from immunosuppressive medications, such as azathioprine [7] and mammalian target of rapamycin inhibitors (e.g., sirolimus and everolimus) [8,9], is well-known and established. Tacrolimus has also been recognized to cause lung injury in patients with collagen vascular disease [10,11]. On the other hand, mycophenolate mofetil (MMF) induced lung disease has been reported in only a few isolated reports [12–19]. We describe a case of fatal respiratory failure induced by MMF after kidney transplantation.

## Case Report

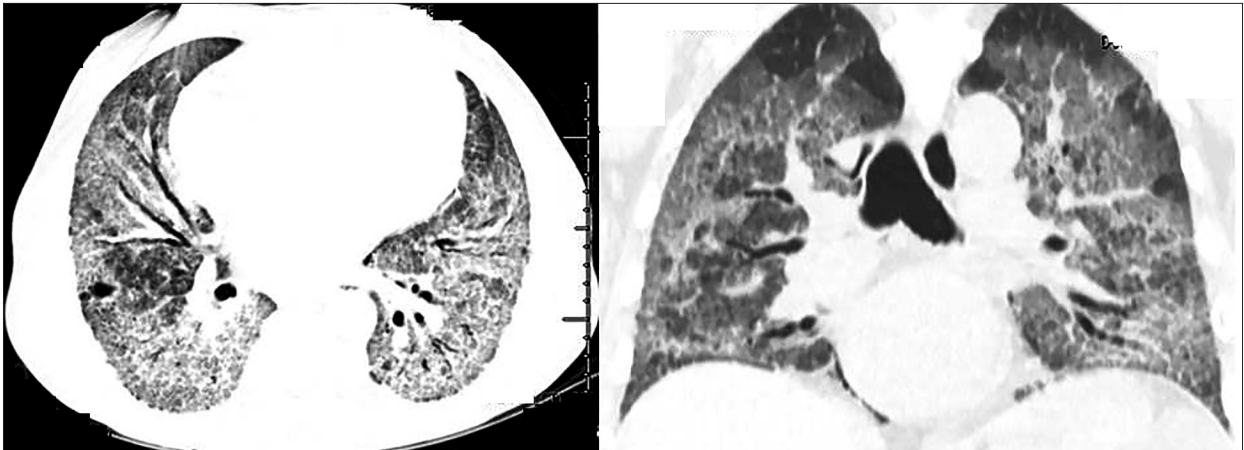
A 50-year-old Hispanic male with a history of end-stage renal disease secondary to hypertension was evaluated for deceased donor kidney transplantation. His preoperative evaluation revealed a 30-year history of smoking. Preoperative pulmonary and cardiac assessments were normal except for a chest x-ray (CXR), which revealed bilateral interstitial opacities (Figure 1). His Karnofsky performance status score was 90. His cytomegalovirus (CMV) IgG was negative. A blood group-compatible kidney from a standard criteria donor (36-year-old female, cause of death from cerebrovascular accident, CMV IgG positive) was transplanted. The surgery was uncomplicated with a cold ischemic time of 11 hours 59 minutes and a warm ischemic time of 63 minutes. His immediate post-operative period was uncomplicated and he developed immediate graft function. Basiliximab 0.2 mg was given on the day of transplantation and postoperative day (POD) 4. Valganciclovir 900 mg and sulfamethoxazole/trimethoprim 800/160 mg once a day were started as prophylaxis. Methylprednisolone 250 mg once a day, tacrolimus 2 mg twice a day, and MMF 1,000 mg twice a day were started on the day of surgery. He was discharged on POD 5. He received 2–4 mg of tacrolimus once a day and his trough levels ranged from 12.8–21.4 ng/mL. He received methylprednisolone 250 mg on POD 1 and 2, which was switched to prednisone 80 mg on POD 3 and tapered down to 60 mg on POD 4, 40 mg on POD 5, 30 mg on POD 6, and finally to 20 mg once a day on POD 7.

One month later, he presented to the emergency department with shortness of breath and cough. His respiratory condition rapidly deteriorated with signs of impending respiratory failure.

