Interstial Lung Disease Associated with Agaricus blazei Murill in a Patient with Pancreatic Ductal Adenocarcinoma Receiving Gemcitabine-Based Therapy

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Keywords
Agaricus blazei Murill · Dietary supplementation · Interstitial lung disease · Pancreatic ductal adenocarcinoma · Gemcitabine

Abstract
A male in his sixties with locally advanced pancreatic ductal adenocarcinoma (PDAC) was administered gemcitabine plus nab-paclitaxel therapy. Computed tomography (CT) scans after five courses revealed nonspecific interstitial pneumonitis in addition to PDAC aggravation. No evidence of respiratory infection was detected, and his condition was stable and asymptomatic at diagnosis. Sputum test and interferon-gamma release assay revealed no evidence of tuberculosis. Through careful history taking, the patient was found to be taking dietary supplementation with Agaricus blazei Murill extract for approximately 1 month. Drug-induced lymphocyte stimulation tests for gemcitabine and nab-paclitaxel were negative, whereas those for Agaricus blazei Murill were positive. CT scans after withdrawal showed improved pneumonitis. These findings suggest a possibility that the dietary supplementation may lead to drug-induced interstitial lung disease (ILD). This patient indicates that pertinent diagnostic interviews are essential for the identification of drug-induced ILD.
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a 5-year overall survival rate of <10% [1, 2]. Patients with PDAC are commonly treated with gemcitabine-based chemotherapy [3, 4]. Interstitial lung disease (ILD) is a pivotal complication of gemcitabine-based chemotherapy, with the crude incidence rate of 1.7% in a survey using a Japanese nationwide database [5]. Thus, gemcitabine-induced ILD should be considered as a diagnostic workup in patients with PDAC presenting with respiratory symptoms.

In the clinical setting, cancer patients tend to use complementary and alternative medicine to achieve the anticancer effects. In addition, approximately 60% of cancer patients are reported to use complementary and alternative medicine without consulting their attending physicians [6]. Therefore, attending physicians should focus on the medication history of dietary supplementation. Herein, we describe a patient with PDAC who showed drug-induced ILD associated with *Agaricus blazei* Murill when he was treated with gemcitabine-based therapy.

Case Report

A male in his sixties complaining of abdominal pain was diagnosed with a 30-mm locally advanced pancreatic cancer, located in the body through contrast-enhanced computed tomography (CT) (Fig. 1a, white arrow). Endoscopic ultrasound-guided fine needle aspiration was performed (Fig. 1b), and the specimen revealed PDAC (Fig. 1c). Thus, he was administered gemcitabine plus nab-paclitaxel. CT scans after five courses of regimens showed that the treatment response was classified as the progressive disease. Although the previous CT scan, 1 month before presentation, showed no evidence of pneumonitis (Fig. 2a), current CT scans revealed nonspecific interstitial pneumonitis in the right upper lobe of the lung (Fig. 2b). No evidence of respiratory infection was detected, and his condition was stable and asymptomatic at diagnosis. Sputum test and interferon-gamma release assay revealed no evidence of tuberculosis. The serum level of KL-6 was 476 U/mL. The serum level of surfactant protein D was 100.3 ng/mL and that of surfactant protein A was 71.1 ng/mL. The various kinds of antibody tests such as the antinuclear antibody were negative (Table 1). Through careful history taking, it was found that he had been taking dietary supplementation with *Agaricus blazei* Murill extract for approximately 1 month. Subsequently, the drug-induced lymphocyte stimulation test (DLST) was performed with respect to gemcitabine, nab-paclitaxel, and *Agaricus blazei* Murill extract. DLST results for gemcitabine and nab-paclitaxel were negative. In contrast, the DLST for *Agaricus blazei* Murill extract yielded a positive result, and the stimulation index was 15.8 (reference value, <1.6). Dietary supplementation with *Agaricus blazei* Murill extract was discontinued. CT scans after 2 and 6 weeks of withdrawal showed that the nonspecific interstitial pneumonitis had improved (Fig. 2c, d). After the pneumonitis improved, S-1 (100 mg/day on weekdays) and concurrent radiotherapy (50 Gy in 25 fractions) were administered.

Discussion

PDAC is a life-threatening disease characterized by difficulty in early detection and the rapid progression [2]. Its 5-year overall survival rate is <10% [1]. Patients with PDAC are often diagnosed at a locally advanced or metastatic stage because of a lack of methods for early detection. Gemcitabine monotherapy has been recognized as a reference treatment for PDAC [3]. Multi-agent chemotherapeutics such as gemcitabine plus nab-paclitaxel have
Fig. 1. The diagnosis of PDAC. Contrast-enhanced CT revealed a 30-mm locally advanced pancreatic cancer located in the body (a: white arrow). b Endoscopic ultrasound-guided fine needle aspiration was performed. c Histology of the specimen revealed PDAC (hematoxylin and eosin staining; ×400). CT, computed tomography.

