

# Thin-Section CT Characteristics and Longitudinal CT Follow-up of Chemotherapy Induced Interstitial Pneumonitis

## A Retrospective Cohort Study

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**Abstract:** To describe the computed tomography (CT) features of chemotherapy-induced interstitial pneumonitis (CIIP) with longitudinal follow-up.

The study was approved by the local ethics committee. One hundred consecutive patients with CIIP between May 2005 and March 2015 were retrospectively enrolled. The initial CT was reviewed by 2 independent chest radiologists and categorized into 1 of 4 CT patterns in accordance with the 2013 guidelines for idiopathic interstitial pneumonia: nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), hypersensitivity pneumonitis (HP) mimicking desquamative interstitial pneumonitis, and diffuse alveolar damage (DAD). We assessed semi-quantitative analysis on a 5% scale to assess the extent of parenchymal abnormalities (emphysema, reticulation, ground-glass opacity, consolidation, honeycombing cyst) and their distribution on initial (n = 100), subsequent (n = 87), and second follow-up CT (n = 48). Interval changes in extent on follow-up CT were compared using paired *t* test. The clinic-radiologic factors were compared between Group 1 (NSIP and OP patterns) and Group 2 (HP and DAD patterns) using  $\chi^2$  and independent *t* tests.

The most common pattern of CIIP on the initial CT was HP (51%), followed by NSIP (23%), OP (20%), and DAD (6%). Diffuse ground-glass opacity was the most common pulmonary abnormality. The predominant distribution was bilateral (99%) and symmetric (82%), with no craniocaudal (60%) or axial (79%) dominance. Subsequent and second follow-up CTs showed decreased extent of total pulmonary abnormalities ( $P < 0.001$ , respectively). In comparison with Group 1 CIIP, Group 2 CIIP was more likely to be caused by molecularly targeted drugs ( $P = 0.030$ ), appeared earlier ( $P = 0.034$ ), and underwent

more complete resolution ( $P < 0.001$ ). Use of a CT pattern-recognition approach to CIIP is appropriate and practical in interpreting radiological findings.

(*Medicine* 95(2):e2460)

**Abbreviations:** CIIP = chemotherapy-induced interstitial pneumonitis, DAD = diffuse alveolar damage, GGO = ground-glass opacity, HP = hypersensitivity pneumonitis, ICC = intraclass correlation coefficient, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia.

## INTRODUCTION

Chemotherapy-induced interstitial pneumonitis (CIIP) is recognized as a frequent and important complication of chemotherapy in oncology patients and is reported to occur in up to approximately 10% of patients treated with an antineoplastic agent.<sup>1,2</sup>

CIIP should be considered if respiratory symptoms present temporarily during chemotherapy and resolve after discontinuation of the specific drug. Diagnosis of CIIP is important in determining whether use of the current chemotherapeutic agents can continue and in enabling prompt management such as drug withdrawal and/or steroid medication for patients who undergo acute deterioration.<sup>1,3,4</sup> However, the diagnosis of CIIP remains a challenge for both the clinician and the radiologist. There are no pathognomic clinical, radiological, or pathological findings. Other pulmonary diseases that mimic CIIP, such as pulmonary infection, pulmonary edema, and idiopathic interstitial pneumonia, are more common than CIIP in routine practice and should be initially excluded for the diagnosis of CIIP.

Thin-section computed tomography (CT) findings in CIIP reflect underlying histopathologic processes that include nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), hypersensitivity pneumonitis (HP), diffuse alveolar damage (DAD), eosinophilic pneumonia, obliterative bronchiolitis, or pulmonary hemorrhage.<sup>5,6</sup>

New antineoplastic agents are constantly being developed and there are many reports of CIIP caused by specific types of drug.<sup>1,7-10</sup> However, combination chemotherapy is common and the CT characteristics of CIIP are too diverse and complex in current chemotherapy. So we believe that in terms of CIIP, the pattern approach for interpretation of CT findings is more reasonable and practical to radiologists than that by the individual chemotherapeutic regimen. Furthermore, published thin-section CT findings in CIIP according to pattern approach are very few in number.<sup>11</sup> The purpose of this study was to describe the features of CIIP in thin-section CT with longitudinal CT follow-up.

Editor: Sanket Patel

Received: September 1, 2015; revised: November 25, 2015; accepted: December 14, 2015.

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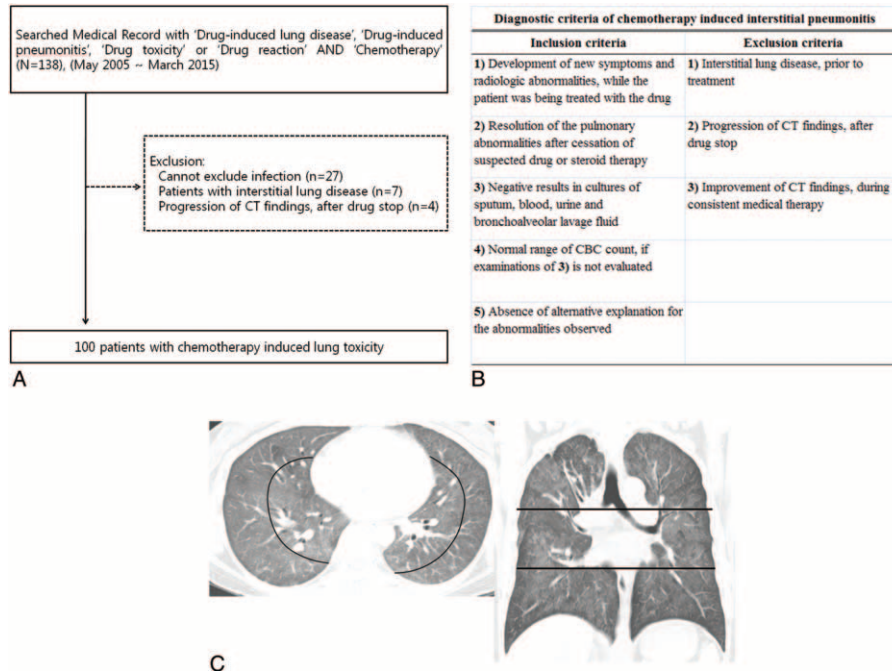
The authors have no funding and conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002460



