



Case report

A case of delayed exacerbation of interstitial lung disease after discontinuation of temsirolimus



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ABSTRACT

Temsirolimus is an inhibitor of mammalian target of rapamycin and interstitial lung disease (ILD) is known to be one of the adverse events associated with temsirolimus, which usually improves rapidly after discontinuation of the drug and rarely worsens thereafter. Herein, we report a case of delayed exacerbation of ILD after discontinuation of temsirolimus for metastatic renal cell carcinoma in an 86-year-old male with chronic ILD. The patient developed gradually worsening dyspnea five weeks after an initiation of temsirolimus and was admitted to our facility. On his admission, although a pulmonary function test revealed a decreased diffusion capacity, there was no obvious progression of ILD on HRCT scan. His dyspnea once improved after discontinuation of temsirolimus, but it recurred and acute exacerbation of ILD was diagnosed 40 days after his last administration of temsirolimus. He received high-dose steroid therapy, however, he deteriorated and died. Histopathological examination of the lungs at autopsy revealed overlapping diffuse alveolar damage with chronic interstitial changes. In the present case, since there were no specific factors that could have caused acute exacerbation of ILD except for temsirolimus, it was considered to contribute to the exacerbation of underlying ILD. In conclusion, physicians should be aware of the possibility of temsirolimus-induced ILD not only while the medication is administered, but also even after it is discontinued. It is important to carefully interview the patient and to recognize the value of physiological tests, such as respiratory function tests and blood gas analysis, as well as imaging findings on HRCT.

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1. Introduction

Temsirolimus is an inhibitor of mammalian target of rapamycin

Abbreviations: AaDO₂, alveolar-arterial oxygen gradient; CMV, cytomegalovirus; CRP, C-reactive protein; DAD, diffuse alveolar damage; DILD, Drug-induced interstitial lung disease; DLCO/VA, diffusion capacity for carbon monoxide corrected for alveolar volume; GGO, ground glass opacities; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LD, lactate dehydrogenase; mPSL, methylprednisolone; mTOR, mammalian target of rapamycin; NPPV, noninvasive positive pressure ventilation; PaCO₂, carbon dioxide partial pressure; PaO₂, oxygen partial pressure; UIP, usual interstitial pneumonia.

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(mTOR), a key player in the cell growth and proliferation signaling pathways that regulate protein synthesis [1]. In Japan, temsirolimus is administered to patients with unresectable and/or metastatic renal cell carcinoma. Although interstitial lung disease (ILD) is reported to be one of the most common adverse events associated with temsirolimus, it usually improves rapidly after discontinuation of the drug and rarely worsens thereafter [2]. Herein, we present a case in which ILD had remained exacerbated for over a month after discontinuation of temsirolimus.

2. Case report

An 86-year-old Japanese man with recurrent renal cell carcinoma developed gradually worsening dyspnea and was admitted to our facility. He had undergone radical nephrectomy for right

renal cell carcinoma 2 years previously, which recurred as multiple metastases in the cervical lymph nodes a year later. He had been treated with temsirolimus (25 mg per week) for 5 weeks prior to admittance. The patient had smoked 20 cigarettes daily for 26 years and quit smoking 40 years previously. He had a history of hypertension for 6 years and had been treated with amlodipine 5 mg/day and losartan 50 mg/day. He was also found to have ground glass opacities (GGO) in both lower lobes on chest X-ray film a year before admission. A high-resolution computed tomography (HRCT) scan of the chest showed reticular abnormality with the subpleural and basal dominance that was consistent with possible usual interstitial pneumonia (UIP) pattern (Fig. 1A, E). Together with the patient's clinical context such as bibasilar inspiratory fine crackles and the duration of illness over three months, his lung abnormality was concluded to be probable idiopathic pulmonary fibrosis (IPF), although lung biopsy was not performed in consideration of the risk of exacerbation of ILD. He had not been receiving any treatment for his probable IPF because it had been stable.