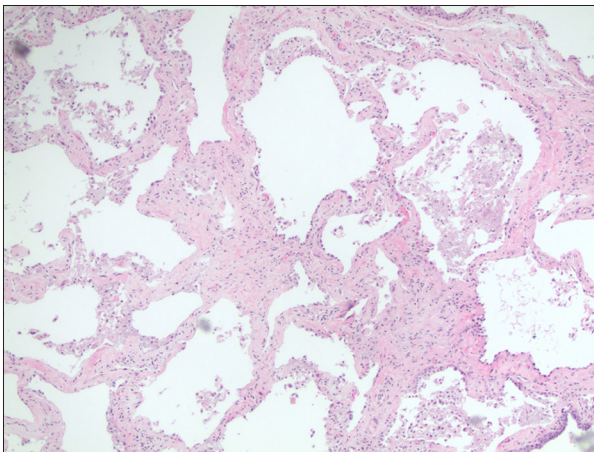


**Figure 1.** Preoperative chest X-ray (CXR). Preoperative CXR demonstrated bilateral interstitial opacities.

His arterial blood gas showed: pH of 7.33,  $pO_2$  of 61 mm Hg,  $pCO_2$  of 38 mm Hg, and  $HCO_3^-$  of 18.9 mEq/L ( $FiO_2$  50%). He was immediately admitted to the intensive care unit and intubated. CXR revealed diffuse airspace disease, and CT demonstrated patchy ground-glass opacities with interlobular septal thickening, associated with bronchiectasis (Figure 2). Findings from bronchoscopy were unremarkable and bronchoalveolar lavage samples were negative for all microbiologic cultures and stains including aspergillus, pneumocystis pneumonia, CMV, legionella, and mycobacterium. Polymerase chain reactions for CMV, influenza A and B, respiratory syncytial virus, rhinovirus, and adenovirus were also negative. Immunologic markers such as anti Scl-70 antibody, anti-nuclear antibody, rheumatoid factor, and anti-neutrophil cytoplasmic antibody were all negative. Echocardiogram revealed an ejection fraction of 65% without evidence of right heart strain. Cardiac catheterization was unremarkable, with a cardiac index of 4.5 L/min/m<sup>2</sup>, mean pulmonary arterial pressure of 18 mm Hg, pulmonary capillary wedge pressure of 15 mm Hg, and central venous pressure of 5 mm Hg. A diagnosis of ARDS secondary to infection was considered and vancomycin 1.5 g once a day, cefepime 1 mg once every 12 hours, and oseltamivir 150 mg once every 12 hours were started empirically. Tacrolimus and MMF were discontinued, and prednisone 20 mg was changed to a stress dosage of methylprednisone 100 mg once every eight hours. Aggressive diuresis with furosemide was initiated with successful extubation two days later. Arterial blood gas immediately post-extubation showed a  $pO_2$  of 89.8 mm Hg,  $pCO_2$  of 33.7 mm Hg, pH of 7.44, and a  $HCO_3^-$  of 22.7 mmol/L ( $FiO_2$  35%), which improved to  $pO_2$  of 101 mm Hg,  $pCO_2$  of 38.3 mm Hg, pH 7.42 and a  $HCO_3^-$  of 24.1 mmol/L ( $FiO_2$  30%), the following day. Since we considered tacrolimus alone to be the most likely cause of the respiratory distress, MMF was subsequently resumed. After two doses of MMF, the patient started to develop respiratory distress. Despite aggressive diuresis, his condition



**Figure 2.** Chest computer tomography (CT) on readmission. CT showed patchy ground-glass opacities with interlobular septal thickening, associated with bronchiectasis.



**Figure 3.** Open lung biopsy. Open lung biopsy showing extensive areas of interstitial fibrosis. Normal alveolar parenchyma essentially not seen with most of the alveolar walls thickened due to diffuse fibrosis (Hematoxylin-Eosin,  $\times 4$ ).

continued to deteriorate over the next two days eventually leading to severe hypoxia at  $pO_2$  44.5 mm Hg,  $pCO_2$  36.5 mm Hg, pH 7.48,  $HCO_3^-$  26.8 mmol/L, ( $FiO_2$  50%), which required re-intubation. All of his immunosuppressive drugs were discontinued except for methylprednisone. Airway pressures remained elevated with an inability to decrease oxygen below a  $FiO_2$  of 90%. Open lung biopsy was performed, which revealed extensive areas of interstitial fibrosis (Figure 3). Normal alveolar parenchyma was virtually nonexistent and nearly all alveolar walls were thickened due to diffuse fibrosis. There was no evidence of granulomatous disease, malignancy, or graft versus host disease. Grocott's methenamine silver stain, Ziehl-Neelsen stain for acid fast bacilli, and special immunostaining for CMV and herpes simplex virus-1 were all negative. He subsequently developed gram negative sepsis and died four weeks after admission. His lung autopsy revealed a picture of

extensive intra-alveolar hemorrhages and interstitial fibrosis with thickening of the alveolar septa.

