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Case Report

Sirolimus Induced Pulmonary Toxicity-Case Report

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Abstract

Sirolimus is an immunosuppressive agent used in renal transplantation to reduce renal toxicity. It is a rare cause of interstitial pneumonitis, organizing pneumonia and alveolar hemorrhage. We present a case of hypersensitivity pneumoniatis in a patient using sirolimus following renal transplantation. She presented with pulmonary symptoms seven years after transplantation. Other possible etiologies were excluded and the diagnosis was histopathologically proven. She was successfully treated just by withdrawal of the drug.

Keywords: *Kidney Transplant Recipient; Sirolimus; Lung Toxicity*

Abbreviations

ESRD: End Stage Renal Disease; CT: Computed Tomography; BAL: Bronchoalveolar Lavage

Introduction

Sirolimus is an immunosuppressive agent used in renal transplantation to reduce renal toxicity [1]. Dose related myelosuppresion and hyperlipidemia are the most common side effect [2]. Sirolimus can cause interstitial pneumonitis, organizing pneumonia and alveolar hemorrhage [3]. The risk of sirolimus-induced pneumonitis remains poorly understood [4]. The diagnosis is usually made by exclusion of other causes [5]. Cases resolve with drug withdrawal but late diagnosis may be fatal [6].

We present a case of hypersensitivity pneumonitis in a patient using sirolimus for renal transplantation.

Case Report

Our patient is a 58-year old woman, with a past medical history of hypertension and ESRD had received a of living donor kidney seven years ago. Her immunsuppresive treatment consisted of sirolimus (1 mg/day), mycophelonate mofetil (1 gr/day), deltacortil (5 mg/day) which had not been change for seven years. The trough level of sirolimus was normal (6 ng/ml). She maintained normal graft function with close follow-up and monitoring of drug levels.

She presented with fever, productive cough, shortness of breath lasting for two months. She was non-smoker and did not have history of alcohol consumption. She did not have history of tuberculosis contact. Before admission, she had received broad spectrum antibiotics but showed no improvement. At the time of admission, blood pressure was 130/80 mmHg, body temperature was 38.5°C, heart rate was 98 beat/minute, respiratory rate was 22/minute and peripharel oxygen saturation was 98%. Physical examination of the lung revealed

expiratory rhonchi and bibasilar crackles. Her chest computed tomography (CT) revealed bilateral irregular patchy alveolar infiltrates with ill-defined margins (Figure 1). Laboratory findings is shown in table 1. Repeat sputum, urine and blood cultures remained negative for bacteria and fungi. Galactomannan and cytomegalovirus polymerase chain reaction were negative. Urinary legionella antigen was negative. Sputum acid fast basillus staining and tuberculosis cultures were negative. Tuberculin skin test was negative. Serologic tests including antinuclear antibody, cytoplasmic antinuclear antibody, perinuclear antibody, anti-glomerular basement membrane antibody were all negative. Pulmonary function tests showed slight restrictive pattern (Table 2).

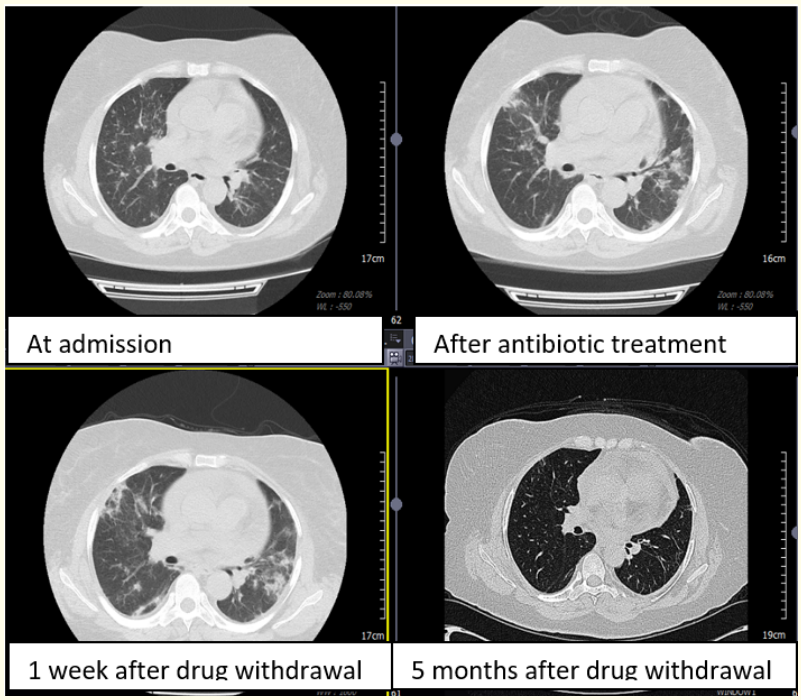

Figure 1

	On admission	1-week after cessation of sirolimus	5-months after cessation of sirolimus
Leucocyte (/uL)	10300	8800	6700
Hemoglobin (g/dL)	10	11.2	13
CRP (mg/L)	123	10.4	5.05
ESR (mm/hour)	87	45	27
Procalcitonin (ng/mL)	0.183	0.118	0.102
Serum urea (mg/dL)	61	50	36
Serum creatinine (mg/dL)	1.1	0.8	0.8
FVC (%)	78	92	103
FEV1 (%)	80	92	102
FEV1/FVC	82	83.5	83
DLCO adj (%)	85	93	94
KCO adj (%)	86	94	94

