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Respiratory Medicine Case Reports

Drug-related pneumonitis with radiographic hypersensitivity pneumonitis pattern: Three case series

Yukihiro Nakamura [a], Takayuki Takimoto [a,*], Takehiko Kobayashi [a], Kazunobu Tachibana [a], Takahiko Kasai [b], Masanobu Akira [c], Toru Arai [d], Yoshikazu Inoue [d]

[a] Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-Cho, Kita-Ku, Sakai City, Osaka, 591-8555, Japan
[b] Department of Pathology, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-Cho, Kita-Ku, Sakai City, Osaka, 591-8555, Japan
[c] Department of Radiology, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-Cho, Kita-Ku, Sakai City, Osaka, 591-8555, Japan
[d] Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-Cho, Kita-Ku, Sakai City, Osaka, 591-8555, Japan

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ABSTRACT

Novel therapies have recently emerged for various diseases, and the management of drug-related pneumonitis (DRP) has become increasingly important. In particular, the hypersensitivity pneumonitis (HP) pattern of DRP has been increasingly recognized due to development of new therapeutic strategies, such as immunotherapy. However, literature describing detailed clinical cases is still lacking.

Herein, we report three cases of DRP with typical HP radiographic pattern. These patients were treated with different drugs, namely nano albumin-bound (nab)-paclitaxel, everolimus, or nivolumab, but had common clinical features, including a good prognosis.

1. Introduction

In the clinical setting, we frequently encounter drug-related pneumonitis (DRP), which is reported at rates of 2.6–5% in interstitial lung disease (ILD) cohorts [1] and the prevalence is 19.4 per 100,000 per year [2]. Computed tomography (CT) patterns of DRP are classified based on the American Thoracic Society (ATS)/European Respiratory Society international multidisciplinary classification of interstitial pneumonia (IP), as acute interstitial pneumonia/diffuse alveolar damage (DAD) pattern, hypersensitivity pneumonitis (HP) pattern, cryptogenic organizing pneumonia pattern, nonspecific interstitial pneumonia (NSIP) pattern, or others [3,4]. These categories are useful when considering differential diagnosis, response to treatment, and prognosis.

DRP is relatively rare, and an HP pattern is even less frequent, although HP patterns are established in radiologically categorized patterns of DRP. Moreover, it is important to discriminate such cases from other diseases, including acute HP (non-fibrotic HP) or infectious diseases, such as pneumocystis pneumonia and tuberculosis. To date, there has been little research and insufficient evidence regarding the frequency, prognosis, and mechanism of DRP with HP pattern.

The aim of this study was to examine DRP with a radiographic HP pattern through case reports. We queried our hospital's electronic medical record to retrospectively identify all adult patients with "drug-related pneumonitis", between October 2013 and October 2019. Of the 133 patients with "definite or suspected drug related pneumonitis", three patients (2.3%) were classified as having an HP pattern by a radiologist, according to the consensus criterion for the diagnosis [3,4]: small, poorly defined centrilobular nodules with or without widespread areas of ground-glass opacity (GGO).

DRP was diagnosed based on the correct identification of the drug, exclusion of other causes, and earlier observations with the drug, based on the literature. To validate DRP, we used the Naranjo Adverse Drug Reaction Probability Scale (Naranjo Scale) [5], which is a helpful assessment tool for causality in adverse drug events.

To validate the HP radiographic pattern, we also referred to an official ATS/Japanese Respiratory Society (JRS)/Asociaci'on Latinoamericana del T'orax (ALAT) clinical practice guideline for diagnosis of HP in adults, recently published in 2020 [6]. The revised guidelines showed a diagnostic algorithm and confidence levels for the diagnosis of HP. Based on the high-resolution computed tomography (HRCT) scan

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findings and histopathological features, patients were categorized has having three patterns (i.e., typical HP, compatible with HP, and indeterminate for HP) with diagnostic confidence in multidisciplinary discussion. In all three presented cases, the HP patterns were radiographically defined as a typical non-fibrotic HP pattern.

We herein report three cases of DRP with HP radiographic pattern by presenting their background characteristics and clinical courses.

