Life-Threatening Everolimus-Associated Pneumonitis: A Case Report and a Review of the Literature

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ABSTRACT

Introduction. Noninfective pneumonitis is a class-related effect within mammalian target of rapamycin (mTOR) inhibitors, including everolimus, and can occasionally be severe.

Case Report. A 62-year-old man, medicated with everolimus due to a heart transplantation 17 years previously and with chronic kidney disease, was admitted to the intensive care unit (ICU) with acute respiratory failure, cardiovascular shock, and impaired renal function requiring dialysis. Computed tomography (CT) scan revealed right upper lobe consolidation. Extensive microbiological workup, autoimmune testing, and cytology were negative and echocardiography showed preserved heart function. Everolimus levels were normal (5.7–6.1 ng/mL) and the drug was suspended at day 9. The patient was difficult to ventilate and responded poorly to broad-spectrum antibiotic and antifungal therapy. On day 25, CT scan and bronchoscopy revealed left-sided alveolar hemorrhage, and corticosteroid pulses were performed. The patient gradually improved. After discharge and 6 months of follow-up, clinical recovery was complete and chest imaging substantially improved.

Discussion. Pneumonitis occurs in up to 4.3% of transplant recipients using everolimus for immunosuppression. Despite usually presenting as a mild and self-limited disease, severe cases have been described. Alveolar hemorrhage can occur and is associated with poor outcome. Everolimus levels do not seem to accurately predict toxicity. Corticosteroid therapy has been used with success in severe disease. We review the pathophysiological, clinical, and management-related aspects of this entity with emphasis on its potential severity.

Conclusion. Our case was a rare occurrence of severe life-threatening pulmonary disease related to everolimus. Awareness of the potential severity of this entity is important for the management of patients using mTOR inhibitors.

EVEROLIMUS is a nonselective mammalian target of rapamycin (mTOR) inhibitor with clinical use as an immunosuppressant in solid organ transplantation (heart, lung, and kidney) and as an antineoplastic agent [1,2].

Noninfective pneumonitis is a class-related side effect within mTOR inhibitors. It has mostly been associated with sirolimus, with a prevalence of up to 16.7% [3], and it is probably underdiagnosed [4].

Cases of noninfective pneumonitis have also been described both in patients using everolimus as an antineoplastic agent [5] and, to a lesser extent, in patients medicated with its lower-dose formulation as an immunosuppressant after heart, kidney, and lung transplantation [6–9].

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This entity usually presents with cough and shortness of breath and is occasionally associated with systemic symptoms such as malaise or fever [10]. Diagnosis is based on the presence of a temporal association between everolimus exposure and onset of symptoms, imaging and laboratory studies suggestive of pneumonitis, and exclusion of alternative causes, particularly infection [4].

Usually, respiratory symptoms are mild to moderate and resolve spontaneously after suspension of the drug [11]. Rarely, it can progress to severe and potentially life-threatening disease requiring mechanical ventilatory support [12].

CASE REPORT

We report the case of a 62-year-old man, residing in Portugal for 1 year, with a history of heart transplantation in France in 1999 due to dilated cardiomyopathy and under chronic immunosuppression with everolimus 0.25 + 0.5 mg/d for several years, associated with cyclosporine 25 + 50 mg/d and prednisolone 10 mg/d. He presented the following comorbidities: National Kidney Foundation (NKF) stage III chronic kidney disease and proteinuria due to severe hypertensive nephroangiosclerosis (confirmed in renal biopsy in 2016), prostatic adenocarcinoma treated with surgery and radiotherapy in 2007, placement of stent in the right iliac external artery in 2014, type 2 diabetes mellitus, severe arterial hypertension, and dyslipidemia. He was medicated with metformin, aspirin, bisoprolol, perindopril, amlodipine, indapamide, and simvastatin/ezetimibe. His most recent coronariography (2014) revealed no angiographic coronary disease.

He had no records about screening for latent tuberculosis prior to transplantation or previous pneumococcal vaccination and was not under *Pneumocystis jirovecii* pneumonia prophylaxis.