**FIGURE 1.** (A) Flow diagram of the patient selection process. (B) Diagnostic criteria for chemotherapy-induced interstitial pneumonitis. (C) The levels of the “carina” and “lower pulmonary vein” are landmarks in coronal CT scans and lines indicate imaginary lines dividing the central and peripheral lung in axial CT scans. CT=computed tomography, ILD=interstitial lung disease.

**MATERIALS AND METHODS**

**Patient Characteristics**

This retrospective study was performed at the Asan Medical Center, a 2700-bed tertiary-care teaching hospital, between May 2005 and March 2015. The study was approved by our hospital’s institutional review board (approval number: 2015–0524) and informed consent was waived because of retrospective study.

Using in-house searching software (ABLE, Asan Medical Center, Seoul), we retrospectively searched electronic medical records and found 138 consecutive oncology patients undergoing chemotherapy with “drug-induced lung disease,” “drug-induced pneumonitis,” “drug toxicity,” or “drug reaction.”

Patients with other causes for the pulmonary abnormality, such as pulmonary infection or pulmonary edema, were excluded on the basis of bronchoscopy with bronchoalveolar lavage (BAL), echocardiography, and laboratory tests by clinicians. Accordingly, 27 patients who were finally diagnosed as having pulmonary infection and 7 patients with underlying idiopathic interstitial lung disease on thin-section CT images taken before the start of chemotherapy were excluded. A further 4 patients who showed progression of lung lesion, despite discontinuation of chemotherapy, were also excluded. Finally, 100 consecutive patients with CIIP (51 males, 49 females; median age 61.0 years, range 14–81) were included (Figure 1A). Inclusion and exclusion criteria are summarized in Figure 1B.<sup>11,12</sup>

All patients in the study met the clinical diagnostic criteria for CIIP. Bronchoalveolar lavage was performed with culture of samples in 72 of 100 patients. Remaining 28 patients showed normal range of white blood cell count. Tissue confirms were taken in 7 patients by either bronchoscopy or wedge resection of lung for cases, which were difficult to differentiate from some

other idiopathic diffuse interstitial lung diseases or clinically and radiologically undetermined pulmonary lesions.

We reviewed the demographics, smoking history, and clinical symptoms of the patients, focusing on dyspnea, fever, and cough. The onset of CIIP was defined as the interval between the date of the initial thin-section CT (Time1CT) and the date of initial chemotherapy as follows: within 1 week, 1 week to 1 month, 1 to 3 months, >3 months. Chemotherapeutic agents and underlying malignancies were reviewed. Drugs were divided into 2 categories according to the underlying mechanisms: molecularly targeted drugs and cytotoxic drugs (Supplementary Table 1, <http://links.lww.com/MD/A609>). We also assessed the history of steroid therapy and endotracheal tube insertion in patients with acute deterioration.

**Evaluation of CTs**

Chest thin-section CT studies were undertaken in the 100 patients as follows: 84 pretreatment thin-section CTs for staging underlying disease (Time 0), 100 initial thin-section CTs of CIIP (Time1), 87 subsequent thin-section CTs (Time2), and 48-second follow-up thin-section CT (Time3). Thus, a total of 319 thin-section CT scans were collected and randomized by a thoracic radiologist (H.N.L., 5 years’ experience in radiology).

**1) Evaluation of Initial CT**

Two radiologists (M.Y.K and H.N.L, 23 and 5 years’ experience in radiology, respectively) independently assessed and scored the extent of parenchymal abnormalities including emphysema, reticulation, ground-glass opacity (GGO), consolidation, and honeycombing cysts in 100 Time1CT images. The extent of the abnormalities was determined on axial CT images, using a 5% volumetric scale for 6 zones from: (1) the lung apex to the carina, (2) the carina to the lower pulmonary vein, and (3)

