[6] also reported a case of eosinophilic pneumonia. While immunoallergic mechanisms were implicated in these cases, Rosado et al. [4] reported a case in which pathological findings were compatible with nonspecific interstitial pneumonia, suggesting that imatinib-induced pneumonitis is a heterogeneous condition.

In the present case, the patient gradually developed symptoms after readministration of imatinib, and a chest X-ray taken 1 month after readministration showed the development of bilateral ground-glass opacities. Apart from imatinib, no other medication was introduced during the month preceding the patient's admission. Furthermore, no clinical evidence of respiratory infection, collagen disease or systemic vasculitis was detected. Hypersensitivity pneumonitis and acute exacerbation of IPF were also considered in the differential diagnosis. However, a negative provocation test after hospital discharge did not support the possibility of hypersensitivity pneumonitis. Moreover, the patient exhibited a relatively good response to steroid therapy, which is not the usual case with acute exacerbation of IPF. A diagnosis of imatinib-induced interstitial pneumonitis is supported by the above findings. The present patient received a reduced dose (200 mg/day) of imatinib because of the adverse effects observed at the initial administration. Although this dose was lower than that administered in other case reports (400–600 mg/day) [3–7], we believe it was sufficient to induce pneumonitis.

The mechanism of drug-induced pneumonitis is considered to involve either cytotoxic or idiosyncratic reactions; the latter include allergic reactions to medications. It is possible that an immunoallergic mechanism is implicated in the present case. Although a drug lymphocyte stimulation test yielded negative results for imatinib, the onset of pneumonitis after readministration of imatinib and the responsiveness to steroid therapy is in support of the postulated mechanism. Histopathologic examination of TBLB specimens failed to demonstrate a significant lymphocyte and eosinophil infiltration, one of the pathologic feature indicating allergic reactions. However, as TBLB was delayed owing to the severity of the patient's condition, the possibility exists that the antecedent steroid therapy modified the pathologic features. Accordingly, it is possible that by the time biopsy was feasible, only a modest infiltration of inflammatory cells was apparent.

The present case is characteristic in that the patient had preexisting interstitial lung disease; however, this is the first report of imatinib-induced pneumonitis in a patient with IPF. Because imatinib also inhibits c-kit and platelet-derived growth factor (PDGF) receptor tyrosine kinases, the spectrum of diseases that may respond to this agent is growing [8–10]. PDGF is a potent mitogen and chemoattractant for fibroblasts and smooth muscle cells and also stimulates fibroblast collagen synthesis. It is hence thought to be an important contributing factor to the development of lung fibrosis. In IPF, local production of PDGF is increased [11]. In accordance with exaggerated production of this cytokine, its specific receptor, the PDGF receptor, is also upregulated in various pulmonary cells including alveolar epithelial cells at early-stage IPF [12]. Although the precise role of PDGF receptor upregulation in the alveolar epithelium is unclear in lung fibrosis, it might represent one of the mechanisms facilitating re-epithelialzation of injured tissue. On the other hand, in vitro, imatinib actually suppresses the proliferation of type-II-like epithelial cells and this effect is likely mediated through inhibition of PDGF receptor phosphorylation [13]. Hence, the influence of imatinib on tissue repair in lung fibrosis remains to be determined.

In this regard, attention should be drawn to the recent issues related to gefitinib, a new molecular-targeting anticancer agent. Gefitinib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, has been shown to be effective against advanced non-small cell lung cancer [14]. However, acquired acute lung injury has been correlated with gefitinib treatment in a significant number of patients in Japan [15]. The precise mechanism of action of this drug in relation to its adverse effect on the lung parenchyma remains unclear. However, one possible explanation is provided by Suzuki et al. [16] who found that inhibition of epidermal growth factor receptor phosphorylation augmented lung fibrosis in vivo by reducing regenerative epithelial proliferation. Therefore, caution is advised against the use of gefitinib in cancer patients with interstitial lung disease. It remains to be determined whether imatinib acts in a similar manner through inhibition of PDGF receptor phosphorylation. We do advocate, however, that all drugs which have the potential to modulate epithelial cell proliferation be used with caution in patients with lung fibrosis.