On admission, temsirolimus was suspended due to suspicion of dyspnea as an adverse effect. The physical examination did not show any abnormal findings, except for fine crackles which were audible at the base of both lungs but had changed very little since before admission. Arterial blood gas on room air showed an oxygen saturation of 95%, oxygen partial pressure (PaO₂) of 88.6 mmHg and carbon dioxide partial pressure (PaCO₂) of 28.2 mmHg. The ratio of PaO₂ to fractional inspired oxygen (PaO₂/FiO₂) and the alveolar-arterial oxygen gradient (AaDO₂) were calculated and their values were 421 and 25.9 mmHg, respectively. Although lactate dehydrogenase (LD) and C-reactive protein (CRP) were slightly elevated, at 309 U/L (>222 U/L) and 2.37 mg/dL (>0.3 mg/dL), respectively, the Krebs von den Lungen-6 (KL-6) level was 435 U/mL (<500 U/mL). The remainder of the hematological examination, including serum autoantibodies, revealed no abnormalities. No infectious agents were revealed in the patient's sputum cultures.

An HRCT scan of the chest showed bilateral reticular shadows in both lower lung lobes, which slightly spread, but not significantly differed from that before administration of temsirolimus (Fig. 1A, B, E, F). A pulmonary function test demonstrated a normal range of vital capacity (VC; 2.83 L, percentage of predicted VC; 96%) and normal forced expiratory volume in 1 second (FEV_{1.0}; 1.98 L, FEV_{1.0}/FVC ratio: 70.1%, percentage of predicted FEV_{1.0} 111%) with

moderately reduced diffusion capacity for carbon monoxide corrected for alveolar volume (percentage of predicted DLCO/VA 75%) compared with that before administration of temsirolimus (%DLCO/VA 91%). After discontinuation of temsirolimus, the dyspnea spontaneously subsided without any additional treatment and the patient was discharged. His modified medical research council dyspnea scale improved from grade 4 to grade 2 and chest X-ray film showed no significant deterioration of GGO in both lower lung fields after discharge (Fig. 2). Temsirolimus was not restarted after discharge, considering the risk of recurrent dyspnea and deterioration of ILD.

Forty days after his last administration of temsirolimus, the patient returned to the hospital due to rapidly progressive dyspnea. On his second admission, he was conscious, with a body temperature of 37.1 °C, pulse rate of 99 beats/min, and blood pressure of 126/66 mmHg. He had no arthralgia or thoracic pain. Pulmonary auscultation revealed fine crackles in the lower lung fields bilaterally and coarse crackles in the left lower lobe. He did not have lower leg edema. His ambulatory pulse oximetry on room air decreased to 88% and improved to 95% on 2 L/min supplemental oxygen administered via a nasal cannula. Arterial blood gas analysis on 2 L/min supplemental oxygen administered intranasally showed hypoxia (pH 7.470, PaCO₂ 27.8 mmHg, PaO₂ 89.1 mmHg, and HCO₃ 19.8 mmol/L). The calculated PaO₂/FiO₂ was 318. An electrocardiogram was within normal limits. Laboratory tests showed a white blood cell count of 11,400 cells/μL, hemoglobin level of 8.1 g/dL, and platelet count of 281,000/μL. Although KL-6 was not elevated (280 U/mL), CRP, LD, and surfactant protein D were elevated to 12.30 mg/dL, 308 U/L, and 152.7 ng/mL (>110 ng/mL), respectively. Brain natriuretic peptide was slightly elevated to 188.9 pg/mL (>18.4 pg/mL) from his first admission (63.3 pg/mL). However, a transthoracic echocardiogram showed preserved ejection fraction and no motion abnormalities, suggesting the little possibility of acute heart failure. An ultrasonographic examination of lower legs did not detect any venous thromboembolism despite the fact that D-dimer was elevated to 7.6 μg/mL (>0.9 μg/mL) on his second admission, which was lower than that on his first admission (11.9 μg/mL). Cytomegalovirus (CMV)-pp65 antigen, procalcitonin and β-D glucan levels were within normal limits. Urine antigen testing for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. No pathological microorganisms were found in