**TABLE 1.** Baseline Characteristics of Patients With Chemotherapy-Induced Interstitial Pneumonitis

| Characteristic              | Total         | NSIP Pattern  | OP Pattern     | HP Pattern    | DAD Pattern   | Group 1       | Group 2       | P   |
|-----------------------------|---------------|---------------|----------------|---------------|---------------|---------------|---------------|---|
| n                           | 100 (100.0)   | 23 (23.0)     | 20 (20.0)      | 51 (51.0)     | 6 (6.0)       | 43 (43.0)     | 57 (57.0)     |   |
| Male                        | 51 (51.0)     | 15 (65.2)     | 10 (50.0)      | 25 (49.0)     | 1 (16.7)      | 25 (58.1)     | 26 (45.6)     | 0.215 <sup>†</sup>                        |
| Age (y) <sup>*</sup>        | 61 (14–81)    | 61 (23–81)    | 59.5 (14–75)   | 60 (33–79)    | 65.5 (59–76)  | 61 (14–81)    | 60 (33–79)    | 0.574 <sup>§</sup><br>N/A                 |
| Smoking habit               |               |               |                |               |               |               |               |   |
| Never                       | 64 (64.0)     | 10 (43.5)     | 14 (70.0)      | 34 (66.7)     | 6 (100.0)     | 24 (55.8)     | 40 (70.2)     |   |
| Ex                          | 35 (35.0)     | 13 (56.5)     | 6 (30.0)       | 16 (31.4)     | 0 (0.0)       | 19 (44.2)     | 16 (28.1)     |   |
| Current                     | 1 (1.0)       | 0 (0.0)       | 0 (0.0)        | 1 (2.0)       | 0 (0.0)       | 0 (0.0)       | 1 (1.8)       |   |
| Pack years <sup>*</sup>     |               | 27.0 (10–45)  | 30.0 (10–72)   | 36.0 (10–80)  | 0.0 (0)       | 30 (10–72)    | 36 (10–80)    | 0.582 <sup>§</sup><br><0.001 <sup>†</sup> |
| Symptoms                    |               |               |                |               |               |               |               |   |
| Dyspnea                     | 57 (57.0)     | 16 (69.6)     | 9 (45.0)       | 30 (58.8)     | 2 (33.3)      | 25 (58.1)     | 32 (56.1)     |   |
| Fever                       | 29 (29.0)     | 2 (8.7)       | 4 (20.0)       | 19 (37.3)     | 4 (66.7)      | 6 (14.0)      | 23 (40.4)     |   |
| Cough                       | 14 (14.0)     | 5 (21.7)      | 7 (35.0)       | 2 (3.9)       | 0 (0.0)       | 12 (27.9)     | 2 (3.5)       |   |
| Chemotherapy                |               |               |                |               |               |               |               |   |
| Molecularly targeted        | 52 (52.0)     | 8 (34.8)      | 9 (45.0)       | 31 (60.8)     | 4 (66.7)      | 17 (39.5)     | 35 (61.4)     | 0.030 <sup>†</sup>                        |
| Cytotoxic                   | 48 (48.0)     | 15 (65.2)     | 11 (55.0)      | 20 (39.2)     | 2 (33.3)      | 26 (60.5)     | 22 (38.6)     |   |
| Periods (days) <sup>*</sup> |               |               |                |               |               |               |               |   |
| Period of chemotherapy      | 68.0 (0–1597) | 70.0 (0–217)  | 80.0 (0–380)   | 63.0 (0–1597) | 69.0 (42–125) | 76.0 (0–380)  | 64.0 (0–1597) | 0.908 <sup>§</sup>                        |
| Onset of CIIP <sup>‡</sup>  | 80.5 (4–425)  | 93.0 (24–301) | 101.5 (11–425) | 75.0 (13–417) | 84.0 (4–126)  | 93.0 (11–425) | 76.0 (4–417)  | 0.034 <sup>§</sup>                        |
| Time0CT ~ Time1CT           | 74.5 (5–487)  | 80.0 (9–254)  | 74.0 (16–314)  | 73.0 (5–487)  | 91.0 (48–189) | 76.5 (9–314)  | 73.0 (5–487)  | 0.320 <sup>§</sup>                        |
| Time1CT ~ Time2CT           | 56.0 (7–758)  | 63.0 (10–271) | 58.5 (14–758)  | 51.0 (7–218)  | 35.0 (13–83)  | 62.0 (10–758) | 50.5 (7–218)  | 0.022 <sup>§</sup>                        |
| Time2CT ~ Time3CT           | 65.0 (8–939)  | 75.5 (13–548) | 57.0 (27–179)  | 57.5 (8–939)  | 57.0 (32–73)  | 65.0 (13–548) | 57.0 (8–939)  | 0.566 <sup>§</sup>                        |

Note: Except where indicated, data are numbers of patients, with percentage in parentheses.

