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Case report

Pneumocystis pneumonia in everolimus therapy: An indistinguishable case from drug induced interstitial lung disease

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ABSTRACT

A 66-year-old male treated with everolimus for renal cell carcinoma developed exertional dyspnea. Chest computed tomography revealed diffuse interstitial shadows on both lungs. Bronchoalveolar lavage and the drug-induced lymphocyte stimulation test confirmed the diagnosis of drug-induced interstitial lung disease due to everolimus therapy. However, discontinuation of everolimus in combination with corticosteroid therapy did not prevent disease progression. On the basis of a PCR assay for *Pneumocystis jirovecii* and elevated β-D-glucan levels, trimethoprim-sulfamethoxazole was administered immediately, resulting in a dramatic improvement. This case demonstrated that pneumocystis pneumonia should always be considered and treated during everolimus therapy, even when drug-induced interstitial lung disease is suspected.

1. Introduction

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is an effective antitumor drug for renal cell carcinomas (RCCs), with its use increasing for management of other neoplasms such as breast cancer [1], neuroendocrine tumors [2], and angiomyolipoma [3]. Because of the high incidence of pulmonary adverse effects caused by the drug, this increased use of everolimus is expected to result in an increased number of patients with drug-induced interstitial lung disease (ILD). In fact, drug-induced ILD was reported to occur in 13.5% patients receiving everolimus in a phase III clinical trial for RCC [4]. In addition to its antitumor effects, everolimus has been used as an immunosuppressant to prevent the rejection of heart and kidney transplants [5]. Therefore, scrupulous care must be taken against opportunistic infections whenever everolimus is used; however, to our knowledge, there is only limited information regarding pulmonary infectious complications associated with everolimus therapy. In this paper we describe a case of pneumocystis pneumonia (PCP), which was clinically similar to everolimus-induced ILD and was initially managed with a corticosteroid. The patient was successfully treated with trimethoprim-sulfamethoxazole immediately after being diagnosed with PCP on the basis of a PCR assay for *Pneumocystis jirovecii* and elevated β-D-glucan levels.

2. Case report

A 66-year-old Japanese male with advanced renal cell carcinoma (RCC) visited our respiratory outpatient clinic complaining of progressive exertional dyspnea for 1 month after administration of everolimus. He had suffered from unresectable RCC with multiple bone metastases for 2 years (clear cell carcinoma. cT3cN0M1. stage IV). Previous therapy included sunitinib for 1 year, followed by axitinib for 2 months. This regimen failed to prevent disease progression. Thereafter, third-line therapy with everolimus was initiated. The patient was an exsmoker and had stopped smoking 35 years back. Annual check-ups had revealed that he was asymptomatic for any breathing problems, with no abnormalities in the pulmonary function tests or chest computed tomography (CT) scans. On his first visit to our clinic, he was afebrile but presented with general malaise and tachypnea accompanied by hypoxemia (SpO_2, 96% after inhaling oxygen by mask at 4 L/min). He had slight systemic edema, probably caused by renal insufficiency and/or hypoalbuminemia. Cardiac pulmonary edema was excluded by echocardiography. On chest auscultation, no wheeze or crackle was

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audible. Chest radiograph revealed bilateral infiltration on both lungs, while chest CT revealed diffuse ground glass opacities in both lung fields (Fig. 1A and B). The laboratory findings on admission are presented in Table 1. In brief, we observed mild lymphocytosis, mild anemia, thrombocytopenia, slight liver dysfunction, and renal insufficiency. Lactate dehydrogenase (LDH) and CRP were elevated at 583 IU/L and 16.7 mg/dl, respectively. The serum level of Krebs von den Lungen-6 (KL-6): a sensitive marker for interstitial pneumonia, was also elevated at 735 U/mL (normal range; <500 U/mL), excluding the possibility of atypical pneumonia. On the basis of these findings, we suspected that the patient had everolimus-induced ILD. On the first hospital day, a bronchoalveolar lavage (BAL) was performed to determine the cellular fractionation in the BAL fluid (BALF) as well as to exclude respiratory infections. BALF recovered from right B^{3b} revealed an increased total cell number (3.10×10^5 cells/mL) with lymphocytosis (macrophages, 65.4%; lymphocytes, 29.0%; neutrophils, 4.2%; eosinophils, 1.4%). The CD4/CD8 ratio was 0.9 (normal range in nonsmokers, 0.4–1.0). BALF cultures were negative for bacteria, acid-fast bacilli, and fungi. Unfortunately, we could not perform a transbronchial lung biopsy (TBLB) because of the patient's frequent cough and oxygen desaturation during the bronchoscopic procedure.