The patient presented to a regional hospital's emergency department with a 5-day history of right pleuritic chest pain, daily fever, dry cough, and progressive worsening dyspnea.

On admission, he was fully conscious and hemodynamically stable. Respiratory rate was 32 cycles per minute and auricular temperature was 38.2°C. Pulmonary auscultation revealed diffuse inspiratory crackles on the upper right quadrant. The remaining physical examination was normal.

Laboratory studies showed leukocytosis (18.000/mmc), mildly elevated C-reactive protein (60 mg/dL), and impairment of renal function (creatinine 2.9 mg/dL). Arterial blood gas measurement revealed type 1 respiratory insufficiency (PaO2 47 mm Hg on air) and hypocapnia (PaCO2 23 mm Hg).

Electrocardiogram revealed a sinus tachycardia of 109 beats/min and echocardiogram showed normal biventricular function.

A consolidation on the upper right lung lobe was present on chest x-ray. Chest computed tomography (CT) scan was subsequently performed, which showed consolidation of the superior and middle right lung lobes, air bronchogram, and a thin layer of right-sided pleural effusion.

The patient was admitted to a regional hospital with the diagnosis of community-acquired pneumonia with type 1 respiratory insufficiency and decompensated chronic renal disease and was started on piperacillin/tazobactam due to the severity of the disease and presence of immunosuppression and comorbidities.

Hypoxia worsened within 8 hours of admission and the patient was started on noninvasive ventilation (IPAP 14 cmH_2O, EPAP 8 cmH_2O). Respiratory function failed to improve and on the second day the patient, who had a PaO2/FiO2 ratio <100 mm Hg, was sedated, intubated, and transferred to the intensive care unit (ICU) of our hospital, which is the reference tertiary hospital. Neuromuscular blockade was necessary to ensure adaptation to the mechanical ventilator.

On admission to our hospital, the patient was undergoing mechanical ventilation in pressure control mode, with an inspiratory pressure of 18 cmH_2O and a positive end-expiratory pressure (PEEP) of 10 cmH_2O, achieving tidal volumes of 10 mL/kg, and with a FiO2 of 100% had a PaO2/FiO2 ratio of 70 mm Hg. Chest x-ray performed on admission revealed consolidation of the whole right lung (Fig 1).

At day 1, after blood, urine, and respiratory samples collection (endotracheal aspiration, bronchoscopy, and bronchoalveolar lavage [BAL]) for microbiological investigation, the patient was started on liposomal amphotericin B 300 mg/d and remained on piperacillin/tazobactam. At day 3, piperacillin/tazobactam was switched for meropenem 3 g/d. Vancomycin was added on the 7th day and was dosed to achieve trough levels of 15–20 μg/mL.

On ICU admission, aside from severe pneumonia with difficult mechanical ventilation, the patient had several end-organ dysfunctions (cardiovascular, renal, and hematologic) requiring artificial support. The patient had an APACHE II score of 22 and a SAPS II score of 65.

Microbiological results were negative in repeated endotracheal aspirates, including Gram and Ziehl-Neelsen stains, bacteriological, mycological, and mycobacteriological cultures and *Mycobacterium tuberculosis* nucleic acid amplification tests. Blood cultures for bacteria, fungi and mycobacteria, serum *Cryptococcus* antigen, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae*, testing for influenza RNA in oropharyngeal swabs, and serologies for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Coxiella burnetti* were also negative. Bronchoscopy was performed on admission, on the 6th day, and on the 8th day. Gram and Ziehl-Neelsen stains were negative, along with BAL fluid cultures for bacteria, fungi and mycobacteria, Galactomannan, and nucleic acid amplification tests for *Mycobacterium tuberculosis* complex, *Aspergillus* species, and *Cryptococcus* species. BAL fluid immunofluorescence tests were also negative for *Pneumocystis jirovecii* and virus (adenovirus, respiratory syncytial virus, influenza, parainfluenza, herpes simplex, and cytomegalovirus). Laboratory study for markers of immunity was also fully negative.