2. Case reports

2.1. Case 1: nano albumin-bound–paclitaxel

A 77-year-old man with a smoking history (96 pack-years) was diagnosed with T4aN1M1 liver and peritoneal metastasis, stage IVB advanced gastric cancer (Japanese Classification of Gastric Carcinoma, 15th Edition). He had no recent history of exposure to dust. He was prescribed acetaminophen and acetaminophen, started 3 months before admission, and the newest oral drug was an antipyretic and analgesic drug for fever, postoperative pain, and chemotherapy-related lower limb pain. The patient characteristics are shown in Table 1. He was treated with capecitabine, oxaliplatin, and trastuzumab as first-line chemotherapy. After four cycles, prolonged nausea and fatigue developed. Abdominal CT revealed progression of gastric cancer and gastric dilation with gastric outlet obstruction. He underwent laparoscopic gastrojejunostomy and was discharged 2 weeks after surgery.

Nano albumin-bound (nab)-paclitaxel and ramucirumab were induced as second-line chemotherapy. On day 8 of the first cycle, nab-paclitaxel administration was interrupted because of neutropenia. On day 18, he had a high-grade fever (38 °C) and malaise and was started on levofloxacin. On day 22, the high-grade fever persisted, and chest CT showed an abnormal shadow in the lung fields. He was then referred to our hospital.

On admission, the findings of his physical examination were unremarkable. A peripheral blood test showed elevated levels of C-reactive protein (CRP) (8.44 mg/dL). Krebs von den Lungen (KL)-6 (342 U/mL) and β-D glucan (14.4 pg/mL) were within the normal limits (Table 2). Arterial blood analysis showed that the arterial partial pressure of oxygen (PaO_2) was 86.4 Torr in ambient air. Chest CT showed bilateral diffuse GGO and ill-defined centrilobular nodules (Fig. 1A and B), suggesting a non-fibrotic typical HP pattern. Bronchoscopy for bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed. BAL fluid analysis showed a total cell count of 1.07×10^6 and an increase in lymphocytes (43.8%) with a CD 4/8 ratio of 4.2% and eosinophils (16.6%). Culture of BAL fluid yielded negative results for bacteria, fungi, mycobacteria, and pneumocystis spp. There was no

Table 1
Patient characteristics.

Case number	1	2	3
Sexuality	Male	Female	Male
Age (years old)	77	51	63
Cancer type	Gastric cancer	Breast cancer	Lung cancer
Suspected drug	Nab-paclitaxel	Everolimus	Nivolumab
Time to detection on CT after treatment (days)	22	198	5
Symptoms	Fever	Fever, dyspnea	Fever
CTCAE grade for pneumonia	2	3	2
Past medical history	Macular degeneration	Diabetes	Insomnia Herniated disk of lumbar vertebrae Ureter stone
Family history	None	None	Pancreatic cancer Colon cancer Gastric cancer
Smoking (pack-years)	96	0	31.5
Job	Architect	NA	Transportation
Allergy	None	Lobsters	Tomato Chicken Fish
Suspected findings of CVD	None	None	None
Home	Wooden building 50 years old	NA	NA
Exposure to bird	Down quilt use	None	None
Exposure to dust	None	None	None
Regular medicine	Acetaminophen Lansoprazole Magnesium oxide Sodium ferrous citrate	Sitagliptin	Acetaminophen, Estazolam Mefenamic acid Mosapride Naproxen Sodium alginate Trazodone Triazola, Vonoprazan

CTCAE: Common terminology criteria for adverse events; CVD: collagen vascular diseases; NA: not available.

Table 2
Laboratory data of case 1, 2, 3 at the diagnosis of drug-related pneumonitis.

		case1	case2	case3
Hematology				
WBC	/uL	2910	4000	4000
Neu	%	54.5	82.4	55.7
Lym	%	25	8.3	12.5
Mon	%	12.2	5.5	8.2
Eos	%	8	3.3	23.4
RBC	$\times 10^4$/uL	279	497	285
Hb	g/dL	8.9	11.5	8.9
Ht	%	27.3	37.6	25.6
Plt	$\times 10^4$/uL	12.3	26.6	5
Biochemistry				
AST	U/L	19	13	45
ALT	U/L	14	5	57
LDH	IU/L	198	537	189
BUN	mg/dL	19.7	13.3	17.6
Cre	mg/dL	0.9	0.73	0.9
CPK	IU/L	29	91	10
CRP	mg/dL	8.44	11.58	12.97
KL-6	U/mL	342	398	222
SP-D	ng/mL	177.7	261.9	72.6
SP-A	ng/mL	98.8	112.1	72.2
β-D glucan	pg/mL	14.4	9.5	15.6
CMV C7-HRP	/50000WBC	0	0	0
Anti-*T.asahii* antibody	CAI	0	NA	NA
Parakeet IgG	mgA/L	2.21	NA	NA
Parrot IgG	mgA/L	3.93	NA	NA
Pigeon IgG	mgA/L	4.53	NA	NA
Mycobacterium tuberculosis specific interferon-γ release assay		(−)	NA	(−)
Bronchoalveolar lavage		left B4	NA	NA
cell count	$\times 10^5$/mL	10.71		
Mac	%	38.7		
Lym	%	43.8		
Neu	%	0.9		
Eos	%	16.6		
CD4/8		4.2		