Because drug allergy for everolimus was strongly suspected, we performed a drug-induced lymphocyte stimulation test (DLST) using serum and BALF. Although DLST with serum revealed a negative reaction, the test with BALF was positive with a stimulation index of 204% compared with that in the control (368 cpm for everolimus and 179 cpm for control). Taken together, these clinical findings confirmed the diagnosis of everolimus-induced ILD. Therefore, everolimus therapy was discontinued, and intravenous methylprednisolone administration (1000 mg/day for 3 consecutive days) was initiated immediately after BAL. Oral prednisolone administration (50 mg/day) was followed by steroid pulse therapy. Despite this vigorous therapy, his respiratory distress and radiographic findings rapidly exacerbated day by day (Fig. 2). On the fifth hospital day, the presence of PCR for *Pneumocystis jirovecii* DNA in BALF was established. Moreover, serum (1–3) − β−D-glucan levels were markedly increased at 137.5 pg/mL (normal range; <20 pg/mL). Cytomegalovirus (CMV) pp65 antigenemia in the serum and CMV-DNA in BALF were negative. Therefore, a diagnosis of PCP was confirmed. Intravenous trimethoprim-sulfamethoxazole administration was initiated immediately, and his respiratory symptoms improved dramatically within a week, along with dissolution of the interstitial shadow on radiographs. Unfortunately, everolimus was discontinued even after recovery from PCP owing to intolerable adverse gastrointestinal effects, including nausea and anorexia. The patient was referred to the palliative care unit and died of cancer 5 months later.

Table 1
Laboratory data on admission.

Hematology		Biochemistry		Serology	
WBC	3200/uL	TP	5.5 g/dL	CRP	16.7m g/dL
Neutrophil	70.5%	Alb	2.8 g/dL	KL-6	735 U/mL
Lymphocyte	21.5%	LDH	583 IU/L		
Monocyte	5%	AST	67 IU/L		
Eosinophil	0%	ALT	28 IU/L		
Basophil	3%	ALP	523 IU/L		
RBC	405×10^4/uL	BUN	35m g/dL		
Hgb	10.2 g/dL	Cre	1.66m g/dL		
Hct	31%	Na	134 mEq/L		
Plt	26×10^4/uL	K	3.8 mEq/L		
		Cl	94 mEq/L		

3. Discussion

Everolimus is a potent immunosuppressant prescribed for immunocompromised hosts with malignancies and is known to increase the risk of *Pneumocystis jirovecii* infections. However, to our knowledge, there is only 1 case report of PCP associated with everolimus therapy [6]. As reported in the present case, differentiation of drug-induced ILD and PCP is extremely difficult as they share several of the clinical findings described below. This emphasizes the risk of overlooking or misdiagnosing PCP as common everolimus-induced ILD; these errors might result in treatment delays and a fatal outcome.

3.1. Radiographic findings

The radiographic manifestations of drug-induced ILD by everolimus change over time. In general, CT patterns can be divided into 4 groups: pattern A (nonspecific areas of ground-glass attenuation); B (multifocal areas of airspace consolidation); C (patchy distribution of ground-glass attenuation accompanied by interlobular septal thickening); and D (extensive bilateral ground-glass attenuation or airspace consolidation with traction bronchiectasis) [6]. The A, B, and C patterns are not specific to ILD but are often seen in patients with PCP [7]. In addition, pattern D is difficult to distinguish from PCP, particularly in patients with underlying pulmonary diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and pulmonary fibrosis. The CT findings in the present case correspond with pattern A (nonspecific areas of

