Everolimus-related pulmonary toxicity in a kidney transplant recipient—diagnosis and management

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Introduction

A standard immunosuppressive regimen after kidney transplantation in a low immunological risk recipient consists of a calcineurin inhibitor (CIN), mycophenolic acid derivative and prednisolone. A nephrotoxic effect of CIN and neoplastic or cardiovascular history in kidney recipients are the main reasons for a conversion from a CIN to a proliferation signal inhibitor (PSI) [1]. PSI is a novel group of immunosuppressive agents used after solid organ transplantation. Currently, there are two PSIs available, i.e. sirolimus and everolimus. Everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) is a new PSI/mammalian target of rapamycin (mTOR) inhibitor. Although it is structurally similar to sirolimus, there are a number of important pharmacokinetic differences including a shorter half-life and time to a steady state of everolimus. Both inhibitors of mTOR share a similar side-effect profile, mostly anaemia, dyslipidaemia or proteinuria [2]. The hypersensitivity-like interstitial pneumonitis has mostly been related to sirolimus [3], but there have also been 13 recently published reports of that side effect after everolimus, most of them, however, in heart transplant recipients [8–11,14]. Since the relation in timing between the appearance of pulmonary symptoms and introduction of PSI is variable, the differential diagnosis of such cases could be particularly challenging and it includes a range of pulmonary infections, vasculitis and neoplastic diseases. To illustrate this, we present and discuss a case of pulmonary toxicity (PT) secondary to everolimus in a kidney transplant recipient.

