Case Reports in Gastroenterology

Case Rep Gastroenterol 2022;16:229–234
DOI: 10.1159/000522639
Received: December 28, 2021
Accepted: February 11, 2022
Published online: March 31, 2022

Single Case

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

Naoto Iwai[a, b] Takashi Okuda[a] Ryo Sawada[c] Tomoya Ohara[b]
Chie Hattori[a] Masashi Taniguchi[a] Hiroaki Sakai[a] Kohei Oka[a]
Tasuku Hara[a] Toshifumi Tsuji[a] Toshiyuki Komaki[a] Junichi Sakagami[a, b]
Keizo Kagawa[a, b] Osamu Dohi[b] Hiroaki Yasuda[b] Yoshito Itoh[b]

[a]Department of Gastroenterology and Hepatology, Fukuchiyama City Hospital, Fukuchiyama-city, Kyoto, Japan; [b]Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; [c]Department of Respiratory Medicine, Fukuchiyama City Hospital, Fukuchiyama-city, Kyoto, Japan

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.

Correspondence to:
Naoto Iwai, na-iwai@koto.kpu-m.ac.jp

Case Rep Gastroenterol 2022;16:229–234
DOI: 10.1159/000522639

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

Case Rep Gastroenterol 2022;16:229–234
DOI: 10.1159/000522639

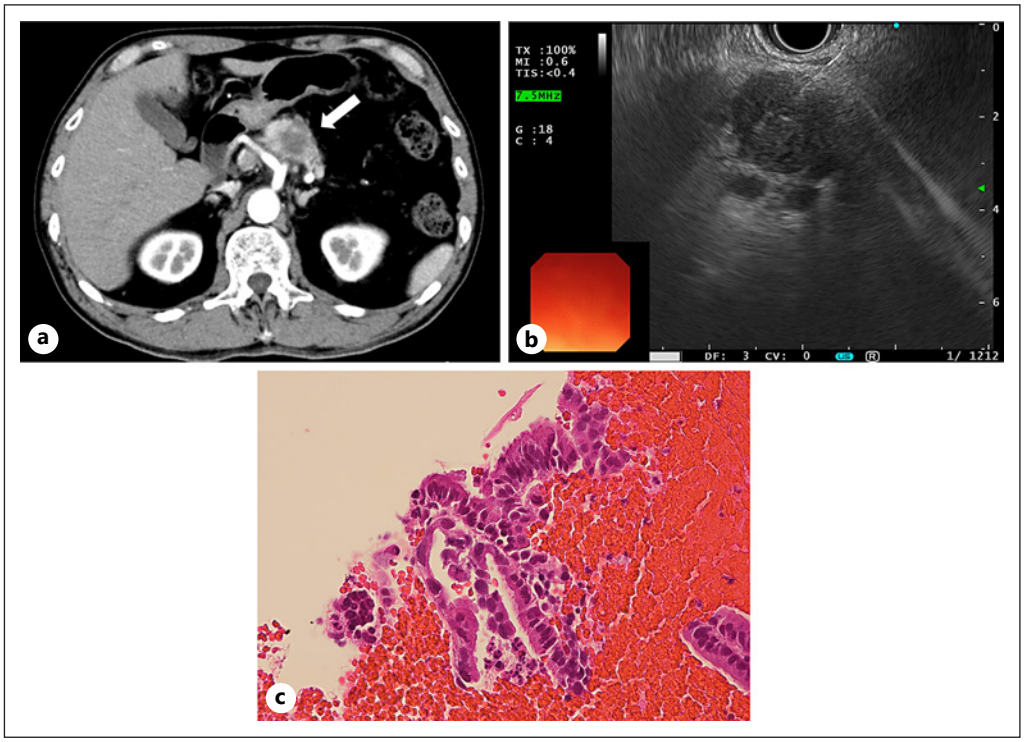

Fig. 1. The diagnosis of PDAC. Contrast-enhanced CT revealed a 30-mm locally advanced pancreatic cancer located in the body (**a**: white arrow). **b** Endoscopic ultrasound-guided fine needle aspiration was performed. **c** Histology of the specimen revealed PDAC (hematoxylin and eosin staining; ×400). CT, computed tomography.