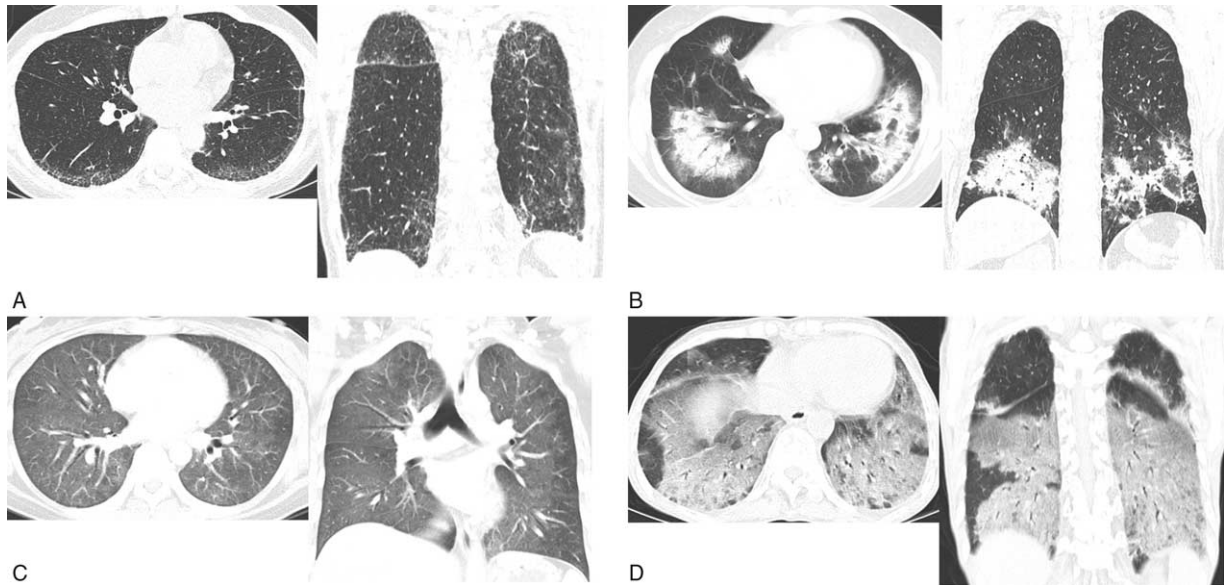
CIIP = chemotherapy-induced interstitial pneumonia, CT = computed tomography, DAD = diffuse alveolar damage, HP = hypersensitivity pneumonitis, N/A = not applicable, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, Time0CT = pretreatment thin-section CT, Time1CT = initial thin-section CT, Time2CT = subsequent thin-section CT, Time3CT = second follow-up thin-section CT.

<sup>\*</sup>Data are medians with ranges in parentheses. *P* values for the analysis of variance comparing Group 1 (NSIP or OP patterns) with Group 2 (HP or DAD patterns).

<sup>†</sup> Chi-square test.

<sup>‡</sup> Onset of CIIP = interval between date of initial thin-section CT and date of initial chemotherapy.

<sup>§</sup> Independent samples *t* test.



**FIGURE 2.** Four representative patterns of chemotherapy-induced interstitial pneumonitis. (A) A 47-year-old woman with ovarian cancer and bleomycin-induced interstitial pneumonitis with the NSIP pattern. Thin-section CT axial and coronal lung images (1-mm reconstruction) show fine interlobular septal thickening and GGO in the subpleural area of the lungs. (B) A 64-year-old woman with colon cancer and oxaliplatin-induced interstitial pneumonitis showing the pattern of OP. Thin-section CT axial and coronal lung images (1-mm reconstruction) show patchy airspace consolidation along the bronchovascular bundle in both lower lobes and the right middle lobe. (C) A 40-year-old woman with lymphoma and rituximab-induced interstitial pneumonitis showing the pattern for HP. Thin-section CT axial and coronal lung images (1 mm reconstruction) show a diffuse area of ill-defined ground-glass opacity with subtle subpleural sparing in the left lung. (D) A 62-year-old woman with lymphoma and rituximab-induced interstitial pneumonitis showing the pattern for DAD. Thin-section CT axial and coronal lung images (1 mm reconstruction) show extensive areas of ground-glass opacity, mild dependent airspace consolidation, and thickening of interlobular septa in both lungs. Biopsy revealed intra-alveolar hyaline membrane with diffuse alveolar damage. CT = computed tomography, DAD = diffuse alveolar damage pattern, GGO = ground-glass opacity, HP = hypersensitivity pneumonitis, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia.

the lower pulmonary vein to the lung base (Figure 1C).<sup>13</sup> The prevalence of traction bronchiectasis, subpleural sparing, and subpleural curvilinear lines was assessed in consensus (M.Y.K. and H.N.L.).

With regard to the distribution of parenchymal abnormalities, the following were evaluated in consensus: 4 instances of craniocaudal dominance (upper, mid, lower, none); referent to carina and right lower pulmonary vein, respectively) (Figure 1C); 3 instances of axial zonal dominance (central, peripheral, none; referent to imaginary middle line) (Figure 1C); bilaterality and symmetry of pulmonary abnormalities.

The initial thin-section CT (Time1CT) images were categorized in consensus (M.Y.K. and H.N.L.) as presenting 1 of the following 4 patterns in accordance with American Thoracic Society/European Respiratory Society guidelines<sup>14</sup>: (1) NSIP pattern, (2) OP pattern, (3) HP pattern, mimicking diffuse desquamative interstitial pneumonitis, and (4) DAD pattern (Figure 2 A–D). The 4 patterns were then recategorized into either Group 1 (NSIP and OP patterns) or Group 2 (HP and DAD patterns) depending on whether or not >50% of pulmonary infiltration composed of GGO.

## 2) Evaluation of Follow-up CTs

Two thoracic radiologists (M.Y.K., H.N.L.) independently assessed and scored the extent of parenchymal abnormalities, including emphysema, reticulation, GGO, consolidation, and honeycombing cysts in 87 subsequent thin-section CT (Time2) images and 48-second follow-up thin-section CT (Time3) images. The extent of these abnormalities was determined in

transverse images using a 5% volumetric scale for 6 zones in the same manner as for the Time1CTs. On the Time2CT images of 87 patients, we classified changes of pulmonary abnormalities as complete resolution or partial resolution.