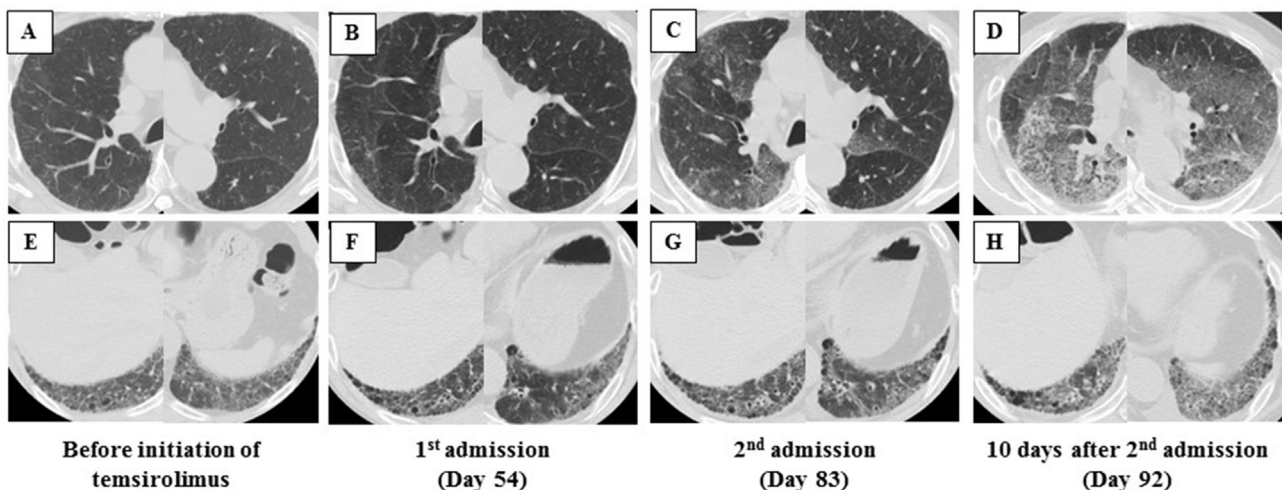


Fig. 1. Chest high-resolution computed tomography (HRCT) scans over the clinical course. HRCT scans before the administration of temsirolimus (A, E) showed bilateral reticular shadows in both lower lobes that were slightly progressed, but not significantly differed from those seen on the patient's first admission (B, F). On the patient's second admission (C, G), a non-segmental ground glass appearance in the right upper and middle lobes was noted, as well as extension of the reticular shadows in the basal lungs bilaterally. On the tenth day of the patient's second admission (D, H), progressive exacerbation of the ground glass opacities was noted to spread throughout most of the lung fields.

