A Case of Sirolimus-Induced Interstitial Lung Disease After Liver Transplantation

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Mammalian target of rapamycin inhibitors (mTORis) are immunosuppression agents that are commonly used in solid organ transplantation. Available mTORis include sirolimus and everolimus. Interstitial lung disease (ILD) is an uncommon side effect of mTORis in liver transplantation. A high index of suspicion is needed, and timely intervention can reverse the disease. We present a case of sirolimus-induced ILD that improved after discontinuation of sirolimus. (J CLIN EXP HEPATOL 2019;9:539–540)

A 50-year-old male underwent living donor liver transplantation for hepatitis C-related cirrhosis (treated, sustained virological response present) and hepatocellular carcinoma (HCC) in June 2017. Pre-transplant pulmonary function test (PFT) was normal, and there was no contributory personal and family history regarding interstitial lung disease (ILD). His chest X-ray was normal before liver transplantation. He had uneventful recovery; posttransplantation immunosuppression consisted of tacrolimus, mycophenolate, and steroids (tapered over 3 months). Sirolimus was introduced at 6 weeks after transplantation in view of pretransplant HCC to decrease chances of HCC recurrence, and tacrolimus slowly tapered off. A repeat PFT was not conducted before the start of sirolimus as it was conducted just 7 weeks back; chest X-ray was normal after transplantation also. His liver functions tests remained stable during the follow-up. He had progressive dyspnea after 6 months of sirolimus introduction. Chest computed tomography (CT) revealed thin subpleural reticular opacities in bilateral lung parenchyma, suggestive of ILD, as shown in Figure 1. The average trough level of sirolimus was 7 ng/ml, the last 2 values being 4.8 and 2.1 ng/ml. A possibility of sirolimus-induced ILD was present, and sirolimus was stopped. Ta-

crolimus was started in place of sirolimus. The patient improved gradually and became asymptomatic at 3 months, and repeat PFT in June 2018 showed improvement of FVC (3.5 L–3.85 L) and FEV1 (2.9 L–3.13 L) values. A repeat CT was not performed as the patient had clinical recovery.

DISCUSSION

ILD is a heterogeneous group of noninfective lung disorders caused by multiple etiologies that include connective tissue diseases, smoking/vasculitis, granulomatous disease, occupational changes, or drug-induced changes; sometimes, the etiology remains idiopathic.¹ Various drugs known to cause ILD are chemotherapy agents, cardiovascular drugs (amiodarone, beta blockers, and statins), some antiinflammatory drugs, antimicrobial agents (nitrofurantoin and amphotericin), and biological agents (etanercept and infliximab).² Mammalian target of rapamycin inhibitors (mTORis) are used in cases of pre-LT tumors (to prevent tumor recurrence) and in cases of CNI-induced renal toxicity.^{3,4} Both sirolimus and everolimus are implicated as the cause of ILD.^{5–8}

In a systemic review of literature, 68 cases of mTORi-induced ILD were identified. Thirteen of these cases occurred in patients receiving everolimus and 55 occurred in patients receiving sirolimus; of these 55 patients, 10 had liver transplantation. Most patients were males, whose age ranged from 9 months to 79 years, with an average being 58 years. ILD was diagnosed after a median period of 4 months (range, 5 days to six years). The most common symptom was dyspnea as in the present case. Discontinuation of mTORi therapy led to resolution 85% of cases, but 2 cases died with progressive respiratory failure.⁹ Sometimes, change of sirolimus to everolimus leads to clinical

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Abbreviations: HCC: hepatocellular carcinoma; ILD: Interstitial lung disease; mTORi: Mammalian target of rapamycin inhibitor

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Figure 1 CT of the chest (lung window) before liver transplantation which is normal (left side) and at onset of dyspnea after liver transplantation (right side) which shows thin subpleural reticular opacities in bilateral lung parenchyma, suggestive of ILD. CT, computed tomography; ILD, interstitial lung disease.

improvement.¹⁰ Everolimus may have lower risk of ILD than sirolimus because of more hydrophilic nature of everolimus.^{6,9} The exact mechanism of mTORi-mediated ILD is not clear; various possibilities suggested dose-dependent toxicity, T cell-mediated delayed-type hypersensitivity reaction, and idiosyncratic cell-mediated autoimmune response.^{9,11–13} The risk factors for ILD in patients on mTORis are late switch (as compared to early introduction), higher age, higher dose, male sex, and allograft dysfunction.^{9,11,14,15} A high index of suspicion and timely withdrawal of sirolimus should be performed. In summary, we present a case of sirolimus-induced ILD which improved upon sirolimus withdrawal.

CONFLICTS OF INTEREST

The authors have none to declare.

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