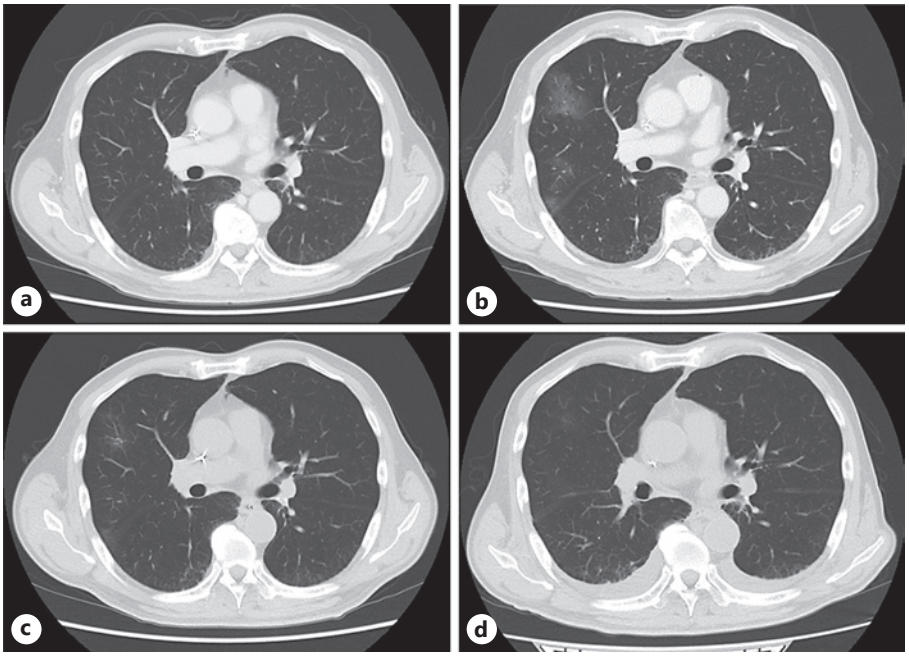

Fig. 2. CT findings of interstitial pneumonitis. **a** CT scans prior to the intake of dietary supplementation with *Agaricus blazei* Murill showed no evidence of interstitial pneumonitis. **b** CT scans revealed a nonspecific interstitial pneumonitis in the right upper lobe of the lung. **c**, **d** CT scans after 2 and 6 weeks of *Agaricus blazei* Murill withdrawal showed that the nonspecific interstitial pneumonitis has improved. CT, computed tomography.

Case Rep Gastroenterol 2022;16:229–234
DOI: 10.1159/000522639

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	$\times 10^4$/μL	PR3-ANCA	(−)	
Hemoglobin	8.8	g/dL	Anti-ARS antibody	(−)	
Hematocrit	27.6	%	Anti-Sm antibody	(−)	
Platelets	11.1	$\times 10^4$/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.

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.

Case Rep Gastroenterol 2022;16:229–234
DOI: 10.1159/000522639

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.

Acknowledgments

The authors thank all the members of the Department of Gastroenterology and Hepatology, Fukuchiyama City Hospital, and all the members of the Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine. We would like to thank Editage (www.editage.jp) for the English language editing.

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.

Funding Sources

There were no funding sources.

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.

References

1 Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016 Nov 28;22(44):9694–705.
2 Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016 Jul 2;388(10039):73–85.
3 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997 Jun;15(6):2403–13.
4 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691–703.
5 Hamada T, Yasunaga H, Nakai Y, Isayama H, Matsui H, Fushimi K, et al. Interstitial lung disease associated with gemcitabine: a Japanese Retrospective Cohort Study. Respirology. 2016 Feb;21(2):338–43.
6 Hyodo I, Amano N, Eguchi K, Narabayashi M, Imanishi J, Hirai M, et al. Nationwide survey on complementary and alternative medicine in cancer patients in Japan. J Clin Oncol. 2005 Apr 20;23(12):2645–54.
7 Ueno H, Ikeda M, Ueno M, Mizuno N, Ioka T, Omuro Y, et al. Phase I/II Study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2016 Mar;77(3):595–603.
8 Gupta N, Ahmed I, Steinberg H, Patel D, Nissel-Horowitz S, Mehrotra B. Gemcitabine-induced pulmonary toxicity: case report and review of the literature. Am J Clin Oncol. 2002 Feb;25(1):96–100.
9 Belknap SM, Kuzel TM, Yarnold PR, Slimack N, Lyons EA, Raisch DW, et al. Clinical features and correlates of gemcitabine-associated lung injury: findings from the RADAR project. Cancer. 2006 May 1;106(9):2051–7.
10 Tamiya A, Endo M, Shukuya T, Igawa S, Tsuya A, Nakamura Y, et al. Features of gemcitabine-related severe pulmonary toxicity: patients with pancreatic or biliary tract cancer. Pancreas. 2009 Oct;38(7):838–40.
11 Hetland G, Tangen JM, Mahmood F, Mirlashari MR, Nissen-Meyer LSH, Nentwich I, et al. Antitumor, anti-inflammatory and antiallergic effects of Agaricus blazei mushroom extract and the related medicinal Basidiomycetes Mushrooms, Hericium erinaceus and Grifola frondosa: a review of preclinical and Clinical Studies. Nutrients. 2020 May 8;12(5):1339.
12 Kimura Y, Kido T, Takaku T, Sumiyoshi M, Baba K. Isolation of an anti-angiogenic substance from Agaricus blazei Murill: its antitumor and antimetastatic actions. Cancer Sci. 2004 Sep;95(9):758–64.
13 Shimizu T, Kawai J, Ouchi K, Kikuchi H, Osima Y, Hidemi R. Agarol, an ergosterol derivative from Agaricus blazei, induces caspase-independent apoptosis in human cancer cells. Int J Oncol. 2016 Apr;48(4):1670–8.
14 Yoshimura K, Kamoto T, Ogawa O, Matsui S, Tsuchiya N, Tada H, et al. Medical mushrooms used for biochemical failure after radical treatment for prostate cancer: an Open-Label Study. Int J Urol. 2010 Jun;17(6):548–54.
15 Mukai H, Watanabe T, Ando M, Katsumata N. An alternative medicine, Agaricus blazei, may have induced severe hepatic dysfunction in cancer patients. Jpn J Clin Oncol. 2006 Dec;36(12):808–10.
16 Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012 May 31;13(1):39.