Everolimus was suspended on admission and immunosuppression was maintained only with cyclosporine. Due to worsening renal

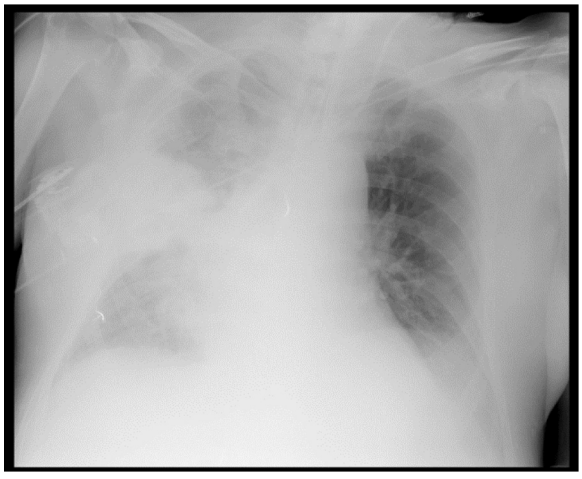

Fig 1. Chest x-ray on admission to our hospital.

function, cyclosporine was temporarily stopped and everolimus was reinitiated on the 4th day. We performed everolimus dosing on the 6th and 8th days, with results within the therapeutic interval (5.7 and 6.1 ng/mL, respectively). The drug was stopped on the 9th day due to its potential pulmonary toxicity and the patient remained on cyclosporine, with close dose monitoring during hospital stay.

Patient evolution is summarized in Table 1. During the first days, respiratory function improved with mechanical ventilation, with PEEP values of up to 15 cmH_2O on day 2 and 12 cmH_2O on the following days. At day 5, the patient's PaO2/FiO2 ratio was 147 mm Hg.

After day 7, PaO2/FiO2 ratio worsened (55 mm Hg) and the patient needed prone position ventilation. On the same day, a right upper lobe pneumothorax was diagnosed and a pleural drain was placed, which prevented further prone positioning. PEEP was diminished to 6–8 cmH_2O and FiO2 was increased again to 100%. CT scan performed on the 8th day revealed consolidation of the whole right lung and a small pneumothorax on the upper right lobe.

PaO2/FiO2 ratio remained <100 mm Hg up to day 14 and improved slowly after that, with values inferior to 150 mm Hg up to day 24. The patient remained under pressure control mechanical ventilation with inspiratory pressure values of 16–20 cmH_2O, with poor tolerance for periods under pressure-assisted modes and frequent episodes of desaturation after changes in positioning. Pleural drains were kept in place due to the development of a bronchopleural fistula.

Due to persisting hypoxia, chest CT scan was repeated at day 23, which revealed improving right lung consolidations and new-onset ground glass consolidations on the upper left lobe and lingula (Fig 2). On the following day, bronchoscopy was performed, and BAL fluid analysis was suggestive of alveolar hemorrhage. Once again, bacteriological, mycobacteriological, and mycological tests were negative but *Herpes Simplex* 1 Virus (HSV-1) immunofluorescence and nucleic acid amplification tests were positive. Vancomycin, meropenem, and amphotericin B were stopped on the 24th day and the patient was medicated with intravenous acyclovir for 14 days.

At that point, a decision was made to perform pulses of intravenous steroids (1 g methylprednisolone) between days 25 and 27. Subsequently, lung function began to improve and PaO2/FiO2 ratio remained >200 mm Hg. On day 29, the chest drain was removed. The patient underwent tracheostomy on day 34, began to tolerate periods of pressure-assisted ventilatory support, and was able to progressively wean mechanical ventilation. Tracheostomy was eventually closed on the 62nd day.

Concerning other dysfunctions, renal function worsened on the first days and urine output was low. On the 3rd day, the patient started continuous venovenous hemofiltration technique, which was suspended on the 29th day. Circulatory shock was present, and the patient remained under up to 0.3 mg/kg/min of noradrenaline during the first 2 weeks. Anemia and coagulopathy also occurred, with necessity for transfusional support and vitamin K administration.

At day 43, the patient was diagnosed with *Pseudomonas aeruginosa* ventilator-associated pneumonia and treated with ceftazidime for 7 days.