Mycobacterium tuberculosis-specific interferon-γ release assay was measured by TSPOT.TB test for case1 and QFT TB test for case3.

KL-6: Krebs von den Lungen - 6.

SP-D: surfactant protein D.

SP-A: surfactant protein A.

Anti-*T.asahii* antibody: Anti *Trichosporon asahii* antibody.

CAI: corrected absorbance index.

CMV C7-HRP: cytomegalovirus antigenaemia C7-horse radish peroxidase.

QFT TB test: quantiferon tuberculosis test.

T-SPOT.TB test: T-SPOT tuberculosis test.
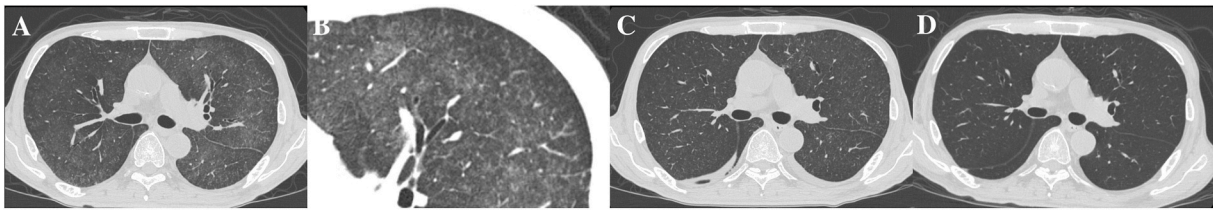
NA: not available.

Fig. 1. High resolution computed tomography (HRCT) in case 1 showed diffuse ground-glass opacity (GGO) and centrilobular nodules at the initial visit (A), (B). (B) Enlarged image of the left upper lobe. The patient improved after steroid pulse treatment (C). Chest computed tomography (CT) after the second steroid treatment (D) showed further improvement of the shadow.

evidence of suspected infectious diseases. TBLB showed fibro-cellular alveolitis and accumulation of histiocytes without granulomas (Fig. 2). He was negative for the *anti-Trichosporon asahii* (*T. asahii*) antibody and parakeet IgG (2.21 mg A/L), parrot IgG (3.93 mg A/L), and pigeon IgG (4.53 mg A/L) were within normal limits. Serum IgG against bird antigens was measured with ImmunoCAP® system (Thermo Fisher Scientific, Uppsala, Sweden).

He was diagnosed as DRP with radiographic HP pattern, probably due to nab-paclitaxel, after excluding other possible ILD caused by infection (pneumocystis spp. or mycobacterium spp.), connective tissue disease, and hypersensitivity pneumonitis (summer type or bird fancier's lung). His DRP was categorized as grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Chemotherapy was discontinued, and his condition was carefully monitored. He had no respiratory symptoms and oxygen desaturation during the 6-min walk test; however, high fever did not improve. On day 33 of the admission, steroid pulse therapy with methylprednisolone (500 mg/day) was started for 3 days. His fever and abnormal shadow improved, without maintenance of steroid therapy (Fig. 1C). He was discharged 8 days after initiation of steroid therapy. Acetaminophen was discontinued after symptom relief. One month after discharge, nivolumab as the third-line therapy was started, and he was diagnosed with nivolumab-related renal failure at the previous hospital. He subsequently underwent temporary hemodialysis and was treated with prednisolone 50 mg per day. Thereafter, his chest CT showed complete resolution of the shadow (Fig. 1D). For a diagnosis of DRP, scores according to the Naranjo Scale were five points (probable confidence). If we judge as exposure to nab-paclitaxel, his ILD could be diagnosed as HP with high confidence (80–89% confidence), according to the ATS/JRS/ALAT HP guideline [6].