## Discussion

The diagnosis of drug-induced lung disease is one of exclusion. Widely accepted criteria consist of five factors: history of drug exposure; clinical patterns consistent with previously observations with the exposed drugs; exclusion of other etiologies leading to pulmonary injury; improvement following discontinuation of the medication; and finally recurrence of symptoms on re-exposure to the drug [20]. Drug induced pulmonary toxicity is a well-established complication among cytotoxic drugs such as bleomycin, busulfan, and methotrexate [21]. Within the transplantation population, azathioprine, sirolimus, and everolimus are well-known in causing interstitial lung disease [7–9], with tacrolimus also being reported to induce lung injury [10,11]. T-cell targeted therapies, such as basiliximab, alemtuzumab, and anti-thymocyte immunoglobulin (ATG) have been associated with non-cardiogenic pulmonary edema in kidney transplant patients [22–25]. MMF-induced lung disease was first reported by Gross et al. in 1997 [12]. They described a case of progressive respiratory failure with extensive bilateral pulmonary infiltrates identified after kidney transplantation. In their report, cultures and immune-stains performed were all negative with a biopsy that showed interstitial fibrosis. Their patient's respiratory symptoms resolved after discontinuation of MMF. In the same year, Elli et al. suggested cough and dyspnea as a potential side-effect of MMF [26]. Since these reports, four separate case reports and three case series have been reported on the effects of MMF on the lung post-transplantation (Table 1) [13–19]. Most cases were identified in kidney transplant recipients. Bronchiectasis was the most commonly reported effect in 15 cases, followed by pulmonary fibrosis in five cases, and pulmonary hemorrhage in

**Table 1.** Reports of mycophenolate mofetil (MMF) related lung disease in organ transplant patients.

Author	Year	Age/gender	Transplant	Immunosuppression	Lung disease	Time to onset*	Outcome
Gross [12]	1997	51/F	Kidney	TAC, MMF	Pulmonary fibrosis	10 days	Alive
Morrissey [13]	1998	61/M	Kidney	CSA, MMF	Pulmonary fibrosis	6 weeks	Died
Shrestha [14]	2002	57/M	Kidney	CSA, MMF	Pulmonary fibrosis	10 days	Alive
Pijnenburg [15]	2004	17/M	Kidney	CSA, MMF	Bronchiectasis	3 years	Alive
		12/M	Kidney	CSA, MMF	Bronchiectasis	1 year	Alive
		11/M	Kidney	CSA, MMF	Bronchiectasis	1 year	Alive
		7/M	Kidney	CSA, MMF	Bronchiectasis	2 years	Alive
		11/F	Liver	CSA, MMF	Bronchiectasis	6 years	Unknown
Rook [16]	2006	51/F	Kidney	MMF	Bronchiectasis	5 months	Alive
		46/F	Kidney	CSA, MMF, ATG	Bronchiectasis	1 months	Alive
		27/M	Kidney	MMF	Bronchiectasis	20 months	Alive
		54/M	Kidney	OKT3, MMF	Bronchiectasis	0 months	Alive
		61/M	Kidney	CSA, MMF	Bronchiectasis	2 months	Alive
Reynold [17]	2007	2/M	Kidney	TAC, MMF	Pulmonary fibrosis	14 months	Alive
Boddana [18]	2010	61/M	Kidney	CSA, AZA, MMF	Bronchiectasis	60 months	Unknown
		51/F	Kidney	ATG, TAC, MMF	Bronchiectasis	32 months	Unknown
		39/F	Kidney	TAC, CSA, AZA, MMF	Bronchiectasis	26 months	Unknown
		70/M	Kidney	CSA, AZA, MMF	Bronchiectasis	84 months	Unknown
		44/M	Kidney	TAC, MMF	Bronchiectasis	12 months	Unknown
		52/M	Kidney	CSA, MMF	Bronchiectasis	95 months	Unknown
Gorgan [19]	2012	51/M	Heart	TAC, MMF	Pulmonary hemorrhage	7 days	Alive
		56/M	Kidney	Basiliximab, TAC, MMF	Pulmonary fibrosis	1 month	Died