Case

A 59-year-old female with end-stage renal disease due to chronic glomerulonephritis received a transplant kidney from a deceased donor after 31 months of uncomplicated chronic peritoneal dialysis therapy. Her primary immunosuppression regimen consisted of steroids, mycophenolate mofetil and cyclosporine (CsA), with through levels of CsA in the range of 100–120 ng/ml from the third month after transplantation. Kidney function had been stable (serum creatinine around 1.0 mg/dl, estimated glomerular filtration rate (eGFR), around 90 ml/min) up to 17 months after transplantation when serum creatinine increased to 2.27 mg/dl (eGFR 38 ml/min). A graft biopsy was performed at that time and revealed mild advanced chronic allograft nephropathy with chronic interstitial inflammation. A cytomegalovirus (CMV) infection was diagnosed (20.6 × 104 of CMV DNA), and the course of i.v. ganciclovir for 3 weeks followed by oral valganciclovir for 90 days was immediately started. One month after discontinuation of the antiviral therapy (CMV DNA negative), the graft function did not improve (eGFR 44 ml/min, serum creatinine 1.95 mg/dl) and, therefore, the patient was immediately switched to everolimus with CsA discontinuation. At the time of everolimus therapy commencement, a chest X-ray was normal, oxygen saturation was 99% on room air and the patient reported good exercise tolerance and was free of any respiratory problems. The level of haemoglobin was 11 g/dl, serum total cholesterol 219 mg/dl and triglycerides 313 mg/dl. Six weeks after conversion, however, she started to complain of dry cough. Four weeks later, the patient was admitted to our hospital due to progressive dyspnoea on minimal exercise, dry cough and subfebrile state. The patient was tachypnoeic at rest and had fine bilateral basal crackles on auscultation. Peripheral oxygen saturation of haemoglobin at rest was (86%) and blood gases showed partial respiratory insufficiency (pH 7.43, pO2 56 mmHg, pCO2 32 mmHg, HCO3 22.8, base excess (BE) −2.7). Laboratory findings showed a white blood cell count of 6.68 × 10³ with a mild increase in monocytes 1.10 × 10³ and eosinophils 0.42 × 10³, anaemia, with haemoglobin 8.9 g/dl, platelets 212 × 10³ and serum creatinine 1.67 mg/dl. Electrolyte
and liver enzymes were in a normal range but serum C-reactive protein (CRP, 56 mg/l) and D-dimers (1645 ng/ml) were elevated. The lipid profile revealed severe disturbances with total cholesterol 345 mg/dl, HDL 51 mg/dl, LDL 207 mg/dl and triglycerides 818 mg/dl. Urinalysis did not reveal any significant abnormality. The everolimus blood level was 7.75 ng/ml and was within the target range (3–8 ng/ml). The through levels of everolimus during the whole treatment period did not exceed the recommended ranges (successive through levels: 4.03, 3.09 and 7.75 ng/ml). Chest X-ray revealed fine, bilateral patchy and linear opacities (Figure 1). Due to relatively low level of D-dimers, lack of right heart overload in Transthoracic echocardiography and normal venous Doppler ultrasonography, the risk of pulmonary embolism was estimated as low, and pulmonary angio-CT scan was not performed. The high-resolution computed tomography of the chest (HRCT) demonstrated extensive bilateral, predominantly basal linear and patchy infiltrations (Figure 2). Lung function tests showed normal spirometry, forced expiratory volume in 1st second (FEV$_1$) 1.71 l (74% of predicted, standardized residuals (SR) −1.61), forced vital capacity (FVC) 2.10 l (76% of predicted, SR −1.51), FEV$_1$/FVC 0.84 and slightly increased diffusion capacity, suggesting latent alveolar haemorrhage (diffusing lung capacity for carbon monoxide corrected for haemoglobin (DLCOc): 7.59 mmol/min/kPa, 99.6% of predicted; DLCOc/alveolar volume (VA)–DLCOc corrected for alveolar volume: 2.06 mmol/min/kPa/l, 145% of predicted). Total lung capacity measured by He dilution method was normal (3.76 l, 79% of predicted, SR −1.61). CMV re-infection was excluded by the negative CMV DNA in serum. The blood serological markers of atypical infections like Chlamydia and Mycoplasma pneumoniae were negative. Bronchoscopy with broncho-alveolar lavage (BAL) was performed by instillation and subsequent withdrawal of 4 × 50 ml of 0.9% NaCl. The microscopic examination of BAL cytospin stained with May–Grünwald–Giemsa stain revealed moderate increase of lymphocytes (30%) and neutrophils (5%). Bronchial aspirate contained a lot of macrophages with foamy cytoplasm as well as few lymphocytes and polymorphonuclear cells (Figure 3). BAL cultures for bacteria, fungi, viruses, Mycobacterium tuberculosis and Pneumocystis carini were negative. A transbronchial peripheral lung biopsy was performed to obtain histological diagnosis. It revealed alveolar wall thickening with interstitial inflammatory infiltrate consisting of foamy macrophages, haemosiderin-laden macrophages and lymphocytes. Moreover, single scattered epithelioid
granulomas were noted (Figure 4). Vacuolated pneumocytes and haemosiderin-laden macrophages in the alveolar lumen were observed (Figure 5). Masson trichrome staining showed mild fibrosis localized in the peribronchiolar parenchyma. No signs of vasculitis were seen. Overall, the microscopic lesions together with the clinical manifestation prompted us to diagnose a drug-associated interstitial pneumonitis.

As everolimus was the most likely causal agent, it was immediately discontinued without increasing the dose of prednisone (it was still 5 mg/day). A calcineurin inhibitor (tacrolimus) was re-initiated. The patient’s condition started to gradually improve within the next few days, and 10 days later all respiratory symptoms such as dyspnoea, cough and exercise intolerance disappeared and pulmonary auscultation symptoms resolved. Blood gases normalized and the patient was discharged from the hospital. The patient was eventually maintained on prednisone 5 mg/day, tacrolimus 2 mg once daily formula and mycophenolate 500 mg twice daily. One month after everolimus withdrawal, she remained asymptomatic. Follow-up HRCT scan revealed a slight improvement of parenchymal changes, and DLCOc/VA was 0.86 mmol/min/kPa/l (61% of predicted, SR −1.14). We also observed improved control of anaemia (Hgb 11 g/dl) and serum lipids (total cholesterol 232 mg/dl, triglyceride 368 mg/dl) but the graft function further worsened (serum creatinine 2 mg/dl, eGFR 40 ml/min).