After 64 days of ICU stay, the patient was discharged to the Infectious Diseases ward, where he remained under vigilance and physical rehabilitation with a favorable clinical evolution. At day 85, the patient was transferred to the hospital of origin in order to proceed with the rehabilitation. On discharge, he had no pulmonary symptoms and had resolution of hypoxia. Re-evaluation CT scan showed improvement of left and right lung infiltrates and persistence of a residual ground-glass consolidation area on the upper left lobe (Fig 2).

The patient presented to our outpatient clinic for a scheduled re-evaluation 2 months after discharge and had no recurrence of his pulmonary symptoms. He was given pneumococcal vaccination and remained on prophylactic doses of acyclovir and trimethoprim/sulfamethoxazole. At 6 months of follow-up, the patient was asymptomatic under immunosuppression with cyclosporine, mycophenolate mofetil, and prednisolone, with stable renal function (creatinine clearance of 33 mL/min) and no proteinuria.

DISCUSSION

Pneumonitis is a common finding in patients who use mTOR inhibitors, with a reported prevalence of up to 16.7% in transplant recipients using sirolimus as an immunossupressor [3]. Everolimus appears to show less pulmonary toxicity, which is thought to be related to its less hydrophilic molecular composition [13].

Although patients with cancer treated with everolimus as an antineoplastic agent show comparable prevalence rates (17%) [4], most case series of everolimus use in lower doses for solid organ transplantation rejection prophylaxis appear to be less affected by pulmonary toxicity (up to 4.3%) [8]. A pooled analysis of 3 clinical trials on everolimus use in transplanted cases found 6 cases of pneumonitis in 1473 patients (0.4%) [8]. Notwithstanding, in a retrospective subanalysis of a clinical trial involving 101 kidney transplant recipients, the proportion of pneumonitis was 12.7% [14].

The pathophysiology behind everolimus-related pulmonary toxicity is yet to be fully explained. Both immune-mediated and direct toxicity mechanisms have been

Table 1. Evolution of Ventilatory and Laboratory Parameters

Day	2	8	15	23	27	38	44	62
PaO2/FiO2	70	54	116	142	208	283	173	232
Ventilatory mode	PC	PC	PC	PC	PC	PC	PA	SB
PEEP	10	6	8	6	5	6	4	
FiO2 (%)	100	100	75	50	60	40	40	28
Hb (g/dL)	11.7	10.9	8.7	7.4	7.7	7.2	7.7	8.1
WBC ($x10^9$/L)	25.57	22.66	15.33	8.82	7.78	13.72	11.04	10.71
CRP (mg/L)	991.9	323.5	169.4	116.5	37	118.1	154.7	66.2
aPTT (sec)	45.4	37.7	26.4	28.2	23.9	28.0	30.4	26.5
Albumin (g/L)	24.4	20.3	19.0	21.0	25.4	24.1	22.9	27.4

Abbreviations: Hb, hemoglobin; WBC, white blood cell; CRP, C-reactive protein; aPTT, activated partial thromboplastin time.

