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Case Report

CASE REPORT

Everolimus induced pneumonitis in a lung transplant recipient

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Abstract

Everolimus is a mechanistic target of rapamycin inhibitor used for the treatment of various cancers and prevention of allograft rejection in solid organ transplantation. We present a case of a lung transplant recipient on everolimus who was admitted with generalized weakness, hypoxia and new onset bilateral pulmonary infiltrates on imaging. Extensive workup revealed no infectious etiology and high levels of serum everolimus levels. Her condition deteriorated over the hospital course with symptoms and signs of systemic everolimus toxicity. She was treated with high-dose steroids with significant improvement. Follow-up imaging showed resolution of infiltrates. Everolimus induced pneumonitis is seldom reported in the lung transplant literature. It is important to recognize early signs of toxicity to intervene and preserve the lung allograft.

INTRODUCTION

Adequate immunosuppression is necessary for the prevention of acute and chronic allograft rejection following lung transplantation. Calcineurin inhibitors (CNIs), tacrolimus and cyclosporine (Cy-A) form the backbone of this immunosuppressive regimen.

Everolimus is a mTOR inhibitor licensed by the FDA to be used in the treatment of various cancers [1, 2]. MTOR inhibitors (sirolimus, everolimus and temsirolimus) block IL-2 as well as IL-12 mediated signal transduction for T-cell proliferation. Their addition (dual therapy) allows dose reduction of the CNIs, potentially reducing the side effects [3].

Non-infectious pneumonitis is a known, class-wide, adverse effect of mTOR inhibitors. It has also been reported with the off-label use of the drug in heart, liver and renal transplant recipients [4]. Its overall occurrence has been reported ranging from 8% to 34% [5, 6].

Herein, we report a case of non-infectious pneumonitis from everolimus use in a lung transplant recipient. To our knowledge, such an occurrence is seldom reported in the literature.

CASE REPORT

A 66-year-old female underwent double lung transplantation in October 2006 for chronic obstructive pulmonary disease. Her post-transplant course was complicated by chronic kidney disease and multiple malignancies including squamous cell carcinoma (SCC) of the skin. Post-transplant, tacrolimus was transitioned to Cy-A due to gastrointestinal side effects. In February 2012, Everolimus was added to the regimen to further lower the dose of Cy-A, especially given development of the skin cancers.

Seven years post-transplant (in 2014), she developed chronic lung allograft syndrome (CLAD) which was consistent with a

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Table 1: Admission laboratory values

	Results	Reference
Hematology		
Hemoglobin	9.2 g/dl	11.5–15.5 g/dl
Hematocrit	27.3%	36.0–46.0%
Platelet	49k/ul	150–400k/ul
Chemistry		
BUN	77 mg/dl	8–25 mg/dl
Creatinine	4.40 mg/dl	0.70–1.40 mg/dl
AST	43 U/l	7–40 U/l
ALT	20 U/l	0–45 U/l
Alkaline phosphatase	160 U/l	40–150 U/l
Lactate dehydrogenase	662 U/l	100–220 U/l
Anion gap	18 mmol/l	0–15 mmol/l
Lactate	0.6 mmol/l	0.5–2.2 mmol/l
Drug levels		
Posaconazole	3.2 ug/ml	≥0.8 ug/ml
Everolimus	20.6 ng/ml	3.0–8.0 ng/ml

Table 2: Spirometry history

	Pred[a]	Value[b]	%
Immediately prior to admission			
FVC	3.25	3.01	93
FEV1	2.48	2.03	82
FEV1/FVC	76.78	67.43	88
Six years prior to admission			
FVC	3.22	4.02	125
FEV1	2.54	3.64	144
FEV1/FVC	78.13	90.41	116

[a]Predicted value.
[b]Measured value.

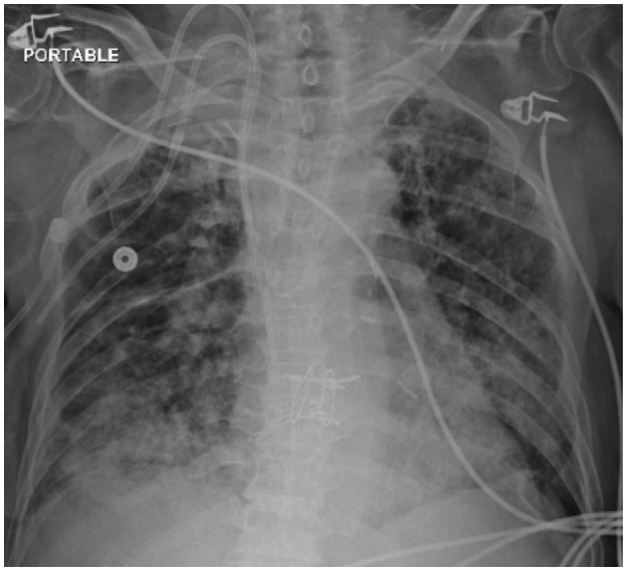

Figure 1: Bilateral diffuse coarse reticular nodular opacities along with alveolar opacities involving mid and lower lung zones

restrictive allograft syndrome, with a 20% reduction in both FEV1 and FVC.