In summary, we report the case of imatinib-induced pneumonitis in a patient with IPF. So far, interstitial pneumonitis related to this drug appears to be rare; however, we should monitor such adverse events closely, as the underlying mechanism remains to be elucidated. Imatinib is one agent that is currently being used in ongoing clinical trials in IPF in the USA (according to the Tulane University website http://www2.tulane.edu/

about.cfm). In the light of the issues surrounding gefitinib, we recommend that further cases be accumulated in order to establish the clinical safety of the administration of imatinib, particularly in patients with interstitial lung disease.

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SCIENTIFIC LETTER

Idiopathic pulmonary fibrosis—results from a Japanese nationwide epidemiological survey using individual clinical records

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Nationwide epidemiological survey of patients with idiopathic pulmonary fibrosis using clinical personal records in Japan
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Key words: clinical personal records, epidemiological survey, idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis, prevalence.

INTRODUCTION

Idiopathic interstitial pneumonias (IIP) were internationally classified into seven types in 2002.[1] In Japan, the fourth revision of clinical diagnostic criteria for IIP was prepared in 2003, and IIP were classified in accordance with the international classification.[2] Since the Specific Disease/Pulmonary Fibrosis Survey/Study Group of the Ministry of Health and Welfare (currently, Study Group on Diffuse Pulmonary Disorders, Scientific Research/Refractory Disease-Overcoming Research Business, Ministry of Health, Labor and Welfare) was established in 1974, epidemiological studies of IIP were made using a questionnaire[3] or in specific areas[4,5]. Currently, a nationwide epidemiological study may be of significance, as the disease entity has now been well established.

METHODS

Among patients with IIP, the subjects were those to whom a certificate of medical benefits was delivered in 2005. As medical benefits for IIP are examined in each prefecture, clinical personal records are collected and submitted to the Disease Strategy Section, Health Bureau, Ministry of Health, Labor and Welfare and then stored in a database in the Ministry. Using this database, we analysed the age at onset, smoking history, dust inhalation, diagnostic methods, disease type, classification of severity, main symptoms, respiratory dysfunction, imaging findings, serum markers and drug therapy in the new patients, and disease type, classification of severity and drug therapy in the updated patients.

In Japan, the severity of IIP was classified by resting PaO_2 and desaturation during exercise: stage I: $PaO_2 \geq 80$ Torr; stage II: $70 \leq PaO_2 < 80$ Torr; stage III: $60 \leq PaO_2 < 70$ Torr; stage IV: $PaO_2 < 60$ Torr. If SpO_2 was below 90% during 6-minute walking test, stage II or III was up to III or IV, respectively.[2]

RESULTS

In 2005, medical benefits were delivered to 4396 patients with IIP. Based on a population of 127 756 815 persons, the prevalence was 3.44 per 100 000 persons. Of the 4396 patients, clinical personal records were collected and available for 1543 (35.1%) patients; new and updated patients were 658 and 885, respectively. Concerning disease type, a total of 1322 (85.7%) patients had IPF (Table 1): 545 new patients and 777 updated patients; 878 were men. The following analysis was performed in the IPF.

Pathological diagnosis was made only in 67 (12%) patients. Concerning disease severity, stage I/II/III/IV were 32/28/177/287 in the new patients and 73/64/229/318 in the updated patients. The mean age at disease onset was 64.5 ± 10.5 years (men: 64.8 ± 9.3

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Table 1 Clinical diagnosis in idiopathic interstitial pneumonias using clinical personal records

Clinical diagnosis	Case	
	New	Updated
IPF	545	777
NSIP	14	82
COP		7
AIP	1	6
DIP	2	
RBILD		1
LIP		1
Others	2	11
Unknown	94	
Total	658	885

AIP, acute interstitial pneumonia; COP, cryptogenic organaizing pneumonia; DIP, desquamative interstitial pneumonia; LIP, lymphoid interstitial pneumonia; NSIP, non-specific interstitial pneumonia; RBILD, respiratory bronchiolitis-associated interstitial pneumonia.

