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LETTER TO THE EDITOR

Sirolimus-related dyspnoea, airway obstruction and pleural effusion after lung transplantation

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Renal insufficiency remains a major side-effect of the treatment with calcineurin inhibitors after organ transplantation and when it appears, switching to a calcineurin inhibitor (CNI)-free regime including sirolimus or everolimus may be a favourable possibility. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor, which has been reported to exhibit less renal toxicity than calcineurin inhibitors [1,2]. However, sirolimus can have other serious side-effects such as dose-dependent myelosuppression, hypertension, hyperlipidaemia, glucose intolerance, dehiscence of the bronchial anastomosis, interstitial pneumonitis and pulmonary vasculitis [3–6]. In this report, we describe a patient who showed deterioration of lung function, after being switched from tacrolimus to sirolimus.

A 47-year-old female, with a smoking history of 20 pack-years, underwent bilateral sequential lung transplantation because of pulmonary emphysema.

After transplantation, she was treated with an immunosuppressive regimen including tacrolimus (initial trough levels 15–20 μg/l), mycophenolate and prednisolone combined with induction therapy with daclizumab (1 mg/kg body weight) on days 0 and 10.

After discharge, her clinical course was unremarkable without signs of acute or chronic rejection. Her FEV_1 increased from 0.40 l (16% predicted, pre-transplantation) to 2.50 l (102% predicted, 9 months post-transplantation). However, a gradual decrease of renal function developed. Two years postoperatively, her serum creatinine had increased to 223 μmol/l and her calculated serum creatinine clearance had dropped to 22 ml/min. At this point, we decided to prescribe sirolimus (initial trough levels 10–15 μg/l) instead of tacrolimus. Her renal function improved significantly, illustrated by a decrease in serum creatinine level to 131 μmol/l (calculated creatinine clearance 40 ml/min) 35 days after the switch. Unfortunately, 21 days after the switch, she presented with shortness of breath. At that time a drop in the FEV_1 was seen, with the lowest FEV_1 of 53% suggesting bronchiolitis obliterans syndrome (BOS) stage 2. Lung function was obstructive as the Tiffeneau index (FEV_1/FVC) decreased from 88% (110% of predicted) to 73% (91% of predicted). Chest X-ray and CT-scan revealed bilateral pleural effusion (see Fig. 1 panels A and D). Furthermore, slight peripheral oedema and proteinuria were observed.

We considered five main causes for the decline in FEV_1 and appearance of pleural effusion. First, we considered acute rejection because sirolimus is generally regarded as a less powerful immunosuppressive agent than calcineurin inhibitors. Although we could prove neither rejection nor interstitial pneumonitis by biopsy, we decided to give high doses of methylprednisolone (1000 mg/day for three consecutive days). This did not result in significant improvement in lung function and therefore the drop in FEV_1 and the pleural effusion were unlikely to be a result of acute rejection.

Second, we considered infection. At the time of admission her C-reactive protein (CRP) was 32 mg/l (reference value <9 mg/l). Elevated CRP-levels have been described earlier possibly attributable to sirolimus therapy, although the authors underlined that CRP remains an unspecific marker [6]. She did not have a productive cough and there was no evidence of bronchitis. On the chest X-ray, there were no signs of pneumonia. Her bronchial lavage fluid showed Haemophilus influenzae, but lung function did not improve upon treatment with either amoxycillin or cefuroxime. Therefore, infection was considered an unlikely cause of the drop in FEV_1. Unfortunately, no thoracentesis was performed.

Third, hypoproteinaemia may be a cause of pleural effusion. However, the proteinuria was not in the nephrotic range (maximal protein loss 4.08 g/l) and lowest serum albumin level was 37 g/l.

Fourth, cardiac dysfunction may result in pleural effusion, but in this patient cardiac evaluation was unremarkable.

Despite polypragmatic treatment, her FEV_1 did not improve and eventually her decline in FEV_1, the appearance of bilateral pleural effusion, in combination with the development of proteinuria and peripheral oedema were all regarded as secondary to sirolimus. Therefore, after 63 days of treatment with sirolimus, we decided to reconvert her to tacrolimus. Thirty-five days after this conversion, her FEV_1 had increased significantly to 84% (BOS