Lung function remained relatively stable until August 2015, when she was hospitalized with generalized weakness and

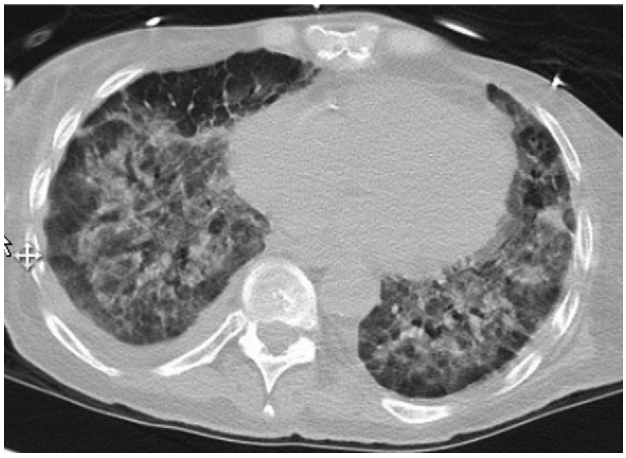

Figure 2: Interval development of multifocal nodular and ground glass opacities in both mid to lower lung zones

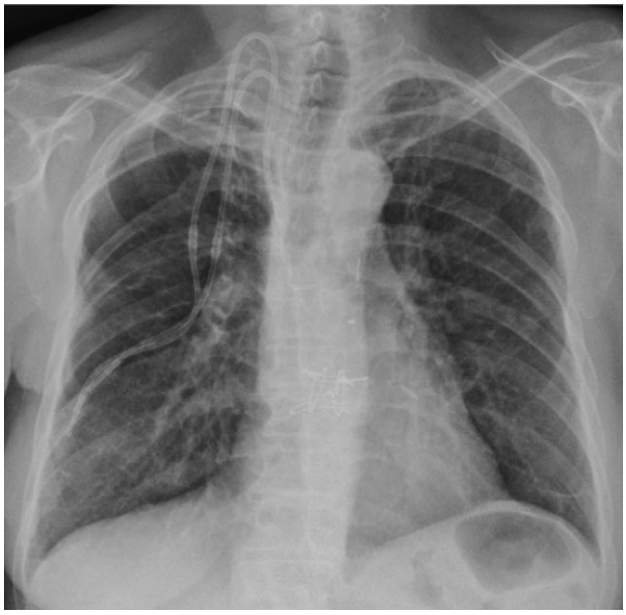

Figure 3: Improved appearance of reticular nodular opacities bilaterally

poor oral intake. Also, she had developed spontaneous epistaxis leading to severe anemia requiring blood transfusions. Upon admission, she required 3 l oxygen via nasal cannula to maintain SpO_2 above 88%. Auscultation of the lungs revealed bilateral end-inspiratory crackles. Her initial lab values, including everolimus level, are depicted in Table 1. Her pulmonary functions are illustrated in Table 2.

Chest X-ray (Fig. 1) was notable for bilateral diffuse coarse reticular nodular opacities along with alveolar opacities involving mid and lower lung zones. Computed tomography (CT) of the chest (Fig. 2) revealed interval development of multifocal nodular and ground glass opacities in both mid to lower lung zones

Bronchoalveolar lavage (BAL) fluid cultures were negative for infectious etiologies. Transbronchial biopsy was not performed due to the thrombocytopenia. There was no evidence of donor-specific antibodies in the serum. The high-everolimus level was attributed to its possible interaction between posaconazole (Table 1).

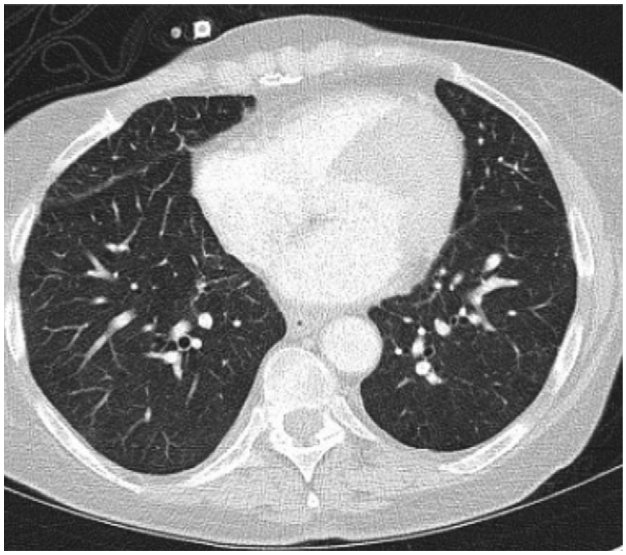

Figure 4: Significant improvement in previously noted multifocal ground glass opacities

