



## Case report

## Spontaneous resolution of thoracic radiation therapy-induced organizing pneumonia: A case series



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## A B S T R A C T

We retrospectively analyzed the data of 9 patients with organizing pneumonia induced by radiation therapy. Radiation therapy had been administered for breast cancer in 8 patients and for lung cancer in 1 patient. Symptoms were detected in 8 patients; however, none of the patients developed hypoxemia or respiratory failure, and the clinical course was good. Steroid therapy was administered to 3 patients; however, all 3 patients developed recurrence. In contrast, none of the 6 patients who received symptomatic treatment developed recurrence. Steroid treatment is often provided for patients with organizing pneumonia; however, the effect of steroid administration on recurrence rate needs to be examined. In addition, none of the patients died and only 1 patient with lung cancer required mechanical ventilation. Therefore, considering the serious side effects of steroid use, initial symptomatic treatment, and not steroid administration, may be best for patients. One exception would be for patients with hypoxemia or those whose symptoms adversely affect the activities of daily living. The incidence of radiation therapy-induced organizing pneumonia in lung cancer patients is higher and its severity is greater than that in breast cancer patients; however, the time to onset may be longer in lung cancer patients. Therefore, more attention should be paid towards the diagnosis and treatment of radiation therapy-induced organizing pneumonia in patients with lung cancer as compared to that in patients with breast cancer.

## 1. Introduction

Organizing pneumonia may occur outside the radiation fields after thoracic radiation therapy, and a number of such cases have been reported in patients undergoing postoperative radiotherapy for breast cancer [1]. The mortality associated with secondary organized pneumonia is higher than that associated with cryptogenic organizing pneumonia [2] and steroid administration is a standard treatment for both forms of the disease. Although steroid treatment is highly effective, there is a reported increase in recurrence and incidence of adverse events as treatment continues over time [3–5]. We encountered 9 patients who developed radiation therapy-induced organizing pneumonia. The radiation therapy was administered for breast cancer in 8 patients and for lung cancer in 1 patient. Herein, we present 2 detailed case reports and a summary of 9 patients with radiation therapy-induced organizing pneumonia with additional information from the published literature. In particular, we examine the validity of steroid-based treatment in patients with breast cancer and lung cancer.

## 2. Case presentation

## 2.1. Case 1

The patient was a 62-year-old female. She received postoperative radiotherapy (total dose of 50 Gy with tangential irradiation) for right breast cancer. Fever and coughing occurred 14 months after completion of radiotherapy. Because antimicrobial therapy failed to improve the symptoms, she was admitted to our hospital. On admission, her vital signs and breath sounds were normal. Chest CT showed consolidation outside the radiation field in the upper, middle, and lower lobes (Fig. 1A). Bronchoscopy was performed and BALF was obtained from the right upper lobe bronchus. There were no malignant findings on smear, a culture test, or following cytodiagnosis of BALF. Lymphocytes in the BALF were increased, and her CD4/8 ratio was decreased. Because of a case that occurred more than 12 months after radiation therapy [6,7], we diagnosed radiation therapy-induced organizing pneumonia. The patient complained of severe respiratory discomfort on exertion, and 500 mg of methylprednisolone was given for 3 consecutive days. Then, 20 mg/day oral prednisolone was administered. The dose of prednisolone was tapered at an outpatient clinic after her respiratory discomfort improved. Eight months after the initiation of

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**Fig. 1.** Computed tomography image course of case 1. (A) Consolidation outside the radiation field in the upper lobe on admission. (B) New consolidation was found in the left upper lobe one month after the end of steroid administration. (C) Consolidation was improved only by follow-up in 3 months.

steroid treatment, the shadows disappeared on chest radiography and steroid administration was discontinued. However, one month later, new consolidation was noted in the left lung, leading to a diagnosis of relapsing organizing pneumonia (Fig. 1B). After a course of symptomatic treatment (because hypoxemia was not found), the shadow completely disappeared in 3 months (Fig. 1C).