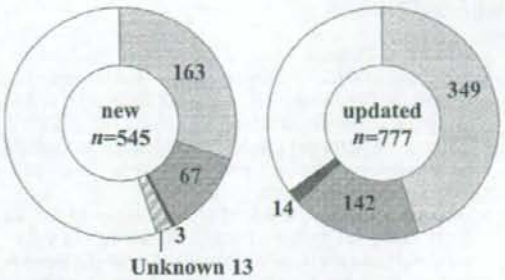

Figure 1 Drug treatment in new and updated patients with IPF. (▨) Corticosteroid; (▩) corticosteroid + immunosuppressant; (■) immunosuppressant.

years, women: 64.0 ± 12.4 years). There was no gender difference. Overall, 59% had a history of smoking (men: 79%, women: 13%). In addition, 13% had a history of dust inhalation (men: 17%, women: 2%). The prevalence was significantly higher in men.

The main symptoms of fine crackles, dry cough, dyspnoea on exertion and finger clubbing were observed in 98%, 94%, 98% and 53%, respectively. Concerning respiratory function, restrictive impairment, reduced diffusion capacity, hypoxemia, an increase in A-aDO_2 and a desaturation after a 6-minute walking test were noted in 86%, 92%, 90%, 80% and 91%, respectively. There was a significantly negative correlation between %VC or %DLco and disease severity. CXR showed bilateral diffuse shadows, predominant lower lung fields and lung volume loss in 99%, 93% and 83%, respectively. HRCT revealed bilateral basal shadow, honeycombing, traction bronchiectasis, ground glass opacities and consolidation in 97%, 91%, 85%, 82% and 43%, respectively. Serological testing showed increases in KL-6, SP-A, SP-D and LDH in 95%, 89%, 86% and 71%, respectively. There was no correlation between serum markers and disease severity.

Drug therapy was performed in 246 (45%) of the 545 new patients and in 505 (65%) of the 777 updated patients. Corticosteroids alone were most frequently administered (Fig. 1). With respect to severity of IPF, the proportion of patients undergoing drug therapy increased with severity among the new patients, whereas in the updated patients, there was a negative correlation. There were no differences in drug therapy among patients with differing severities.

DISCUSSION

The present epidemiological study is the first nationwide report in Japan to utilize clinical personal records. Previous epidemiological studies were conducted using a questionnaire or health check-up in the specific prefectures. In Hokkaido, the prevalence of IIP is 3.4 per 100 000 persons[4]. Based on the results of health check-up in residents over 50 years in Niigata, the prevalence was 2.9 to 4.9 per 100 000 persons[5]. Thus, the prevalence of IIP in Japan has been reported to be approximately five per 100 000 persons. In the present study, the prevalence was estimated to be 3.44 per 100 000, which was consistent with the values previously reported. However, IIP conditions for which medical benefits were delivered corresponded to IPF severity level of III or IV. Therefore, patients with other IIP or mild IPF were not included, and the true prevalence may be higher. In epidemiological studies of IPF in various countries, the prevalence in England,[6] in the USA[7] and in Finland[8] were 3–6, 13–20 and 16–18 per 100 000 persons, respectively. Recently, these prevalence numbers have risen further.[9,10]

The clinical personal records were collected for about 35% of the 4396 patients in our survey. The conditions of most patients with IIP corresponded to stage III or IV IPF. Our subjects showed typical clinical findings, because most patients were diagnosed as having IPF based on clinical findings. Furthermore, a high proportion of patients were positive for three new serum markers, KL-6, SP-A and SP-D, which suggests that they may be useful in the diagnosis of IPF.

In the present study, severe IPF patients predominated, which could raise various concerns. Initially, most patients were diagnosed based on clinical findings, suggesting fibrotic NSIP might be commingled in IPF. Regarding treatment, drug therapy was performed in 65% of our updated patients, reflecting medical treatment might be aimed to prevent disease progression even in stage I or II patients in clinical practice, despite its low efficacy. However, most regimens consisted of corticosteroids alone; combination therapy with immunosuppressants, as recommended in the guidelines,[1,2] was not commonly used. N-acetylcysteine and interferon are not approved for use in the Japanese health system.

This study was based on the data collected in 2005. Future continuous analysis may facilitate the understanding of various features of IIP, especially IPF.