2.2. Case 2: everolimus

A 51-year-old woman, who had never smoked, was diagnosed with advanced breast cancer (liver and bone metastasis), and started on exemestane and everolimus as the seventh-line chemotherapy. She had no recent history of exposure to dust or mold at home. Her only regular medicine was sitagliptin. Other new drugs were not prescribed. Patient characteristics are shown in Table 1. She presented to the previous hospital with a high-grade fever (39 °C) and gradually worsening dyspnea, 7 months after the chemotherapy had started. Chest CT showed diffuse GGO and centrilobular nodules (Fig. 3 A), suggesting a typical non-fibrotic HP pattern. She was referred to our hospital for pneumonia during breast cancer chemotherapy.

Laboratory data showed elevated levels of CRP (11.58 mg/dl), KL-6 (398 U/mL), and surfactant protein D (SP-D) (261.9 ng/mL) in the blood and there was no data to actively suggest infectious disease (Table 2). Arterial blood analysis showed that the PaO_2 was 107 Torr, at 2 L/min nasal cannula. BAL performed at the previous hospital showed no specific findings. The details of the BAL fluid were not evaluated in urgent situations. Chest CT revealed a more increased GGO than the previous chest CT (Fig. 3 B). She was diagnosed with DRP, probably due to everolimus, after excluding other possibilities. Pneumonia was categorized as CTCAE grade 3.

Exemestane and everolimus were interrupted and steroid pulse therapy (methylprednisolone 1000 mg/day for 3 days) was started on the day of admission. Steroids were tapered after steroid pulse therapy. Her symptoms, clinical findings, and radiographic findings (Fig. 3C) were remarkably improved. Laboratory examination at the last visit showed decreased levels of CRP (0.11 mg/dL) and SP-D (28.6 ng/mL). She continued treatment for breast cancer, and steroid therapy was tapered at the previous hospital. For a diagnosis of DRP, scores ac-
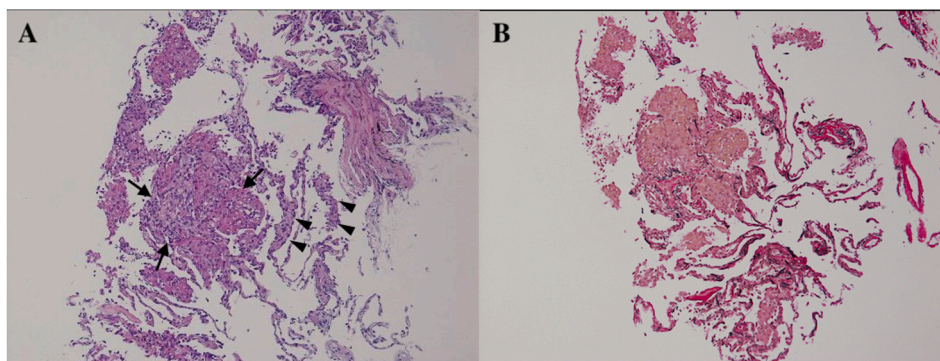

Fig. 2. A transbronchial lung biopsy of case 1 showed fibrocellular alveolitis (arrowheads) and accumulation of histiocytes (arrows). (A. Hematoxylin eosin stain, B. Elastica van Gieson stain, high power field).
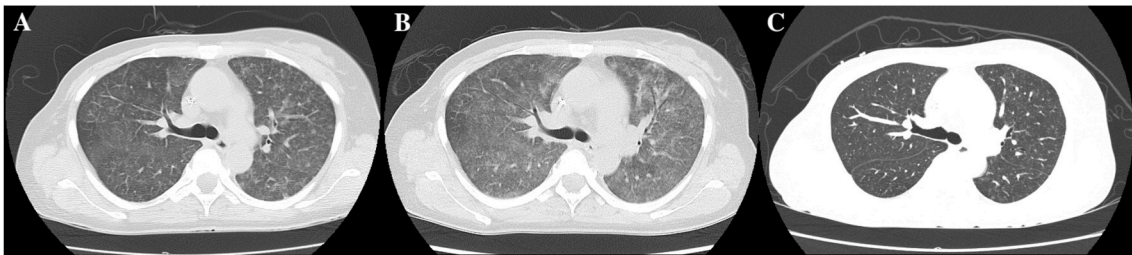
Fig. 3. CT in case 2. Diffuse ground-glass opacity and centrilobular nodules were observed at the initial visit (A), these increased just before steroid treatment (B), and disappeared after steroid treatment (C).

cording to the Naranjo Scale were five points (probable confidence). According to the ATS/JRS/ALAT HP guideline [6], the diagnostic confidence level was moderate for HP (70–79% confidence).