## 2.2. Case 2

The patient was a 64-year-old female with a past medical history significant for pulmonary tuberculosis, and chronic hepatitis C. Thoracic radiation therapy (total dose of 60 Gy with parallel opposed-field irradiation) was performed for lung adenocarcinoma of the right middle lobe. Fever and a cough developed 6 months after the conclusion of radiotherapy and she was hospitalized in our department because of shadowing on chest computed tomography (CT). On admission, her vital signs were normal, and fine crackles were heard at the right lower lobe. Chest CT revealed consolidation outside the radiation field in the middle and lower lobes (Fig. 2A). Despite the administration of antimicrobial agents, her symptoms did not improve, and a bronchoscopy was performed. The findings from transbronchial lung biopsy were consistent with organizing pneumonia, although etiology was uncertain following blood testing, smear culture testing, and cytodiagnosis of the bronchoalveolar lavage fluid (BALF), we diagnosed her with organizing pneumonia induced by radiation therapy. She was not hypoxemic and, given her history of hepatitis C and tuberculosis, we opted to not use steroids in favor of observation only plus anti-tussive agents. The shadow continued to move, eventually crossing over to the other side, and completely disappeared in 5 months (Fig. 2B and C).

## 3. Discussion

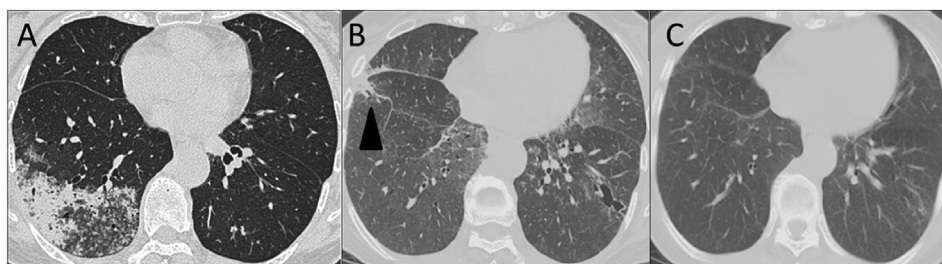
There are reports of a number of cases of radiation therapy-induced organizing pneumonia, especially after breast-conserving surgery [1]. We encountered 9 patients for whom radiation-associated organizing pneumonia in 15 years from 2004 to 2018. Radiation therapy had been performed for breast cancer in 8 patients and for lung cancer in 1. All the cases exhibited consolidation outside the lung fields, and shadowing suggestive of organized pneumonia often moved. Because we could not identify any apparent causes, other than radiation therapy, we diagnosed these patients with organizing pneumonia after radiation therapy based on their clinical courses, radiological findings, hematological test

results, and BALF findings (with the exception of one in whom a histological diagnosis was made).

### 3.1. Radiation therapy-induced organizing pneumonia in patients with breast cancer

The average age of the 8 patients with breast cancer was 56.8 years. The mean duration from completion of radiotherapy to disease onset was 5.6 months. One patient was asymptomatic, while 7 patients developed fever and cough; however, none of the patients exhibited hypoxemia. Steroid therapy was administered to 3 patients, while 5 patients were only administered symptomatic treatment. All patients experienced good outcomes with no impairment of respiratory function. However, all patients who were administered steroid therapy showed recurrence; in addition, the time required for resolution of lung shadow was also longer in these patients (Table 1).