Discussion

Pulmonary side effects related to immunosuppressive therapy are an infrequent complication in solid organ transplant patients [4]. Although infections are the common cause of pulmonary infiltrates and respiratory failure, the differential diagnosis should also take into account the drug-induced pneumonitis. PT from sirolimus was first reported in 2000 [5]. Since then, almost 100 cases of sirolimus-related pneumonitis in organ recipients have been described [6]. The structurally related PSI everolimus was initially thought to be free of this side effect and even several cases of sirolimus-related pulmonary complications resolved after a conversion to everolimus [7]. However, everolimus-induced pneumonitis has also been recently reported but mostly among patients after heart transplantation [8,9,14]. The first case of everolimus-induced PT in kidney transplant recipient was described by Alexandru et al. in 2008 [10] and another five cases with everolimus-related pneumonitis were reported by Rodriguez-Moreno et al. in 2009 [11]. Surprisingly, in their observation of 205 kidney recipients who underwent a late switch from calcineurin inhibitor to PSI inhibitor sirolimus or everolimus, more episodes were related to everolimus (in five patients) than to sirolimus (one case).

Both clinical symptoms and additional examinations performed in our patient were strongly suggestive of the side effect of a PSI. The clinical manifestations of drug-induced pneumonitis are non-specific and include cough, fever, dyspnoea and hypoxaemia [12]. The differential diagnosis...
Teaching points

1. PT should be considered in all patients after solid organ transplantation treated with both mTOR inhibitors sirolimus and everolimus.

2. A worsening anaemia and dyslipidaemia at onset of respiratory problems may provide a hint for early diagnosis of everolimus-induced pneumonitis.

3. The early withdrawal of mTOR inhibitor from immunosuppressive regimens in patients with everolimus-related PT allows to avoid a high dose of steroids in management of this complication.

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Conflict of interest statement. None declared.

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of drug-induced pneumonitis is extensive. Appropriate cultures and serology can be helpful to differentiate pneumonitis from infectious pneumonia. Bronchoscopy with BAL is particularly useful to exclude an infectious process. Transbronchial or open-lung biopsy can be helpful in demonstrating the presence of pneumonitis and excluding alternative diagnoses like carcinomatous lymphangitis, vasculitis and pneumonia. Non-specific pneumonitis, organizing pneumonia, eosinophilic pneumonia, pulmonary fibrosis and diffuse alveolar damage are frequently seen in lung biopsy specimens [13].

Exclusion of infection, lack of improvement after empirical treatment, presence of interstitial bilateral infiltrates of lower lobe in HRCT and lymphocytic alveolitis in BAL allowed us to suspect a drug-induced pneumonitis in our patient. This diagnosis was supported by the fact that the symptoms of PT appeared shortly after the conversion from CIN to everolimus. In the observations of other authors, the time from conversion to onset of pneumonitis ranged from 14 to 491 days [9,11]. Some authors initially suggested dose-related effects [14], but recent publication did not confirm that notion [10,11]. In our patient, the drug level was always maintained in the recommended range and, therefore, no relation between severity of that side effect and drug therapeutic level could be noticed. Other frequent adverse events associated with the PSIs include dyslipidaemia, anaemia and proteinuria, although all of them can be managed without a need for drug withdrawal [2]. In our patient, worsening of both anaemia and dyslipidaemia was observed at the onset of pneumonitis. The patient had lipid disturbances in the past but they were quite well controlled with statins. Furthermore, the degree of anaemia found at that time could not be explained by the graft function that was improving; there was, however, an increase in serum CRP that indicated an inflammation. In other cases of everolimus-induced pneumonitis, no worsening of anaemia and/or dyslipidaemia was reported [8–11,14]. If our observation is confirmed, it could be helpful in the assessment of the risk of pneumonitis in transplant recipients treated with PSI.

The patients with everolimus-induced pneumonitis described so far required both intensification of steroid treatment and PSI withdrawal. Our experience shows that early diagnosis and suspected drug withdrawal allows avoidance of high doses of steroids, and thereby, their detrimental long-term consequences.

Our observation strengthens the notion that there is a need for careful monitoring of the risk of pulmonary adverse events in all patients treated with both mTOR inhibitors sirolimus and everolimus. The worsening of anaemia and dyslipidaemia at the onset of respiratory problems may provide additional diagnostic hints. In case when symptoms of pneumonitis develop, a withdrawal of proliferating signal inhibitor from immunosuppressive regimens should be immediately considered to avoid excessive doses of steroids.