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LETTER TO THE EDITOR

Everolimus-induced pneumonitis: report of the first case in a liver transplant recipient and review of treatment options

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For more than 10 years, two inhibitors of the mammalian target of rapamycin (mTOR), i.e. sirolimus and everolimus, have been in use as immunosuppressive agents in solid organ transplant recipients. Absence of nephrotoxicity and neurotoxicity as well as the anti-tumoral properties of the mTOR inhibitors make these drugs particularly attractive for use in liver transplant patients [1,2]. The side-effect profile compromises myelosuppression, mucosal ulcerations, skin pustulae, hyperlipidaemia and abdominal discomfort [3,4]. Pulmonary complications such as pneumonitis are rare severe adverse events of mTOR inhibitors. So far, this complication has been reported in nine liver transplant patients receiving sirolimus treatment [5–7]. Recently, the first few cases of everolimus-induced pneumonitis were described in heart and renal transplant recipients [8–12]. We hereunder describe the first report of everolimus-induced pneumonitis in a liver transplant recipient.

A 63-year-old woman underwent orthotopic liver transplantation for alcoholic liver disease in 2005. Post-transplantation, the immunosuppresssive regimen consisted of cyclosporine microemulsion (Neoral), mycophenolate mofetil and steroids. Because of deteriorating renal function, the patient was included into a clinical trial investigating the use of everolimus in liver transplant recipients with renal insufficiency (RESCUE, CRAD001H2401, Novartis) 13 months post-transplantation. According to protocol, everolimus was added to the immunosuppressive regimen with stepwise reduction of Neoral to a minimal dose of 10 mg twice daily. Four weeks later she developed a traumatic fracture of her 10th left rib, which caused local pain and persisting cough. Two months after starting everolimus, the patient reported increasing shortness of breath on mild physical exertion and a deterioration of her general well-being. Auscultation revealed wet crackles over the base of the left lung. Computed tomography of the chest demonstrated pulmonary infiltrates in the left lower lung lobe (Fig. 1). Pulmonary function tests revealed a reduction of vital capacity to 80% and a drop in diffusion capacity to 42% when compared with normal values pretransplant. As the blood work up at that time showed normal C-reactive protein and leucocyte count and the patient was afebrile, we did not start an empirical antibiotic treatment. A bronchoscopy with bronchioalveolar lavage and peripheral lung biopsy was performed. Microbiological cultures did not reveal a bacterial, fungal, viral, or pneumocystis carinii infection. On histology, intra-alveolar lymphocytic interstitial inflammation was seen and the diagnosis of bronchiolitis obliterans most likely secondary to everolimus treatment was made (Fig. 2). Everolimus was discontinued and Neoral treatment restarted together with 30 mg prednisolone in a tapering regimen. The CT scans of the chest 4 weeks after discontinuation of everolimus showed partial resolution of infiltrates with complete resolution of the pulmonary changes after 4 months (Fig. 1). Noteworthy, everolimus plasma levels had been within the therapeutic range throughout the whole period (5–12 ng/ml). The patient had no history of pulmonary disease and has not been smoking anytime during her life.

Morelon *et al.* [13] were the first to define four criteria, which support the diagnosis of sirolimus-induced pneumonitis, i.e. (i) onset of symptoms after sirolimus exposure, (ii) exclusion of any other pulmonary disease, (iii) resolution after discontinuation of sirolimus and (iv) pathological findings consistent with drug-induced lung-toxicity. With regard to our patient, symptoms started after initiation of the drug; other causes of pneumonitis were not found and clinical recovery occurred after discontinuation of everolimus. In addition, the histological picture of bronchiolitis obliterans organizing pneumonitis is well in agreement with the diagnosis. In contrast to previous reports on sirolimus-induced pneumonitis, our patient did not have fever or elevated inflammatory blood parameters [5]. The development of pneumonitis has been attributed to elevated plasma drug levels or pre-existing pulmonary disease, but both were not present in our patient. The pathomechanism of mTOR inhibitor-induced pneumonitis is unclear. Interestingly, two recent publications reported discovery of a cross-talk between toll-like receptor and mTOR-signalling, establishing a pro-inflammatory action of mTOR inhibitors in cells of the innate immune system [14,15]. Although only speculative, the rib fracture in our patient might have triggered

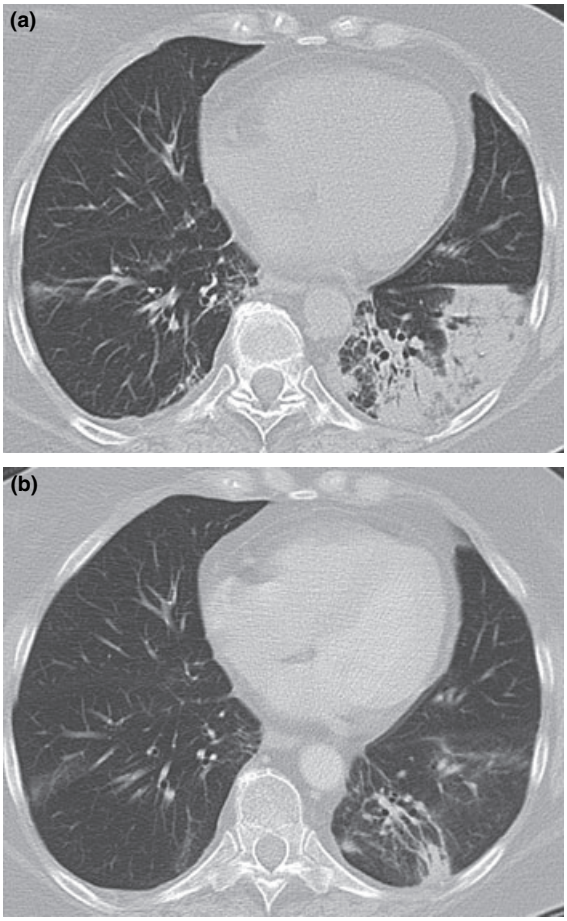

Figure 1 CT Scan at time of diagnosis (a) revealed infiltrates in the left lower lung. Follow-up CT-Scan after 1 month of everolimus discontinuation (b) showed marked regression of infiltrates.

