Case Report

Unusual radiological presentation of sirolimus-associated pneumonitis

Li-Kuo Huang a, Ming-Ji Tsai a, Shi-Chuan Chang a,b,*

a Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
b Institute of Emergency and Critical Care Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Received February 18, 2012; accepted May 16, 2012

Abstract

Sirolimus-associated pneumonitis, a rare but serious drug-induced lung injury, has become a great concern clinically, because of the increasing use of sirolimus (rapamycin) in patients who have been subjected to solid organ transplantation. We report sirolimus-associated pneumonitis in two women who underwent renal transplantation. At variance with previous reports, the radiological findings shown on chest radiographs and computed tomography scans of the chest in these two cases were consolidation lesions mainly with minimal interstitial abnormalities. Our reported cases highlight that awareness of various radiological findings of sirolimus-associated pneumonitis is pivotal for physicians to make early diagnosis of the disorder in patients who have undergone solid organ transplantation.

Copyright © 2013 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

Keywords: lung toxicity; pneumonitis; rapamycin; sirolimus; solid organ transplantation

1. Introduction

Sirolimus (rapamycin) is a potent immunosuppressive agent used widely in patients undergoing solid organ transplantation. Because of the advantage of lack of nephrotoxicity, sirolimus is increasingly used as an alternative to other calcineurin inhibitors. The common side effects of sirolimus therapy include dyslipidemia, thrombosis, oral ulcers, wound complications, and dose-dependent bone marrow suppression.1 A number of case reports of serious pulmonary toxicity caused by sirolimus have attracted more concern regarding the drug’s use in clinical practice.2–13 In this report, we describe sirolimus-associated pneumonitis, which presented with unusual radiological manifestations mimicking lobar pneumonia, in two renal transplants.

2. Case reports

2.1. Case 1

A 65-year-old Chinese woman underwent renal transplantation due to end-stage renal disease caused by Chinese herb medicines on December 20, 2006. She had a history of hypertension, diabetes mellitus, and hypothyroidism controlled well by medications. Her immunosuppression regimen initially included sirolimus 2 mg daily, prednisolone 5 mg daily, tacrolimus 0.5 mg twice a day and mycophenolate mofetil 500 mg twice a day. Because of high serum level of 23.9 ng/mL (reference range, 4–14 ng/mL), the dose of sirolimus was reduced to 1 mg daily beginning March 29, 2008.

At the end of May 2008, the patient began to suffer from fever, dyspnea, and productive cough with whitish sputum for 2 days. She was transferred to our emergency room due to poor response to medications. The vital signs were as follows: blood pressure, 136/90 mmHg; respiratory rate, 20 breaths/min; pulse rate, 72 beats/min; body temperature, 40.3°C. Arterial oxygen saturation was 91% at room air. Sonorous rhonchi were heard over bilateral upper lung fields. Complete
blood counts were as follows: white cell count, $13.5 \times 10^9$/L; hemoglobin, 14.6 g/dL; platelet count, $159 \times 10^9$/L. Abnormal results of blood biochemistries included creatinine, 1.7 mg/dL; sodium, 125 mmol/L; C-reactive protein, 15.33 mg/dL. The trough serum level of sirolimus was 12.8 ng/mL. The chest radiograph at ER showed a consolidation lesion in each upper lobe (Fig. 1A).

The patient was admitted for further management. Empiric antibiotics were administered with intravenous ceftriaxone 2000 mg daily, and then levofloxacin 750 mg daily to combat the pneumonia. Microbiologic studies including cultures of sputum, urine, and blood yielded no growth. Because of progression of the lung lesions and persistent symptoms, thoracic computed tomography was performed 5 days after admission and showed a consolidation lesion mainly in each upper lobe (Fig. 1B).

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was done via the right upper lobe lesion. Total cell count and cell profile of the BAL fluid (BALF) were as follows: total cell count, $7.8 \times 10^7$/L; macrophages, 65%; lymphocytes, 31%; eosinophils, 4%, suggestive of lymphocytic alveolitis (Fig. 2A,B). The cytological smear and microbiologic studies of BALF were negative for bacteria, *Mycobacterium tuberculosis*, virus, fungi, and cytomegalovirus or *Pneumocystis carinii*. Since sirolimus-induced pneumonitis was highly suspected clinically, the regimen of immunosuppressants was shifted as follows: discontinuation of sirolimus, increases in the dose of prednisolone up to 30 mg daily (about 0.5 mg/kg/day) and continued use of other immunosuppressants. Fever and respiratory symptoms subsided, and follow-up chest radiograph 20 days later revealed marked improvement of the lung lesions (Fig. 1C). The patient was discharged and followed-up at the outpatient clinic in a stable condition.