Table 1: *Comparison of the laboratory findings and pulmonary function tests on admission and after withdrawal of sirolimus.*

CRP: C-reactive Protein; ESR: Erythrocyte Sedimentation Rate.

	On admission	1-week after cessation of sirolimus	5-months after cessation of sirolimus
FVC (%)	78	92	103
FEV1 (%)	80	92	102
FEV1/FVC	82	83.5	83
DLCO adj (%)	85	93	94
KCO adj (%)	86	94	94

Table 2: *Comparison of the pulmonary function tests on admission and after withdrawal of sirolimus.*

FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in One Second; DLCO: Diffusing Capacity for Carbon Monoxide Adjusted for Hemoglobin; KCO: Carbon Monoxide Transfer Coefficient Adjusted for Hemoglobin.

Clinical and radiological findings were persistent despite antibiotic and antifungal treatment. Repeat chest CT showed progression of the infiltrates and inflammatory markers were still increased (Table 1). Fiberoptic bronchoscopy was performed, no endobronchial lesion was detected. Bronchoalveolar lavage and transbroonchial lung biopsy were nondiagnostic. The patient subsequently underwent video assisted thoracic surgery and wedge resection revealed organising pneumonia, giant cells and minimal fibrosis. Histopathological findings were persistent with drug reaction. Sirolimus associated lung toxicity was suspected and the drugs was discontinued and replaced by tacrolimus. During the whole disease course, the renal graft function maintained in a normal range. One week after discontinuation of the drug, inflammatory markers started to decrease (Table 1). Five months later chest CT findings significantly recovered (Figure 1). Spirometric measurements and diffusion capacity improved significantly (Table 2). The patient is doing well with no recurrence of any pulmonary symptoms.

Discussion

The current case had histopathologically proven diagnosis of drug toxicity and was successfully treated with discontinuation of the drug. Pulmonary toxicity is a rare but life-threatening complication in renal transplant recipients treated with sirolimus [1]. The frequency of the complication has been reported to be 2.9 - 16.7% [7]. Errasti., *et al.* reported 8/186 cases(4.3%) with pneumonitis associated with sirolimus [5]. The histopathological features from biopsies include lymphocytic interstitial pneumonitis, lympocytic alveolitis, organizing pneumonia, pulmonary alveolar proteinosis or diffuse alveolar hemorrhage [8]. Pathogenic mechanism of sirolimus associated pulmonary toxicity is not known [4]. Autoimmune response is a possible mechanism. Sirolimus hampers the repairment of alveolar epitelium damage, thereby leading to exposure of pulmonary auto-antigen and further initiation of an immune response. Another pathogenic mechanism may be delayed hypersensitivity [6]. In the literature, sirolimus associated pneumonia was reported to occur between 1 and 51 months [1]. It is thought that sirolimus associated pneumonia is not dependent on serum drug levels [9]. Therefore, pneumonia due to sirolimus should be considered as an idiosyncratic mechanism. Dyspnea, fever, fatigue, cough and hemoptysis are the main symptoms [1]. Most frequent radiological finding is the presence of bilateral patchy infiltrates especially in the lower lobes [10]. Bronchoalveolar lavage(BAL) cytology shows lymphocytic alveolitis, a typical finding of sirolimus associated pneumonia [7]. Diagnosis of pneumonitis due to sirolimus is difficult. In the absence of strictly defined diagnostic criteria, the exclusion of infection or alternative pulmonary disease and improvement of symptoms after withdrawal of the drug supports the diagnosis of sirolimus associated pneumonia [7]. Hypervolemia,-male gender, allograft dysfunction, late sirolimus exposure are thought to be risk factors for pulmonary complications [11]. However, the precise etiological factors have not been clearly established [10].

Treatment of sirolimus associated pneumonia is the withdrawal of the drug [12]. In patients who developed diffuse alveolar hemorrhage, steroids showed favorable outcomes [5].

Conclusion

After infection and alternative pulmonary conditions are excluded, drug-associated pneumonia should be in the differential diagnosis these patients. Withrawal of sirolimus can be life saving.

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