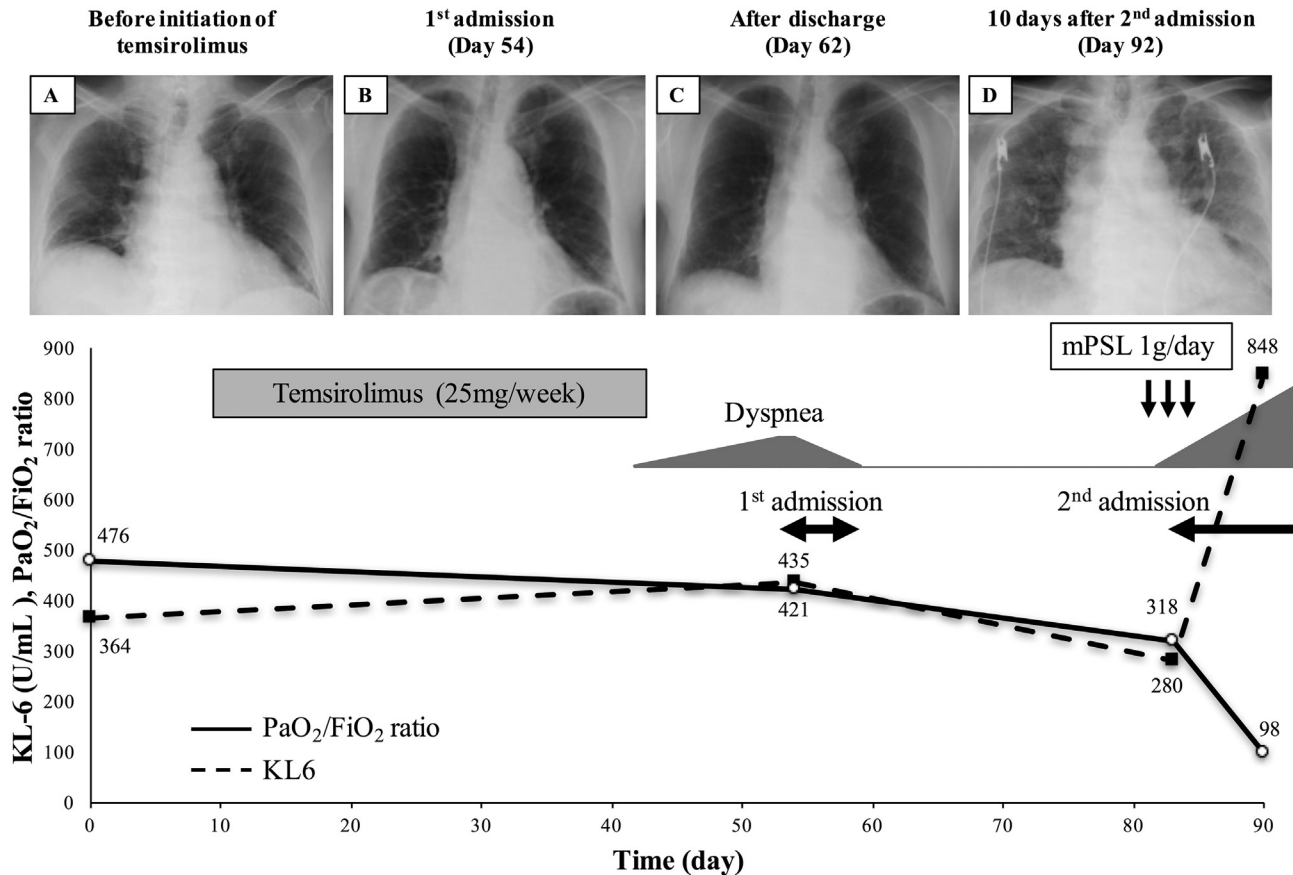


Fig. 2. Clinical course of the patient. Chest X-ray films on the patient's first admission (B) and after discharge (C) did not show significant deterioration of ground glass opacity (GGO) in both lower lung fields compared with that before initiation of tamsirolimus (A). Ten days after the patient's second admission, extended GGOs in the whole lung fields were revealed (D).

sputum or blood culture.

A chest HRCT scan revealed a non-segmental GGO of the right upper and middle lobes, as well as the left lung (Fig. 1C, G), which had not been noted on his previous visit. Moreover, the reticular shadows in the bilateral basal lungs had extended. The patient was diagnosed with acute exacerbation of ILD and high-dose methylprednisolone (mPSL) (1000 mg daily for 3 days) was immediately initiated, as well as ampicillin/sulbactam to prevent progression of bacterial pneumonia that was possibly complicated. Further, noninvasive positive pressure ventilation (NPPV) was initiated to treat respiratory failure. Dyspnea and hypoxemia improved after 3 days of high-dose mPSL, and then the NPPV was withdrawn. However, 9 days later, the patient's dyspnea gradually worsened once more and an HRCT scan of the chest (Fig. 1D, H) showed new consolidations in the bottom of the lungs bilaterally, with an increase in the density of ground glass lesions in the entire lung. Because sputum and blood cultures were positive for *Escherichia coli*, bacterial pneumonia was considered to be complicated. The patient received high-dose mPSL again without improvement. He deteriorated and died on the 20th day of admission.