2.2. Case 2

A 64-year-old woman was a victim of end-stage renal disease caused by hypertension and diabetes mellitus, and underwent renal transplantation on June 3, 2002. The postoperative course was uneventful under immunosuppressant therapy including oral prednisolone 5 mg every other day,
mycophenolate mofetil 500 mg twice a day and tacrolimus 1 mg twice a day. In April 2007, due to elevation of serum creatinine level from 1.1 mg/dL to 1.6 mg/dL, sirolimus 2 mg daily was added, accompanied by reducing the dose of tacrolimus to 0.5 mg twice a day. Sirolimus was then gradually tapered to 3 mg every other day 1 year later. The serum levels of sirolimus were maintained in the range 4.3–10.5 ng/mL.

On April 11, 2009, the patient was admitted due to exertional dyspnea and cough with whitish sputum for 1 month. The vital signs were within normal limits. Sonorous rhonchi were heard over the right posterior lower lung field. The

Fig. 2. Marked lymphocytosis is found in bronchoalveolar lavage fluid obtained from the right upper lobe lesion. (A) Riu-stained and (B) Papanicolaou-stained smears (original magnification ×400).

Fig. 3. (A) Chest radiograph and (B) computed tomography reveal a consolidation lesion over the right lower lobe mainly. Obvious resolution of the lung lesion was found 3 weeks after discontinuation of sirolimus (C).
abnormal results of laboratory tests were as follows: hemoglobin, 9.8 g/dL; C-reactive protein, 8.50 mg/dL. Arterial oxygen saturation was 96% at room air. The trough serum level of sirolimus was 5.0 ng/mL. Chest radiograph (Fig. 3A) and computed tomography (Fig. 3B) showed a consolidation lesion mainly in the right lower lobe (RLL). Empiric antibiotics including cefuroxime 1500 mg every 8 hours and azithromycin 500 mg daily were given. Because of no significant improvement of the symptoms and lung lesion, the patient underwent diagnostic BAL on the sixth day after admission. Total cell count and cell profile of BALF obtained from the RLL was as follows: total cell count, 14.1 \times 10^7/L; macrophages, 52%; lymphocytes, 43%; neutrophils, 1%; eosinophils, 4%, indicative of lymphocytic alveolitis. The ratio of CD4+/CD8+ T lymphocytes in BALF was 4.4. The cytological smears and microbiological studies of BALF were negative for bacteria, virus, mycobacteria, fungi, cytomegalovirus, and Pneumocystis carinii. Since sirolimus-associated pneumonitis was highly suspected clinically, sirolimus was discontinued and the dose of tacrolimus was increased to 1 mg twice a day. Clinical features improved rapidly. The chest radiograph obtained 3 weeks later revealed obvious resolution of the RLL lesion with minimal residual infiltrates (Fig. 3C). The patient was discharged and followed-up at the outpatient clinic.

3. Discussion

Currently, sirolimus appears to be an important immunosuppressive agent in patients subjected to solid organ transplantation, with mechanisms that block interleukin-2-induced proliferation of T-cells and inhibit the protein kinase, causing arrest of cell cycle in the G1 phase. The relevant advantage of sirolimus over other calcineurin inhibitors is its lack of nephrotoxicity.1

More adverse effects have been reported with the increasing use of sirolimus clinically. Of these, pulmonary toxicity, a rare but serious complication, is of great concern. Interstitial pneumonitis related to sirolimus in three renal-transplant recipients was firstly reported by Morelon et al.2 In general, patients with sirolimus-associated pneumonitis present with nonspecific pulmonary symptoms including dyspnea, dry cough, fever, fatigue, and occasionally hemoptysis.3 Diagnostic criteria for sirolimus-induced pneumonitis are suggested as follows8: (1) the use of sirolimus preceding the onset of pulmonary symptoms; (2) clinical exclusion of infection or alternative pulmonary diseases; (3) resolution of lung lesion(s) after sirolimus discontinuation; (4) lymphocytic alveolitis suggested by BALF cytology or compatible pathological findings on the lung tissue specimens.