2.3. Case 3: nivolumab

A 64-year-old man with a smoking history (31.5 pack-years) was diagnosed with T4N1M0 stage IIIA squamous cell carcinoma of the right lung (Union for International Cancer Control TNM Classification 7th edition) at our hospital. He had no recent history of exposure to dust or other new drugs. Patient characteristics are shown in Table 1. Neo-adjuvant chemotherapy (cisplatin 70 mg/m^2, day 1 and vinorelbine 25 mg/m^2, day 1, 8) followed by surgery was started. The primary tumor size enlarged from 76 mm to 92 mm after one cycle of chemotherapy. He was diagnosed with progressive disease (PD) and could not undergo surgery. Subsequently, chemoradiotherapy (weekly carboplatin [AUC = 2], Day 1, 8, 15, 22, 29, 36 and paclitaxel [40 mg/m^2], Day 1, 8, 15, 22, 29, 36) and concurrent radiation therapy (66 Gy/33 fractions) were induced. On day 38 after initiation of chemoradiotherapy, metastasis in the left adrenal gland and left renal metastasis were indicated.

Nivolumab 240 mg/body every 2 weeks was started as the third-line therapy. He suddenly developed high-grade fever (39 °C) 8 hours after administration of chemotherapy. He experienced no shortness of breath or oxygen desaturation. Laboratory examinations showed elevated CRP levels (12.97 mg/dL). Serum KL-6 (222 U/mL) levels were within normal limits and there was no data for suspected infection (Table 2). Chest CT revealed bilateral patchy GGO and ill-defined centrilobular nodules (Fig. 4A and B). The CT pattern of this case was typical non-fibrotic HP pattern. At first, levofloxacin was administered until sputum and blood cultures were negative for bacteria, fungi, and mycobacteria. He was diagnosed with DRP, probably due to nivolumab, after excluding other possibilities. His DRP was categorized as CTCAE grade 2.

On day 8 of admission, prednisolone 30 mg/day (0.5 mg/kg) was administered because a high-grade fever persisted. After steroids were started, symptoms, laboratory data, and chest CT findings all improved (Fig. 4C). Fourth-line chemotherapy was not administered. His DRP did

not recur; however, he died of lung cancer at home 4 months after the onset of DRP. For a diagnosis of DRP, scores according to the Naranjo Scale were six points (probable confidence). According to the ATS/JRS/ALAT HP guideline [6], the diagnostic confidence level was moderate for HP (70–79% confidence).

3. Discussion

In this report, we describe three cases of anticancer therapy-related pneumonitis with an HP radiographic pattern. Considering the characteristics and clinical courses of the patients, and after excluding other causes, we diagnosed them as DRP. We searched previous reports in PubMed and referred to the Naranjo Scale to determine which drug was responsible for DRP, and concluded that the suspected drugs were nab-paclitaxel, everolimus, and nivolumab, all of which can induce an immune or allergic reaction. The common features of these three cases included onset with fever, typical HP radiographic pattern, complete resolution by steroid treatment, and no recurrence during the observation period. From the laboratory data, elevated CRP levels and normal KL-6 levels were also observed. Of note, nab-paclitaxel-related pneumonitis has been very rarely reported [7].

HP is related to immune complex-mediated (type 3) and delayed (type 4) hypersensitivity reactions. Chemokines and cytokines, cluster of differentiation (CD) 8 cytotoxic T-cell responses cause tissue reactions, and these chemokines and cytokines play a role in macrophage activation, granuloma formation, and fibrosis [8]. Although the route of administration is different between intravenous and inhalation, the pathological features of hypersensitivity pneumonitis, poorly formed granulomas, and alveolitis may appear.