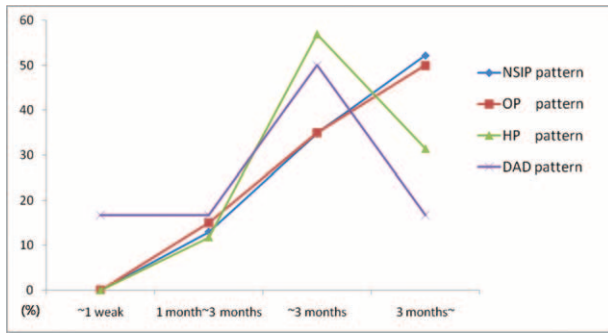
## CT Scanning Protocol

The CT images were obtained with a SOMATOM Sensation (Siemens Medical Solutions, Forchheim, Germany) scanner. The CT parameters were 120 kVp and 100 effective mAs with dose modulation. Reconstruction was done using B60 algorithm (3/5-mm thickness and 3/5-mm increment without a gap), and B50 algorithm (1-mm thickness with 5-mm gap). All 319 CT images were viewed at the mediastinum (width 450 HU; level 50 HU) and the lung (width 1500 HU; level –700 HU) window settings of the axial and coronal images on the picture archiving and communication system.

## Statistical Analysis

Intraclass correlation coefficients (ICCs) were used to analyze interobserver agreement for the extent of pulmonary abnormalities on the Time1 and Time2CTs. ICC values were classified as follows: <0.40, poor agreement; 0.40 to 0.60, moderate agreement; 0.60 to 0.80, substantial agreement; >0.80, good agreement.<sup>15</sup> Paired Student *t* tests were used for comparisons between CT findings at Time1CT and Time2CT, and between findings at Time2CT and Time3CT. Various clinical and radiologic factors at Time1CT were compared between Groups 1 and 2 using  $\chi^2$  tests for categorical data and independent samples *t* tests for continuous data. The





**FIGURE 3.** The graph demonstrates peak times of onset of CIIP according to the thin-section pattern. CIIP=chemotherapy-induced interstitial pneumonitis. DAD=diffuse alveolar damage; HP=hypersensitivity pneumonitis; NSIP=nonspecific interstitial pneumonia; OP=organizing pneumonia.

statistical package SPSS version 18.0 (SPSS Inc, Chicago, IL) was used (by K.S.S., 11 years' experience), and the results are expressed as means  $\pm$  standard deviations or medians with ranges. A *P* value  $<0.05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

The clinical characteristics of the 100 patients are given in Table 1. The most common symptom of CIIP was dyspnea (57%), followed by fever (29%) and cough (14%). Fever was more common in Group 2 (40.4%); cough was more common in Group 1 (27.9%; *P*  $<0.001$ ). Most of the patients had cessation of the chemotherapy (97%) and/or the steroid taking (90%), during treatment of CIIP. Only 5 patients (5%) required admission to the intensive care unit and endotracheal intubation.

The most common molecularly targeted drug that induced CIIP was rituximab (28%) in patients with lymphoma (*n* = 28); the second most common was everolimus (9%) in patients with renal cell carcinoma (*n* = 6). Common cytotoxic chemotherapeutic agents that induced CIIP were bleomycin (11%) in patients with lymphoma (*n* = 6) and docetaxel (10%) in patients with breast cancer (*n* = 5) (Supplementary Table 1, <http://links.lww.com/MD/A609>).

The CIIP was more likely to be caused by cytotoxic drugs in Group 1 cases (NSIP and OP patterns) and by molecularly targeted drugs in Group 2 (HP and DAD patterns, *P* = 0.03).

The median interval between starting the drug and the Time1CT date (onset of CIIP) was 80.5 days (range 4–425). In Group 2, the peak incidence of CIIP onset was between 1 and 3 months, in Group 1 it was  $>3$  months (Figure 3). There was also a statistically significant difference in onset of CIIP between Group 1 (median 93.0, range 11–425) and Group 2 (median 76.0, range 4–417) (*P* = 0.034). The interval between the Time1CT and Time2CT was significantly shorter in Group 2 (median 50.5, range 7–218) than in Group 1 (median 62.0, range 10–758) (*P* = 0.022) (Table 1).

### Evaluation of CTs

The ICCs of the radiologic scores were substantial to good degree in Time1CT (0.764–1.000) and Time2CT (0.788–1.000). ICC was relatively low for reticulation (0.764 on Time1CT and 0.788 on Time2CT) with substantial degree. Other scores were  $>0.885$  with good degree (Supplementary Table 2, <http://links.lww.com/MD/A609>). None of the patients showed honeycombing cysts on the Time1CT, Time2CT, and Time3CT.

### Initial CT

The most common pattern of CIIP on the Time1CT was HP (*n* = 51), followed by NSIP (*n* = 23), OP (*n* = 20), and DAD (*n* = 6). When comparing total pulmonary extent, Group 2 showed more extensive extent of CIIP (53.2%) than Group 1 (33.3%) (*P*  $<0.001$ ) (Table 2).

The most common distribution of CIIP was bilateral (99%) with a symmetric distribution (82%), regardless of the pattern. Craniocaudal dominance was generally absent, except in OP pattern. Among the cases with an OP pattern, 50% showed lower lung zone predominance. Axial zonal dominance was also usually absent, except in NSIP. Among cases with an NSIP pattern, 52.2% showed peripheral predominance (Table 3).

Traction bronchiectasis, subpleural sparing, and subpleural curvilinear lines were observed in only 18%, 1%, and 5% of patients, respectively.