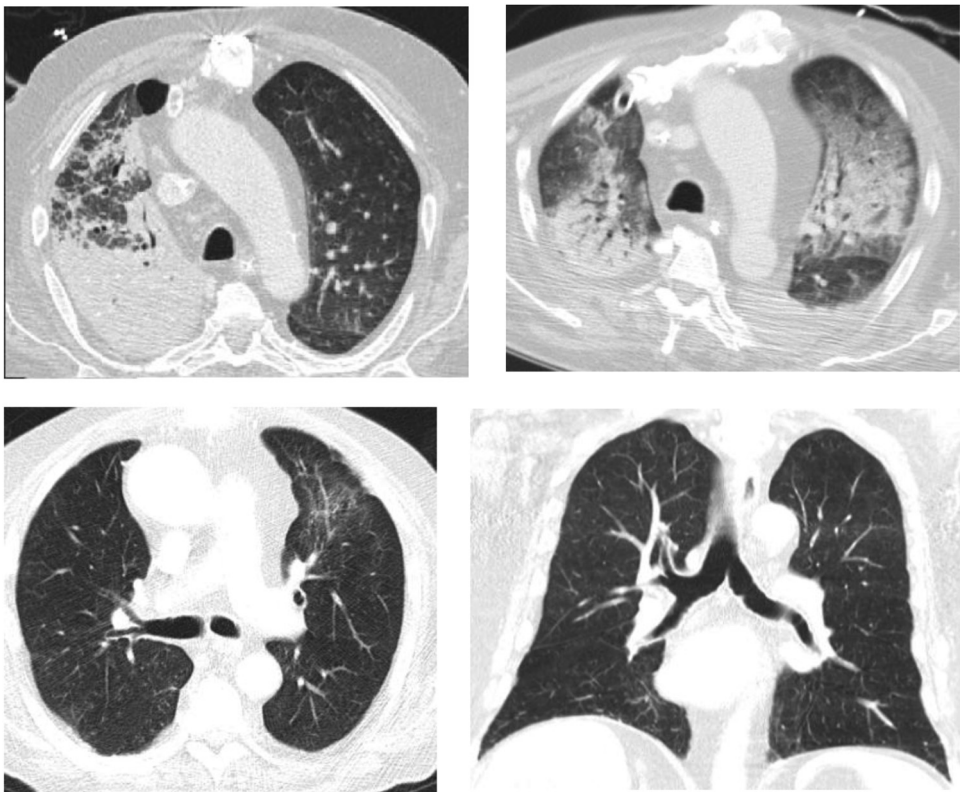

Fig 2. Chest CT scan on day 8 (upper left), day 23 (upper right), and on hospital discharge (lower left and right).

proposed for sirolimus-associated pneumonitis [15]. As stated above, pneumonitis rates are greater in series of patients using higher doses of mTOR inhibitors in oncological settings, rather than the low-dose formulations used for transplant rejection prophylaxis, which favors a dose-dependent mechanism [4,8]. However, although some cases of everolimus-associated pneumonitis occur in patients with supratherapeutic trough drug levels [16,17], other reports of the same condition describe patients with everolimus dosing inside the normal range [6,18]. In a retrospective subanalysis of a randomized clinical trial involving 102 renal transplant recipients, Baas et al found no differences in everolimus serum levels between the 13 patients who developed pneumonitis and in the group with no pulmonary toxicity [14]. Therefore, it is unlikely that everolimus pulmonary toxicity is simply related to higher drug exposure. In our case, serum everolimus levels during the acute phase of the disease were not elevated and everolimus was suspended at day 9 of ICU stay. Renal failure might have contributed to a prolonged everolimus exposure after suspension and delayed recovery.

Pulmonary symptoms usually begin in the first months after initiation of everolimus. Nevertheless, cases described in the literature vary in this aspect, and pneumonitis has been reported up to 6 years after first exposure to everolimus [8,19,20].

Despite being a common feature of mTOR inhibitor use, most of the pulmonary toxicity cases previously described are mild in severity [4,8]. However, severe life-threatening and fatal cases have been described in patients medicated with everolimus, even with the lower dosages used for transplant rejection prophylaxis [12,21–23]. We reported a particularly severe case of noninfectious pneumonitis with alveolar hemorrhage and multiorgan failure (respiratory, cardiovascular, hematologic, and renal), needing ICU admission and mechanical ventilator and renal, cardiovascular, and transfusion support. APACHE II score was 22 and SAPS II score was 65, with an associated predicted in-hospital mortality rate of 42.43% and 76.94%, respectively.

Imaging studies showed a diffuse ground-glass pattern compatible with diffuse alveolar hemorrhage, which was confirmed using bronchoscopy. This clinical picture is compatible with previous descriptions of the disease and is associated with a poor outcome [12,22–24].

Other histological patterns frequently associated with this entity are interstitial pneumonitis with or without fibrosis, bronquiolitis obliterans with organizing pneumonia, and linfointersticial pneumonia. Desquamative interstitial pneumonia, pulmonary vasculitis, and pulmonary alveolar proteinosis patterns have also been described [4,15,25,26]. The severity of our case precluded the realization of biopsy.