In case 1, we considered nab-paclitaxel–related pneumonitis, although ramucirumab was administered in combination with nab-paclitaxel. Ramucirumab is an anti-vascular endothelial growth factor 2 receptor antibody and is effective at treating several cancers, similar to nab-paclitaxel. In combination therapy with ramucirumab, DRP has been reported in some studies; however, ramucirumab monotherapy related pneumonitis has rarely been reported, even in large studies, and ramucirumab-related pneumonitis with HP pattern has never been
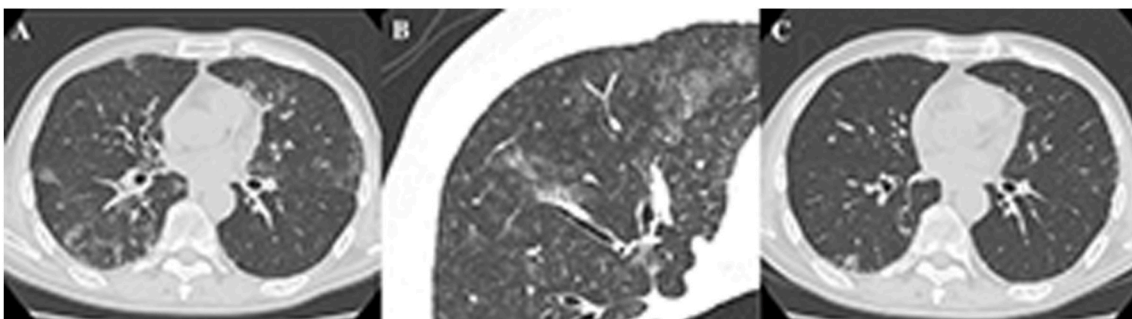

Fig. 4. HRCT in case 3 showed bilateral patchy ground-glass opacity and centrilobular nodules at the onset (A), (B). (B) indicates representative abnormal shadow in the right upper lobe on the same CT of (A). His shadow improved after steroid pulse treatment (C).

reported. Furthermore, DRP with HP pattern induced by first-line chemotherapy (capecitabine, oxaliplatin, and trastuzumab) was not found in the literature. On the other hand, nab-paclitaxel is 130 nm albumin-bound paclitaxel, which is categorized as taxanes. The anti-tumor mechanism involves stabilization of the tubulin polymer and promoting microtubule assembly effectively mitosis, motility, and transport within cancerous cells. Past clinical trials of cancer showed that other taxanes, solvent-based paclitaxel and docetaxel, were reported to induce DRP with a radiographic HP pattern [9–12]. Our previous study also reported centrilobular nodules and GGO on CT in some cases of taxan-related pneumonitis [13]. Nab-paclitaxel-related pneumonitis occurred in 1–4% of cases [14,15]. Kashiwada et al. indicated that radiographic DAD or OP patterns were observed in 9 nab-paclitaxel-related pneumonitis patients [16]. We have found only one case report describing nab-paclitaxel related pneumonitis with an HP pattern [7]. In this report, combination therapy with carboplatin and nab-paclitaxel was induced in a male patient with lung cancer. On day 31 of the first cycle, DRP was detected on chest CT. Chest abnormal shadow was improved without steroids, despite CTCAE grade 3 pneumonia. In two cases, including our case, nab-paclitaxel-related pneumonitis with HP pattern had a good prognosis.

The mechanism underlying nab-paclitaxel-related pneumonitis probably involves allergic, hypersensitivity reaction, and cell-mediated cytotoxic reaction, similar to other taxanes [12]. Nab-paclitaxel is free of cremophor® , a solvent of paclitaxel responsible for side effects, including an acute hypersensitivity reaction, which results in improvement of transferability to tumor and reduction risk of hypersensitivity reaction [17]. If nab-paclitaxel was responsible for HP, we supposed that paclitaxel itself may be important to induce HP-like reactions, because solvents, such as cremophor® , are not contained.

In case 2, everolimus was administered in combination with exemestane. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor. Everolimus-related pneumonitis has relatively higher incidence rates (of 13.5%)compared to other chemotherapeutic drugs, as White et al. indicated [18]. The incidence rate of everolimus-related pneumonitis, with CTCAE grade 3 or 4 was 0–9% [19]; however, OP and NSIP patterns are common and the HP pattern is rare [20]. Several cases with HP pattern have been reported [21,22], although this pattern after exemestane has never been reported. Based on this evidence, we considered everolimus to be the causative agent. Several mechanisms underlying mTOR inhibitor-related pneumonitis have been proposed. Willemsen et al. suggested a dose-related and direct toxic effect. This direct toxic effect leads to epithelial and endothelial injury, resulting in surfactant lipid accumulation. Immunological reactions have also suggested. These reactions are mediated by exposure to cryptic antigens, a delayed-type hypersensitivity reaction, and cytokine production [19, 23].