Pham et al reported that the disease onset of sirolimus-associated pneumonitis in 43 patients might range from 2.5 months to 12 months.3 However, subsequent reports indicated that the onset of sirolimus-associated pneumonitis might occur early within 1 month4–7 or late at 51 months9 after the use of sirolimus. It remains unclear why the time period between the drug initiation and the occurrence of pulmonary symptoms in patients with sirolimus-associated pneumonitis so varies widely. The insidious onset of the disease, physicians’ unawareness or lack of familiarity of the disease, nonspecific clinical manifestations, and a lack of characteristic laboratory and radiological findings of sirolimus-associated pneumonitis may contribute to a delayed diagnosis. Furthermore, the list of differential diagnoses of including a broad spectrum of infectious and noninfectious etiologies in such non-HIV immunocompromised patients can be a difficult challenge for clinicians.14,15

Although the risk factors for sirolimus-induced pneumonitis have not yet been well established, late administration of sirolimus (switched use),4,9,10 concomitant use of additional immunosuppressants,4,9,10 high sirolimus dose (>5 mg/day),4,10 and high sirolimus trough level (>15 ng/mL) at the occurrence of clinical symptoms10 are suggested. Two mechanisms of sirolimus-associated pneumonitis have been proposed,8 including direct alveolar cytotoxicity and immune-mediated toxicity. The evidence supporting the primary cytotoxic effect includes resolution of symptoms after reducing the dose of sirolimus and the supratherapeutic drug level (>15 ng/mL).4,5 However, the immune-related mechanism is more favored in other studies. A wide range of time course from the initiation of sirolimus treatment to the onset of pulmonary complications and a wide range of trough serum levels of sirolimus in the reported cases suggest an idiosyncratic mechanism.11 Pham et al3 regarded sirolimus as a hapten that elicits an immune response after binding to plasma proteins. Moreover, Howard et al reported that the histopathological findings of noncaseating granuloma with CD4+ T-lymphocytes infiltrates shown on transbronchial lung biopsy specimens in a liver transplant recipient with sirolimus-associated pneumonitis are highly suggestive of a hypersensitivity reaction rather than direct dose-related toxicity.6 Of note, the cell profile of BALF may be related to the onset of pulmonary complications after the use of sirolimus. Among cases with more rapid onset, particular in those with onset within 1 month, an increase of alveolar macrophages in BALF5–7,11,12 and a higher incidence of alveolar hemorrhage were noted.4,7 On the contrary, lymphocytic alveolitis is more common seen in those with later onset of sirolimus-induced pneumonitis.11,13 However, it remains unknown whether the two mechanisms act independently or interact in the development of sirolimus-induced pneumonitis. The issue deserves further studies with a large population.

In our reported cases, marked lymphocytosis found in the cytological smear of BALF was highly suggestive of drug-induced lung disease,16 and CD4+/CD8+ T-cell predominance with a high CD4+/CD8+ ratio in BALF as shown in case 2 was compatible with BALF findings in previous reports.4,12 In addition, the low dose used (1 mg daily in Case 1, and 3 mg every other day in Case 2) was associated with a low therapeutic trough level (<15 ng/mL) of sirolimus at the occurrence of pneumonitis in the two reported cases indicates that direct cytotoxicity was less likely.

In general, bilateral, asymmetrical, alveolar or mixed alveolar—interstitial opacities with a predilection at lower lobes...
or diffusely distribution are the predominant radiological findings in most reported cases of sirolimus-associated pneumonitis.\textsuperscript{3,8,11,13} The study with the largest number of reported cases indicated that a pattern of bronchiolitis obliterans organizing pneumonia was found in 19 of 24 patients.\textsuperscript{9} Accordingly, the consolidation lesion mainly shown on both chest radiography and CT scans in our reported Case 2 might easily masquerade as lobar pneumonia. Of note, a consolidation lesion mainly in each upper lobe as shown in Case 1, to our knowledge, has not yet been reported previously. A consolidation lesion may be not usual in sirolimus-associated pneumonitis; however, a consolidation lesion appearing as an isolated lesion or in the bilateral upper lobe is quite unusual or rare in sirolimus-associated pneumonitis. Unawareness of protean radiological manifestations of sirolimus-associated pneumonitis may delay the diagnosis and appropriate treatment.

One may argue that the use of antibiotics in our reported cases may have interfered with the results of infectious workups including cytological smears and microbiological studies of BALF. Negative results of cytological smears for identifying cytomegalovirus or \textit{Pneumocystis carinii} and microbiological studies of BALF cannot completely exclude the possibility of infections. However, a rapid clinical and radiological improvement after discontinuation of sirolimus and antibiotics based on the results of BALF studies strongly supports a diagnosis of sirolimus-associated pneumonitis clinically.

In conclusion, sirolimus-associated pneumonitis should be suspected when pulmonary infection is considered and shows poor response to antimicrobial agents in patients subjected to solid organ transplantation treated with immunosuppressants including sirolimus. Diagnostic BAL with or without transbronchial lung biopsy can be of considerable help in aiding a diagnosis of sirolimus-associated pneumonitis. Discontinuation of sirolimus is the mainstay of treatment.

References