M – male; F – female; TAC – tacrolimus; CSA – cyclosporine; AZA – azathioprine; ATG – anti-human thymocyte immunoglobulin; \* after starting MMF.

one case. The time of onset ranged from seven days to 95 months after starting MMF. Most of the cases reported the usage of MMF in combination with tacrolimus or cyclosporine, and two cases reported its utilization as a stand-alone treatment. T-cell targeted therapies, including basiliximab, ATG, and OKT3 were used in four cases. Recently, Pencheva et al. stated that the use of MMF was a risk factor for mortality as a result of pulmonary complications [2,4]. Furthermore, the relationship between bronchiectasis and hypogammaglobulinemia induced by MMF was named in an “alert” on the Medicines and Healthcare Regulatory Agency bulletin [27]. Although the precise mechanisms are still unknown, it has been suggested that impaired leucocyte recruitment and dysfunction of pulmonary epithelium cilia might lead to reduced pulmonary clearance of microorganisms, causing the development of bronchiectasis [16]. In our case, it was difficult to prove a direct relationship between MMF and pulmonary fibrosis since the patient

might have already had some level of pulmonary fibrosis pre-operatively as observed from his CXR. However, the patient did show temporal improvement after discontinuation of MMF and subsequent respiratory deterioration on resumption, thus meeting all five criteria outlined aforementioned. Hence, MMF was considered to be the most likely etiology of the patient’s respiratory failure; and considering his pathological findings, MMF might have aggravated pre-existing pulmonary fibrosis. It is important to use MMF with utmost care in recipients with underlying lung disease as their pulmonary condition might make them more susceptible to any harmful effects of MMF.

MMF, a prodrug of mycophenolic acid, depletes guanosine and deoxyguanosine nucleotides preferentially in T-cells and B-cells, inhibiting proliferation and suppressing cell-mediated immune responses and antibody formation [28]. It is currently one of the essential drugs for immunosuppression after solid



organ transplantation. Several clinical studies have suggested MMF to be effective for treatment of idiopathic and connective tissue disease-associated interstitial lung disease [29–31]. In our case, the question remains: why did MMF cause pulmonary toxicity? There are two explanations to consider. First, although the patient was clinically negative for respiratory symptoms preoperatively, he had 30 years of smoking history and a CXR showing bilateral interstitial opacities, suggesting existence of underlying lung disease. This likely made his pulmonary condition susceptible to any harmful effects of MMF. In retrospect, it would have been prudent to assess his pulmonary condition more extensively, and consider the use of alternative immunosuppressant medications postoperatively. Second, MMF might have reached toxic levels because of its usage in combination with tacrolimus. The ability of tacrolimus to augment drug levels and the immunosuppressive effects of MMF in renal transplant patients has been demonstrated by Zucker et al. [32]. Their investigation found that tacrolimus increases the bioavailability of MMF by up to 50%. Since tacrolimus levels were elevated in our case, MMF might have been augmented to toxic levels, thus inducing pulmonary injury. Patient MMF levels are not routinely measured; hence, it is unknown whether toxic levels were reached in our patient.

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It is important to be aware of the fact that immunosuppressants can interact with other medications and cause serious side-effects.

## Conclusions

We experienced a rare case of fatal respiratory failure induced by MMF after kidney transplantation, which might be related to pulmonary fibrosis. An awareness of pulmonary toxicity is important for all clinicians administering MMF. Clinicians need to consider discontinuation of MMF in transplant recipients who develop respiratory failure with negative pulmonary, cardiac, infectious, and immunological evaluations. This is especially important in recipients with underlying lung disease, whose baseline pulmonary function is poor.

## Conflict of interest statement:

The authors who have taken part in this study declare that they do not have anything to disclose regarding funding and conflicts of interest with respect to this manuscript.

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