A Patient with Everolimus-Associated Pneumonitis

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Abstract: Interstitial pneumonitis has been observed as adverse effect in patients under immunosuppressive treatment with Sirolimus. Everolimus is the successor of Sirolimus and complications are less known. We report a case of pneumonitis that was observed in a patient with a kidney transplant and immunosuppression by Everolimus. The patient recovered after Everolimus was suspended, suggesting that it causes interstitial pneumonitis similar to Sirolimus.

CASE REPORT

We report the findings of Everolimus-associated pneumonitis in a 39-year-old male patient with IgA nephropathy who received a kidney allograft in 1994 for terminal renal failure. Concomitant disorders were chronic anemia and an intestinal hook worm infection successfully treated in 1992. In 1998, kidney biopsy revealed mild signs of rejection and a recrudescence of his nephropathy. A treatment with Prednisolon had to be stopped in 2001, but was resumed three months later due to a worsening of graft function. In 2002, the immunosuppression was changed from a combination of cyclosporine and azathioprin to a combination of cyclosporine with mycophenolat-mofetil. A further biopsy of the kidney transplant in October 2005 revealed fibrosis, tubular atrophy and small vessel disease. Therefore, in April 2006, immunosuppresion was switched to Everolimus. Shortly after, the patient developed atypical eczema and anemia that recurred during the next months. In October 2006, the patient had dyspnea and the chest X-ray presented reticular opacities (Fig. **1**). The lung function tests yielded a moderate ventilation disorder and a restricted ventilation capacity (Table **1**. column 'Everolimus').

A CT-scan showed changes of the interstitium and air space including the differential diagnosis of bacterial, fungal or viral infection (Fig. **2**). At bronchoscopy no airways abnormalities were found, such as bronchial obstruction or inflammation. However, signs of interstitial inflammation with giant cells, lymphocytes and histiocytes were found in the transbronchial biopsy specimen and bronchioalveolar lavage. There were no definite signs of bacterial or fungal infection and this finding suggests either an allergic process or the complication of treatment. Based on the findings of biopsy and bronchioalveolar lavage and because of the imaging pattern which is similar to Sirolimus-associated Pneumonitis, the diagnosis of Everolimus-associated Pneumonitis was made in this patient.

The treatment with Everolimus was stopped and an immunosuppressive therapy with Myfortic and Prednisolon was initiated. The subsequent CT-scan in November 2006 showed a substantial resolution of the opacities with only slight residues (Fig. **3**). The patient's condition improved and the lung function test was repeated in December 2006 showing an improvement of CO-diffusion and total lung capacity (Table **1** column 'Myfortic and Prednisolon').

DISCUSSION

Sirolimus and Everolimus are rapamycin derivatives that are used as an alternative medication to cyclosporine after kidney or heart transplantation because of their lower nephrotoxicity. Both are inhibitors of the mammalian target of rapamycin (mTOR), which leads to the Inhibition of the responses to Interleukin 2 (IL2), and, eventually, to a reduction of lymphocyte proliferation [1, 2]. Everolimus is more hydrophilic compared to Sirolimus due to an additional hydroxyl group. Sirolimus-induced pneumonitis is a combination of bronchiolitis obliterans type pneumonia with interstitial infiltration and intra-alveolar granulomatosis, both patterns seen in our patient [3, 4]. The CT scan reveals a combination of signs compatible with interstitial disease as the thickening of septa, nodular changes and peribronchial cuffing as well as air space changes with patchy consolidations and ground glass opacities. Elderly patients, patients with late onset of treatment and those treated with a high dose of Sirolimus are at risk of developing this type of pneumonitis. In our patient the treatment with Everolimus was started 12 years after kidney transplantation and he was treated with a high dose. The outcome of Sirolimus-induced pneumonitis is variable and mild and fulminant courses have been described [5]. However, Sirolimus-induced pneumonitis is a complication of the treatment with possible lethal outcome. A supporting treatment with corticosteroids is recommended [5]. While no reports of Everolimus-induced pneumonitis were known at the time, the resolution of Sirolimus-induced pneumonitis has been described after switching to Everolimus [6]. The development of pneumonitis in patients treated with Everolimus, the successor medication of Sirolimus, is still less known [7]. In our patient all CT features resolved without any residues indicating an acute inflammatory reaction without the typical signs of chronic alterations of lung tissue such as fibrosis.