Following consent from the patient's family, an autopsy was performed. Macroscopically, the weight of both lungs was increased (left: 729 g, right: 814 g) and consolidation was evident in mainly the upper and middle lobes. A honeycomb structure was noted at the bottom of both lungs (Fig. 3). Microscopically, a diffuse organization with regional fibrin exudation was observed, which is consistent with the organizing phase of diffuse alveolar damage (DAD) (Fig. 4A). Chronic interstitial changes were focally identified

in the subpleural area at the bottom, which showed fibrosis with alveolar collapse, expansion of remaining air spaces with epithelial metaplasia, and hyperplasia of the smooth muscles (Fig. 4B–D). In addition to these organizing and chronic interstitial changes, alveolar pneumonia with neutrophil infiltration and gram-negative bacteria was observed mainly in both lower dorsal lungs.

3. Discussion

Drug-induced interstitial lung disease (DILD) can be caused by chemotherapeutic agents, antibiotics, antiarrhythmic drugs, and immunosuppressive agents. DILD has no distinct physiologic, radiographic, or pathological symptoms and is usually diagnosed when a patient with ILD is exposed to medication known to result in lung disease. The treatment for DILD is avoidance of further exposure, and systemic corticosteroids are sometimes administered to patients with the progressive or disabling disease. The prognosis is variable and depends on the specific drug and underlying clinical, physiologic, and pathological severity of the lung disease. Unfortunately, if the initiating injury or abnormal repair of injury is not halted, progressive tissue damage can lead to worsening physiologic impairment and even death [3]. In the present case, the patient's underlying ILD was thought to remain exacerbated for over a month after discontinuation of tamsirolimus.

Several factors have been reported to induce acute exacerbation of ILD such as preceding respiratory tract infection, invasive examinations to the lung, tapering the dosage of corticosteroid, and drugs, though more than half of the causes are unknown [4]. In the

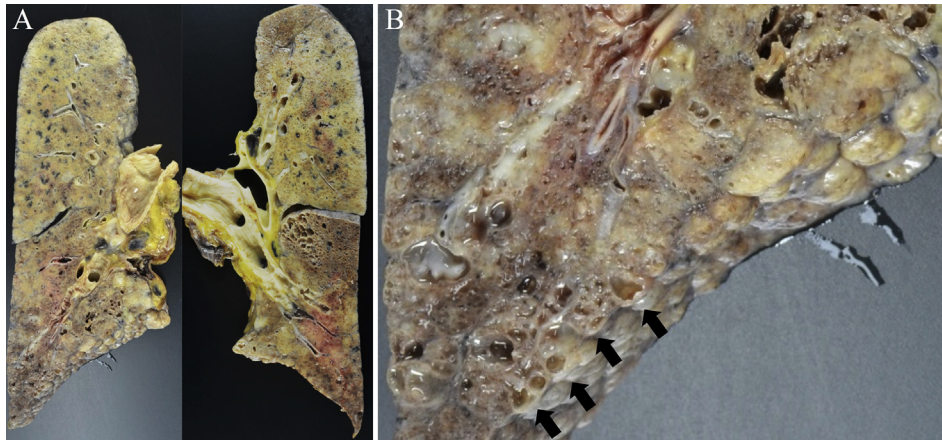


Fig. 3. Macroscopic pathological findings of the lungs at autopsy. Consolidation was noted mainly in the right middle and both upper lobes (A). A honeycomb structure (black arrow) was present at the bottom of the lung (B).