By Day 3, her oxygen requirements gradually increased to 10l/ min and continued to deteriorate. By ruling out other etiologies of diffuse pulmonary infiltrates, a diagnosis of non-infectious pneumonitis from everolimus was suspected. The drug was discontinued while placing the patient on methylprednisolone 40 mg intravenous daily. Following initiation of steroids, her mental status improved, epistaxis resolved, APTT/INR and LFTs normalized, and platelets rose to above 150,000/ cmm, oxygenation improved. She was switched back to a tapering dose of oral prednisone on Day 5. By Day 16, she was down to prednisone 5 mg/ day maintenance therapy.

Everolimus was not resumed, and the Cy-A dose was increased. A follow-up CT scan and Chest X-ray (Figs 3 and 4) at 8 months confirmed total resolution of the infiltrates. Our patient passed away 1 year after this hospitalization and 10 years after her bilateral lung transplant, with an episode of acute bacterial pneumonia and chronic rejection which was seen on autopsy.

DISCUSSION

We believe that our patient's clinical presentation was consistent with a unifying diagnosis of everolimus toxicity with systemic manifestation. Our conclusion is based on clinical presentation findings of aphthous mouth ulcers, epistaxis, anemia, thrombocytopenia, kidney injury, high-lactate dehydrogenase and high-everolimus level. Discontinuation of everolimus and initiation of steroid therapy resulted in dramatic clinical improvement.

Everolimus-related pneumonitis has been reported in the recipients of other solid organ transplantation [4]. Its clinical use has been increasing lately because of its potential benefits in patients with renal dysfunction and anti-neoplastic properties [5]. Data analysis from three large controlled trials in solid organ transplantation (heart, liver and renal) published by Lopez *et al.* [4] in 2014 showed an incidence of everolimus-related interstitial lung disease to be 0.4% (6/1473). Of the six patients, four were heart transplant recipients and one of each, renal and liver transplant recipients. In large clinical trials with everolimus in heart transplant patients involving 400 patients, no pneumonitis was reported at 24 months [7].

Although interstitial pneumonitis is a known side effect of mTOR inhibitors, its pathogenesis is not fully understood and remains speculative. Significant side effects of everolimus toxicity to be recognized are stomatitis/oral mucositis, anemia, thrombocytopenia, hypertriglyceridemia, epistaxis, hypercholesterolemia, hyperglycemia, raised creatinine and an increased risk of opportunistic infections [8].

Dose-dependent everolimus toxicity hypothesis is supported by the higher incidence of pneumonitis observed in patients on everolimus 10 mg/day [4]. However, there have been cases of everolimus toxicity where the drug levels were in the normal range [9]. Also, the time of onset of symptoms after initiating therapy may vary significantly from a few days to as long as 2 years as seen in our case.

Although, outcomes in most cases are favorable, mortality from everolimus-related interstitial pneumonitis has been reported [4]. Follow-up pulmonary function tests in our case showed a progressive decline from an FEV1 of 2.03–1.65 (3 months after withdrawal of everolimus) and 1.43 (8 months later) which most likely was related to progressive CLAD.

Recognition of everolimus induced pneumonitis in lung transplant patients is of higher clinical relevance due to the increased risk of graft dysfunction and development of CLAD after any lung injury. Our case also highlights possible drug interaction between everolimus and posaconazole. To our knowledge, there has been only one report of everolimus pulmonary toxicity in a lung transplant recipient, which was a case of pulmonary alveolar proteinosis [9].

It is essential for all lung transplant physicians to recognize early signs of systemic side effects and pneumonitis from everolimus. Toxicity might occur at any time point during the course of treatment with everolimus. In our opinion, among patients receiving everolimus close radiological screening should be considered and the drug toxicity should be placed in the differential diagnosis of new-onset pulmonary infiltrates. The treatment involves the withdrawal of the drug in extreme cases and initiation of steroid therapy.

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CONFLICTS OF INTEREST

None declared.

FUNDING

None.

ETHICAL APPROVAL

No ethical approval required.

INFORMED CONSENT

Patient has deceased. Difficulty tracing relative at the moment. Case report has been anonymised.

GUARANTOR

Amabalavanan Arunachalam MD is a guarantor for the paper.

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