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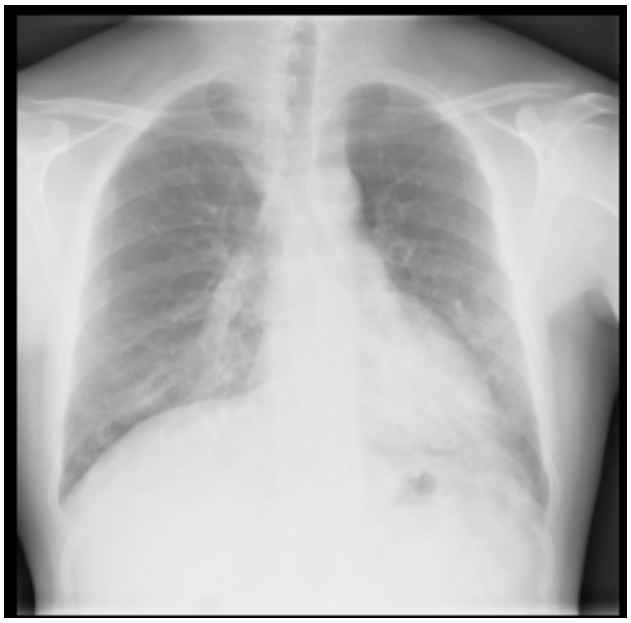

Fig. (1). Initial Chest X-ray The chest X-ray reveals symmetric involvement of both lower lungs with patchy opacities. There are no pleural effusions and only minor hilar adenopathy.

Table 1. Lung Function Test – Development Through Change of Medication

Lung Function Test	Everolimus		Myfortic and Prednisolon	
FVC (liters)	2.91	66%	3.06	70%
FEV1 (liters)	2.45	67%	2.43	66%
FEV1/FVC	-	84%	-	79%
IVC (liters)	3.11	68%	N/A	N/A
TLC (liters)	3.97	62%	4.41	69%
RV (liters)	0.86	47%	1.28	69%
RV/TLC	-	22%	-	29%
TLCO	6.71	66%	7.86	77%

Table: FVC, forced vital capacity; FEV1, forced expiratory volume in the first second of the forceful exhalation; IVC, inspiratory vital capacity; TLC, total lung capacity; RV, residual volume; TLCO, transfer factor of the lung for carbon monoxide; N/A, Not available

CONCLUSION

We report the findings in a patient with recurrent pneumonitis that occurred under Everolimus treatment and resolved after discontinuation of this medication. In our patient the symptoms and course of this pneumonitis were somewhat mild. To date it is not clear if Everolimus would cause a less severe pneumonitis in affected patients than Sirolimus where pneumonitis is a potentially lethal complication. However, treatment induced pneumonitis should always be suspected in the relevant clinical setting. CT imaging can characterize lung changes of the interstitium and air space, thus, narrowing the differential diagnosis and may document the resolution of acute changes after stopping the treatment.

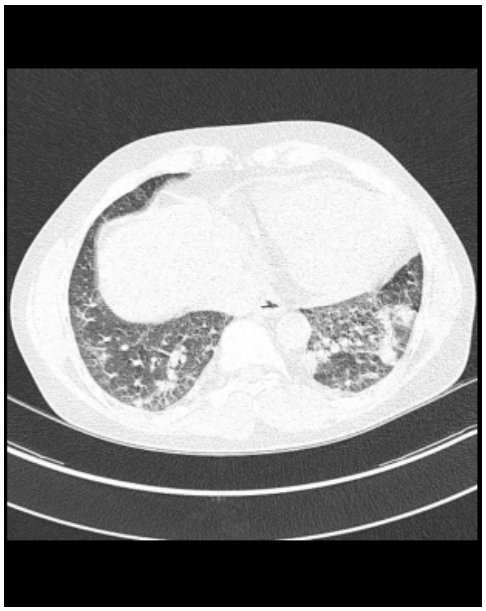

Fig. (2). Initial CT scan The CT scan reveals a patchy consolidative pattern, ground glass appearance as well as thickened interstitial septa, nodular components and peribronchial cuffing. This indicates acute interstitial inflammatory component and air spaces filled with liquid.

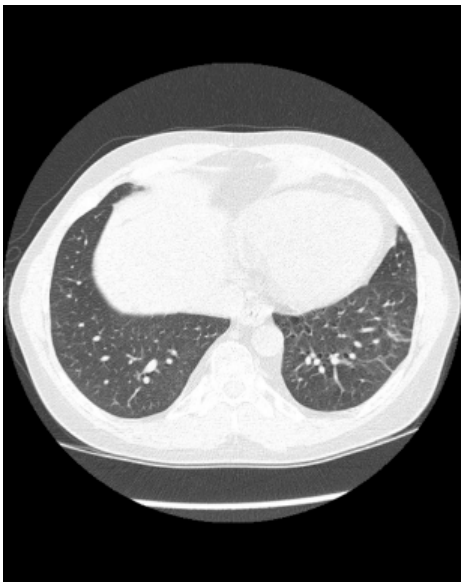

Fig. (3). Follow-up CT scan after change of medication After suspension of Everolimus all inflammatory reactions of the lung resolved without any residues.

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