Our literature search identified 173 cases of breast cancer who developed radiation therapy-induced organizing pneumonia worldwide between 1995 and 2018 [1,3,5–32]. The incidence was 1.1%–2.9%, and the average age range of patients was 52–59 years. The time to onset was 3.1–7.3 months [3,5,7,24,25,27]. As for the risk factors, age, smoking history, history of radiation pneumonitis, and central lung distance have been reported (central lung distance refers to the farthest distance between the posterior border of the irradiation field and the chest wall on approved linacography) [21,25,27]. Out of 173 patients, 159 (92%) were symptomatic. The most common symptoms were cough (95.6%), fever (73.7%), and dyspnea (27%). Twenty-one patients (12%) developed hypoxemia ( $SpO_2 < 95\%$  or  $PaO_2 < 80$  mmHg); however, only 3 patients developed respiratory failure ( $PaO_2 < 60$  mmHg) (1.7%). Therefore, despite a high proportion of symptomatic patients, serious hypoxemia seems to be rarely associated with this condition. Indeed, none of these patients died of radiation therapy-induced organizing pneumonia or required mechanical ventilation. Steroids were used in 105 out of the 173 patients (60.7%). The rate of recurrence in the steroid treatment group (59 of 105 cases, 56.2%) was clearly higher than that in the symptomatic treatment group (10 of 68 cases, 14.7%) (Table 2). Steroid administration is a standard treatment for cryptogenic organizing pneumonia, and the mortality of secondary organized pneumonia appears higher than cryptogenic organizing pneumonia [2]. Therefore, steroid administration is often performed for patients with this disease. Otani et al. reported that no significant difference was found between the steroid group (1.6 months) and the nonsteroidal group (1.7 months) for the time symptom improvement.



**Fig. 2.** Computed tomography image course of case 2. (A) Consolidation was found outside of the radiation field in right lower lobe on admission. (B) Consolidation of the right lower lobe moved, and showed improvement 3 months later (black arrow). (C) Consolidation disappeared following symptomatic treatment in 5 months.

**Table 1**  
Summary of 8 patients with breast cancer who developed thoracic radiation therapy-induced organizing pneumonia.

Case	1	2	3	4	5	6	7	8
Age (years)	62	53	68	47	72	52	52	48
Smoking history	–	–	–	+	–	–	–	–
Irradiation method	Tangential port	Tangential port	Parallel opposing portals	Tangential port	Parallel opposing portals	Parallel opposing portals	Tangential port	Tangential port
Dose (Gy)	50	50	60	50	50	50	50	60
Combination drug	–	–	–	Gn-RHa + Tamoxifen	–	Docetaxel + Trastuzumab	–	Toremifene
History of radiation pneumonitis	–	–	+	–	–	–	–	–
Onset	14 months	3 months	3 months	8 months	4 months	3 months	4 months	6 months
Symptoms	Fever, cough	Fever, cough	Fever, cough	Fever, cough	–	Fever, cough	Fever, cough	Fever, cough
WBC (/ $\mu$ L)	7200	6300	8700	12800	5400	6800	6400	5200
CRP (mg/dL)	17.5	10.8	7.9	4.6	0.7	6	2.5	1.7
KL-6 (U/mL)	–	383	908	105	433	390	167	277
Movement of the shadow	+	+	+	+	+	+	+	+
Treatment	Steroid therapy	Steroid therapy	Steroid therapy	Observation	Observation	Observation	Observation	Observation
Recurrence	+	+	+	–	–	–	–	–
Time elapsed from onset to resolution of shadow	13 months	6 months	8 months	4 months	2 months	5 months	2 months	2 months

WBC, white blood cell; CRP, C-reactive protein.

**Table 2**  
Summary of the symptoms, treatment, and the prognosis of previously reported cases of breast cancer who developed radiation therapy-induced organizing pneumonia.

	N = 173
Symptomatic patients	159
Cough	131
Fever	101
Dyspnea	37
Unknown	22
Asymptomatic patients	14
Hypoxemia (SpO <sub>2</sub> < 95% or PaO <sub>2</sub> < 80 mmHg)	21
Respiratory failure (PaO <sub>2</sub> < 60 mmHg)	3
Patients who received Steroid therapy	105
Recurrence	59
Patients who did not receive steroid therapy	68
Recurrence	10

Furthermore, there was a significant between-group difference the duration of time from symptom improvement to the end of treatment, with 17.1 months for the steroid group and 2.3 months for the non-steroidal group. In addition, rate of recurrence was high in the steroid group, suggesting that steroids are critical factors related to the recurrence of radiation therapy-induced organizing pneumonia [5]. Furthermore, steroid treatment might induce resistance to treatment for solid cancers [33–35], in addition to other steroid-related adverse events. We thought the radiation therapy-induced organizing pneumonia in breast cancer that symptomatic treatment should be first-line from these results. Steroids should only be introduced upon onset of hypoxemia, respiratory failure, or unbearable symptoms.