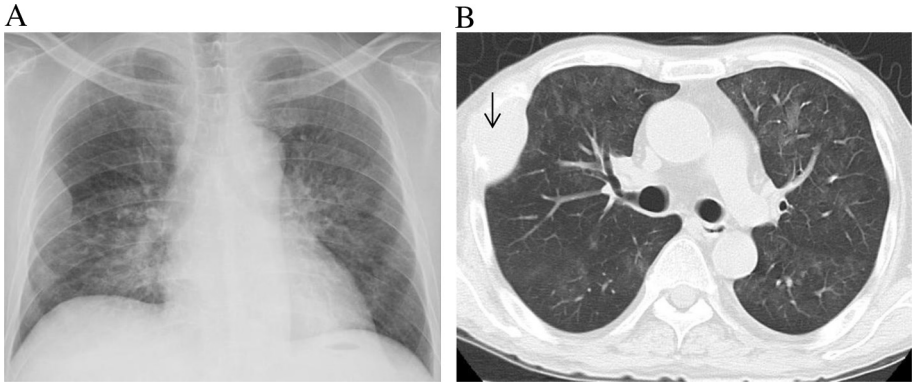

Fig. 1. Chest radiograph (A) and chest CT (B) on the first hospital day. Diffuse ground-glass opacity with an irregular distribution without volume loss is apparent in both lung fields. Metastasis to the thoracic wall was also evident (arrow head).

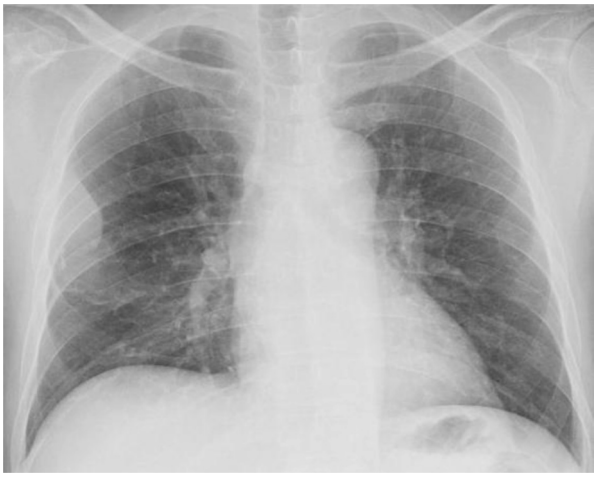

Fig. 2. Chest radiograph on the third hospital day. Despite steroid pulse therapy, the interstitial shadow expanded rapidly in both lung fields. BAL was performed from the right B^{3b}. Trimethoprim-sulfamethoxazole was administered immediately following this procedure.

GGO) findings, which were consistent with the findings of both drug-induced ILD and PCP.

3.2. BAL finding

The cellular pattern of BALF in drug-induced lung toxicity is classified into 5 groups: cellular pneumonitis, eosinophilic pneumonia, organizing pneumonia, cytotoxic reaction, and diffuse alveolar damage [8]. The mechanism of everolimus-induced lung toxicity remains unknown but is thought to be a delayed hypersensitivity reaction [9]. Accordingly, the most characteristic BAL finding of everolimus-induced ILD is cellular pneumonitis with increased lymphocytes. This usually predicts a favorable response to corticosteroid therapy. The present case revealed a typical cellular pneumonitis with an increase in total cell number and lymphocyte dominance as high as 30%. However, lymphocytosis or eosinophilia in BALF has also been reported in HIV-negative PCP patients [10]. A recent cohort study demonstrated no significant difference in cell count or differential count in BALF between PCP and non-PCP patients [11]. Therefore, the cell fractionation pattern of BALF *per sé* is not sufficient to exclude PCP.

3.3. Drug-induced lymphocyte stimulation test (DLST)

Of interest, the present case revealed a positive result against everolimus in DLST of BALF. Everolimus is an immunosuppressant that inhibits cell proliferation of B- and T-cells. The routine use of DLST is not recommended except for research purpose, because the interpretation of its results for immunosuppressive agents is often complicated, and its value remains controversial [12]. However, considering the nature of this agent, a false-negative result would be expected more often and in fact has been reported elsewhere [9]. Thus, a positive DLST might indicate a concomitant drug allergy, although it is not sufficient to exclude the possibility of PCP.

3.4. PCR and β-D glucan

A definitive diagnosis of PCP is established on the basis of histological identification of *Pneumocystis jirovecii* organisms in BALF or TBLB specimens. However, identification of the organism in non-AIDS patients is difficult because of an insufficient number of organisms [13]. As an alternative, PCR of *Pneumocystis jirovecii* is a simple and reliable surrogate marker for direct identification of the organism. The sample is obtained simply from sputum or endobronchial washings and not by a full BALF; further, this test is now also used in patients with general respiratory distress. Moreover, serum β−D glucan levels are a credible marker for PCP, with a sensitivity of 92% and specificity of 86% [13]. The present case was diagnosed conclusively as PCP, primarily on the basis of the PCR findings in BALF and the elevated β−D glucan levels along with the lack of response to corticosteroid therapy. The main drawbacks of these laboratory markers are the time delay in diagnosis, which might help in initiation of appropriate therapy. PCP in non-HIV patients progresses very rapidly, with treatment delays often resulting in a fatal outcome [14,15]. Therefore, chemoprevention or prophylactic administration of trimethoprim−sulfamethoxazole are recommended in these patients, at least until the examination results are obtained.