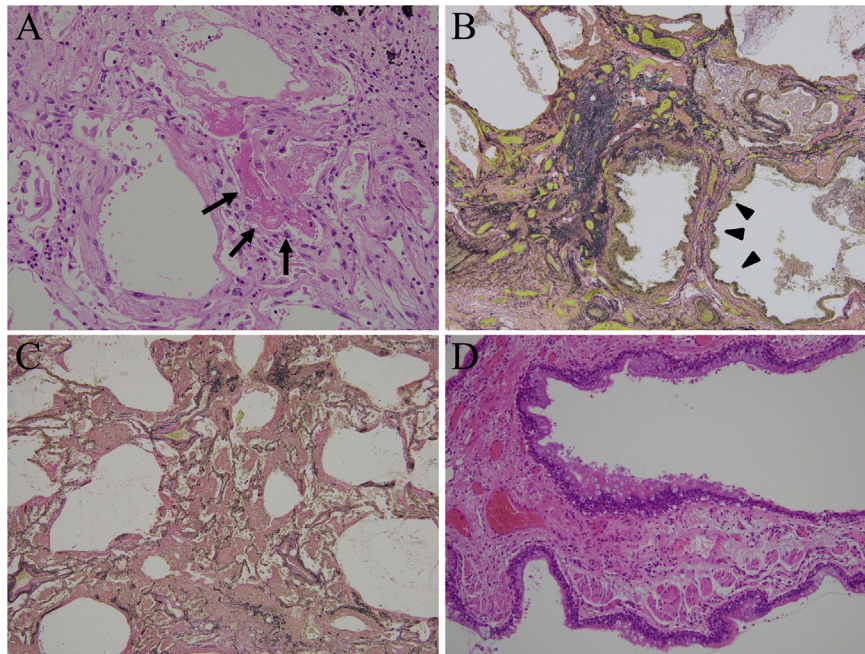


Fig. 4. Microscopic pathological findings of the lungs at autopsy. A diffuse organizational pattern with regional fibrin exudation (black arrow) was revealed in the alveolar region on hematoxylin and eosin staining (A). Expansion of remaining air spaces with epithelial metaplasia (arrow head) (B) and fibrosis with alveolar collapse (C) was identified on elastic-van Gieson staining. Hyperplasia of smooth muscles was shown on hematoxylin and eosin staining (D).

current case, the patient had revealed gradually worsening dyspnea after the initiation of temsirolimus, and then got better as the withdrawal of the drug. This clinical course indicated the possible relation of temsirolimus to the exacerbation of pre-existing ILD, although more than 40 days after discontinuation of the drug was not typical as the onset of temsirolimus-induced ILD [5]. As for the other factors than temsirolimus that could induce acute exacerbation of ILD, firstly, no infectious agents were revealed in the patient's blood and sputum cultures on his second admission. Although sputum and blood cultures turned to positive for *Escherichia coli* ten days after the admission and alveolar pneumonia with gram-negative bacteria was found in autopsy lung, these findings could be the results from secondary pneumonia due to *Escherichia coli*, the onset of which was after the patient's second admission. Additionally, CMV-pp65 antigen and β -D glucan levels were within normal limits, suggesting that *Pneumocystis jirovecii*

and CMV pneumonia were less likely to occur. Next, any invasive examinations to the lung such as lung biopsy and bronchoalveolar lavage were not performed in the patient between his first and second admission, considering the risk of exacerbation of ILD triggered by them. Also, the patient had not taken corticosteroid for his pre-existing ILD, because it had been stable before administration of temsirolimus. Finally, even though there were no specific factors that induced acute exacerbation of ILD, idiopathic acute exacerbation remains a possible cause of acute exacerbation of underlying ILD [6]. However, in short, it is feasible that temsirolimus contributed to the exacerbation of ILD from the perspective of its strong link to the patient's clinical course.

Temsirolimus can cause several adverse effects, including anemia, hyperglycemia, hypophosphatemia, and stomatitis. Another representative adverse effect caused by temsirolimus is ILD [5]. Temsirolimus has been reported to result in ILD in 15–30% of

patients who receive the drug. This incidence is higher than that of tyrosine kinase inhibitors (5%), which are the medications most likely to induce ILD [7]. According to the past report, temsirolimus-induced ILD frequently occurs from 1 to 6 months after initiation of the drug [8]. The prognosis of patients with ILD caused by temsirolimus is relatively favorable as they usually recover after the medication is withdrawn. In the present case, though the patient had underlying ILD, he did not have any respiratory symptoms and abnormalities in pulmonary function test before initiation of temsirolimus. Hence, temsirolimus was decided to be administered carefully. However, five weeks after initiation of temsirolimus, the patient developed dyspnea. This onset of dyspnea was consistent with that in the previous report as described above [8]. However, it is worthy of notice that the exacerbation of ILD could progress subclinically for over a month even after the discontinuation of temsirolimus, and then it became clinically significant. To our knowledge, there has been no report of ILD that developed more than a month after discontinuation of temsirolimus.