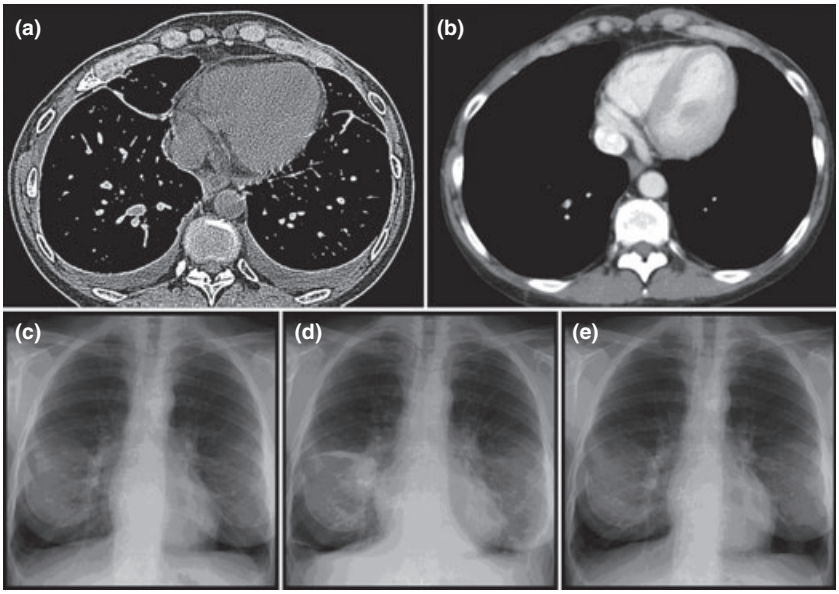

Figure 1 Panel a: CT scan (slice thickness 5 mm), 21 days after switch to sirolimus, with bilateral pleural effusion. Panel b: CT scan (slice thickness 1 mm), 7 months after reconversion to tacrolimus, without signs of pleural effusion. Panel c: Chest X-ray, 7 days before switch to sirolimus. Panel d: Chest X-ray, 49 days after switch to sirolimus, with pleural effusion in the left vertebrophrenic angle, right major fissure and lateral costophrenic sinuses. Panel e: Chest X-ray, 6 months after reconversion to tacrolimus, without signs of pleural effusion. Please note the breast implants visible on the chest films in panels c, d and e.

grade 0p). In addition, her Tiffeneau index improved to 89% (112% of predicted) (see Fig. 2). However, it took almost 6 months for the pleural effusion to resolve completely (see Fig. 1 panels B and E). Unfortunately, her calculated creatinine clearance decreased to the pre sirolimus levels again.

To our knowledge, this is the first time sirolimus-related pleural effusion and decline in FEV_1 are described in a patient after lung transplantation. Pleural effusion, ascites and peripheral oedema have been described in patients on sirolimus after liver transplantation [7] whereas pericardial effusion has been described in patients on sirolimus after heart transplantation [8].

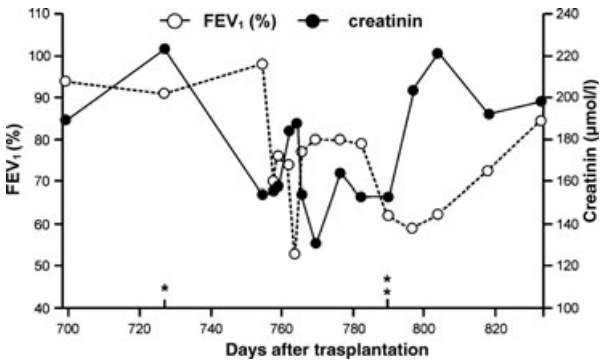

Figure 2 The left ordinate shows the FEV_1 BOS score in percentage, the right ordinate shows the serum creatinine levels in µmol/l. On the abcis the time in days after transplantation is shown. The asterisk at 727 days after transplantation shows the time point of the switch from tacrolimus to sirolimus. The double asterisk at 790 days after transplantation shows the conversion from sirolimus to tacrolimus. After the switch a drop in the BOS score FEV_1 and concomitantly an improvement of the kidney function can be observed. After the conversion an improvement is seen in the FEV_1 BOS score, and concurrently an increase in the serum creatinine levels.

The mechanism by which sirolimus may induce pleural effusion is not clear, but it may be similar to other adverse effects of sirolimus such as proteinuria, peripheral oedema, vasculitis, pericardial effusion and ascites [6–8]. Several hypotheses have been described, including organ-specific autoimmune reactions, both immune- and non-immune-mediated hypersensitivity [9]. However, pleural effusion in our patient was not likely to be mediated through one of these mechanisms, as it did not improve after high doses of methylprednisolone.

In conclusion, sirolimus toxicity should be considered in lung transplant patients with pleural effusion or deterioration of lung function suspected of rejection.

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