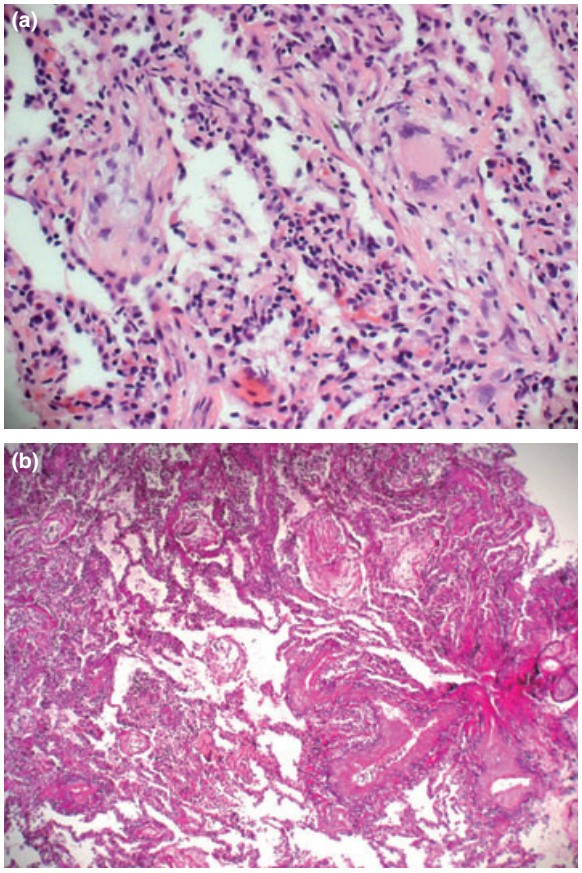

Figure 2 Lung biopsy showing intra-alveolar lymphocytic interstitial inflammation [hematoxilin/eosin (a – 200× magnification) and Elastica van Gieson (b – 100× magnification) staining].

a local inflammatory response, promoting the development of pneumonitis as a rare side-effect of everolimus.

A standard management of mTOR inhibitor-induced pneumonitis is not yet established. We reviewed all published cases of sirolimus- and everolimus-induced pneumonitis in solid organ transplant recipients indexed in PubMed, where sufficient data on management and outcome were available [5–13, and Supplementary references]. From the total of 104 cases in the literature, 87 patients had sirolimus withdrawn, once the diagnosis was established (Table 1A). Of these, 82 showed a complete resolution, one showed only partial resolution and four patients died. Of the 13 patients who were continued on sirolimus at a reduced dose, eight showed a complete resolution, but the remaining five patients either had persistent symptoms or relapse on follow-up. All these five patients had a complete resolution when the drug was finally discontinued. Four patients were managed by switching from sirolimus to everolimus, which led to complete resolution in all patients short-term. However, one of these patients developed a relapsing pneumonitis on follow-up. Twenty two of the 104 transplant patients were given additional steroids following the diagnosis of sirolimus-induced pneumonitis. However, from the available data, there is no clear benefit from the addition of steroids in terms of improvement of symptoms. Out of the nine patients with everolimus-induced pneumonitis, the drug was withdrawn in eight patients and continued in one patient without reducing the dose (Table 1B). Eight patients received a concomitant steroid treatment and all nine had a complete recovery.

In conclusion, drug-induced pneumonitis seems to be a class-related side-effect of both the currently available mTOR inhibitors (i.e. sirolimus and everolimus) and does not appear to be solely restricted to sirolimus. Therefore, clinical suspicion needs to be high in every patient treated with a mTOR inhibitor presenting with new onset of pulmonary symptoms. Given the high rate of relapse when mTOR inhibitors are continued, we recommend the

Table 1. Summary of 104 cases of sirolimus-induced pneumonitis (A) and everolimus-induced pneumonitis (B) in organ transplant receipients with regard to management (Withdrawal WD, Dose Reduction DR, Switch SW, Continuation C) and outcome.

Organ	Patients	Treatment Management	Steroids	Outcome Resolution	Persistence	Relapse	Death
A							
Kidney	78	WD 62 (79%)	15 (19%)	60 (96%)	1 (2%)		1 (2%)
		DR 13 (17%)		8 (62%)	2 (15%)	3 (23%)	
		SW 3 (4%)		2 (67%)		1 (33%)	
Liver	9	WD 8 (89%)	1 (13%)	8 (100%)			
		SW 1 (11%)		1 (100%)			
Heart	17	WD 17 (100%)	6 (43%)	14 (82%)			3 (18%)
Total	104	WD 87 (84%)	22 (21%)	82 (95%)	1 (1%)		4 (4%)
		DR 13 (12%)		8 (62%)	2 (15%)	3 (23%)	
		SW 4 (4%)		3 (75%)		1 (25%)	
B							
Kidney	2	WD 1 (50%)	1 (100%)	1 (100%)			
		C 1 (50%)	1 (100%)	1 (100%)			
Liver	1	WD 1 (100%)	1 (100%)	1 (100%)			
Heart	6	WD 6 (100%)	5 (83%)	6 (100%)			
Total	9	WD 8 (89%)	8 (89%)	8 (100%)			
		C 1 (11%)		1 (100%)			

immediate withdrawal of the drug, once the diagnosis has been established.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary references.

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