Fig. 2. CT findings of interstitial pneumonitis. a CT scans prior to the intake of dietary supplementation with Agaricus blazei Murill showed no evidence of interstitial pneumonitis. b CT scans revealed a nonspecific interstitial pneumonitis in the right upper lobe of the lung. c, d CT scans after 2 and 6 weeks of Agaricus blazei Murill withdrawal showed that the nonspecific interstitial pneumonitis has improved. CT, computed tomography.
recently been developed and widely used [4]. The efficacy and safety of gemcitabine plus nab-paclitaxel have been validated in Japanese populations, with a median overall survival of 13.5 months [7]. In this patient, gemcitabine plus nab-paclitaxel therapy was administered. In contrast, ILD is known to be the major adverse consequence of gemcitabine [5, 8–10]. A previous study, using the nationwide administrative database in Japan, revealed that the crude incidence rate of gemcitabine-associated ILD was 1.7% [5]. In addition, the study reported that the median onset time of the ILD was 65 days after gemcitabine initiation. In this case, the pulmonary injury occurred 5 months after gemcitabine initiation, and the DLST for gemcitabine was negative. These findings suggest that gemcitabine may not be involved in the onset of the pulmonary injury.

Agaricus blazei Murill is a mushroom with diverse biological actions and has been employed as a dietary supplement for its immunomodulating and anticancer effects [11]. Previous studies revealed that ergosterol, an Agaricus blazei Murill component, inhibits tumor neoangiogenesis and induces apoptosis [12, 13]. Agaricus blazei Murill is a popular dietary supplement in Japanese cancer patients; however, few well-designed clinical trials have revealed its efficacy in cancer patients [14]. In addition, a previous study reported that Agaricus blazei Murill may cause liver dysfunction [15]. This patient indicates that dietary supplementation with Agaricus blazei Murill may possibly lead to drug-induced ILD.

Table 1. Laboratory findings

| White blood cells | 4,890 | /µL | KL-6 | 476 | U/mL |
|-------------------|-------|-----|------|-----|------|
| Neut              | 63.2  | %   | SP-D | 100.3 | ng/mL |
| Lymph             | 27.8  | %   | SP-A | 71.1 | ng/mL |
| Mono              | 6.1   | %   | T-SPOT/TB |      |      |
| Eos               | 2.5   | %   | ANA  |      |      |
| Baso              | 0.4   | %   | MPO-ANCA |      |      |
| Red blood cells   | 283 x 10⁴/µL | PR3-ANCA |      |      |
| Hemoglobin        | 8.8   | g/dL | Anti-ARS antibody |      |      |
| Hematocrit        | 27.6  | %   | Anti-Sm antibody |      |      |
| Platelets         | 11.1 x 10⁴/µL | Anti-U1-RNP antibody |      |      |
| Total protein     | 6.6   | g/dL | Anti-SS-A/Ro antibody |      |      |
| Albumin           | 3.7   | g/dL | Anti-SS-B/La antibody |      |      |
| BUN               | 12    | mg/dL | Anti-Scl-70 antibody |      |      |
| Creatinine        | 0.86  | mg/dL | Anti-Jo-1 antibody |      |      |
| Total bilirubin   | 0.5   | mg/dL | Anti-MDA5 antibody |      |      |
| AST               | 20    | IU/L |      |      |      |
| ALT               | 18    | IU/L |      |      |      |
| ALP               | 270   | IU/L |      |      |      |
| γ-GTP             | 35    | IU/L |      |      |      |
| LDH               | 206   | IU/L |      |      |      |

BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; KL-6, Krebs von den lungen-6; SP-D, surfactant protein-D; SP-A: surfactant protein-A; ANA, antinuclear antibody; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibody; ARS, aminoacyl tRNA synthetase; RNP, ribonucleoprotein; SS, Sjögren’s syndrome; MDA5, melanoma differentiation-associated gene 5.
Making a definitive diagnosis of drug-induced ILD in cancer patients could be difficult because they are generally treated with various anticancer agents [16]. DLST is an in vitro test system that can demonstrate the existence of drug-sensitized lymphocytes using suspected antigens and blood samples. In this case, positive DLST results for *Agaricus blazei* Murill, in addition to negative results for gemcitabine and nab-paclitaxel, suggest that ILD may occur because of *Agaricus blazei* Murill. A previous nationwide survey in Japan showed that approximately 60% of cancer patients used complementary and alternative medicine without consulting their attending physicians. In this case, the attending physician did not receive a consultation with the patients, and the pertinent diagnostic interview was essential in identifying the causative agent. This case shows that the diagnosis of drug-induced ILD in cancer patients requires careful history taking with regard to medications including dietary supplementation.

In conclusion, we encountered a case of drug-induced ILD associated with *Agaricus blazei* Murill when he was treated with gemcitabine-based therapy for PDAC. Therefore, this patient indicates that the pertinent diagnostic interview can be useful for the identification of drug-induced ILD.

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**Statement of Ethics**

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This study was reviewed and approved by the Ethics Committee of Fukuchiyama City Hospital, approval number 3-52.

**Conflict of Interest Statement**

The authors have no conflicts of interest.

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**Author Contributions**

Naoto Iwai, Takashi Okuda, Ryo Sawada, Tomoya Ohara, Chie Hattori, Masashi Taniguchi, Hiroaki Sakai, Kohei Oka, Tasuku Hara, Toshifumi Tsuji, Toshiyuki Komaki, Junichi Sakagami, and Keizo Kagawa conducted the diagnosis and treatment and contributed to the study design. Naoto Iwai, Junichi Sakagami, Osamu Dohi, and Hiroaki Yasuda drafted the manuscript. Keizo Kagawa and Yoshito Itoh reviewed the draft. All authors approved the final manuscript.
Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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