### 3.2. Radiation therapy-induced organizing pneumonia in lung cancer

Our literature search identified 21 cases of lung cancer who developed radiation therapy-induced organizing pneumonia worldwide between 1995 and 2018 [23,36–43]. We report the summary of 22 cases (including our case). The incidence was 5.2%–6.4% [40,41], and the average age of patients was 74.3 years; both these variables were higher than that in patients with breast cancer. There was a greater proportion of male patients. Many cases developed radiation therapy-induced

organizing pneumonia > 6 months after irradiation, which is longer than that observed in patients with breast cancer. The predominant irradiation method was stereotactic ablative radiotherapy. History of radiation pneumonitis was found in 18 out of the 22 patients (81.8%). History of symptomatic radiation pneumonitis has been reported as a risk factor [40,41]. The high incidence of organizing pneumonia in patients with lung cancer may be associated with high incidence of radiation pneumonitis. In addition, there were many superior lobes in the irradiation site. Ochiai et al. postulated that radiation injury to subpleural region of the lung and pleura may serve as the primer for organizing pneumonia through radiation pneumonitis [41]. Out of the 21 patients, 18 (85.7%) were symptomatic. The main symptoms were dyspnea (88.9%), fatigue (77.8%), fever (55.6%), and cough (15%). Two patients (9.1%) developed hypoxemia (SpO<sub>2</sub> < 95% or PaO<sub>2</sub> < 80 mmHg) and respiratory failure (PaO<sub>2</sub> < 60 mmHg). One patient was administered mechanical ventilation. Murai et al. reported that the symptoms were sometimes more severe than those of breast cancer [40]. However, none of the patients died. Steroid therapy was administered to 13 patients, while 9 patients were only administered symptomatic treatment. The rate of recurrence in the steroid group (8 of 13 cases, 61.5%) was clearly higher than that in the symptomatic treatment group (1 of 9 cases, 11.1%) (Table 3).

### 4. Conclusion

Symptomatic treatment should be the first-line treatment for patients with radiation therapy-induced organizing pneumonia. Steroids should only be introduced upon onset of hypoxemia, respiratory failure, or unbearable symptoms. The incidence of radiation therapy-induced organizing pneumonia in lung cancer patients is higher and its severity greater than that in breast cancer patients; however, the time to onset may be longer in lung cancer patients. Therefore more attention should be paid towards the diagnosis and treatment of radiation therapy-induced organizing pneumonia radiation in patients with lung cancer as compared to that in patients with breast cancer.

### Declarations of interest

None.

**Table 3**  
Summary of radiation therapy-induced organizing pneumonia in patients with lung cancer.

	N = 22
Age, range (average)	59–85 (74.3)
Sex	
Male	14
Female	8
Histologic type	
Squamous adenocarcinoma	4
small cell	3
Unknown	1
Irradiation method	14
SABR	15
Parallel opposing portals	3
Others	4
Dose, range (average)	48–60 (50.2)
Irradiation site	
Superior lobe	8
middle lobe	1
Inferior lobe	1
Others	3
Unknown	9
Combination drug	2
History of symptomatic radiation pneumonitis	18
Onset	
> 6 months	4
< 6 months	18
Symptomatic patients	18
Dyspnea	16
Fatigue	14
Fever	10
Cough	9
Asymptomatic patients	3
Hypoxemia (SpO <sub>2</sub> < 95% or PaO <sub>2</sub> < 80 mmHg)	2
Respiratory failure (PaO <sub>2</sub> < 60 mmHg)	2
Patients who received steroid therapy	13
Recurrence	8
Patients who did not receive steroid therapy	9
Recurrence	1

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