In case 3, nivolumab administered alone should be responsible for the pneumonitis. Nivolumab or ICI-related HP-pattern pneumonitis has been more frequently reported than the other two drugs presented in cases 1 and 2. ICI-related pneumonitis is observed in about 1–5% of cases in major ICI studies, including combination therapy [24–27]. Nishino et al. also reported an incident rate of 0–10.6% [28]. Delaunay et al. reported that the HP-pattern was 15.6% in all ICI-related pneumonitis cases [29]. Enhancement of the immune system would be the mechanism underlying this phenomenon. Dysregulated effector and regulatory T cells in the pulmonary interstitium are activated, ultimately leading to an inflammatory response [30].

All three cases in this report had a good response to steroids. DRP was different in mortality among their types or suspected drugs [31,32]. Mortality is not available in DRP with an HP-pattern induced by nab-paclitaxel, everolimus, or nivolumab. The mortality of nab-paclitaxel-related pneumonitis is also unknown. The mortality rate of ICI-related pneumonitis, in which HP pattern is frequently observed, was reported as 0.2–2.3% [28]. In DRP, the DAD pattern had higher mortality rates and less favorable response to steroids than other

patterns of DRP [31,32]. The HP pattern probably has a relatively better prognosis than the DAD pattern [31,33,34]. The cause of this better prognosis would be mainly responsible for the mechanism involving inflammation and immune response, and a good response to steroids. Although there is little evidence that the HP pattern has a better prognosis, we speculate that most cases of DRP with HP pattern probably have a favorable prognosis, based on our case series and previous reports [9–11]. On the other hand, HP pattern cases are not always cured, and several reports showed severe clinical course in DRP with HP pattern [12]; therefore, we should carefully treat DRP patients.

We evaluated DRP patients using the Naranjo Scale and the revised HP guideline. The Naranjo Scale has relatively low confidence for adverse drug events [5]. On the other hand, when we applied our 3 cases to the ATS/JRS/ALAT HP guideline, the diagnostic confidence levels of HP were high or moderate [6]; however, the guideline is not intended to evaluate DRP, and thus, the validity of applying this guideline to DRP with HP pattern should be investigated in future studies.

This study has several limitations. First, in cases 1 and 2, combination chemotherapy was performed, and it was difficult to decide which drug was the cause of DRP. The drug-induced lymphocyte stimulation test was not performed because of its diagnostic accuracy and high cost of anticancer drugs. Second, pathological information was only obtained by TBLB in case 1 and not in cases 2 and 3; therefore, the pathological findings of HP cannot be determined. The specimens of case 1 might have been insufficient to be examined. There were no typical features of HP, such as granuloma, and were non-specific features of inflammation. It is difficult to completely discriminate pathological HP from the micronodular pattern of organizing pneumonia, which shows radiographically similar manifestations to HP but pathologically indicates organizing pneumonia [35–37]. In the clinical setting, bronchoscopy or surgical lung biopsy is not always performed because of respiratory failure. Third, in our study, only three of the 133 cases (2.3%) satisfied the radiographic criteria. We could not find as many HP pattern cases as previously reported (9–33.3% [33,38,39]). This is because we restricted the HP pattern to diffuse GGO and ill-defined centrilobular nodules on CT findings, which was eventually confirmed as typical HP according to the ATS/JRS/ALAT HP guideline for HP.

In conclusion, we reported three cases of DRP with a radiographic HP pattern. Nab-paclitaxel could induce this pattern of DRP. Our report further supports the evidence that this pattern has a good prognosis and that classifying radiographic patterns would be useful in clinical settings. However, further investigation is warranted in DRP with HP pattern.

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Author contributions

Writing original draft and study design: Yukihiro Nakamura and Takayuki Takimoto.
Data collection: Yukihiro Nakamura.
Conceptualization and critical review: all authors.
Validation: Takahiko Kasai and Masanobu Akira.
Supervision: Yoshikazu Inoue.

Ethics approval

The present study was approved by the institutional review board of the Kinki-Chuo Chest Medical Centre, Sakai City, Osaka, Japan (approval numbers: 2020-074).

Declaration of competing interest

The authors declare no conflicts of interest associated with this study

(COI).

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