### Subsequent and Follow-up CTs

On the Time2CT, all the parenchymal abnormalities except emphysema were significantly decreased in extent: from 45.4%

**TABLE 2.** CT Characteristics of Patients With Chemotherapy-Induced Interstitial Pneumonitis on Initial CT

| Thin-Section CT Findings | Total       | NSIP Pattern | OP Pattern | HP Pattern | DAD Pattern | Group 1   | Group 2   | <i>P</i> |
|--------------------------|-------------|--------------|------------|------------|-------------|-----------|-----------|----------|
| <i>n</i> *               | 100 (100.0) | 23 (23.0)    | 20 (20.0)  | 51 (51.0)  | 6 (6.0)     | 43 (43.0) | 57 (57.0) |          |
| Extent, %                |             |              |            |            |             |           |           |          |
| Emphysema                | 1.5         | 2.7          | 0.5        | 2.6        | 0.0         | 1.6       | 2.4       | 0.333    |
| Reticulation             | 7.0         | 14.2         | 5.3        | 6.4        | 1.9         | 10.0      | 5.9       | 0.006    |
| GGO                      | 30.0        | 13.9         | 14.2       | 42.3       | 49.4        | 14.0      | 43.1      | $<0.001$ |
| Consolidation            | 6.1         | 2.9          | 13.0       | 1.1        | 7.5         | 7.6       | 1.8       | $<0.001$ |
| Total                    | 44.5        | 33.7         | 32.9       | 52.5       | 58.9        | 33.3      | 53.2      | $<0.001$ |

Note: Except where indicated, data indicate extent of pulmonary parenchymal lesions, expressed as a percentage of the mean value.

CT=computed tomography, DAD=diffuse alveolar damage, GGO= ground-glass opacity, HP=hypersensitivity pneumonitis, NSIP=nonspecific interstitial pneumonia, OP=organizing pneumonia.

\*Data are numbers of patients, with percentage in parentheses. *P* values for analysis of variance comparing Group 1 (NSIP or OP patterns) with Group 2 (HP or DAD patterns) in independent samples *t* test.

**TABLE 3.** CT Characteristics of Patients With Chemotherapy-Induced Interstitial Pneumonitis on Initial CT

| Thin-Section CT Findings | Total       | NSIP Pattern | OP pattern | HP Pattern | DAD Pattern | Group 1   | Group 2    | P      |
|--------------------------|-------------|--------------|------------|------------|-------------|-----------|------------|--------|
| n                        | 100 (100.0) | 23 (23.0)    | 20 (20.0)  | 51 (51.0)  | 6 (6.0)     | 43 (43.0) | 57 (57.0)  |        |
| Distribution             |             |              |            |            |             |           |            |        |
| Craniocaudal             |             |              |            |            |             |           |            |        |
| Upper                    | 13 (13.0)   | 3 (13.0)     | 3 (15.0)   | 6 (11.8)   | 1 (16.7)    | 6 (14.0)  | 7 (12.3)   | N/A    |
| Middle                   | 1 (1.0)     | 0 (0.0)      | 1 (5.0)    | 0 (0.0)    | 0 (0.0)     | 1 (2.3)   | 0 (0.0)    |        |
| Lower                    | 26 (26.0)   | 8 (34.8)     | 10 (50.0)  | 7 (13.7)   | 1 (16.7)    | 18 (41.9) | 8 (14.0)   |        |
| None*                    | 60 (60.0)   | 12 (52.2)    | 6 (30.0)   | 38 (74.5)  | 4 (66.7)    | 18 (41.9) | 42 (73.7)  |        |
| Axial                    |             |              |            |            |             |           |            | N/A    |
| Central                  | 1 (1.0)     | 0 (0.0)      | 1 (5.0)    | 0 (0.0)    | 0 (0.0)     | 1 (2.3)   | 0 (0.0)    |        |
| Peripheral               | 20 (20.0)   | 12 (52.2)    | 8 (40.0)   | 0 (0.0)    | 0 (0.0)     | 20 (46.5) | 0 (0.0)    |        |
| None*                    | 79 (79.0)   | 11 (47.8)    | 11 (55.0)  | 51 (100.0) | 6 (100.0)   | 22 (51.2) | 57 (100.0) |        |
| Bilateral                | 99 (99.0)   | 23 (100.0)   | 19 (95.0)  | 51 (100.0) | 6 (100.0)   | 42 (97.7) | 57 (100.0) | 0.430  |
| Symmetric                | 82 (82.0)   | 20 (87.0)    | 9 (45.0)   | 47 (92.2)  | 6 (100.0)   | 29 (67.4) | 53 (93.0)  | 0.001  |
| Outcome on Time2CT       |             |              |            |            |             |           |            |        |
| Complete resolution      | 32 (32.0)   | 2 (8.7)      | 2 (10.0)   | 26 (51.0)  | 2 (33.3)    | 4 (9.3)   | 28 (49.1)  | <0.001 |
| Partial resolution       | 55 (55.0)   | 16 (69.6)    | 18 (90.0)  | 18 (35.3)  | 3 (50.0)    | 34 (79.1) | 21 (36.9)  |        |
| No follow-up             | 13 (13.0)   | 5 (21.7)     | 0 (0.0)    | 7 (13.7)   | 1 (16.7)    | 5 (11.6)  | 8 (14.0)   |        |

Note: Numbers of the data are numbers of patients, with percentages in parentheses. P values for the test of independence comparing Group 1 (NSIP or OP patterns) with Group 2 (HP or DAD patterns) with  $\chi^2$  test.

Abbreviation as in Table 1.