As mentioned previously, the incidence of everolimus-induced ILD is exceptionally high with other immunosuppressant and anticancer drugs. The severity of respiratory toxicity that is induced by everolimus ranges from very subtle to severe respiratory failure [15.16]. Most patients are asymptomatic despite the high incidence of interstitial shadows on chest CT [15]. The management algorithm for everolimus-induced ILD is different from that of other drug-induced ILDs. For example, discontinuation of everolimus is not necessary for asymptomatic patients (CACTE Grade1) or those with mild radiographic findings. Further, patients with mild symptoms (CACTE Grade 2) can be rechallenged with everolimus soon after recovery following tentative drug discontinuation. Thus, there is considerable risk of overlooking PCP or managing the condition with corticosteroids as drug-induced ILD; these errors might exacerbate the respiratory distress.

Because everolimus is now used to treat patients with various types of cancer and backgrounds, this manifestation of PCP might increase in the future. Thus, it is important to make all possible efforts to survey and monitor opportunistic infections of PCP whenever everolimus is used and to initiate therapy at appropriate times throughout the treatment course.

Conflict of interest

The authors state that they have no conflict of interest.

References

[1] Vinayak S, Carlson RW. mTOR inhibitors in the treatment of breast cancer. Oncol (Williston Park) 2013;27:38–44.
[2] Yao JC, Reidy Lagunes D, Kulke MH. Targeted therapies in neuroendocrine tumors (NET): clinical trial challenges and lessons learned. Oncologist 2013;18:525–32.
[3] Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817–24.
[4] White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. Am J Respir Crit Care Med 2010;182:396–403.
[5] Eisen HJ, Kobashigawa J, Starling RC, Pauly DF, Kfoury A, Ross H, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am J Transplant 2013;13:1203–16.
[6] Saito Y, Nagayama M, Miura Y, Ogushi S, Suzuki Y, Noro R, et al. A case of pneumocystis pneumonia associated with everolimus therapy for renal cell carcinoma. Jpn J Clin Oncol 2013;43:559–62.
[7] Hidalgo A, Falco V, Mauleon S, Andreu J, Crespo M, Ribera E, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non-Pneumocystis carinii pneumonia in AIDS patients. Eur Radiol 2003;13:1179–84.
[8] Costabel U, Uzaslan E, Guzman J. Bronchoalveolar lavage in drug-induced lung disease. Clin Chest Med 2004;25:25–35.
[9] Mizuno R, Asano K, Mikami S, Nagata H, Kaneko G, Oya M. Patterns of interstitial lung disease during everolimus treatment in patients with metastatic renal cell carcinoma. Jpn J Clin Oncol 2012;42:442–6.
[10] Fleury-Feith J, Van Nhieu JT, Picard C, Escudier E, Bernaudin JF. Bronchoalveolar lavage eosinophilia associated with Pneumocystis carinii

pneumonitis in AIDS patients. Comparative study with non-AIDS patients. Chest 1989;95:1198–201.
[11] Tasaka S, Hasegawa N, Kobayashi S, Yamada W, Nishimura T, Takeuchi T, et al. Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 2007;131:1173–80.
[12] Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004;59:809–20.
[13] Azoulay E, Bergeron A, Chevret S, Bele N, Schlemmer B, Menotti J. Polymerase chain reaction for diagnosing pneumocystis pneumonia in non-HIV immunocompromised patients with pulmonary infiltrates. Chest 2009;135:655–61.
[14] Thomas Jr CF, Limper AH. Pneumocystis pneumonia. N Engl J Med 2004;350:2487–98.
[15] White DA, Schwartz LH, Dimitrijevic S, Scala LD, Hayes W, Gross SH. Characterization of pneumonitis in patients with advanced non-small cell lung cancer treated with everolimus (RAD001). J Thorac Oncol 2009;4:1357–63.
[16] Depuydt P, Nollet J, Benoit D, Praet M, Caes F. Fatal acute pulmonary injury associated with everolimus. Ann Pharmacother 2012;46:e7.