There are two main mechanisms proposed for the pathophysiology of ILD caused by mTOR kinase inhibitors such as temsirolimus. The first hypothesis reflects a direct toxic effect of temsirolimus in the lung [9–11]. A mouse model showed that temsirolimus treatment resulted in alveolar epithelial and endothelial injury, causing pulmonary inflammation. Second, an immunological origin is suggested [9,12]. This hypothesis is supported by the fact that alveolitis often develops in patients treated with sirolimus, an mTOR kinase inhibitor, and bronchoalveolar lavage fluid shows an increase in lymphocytes, especially CD41 cells, and sometimes eosinophils. Some immunological mechanisms are considered to give rise to these findings. For example, mTOR kinase inhibitors might expose cryptic antigens that are normally shielded by the immune system. A delayed hypersensitivity reaction has also been proposed. mTOR kinase inhibitors have a high affinity for plasma proteins and can, therefore, form an mTOR kinase inhibitor-protein complex that acts as a hapten, inducing an immunologic reaction mediated by T-cells [13]. These hypothesized pathways in temsirolimus-induced ILD could be influenced by various host factors, such as genetics, age, existing lung disease, and interactions with other drugs [14]. In the present case, an immunologic interaction is considered to be a more feasible as a mechanism underlying the development of ILD rather than a direct toxic effect of the drug, because the patient's ILD was exacerbated after a period of stability.

In the present case, it was possible that the underlying ILD had already worsened prior to the patient's first admission. A chest X-ray and HRCT scan showed only a little expansion of GGO on bilateral basal lungs on the first admission despite his dyspnea. However, biochemical and physical examinations showed some evidence of progressive ILD, e.g., an increased AaDO₂ and lower diffusion capacity than usual. Because an acute exacerbation of ILD, which is represented by IPF, is defined by increasing dyspnea and the appearance or extension of GGO or consolidation [15], it was difficult to diagnose acute exacerbation of ILD without significant change in HRCT findings at that time. On the other hand, some researchers have reported that early-stage temsirolimus-induced ILD often causes few changes on chest CT [16]. Therefore, it is important for clinicians to monitor these patients carefully and pay attention to changes in AaDO₂ and/or DLCO relative to baseline, as well as imaging findings on HRCT. These can help to detect early exacerbation of ILD in patients treated with temsirolimus who develop dyspnea.

The histopathological findings of the lungs at autopsy in the present case showed chronic interstitial changes and a new onset of DAD. Chronic interstitial changes were composed of architectural distortion and patchy fibrotic involvement of the lung parenchyma

as well as honeycombing, meeting the criteria for probable UIP pattern [17]. Integrating these pathologic findings with the radiological and clinical features, the diagnosis of pre-existing ILD in the current case is confirmed as IPF, in which the risk of acute exacerbation was reported to be higher than the other idiopathic interstitial pneumonias [18,19]. DAD is a pathological state of the lung seen when type I pneumocytes and microvascular endothelial cells are injured. DAD is pathologically divided into an exudative phase, a hyaline membrane production phase, and an organizing phase [17]. It is generally detected in acute exacerbation of IPF, acute respiratory distress syndrome, viral pneumonia, and acute interstitial pneumonia [20]. In our case, organized exudate and macrophages were detected in the airspace, which was consistent with the pathological findings of the organized stage of DAD and distinguished the findings from chronic interstitial change. Therefore, the pathological findings reflected relatively new lung injury, indicating overlapping acute exacerbation with underlying chronic ILD.

In conclusion, we present a rare case of delayed exacerbation of ILD after discontinuation of temsirolimus. Physicians should be aware of the possibility of temsirolimus-induced ILD not only while the medication is administered, but also even after it is discontinued. Since it is sometimes difficult to detect early exacerbation of temsirolimus-induced ILD without positive imaging results, it is important for clinicians to carefully interview the patient and to recognize the value of physiological tests, such as respiratory function tests and blood gas analysis.

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The authors state that they have no conflicts of interest.

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