\*None = no predominant distribution.

to 11.6% ( $P < 0.001$ ). On the Time3CT, GGOs and consolidations were reduced ( $P = 0.002$ ,  $P = 0.008$ , respectively), whereas reticular opacities increased ( $P < 0.001$ ) (Table 4).

Although the median interval between Time1CT and Time2CT was shorter in Group 2 (50.5 days, range 7–218) than in Group 1 (62.0 days, range 10–758) ( $P = 0.022$ ), complete resolution of the pulmonary abnormalities on the Time2CT was seen more frequently in Group 2 (n = 28, 49.1%) (Figure 4) than in Group 1 (n = 4, 9.3%) ( $P < 0.001$ ) (Figure 5).

### DISCUSSION

The list of new drugs is growing and the number of recognized pulmonary side effects is increasing. Radiologists relatively frequently encounter CIIP and make a differential diagnosis such as drug reaction or drug toxicity despite the

varied spectra of CIIP on thin-section CT imaging. Diagnosis of CIIP remains a challenge to both radiologists and clinicians. More importantly, the diagnosis depends on exclusion of other cause.

The thin-section CT findings associated with each chemotherapeutic agent such as bleomycin<sup>16,17</sup> are well described, but not histopathologic patterns associated with many kinds of chemotherapeutic agents.

Chemotherapeutic drugs can cause 4 main types of lung reaction: interstitial pneumonitis and fibrosis, OP, hypersensitivity reactions, and acute respiratory distress syndrome.<sup>18</sup> Above we classified the thin-section CT findings for CIIP into 4 patterns: NSIP, OP, HP, and DAD, modification of the classification of idiopathic interstitial pneumonias on thin-section CT scans.<sup>19</sup> We assumed that (1) a NSIP pattern with smooth interlobular septal line thickening was explained by

**TABLE 4.** Comparison of Initial, Subsequent, and Second Follow-up Thin-Section CT Findings in Chemotherapy-Induced Interstitial Pneumonitis

|                   | Time1CT | Time2CT | Time3CT | P (Time1CT vs Time2CT) | P (Time2CT vs Time3CT) |
|-------------------|---------|---------|---------|------------------------|------------------------|
| n*                |         | 87      | 48      |                        | 87                     |
| Extent, %         |         |         |         |                        |                        |
| Emphysema         | 1.9     | 1.8     | 2.1     | 0.132                  | 0.136                  |
| Reticular opacity | 7.5     | 5.4     | 6.2     | 0.004                  | 0.001                  |
| GGO               | 31.4    | 3.7     | 2.3     | 0.000                  | 0.002                  |
| Consolidation     | 4.7     | 0.8     | 0.8     | 0.000                  | 0.008                  |
| Total             | 45.4    | 11.6    | 7.3     | 0.000                  | <0.001                 |

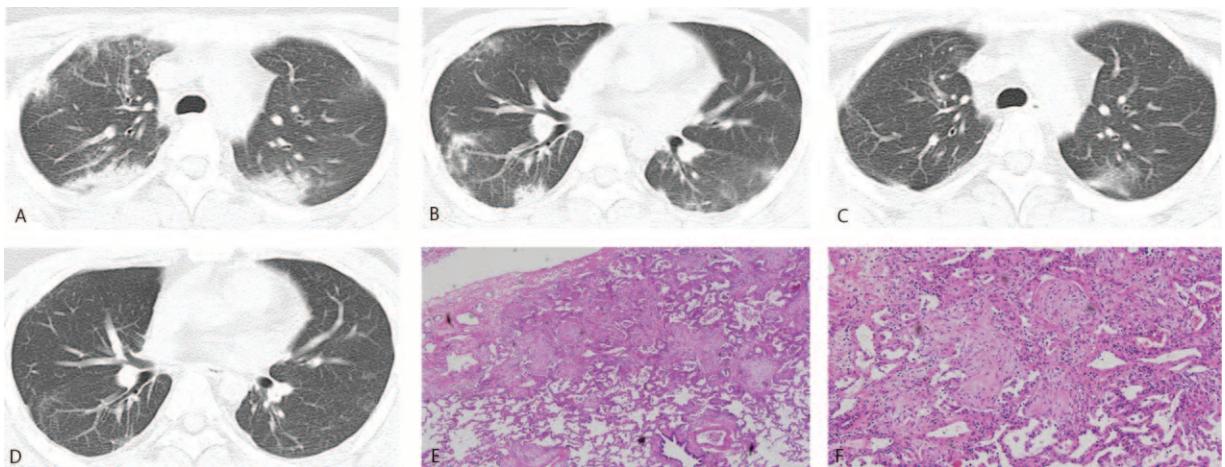
Note: —Except where indicated, data indicate extent of pulmonary parenchymal lesions, expressed as a percentage of the mean value.

CT = computed tomography, GGO = ground-glass opacity, Time1CT = initial thin-section CT, Time2CT = subsequent thin-section CT, Time3CT = second follow-up thin-section CT.

\*Data are numbers of patients. P values for the analysis of variance comparing Time1CT versus Time2CT and Time2CT versus Time3CT with paired t test.



**FIGURE 4.** CT images obtained in a 59-year-old man with lymphoma and rituximab-induced interstitial pneumonitis with the hypersensitive pneumonitis pattern. (A, B) Thin-section CT axial and coronal images (1-mm reconstruction) show diffuse area of GGO without sparing in both lungs. (C, D) Follow-up thin-section CT axial and coronal images (1-mm reconstruction) at the same levels 43 days later show complete resolution after cessation of chemotherapy and initiation of steroid therapy. CT = computed tomography, GGO = ground-glass opacity.