In the absence of strictly defined diagnostic criteria, exclusion of an alternative infectious etiology is essential for diagnosis of noninfectious everolimus–associated pneumonitis [4,11]. In the present case, a thorough microbiological

Table 2. Bronchoscopies Performed

Bronchoscopy Results	1st Day	6th Day	8th Day	25th Day
Bacterial culture	Negative	Negative	Negative	Negative
Fungal culture	Negative	Negative	Negative	Negative
Mycobacterial culture	Negative	Negative	Negative	Negative
Virus immunofluorescence	Negative	Negative	Negative	Positive for HSV-1
Pneumocyistis jiroveci immunofluorescence	Negative	Negative	Negative	Negative
Legionella immunofluorescence	Negative	Negative		
Galactomannan	Negative	Negative	Negative	Negative
Mycobacterium Tuberculosis PCR	Negative	Negative	Negative	Negative
Aspergillus Fumigatus PCR	Negative	Negative	Negative	Negative
Mycobacterium Avium and *Intracellulare* PCR	Negative	Negative	Negative	Negative
Influenza PCR	Negative			Negative
CMV PCR	Negative			Negative
Pneumocyistis jirovecii PCR	Negative	Negative	Negative	Negative
Cryptococcus PCR	Negative			Negative
Herpes Simplex PCR	Negative	Negative	Negative	Positive
Nocardia species PCR	Negative	Negative	Negative	Negative

Abbreviations: PCR, polymerase chain reaction; CMV, cytomegalovirus.

study was repeatedly performed on both noninvasive and invasive respiratory samples, and, therefore, the results were expected to have a high negative predictive value for the exclusion of an infectious etiology [27–29]. HSV-1 nucleic acid amplification and immunofluorescence testing were positive in fluid samples collected on the fourth bronchoscopy (Table 2). Positivity for HSV-1 in critically ill patients with acute respiratory disease has an unclear meaning and the possible pathogenic role of HSV-1 is yet to be accurately defined [30,31]. Therefore, we concluded that this finding could not explain our patient's clinical picture. All of the remaining microbiological study was negative.

BAL fluid cytology was negative for malignant cells and imaging studies performed after significant improvement of the lung infiltrates revealed no lesions suggestive of malignancy. Auto-immune study was also negative. Therefore, the hypothesis of an infectious, immunologic or oncologic etiology was considered unlikely. The patient's remaining medication had been the same for several years and no association has been described between any of the other drugs and alveolar hemorrhage.

The clinical approach to everolimus-associated pneumonitis depends on the severity of its presentation. In the usual mild to moderate cases, management should be based on vigilance, everolimus dose reduction or suspension, and/or oral corticosteroid therapy with up to 1 mg/kg/d of prednisolone [10,11]. Substitution of everolimus by other mTOR antagonists has been performed without recrudescence of pulmonary toxicity [13]. In severe or life-threatening situations, apart from suspension of everolimus, successful use of very high doses of corticosteroids has been described [4,12,22,23]. In our report, pneumonitis persisted for days after everolimus suspension and respiratory improvement coincided with the administration of corticosteroid pulses. Other factors, such as renal failure, prolonged invasive ventilation, critical illness myopathy, and occurrence of pneumothorax and ventilator-associated pneumonia, contributed to a delayed clinical resolution.

To evaluate the plausibility of the association between the described clinical picture and everolimus toxicity, we applied the Naranjo drug adverse reaction probability scale, which classified this relationship as "probable" [32].

In conclusion, our report consisted of a probable case of everolimus-associated pneumonitis associated with difficult mechanical ventilation, severe multiorgan dysfunction, and very poor prognosis in a patient 17 years after heart transplantation, with a favorable outcome. The patient improved slowly even after everolimus suspension, but corticosteroid pulses seemed to have a beneficial effect.

In patients undergoing immunosuppression, respiratory symptoms are associated with a wide array of differential diagnoses, mostly infectious. Pulmonary toxicity associated with mTOR inhibitors is frequent and can be severe or life-threatening. Therefore, knowledge of this entity, its predictable reversibility after everolimus suspension, and its usual favorable response to corticosteroid therapy are important for a correct clinical approach of patients medicated with drugs of this class presenting with pulmonary complaints, mostly when no alternative diagnosis is found.

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