**FIGURE 5.** CT images obtained in a 14-year-old adolescent girl with immature teratoma of ovary and bleomycin-induced interstitial pneumonitis with OP pattern. (A, B) Thin-section CT axial lung images (1-mm reconstruction) obtained at the level of carina and superior segmental bronchi of both lower lobes. CT images show multifocal patchy consolidations in subpleural area of both lungs. (C, D) Follow-up thin-section CT axial lung images (1-mm reconstruction) at the same levels 101 days later show markedly decreased patchy airspace consolidations and mild residual lesion in left upper lobe after cessation of chemotherapy and initiation of steroid therapy. (E, F) Wedge resection was performed and revealed organizing pneumonia. Photomicrographs show interstitial inflammation and occlusion of terminal bronchioles with plugs (original magnification,  $\times 40$  and  $\times 100$ ; hematoxylin-eosin stain, respectively). CT = computed tomography, OP = organizing pneumonia.



persistent interstitial edema or interstitial fibrosis; (2) an OP pattern with multifocal patchy subpleural or peribronchovascular consolidation was explained by various causes of secondary OP; (3) a HP pattern with diffuse GGO was explained by a hypersensitivity reaction; and (4) a DAD pattern with extensive bilateral airspace consolidation mainly in dependent lungs, with diffuse GGO generally in nondependent lungs, was explained by drug-induced acute respiratory distress syndrome or acute lung injury.<sup>20</sup>

In our study, the most common pattern was HP (51%) with diffuse GGO, as reported.<sup>11,21</sup> Most of the CIIP had bilateral and symmetric distributions,<sup>22</sup> and most lacked craniocaudal dominance. However, the NSIP pattern of CIIP has been found to show lower lung dominance,<sup>18,20</sup> but those studies only included CIIP caused by cytotoxic drug such as bleomycin, which usually caused reticulation in lower lung peripheral zone.

In this study, all parenchymal abnormality, except emphysema, showed significant decrease in extent overtime. This result reflects that CIIP is a reversible disease, if proper diagnosis and management are performed. Therefore, the reticulation in CIIP can be differentiated from idiopathic interstitial pneumonia. However, reticulation increased somewhat between Time2CT and Time3CT, perhaps due to a minimal evolution of GGO or consolidation, or due to observational error. Another important differential point is that not all patients had honeycomb cysts, with relatively common in idiopathic pulmonary fibrosis.

The main differential diagnosis differs according to the CIIP patterns. For example, atypical pneumonia, such as *Pneumocystis carinii* pneumonia, or viral pneumonia should be excluded in the HP patterns.<sup>23,24</sup> With an NSIP pattern, idiopathic NSIP, interstitial fibrosis, sequela of atypical pneumonia, and lymphangitic carcinomatosis should be considered<sup>25,26</sup>; with an OP pattern, secondary OP or multifocal infection should be considered<sup>27</sup>; and with a DAD pattern, adult respiratory distress syndrome or acute lung injury from other causes is possible.<sup>28</sup>

We divided 4 CT patterns into 2 groups based on extent of GGO. GGO generally indicates the presence of an ongoing and potentially treatable process. So we expected different temporal changes between them. Indeed, Group 2 usually showed more active and acute manifestation than Group 1 regarding initial presentation and evolution of diffuse lung disease. Although most of the CIIP followed the course of a subacute or chronic disease, in Group 1 (NSIP or OP patterns), mainly caused by cytotoxic agents, most of the CIIP occurred after 3 months, whereas in Group 2 (HP or DAD patterns), mainly caused by molecularly targeted agents, it was mostly restricted to the first 3 months. This difference may be partly explained by the fact that the effects of cytotoxic drugs are dose dependent, whereas molecularly targeted drugs have no cumulative dose effect.<sup>21</sup> Our patients had symptoms of dyspnea, fever, and cough, which are frequent symptoms of CIIP.<sup>5,6,29,30</sup>

Our study has several limitations. First, the study was retrospective and the intervals between follow-up CT scans varied. Second, analysis of thin-section CT images by radiologists could be subjective; disease was confirmed by biopsy and correlated with histopathology in only 7 patients. Third, when a combination of drugs had been used or stopped at the same time, the drug most known for pulmonary toxicity was considered the cause of the CIIP. Fourth, there was no case of CIIP manifesting eosinophilic pneumonia or bronchiolitis obliterans; this means that such cases were underestimated or rare. Only 4 patients whose CT findings worsened after discontinuation of drugs were excluded: 3 died after cardiac arrest, pulmonary embolism,

and coinfection, respectively; the 1 survivor had an unknown superimposed pneumonia. However, such cases may be unavoidable when diagnosing CIIP and can be neglected because of their small number. We included the patients by a word search for the final diagnosis and inevitably are missing minor cases of drug reactions. However, chemotherapy agents can continue to be used for asymptomatic patients, thus it is difficult to diagnose the CIIP without clinical significance.

Despite these limitations, to our knowledge our study is the largest recent study to describe CT findings of CIIP with follow-up CT scans, according to patterns. In conclusions, the diagnosis of CIIP should be considered if CT imaging reveals reversible diffuse, bilateral, and symmetric lung lesions accompanying chemotherapy. A pattern approach in diagnosing CIIP is more appropriate and effective in routine practice.

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