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Acute eosinophilic pneumonia: Thin-section CT findings in 29 patients

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Abstract

Purpose: To determine thin-section computed tomography (CT) characteristics of acute eosinophilic pneumonia (AEP).
Materials and methods: Thin-section CT scans of 29 patients (14 males, 15 females; mean age, 26 ± 15 years; age range, 15–72 years) with AEP were included this retrospective study. The clinical diagnosis of AEP was established by Allen's criteria. Each thin-section CT was reviewed by two observers.
Results: Bilateral areas with ground-glass attenuation were observed on thin-section CT in all patients. Areas of air-space consolidation were present in 16 (55%) of 29 patients. Poorly defined centrilobular nodules were present in 9 patients (31%). Interlobular septal thickening was present in 26 patients (90%). Thickening of bronchovascular bundles was present in 19 patients (66%). Pleural effusions were present in 23 patients (79%) (bilateral = 22, right side = 1, left side = 0). The predominant overall anatomic distribution was central in only 2 (7%) of 29 patients, peripheral in 9 patients (31%), and random in 18 patients (62%). The overall zonal predominance was upper in 4 patients (14%), lower in 8 patients (28%), and random in 17 patients (58%).
Conclusion: CT findings in AEP patients consisted mainly of bilateral areas of ground-glass attenuation, interlobular septal thickening, thickening of bronchovascular bundles, and the presence of a pleural effusion without cardiomegaly. The most common overall anatomic distribution and zonal predominance of the abnormal CT findings were random.

Keywords: Acute eosinophilic pneumonia; Radiography; Thin-section CT

1. Introduction

The concept of acute eosinophilic pneumonia (AEP) was first suggested by Allen et al. in 1989 [1]. AEP has an acute onset and the time from onset to the peak of disease is usually less than a week. Patients present with respiratory insufficiency, hypoxemia, fever, diffuse pulmonary infiltrates, increased eosinophil count (>25%) on bronchoalveolar lavage (BAL), and no evidence of infection or previous atopic illness. AEP is also characterized by a rapid response to corticosteroids with no relapses and improvement of radiographic abnormalities without fibrosis [1,2]. Some case reports have stated that inhalation of various materials could provoke AEP [3–6]. Currently, researchers, particularly Japanese investigators, consider

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that cigarette smoking is an important causative agent of AEP [7–10].

Characteristic chest X-ray findings of AEP have been reported, including bilateral diffuse areas with ground-glass attenuation, smooth interlobular septal thickening, defined nodules, and pleural effusion without cardiomegaly [11–14]. However, these studies are based on only a small number of AEP patients and their CT findings were incompletely characterized with respect to their anatomic distribution and zonal predominance. The aim of this study was to determine the characteristic findings on thin-section CT of AEP patients, with particular attention to the distribution of the various abnormal findings.

2. Materials and methods

2.1. Study population

Twenty-nine consecutive patients who had a definitive diagnosis of AEP and had thin-section CT at our six institutions in the previous 15 years were entered into the study. The patients included 14 males and 15 females, aged 26 ± 15 years (mean ± S.D.) (range: 15–72 years). The institutional review board gave full approval and waived informed consent for our retrospective study.

All patients fulfilled Allen's diagnostic criteria as mentioned in Section 1 [2], and all cases had pulmonary infiltration of eosinophils based on BAL. Thus, patients with other infectious or non-infectious processes associated with other eosinophilic diseases were excluded.

2.2. Thin-section CT techniques

Sequential CT scans were obtained using a variety of scanners. All CT scans were done at the end of inspiration with the patient in the supine position, and no intravenous contrast material was used. Each patient had a single chest CT examination. The CT scans consisted of 1–2-mm collimation sections reconstructed using a high-spatial-frequency algorithm. Images were photographed at window settings appropriate for viewing both the lung (window level from −500 to −800 HU; window width from 1000 to 2000 HU) and the mediastinal (window level from 15 to 40 HU; window width from 300 to 400 HU) windows. The protocols consisted of thin sections obtained at 1-cm intervals (20 patients), 1.5-cm intervals (4 patients), 2-cm intervals (4 patients), or 3-cm intervals (1 patients).

2.3. Evaluation of thin-section CT findings

The CT scans were randomized and then retrospectively analyzed by two chest radiologists (H.S. with 7 years experience and T.D. with 5 years experience). The observers were unaware of any clinical or pathologic findings other than the patient's age and gender. In cases of discordant interpretations, a final decision was reached by consensus of the two observers.

The CT scans were assessed for the presence, extent, and anatomic distribution of areas with ground-glass attenuation, areas of air-space consolidation, nodules, interlobular septal thickening, thickening of bronchovascular bundles, pleural effusion, cardiomegaly, lymphnode enlargement, and the presence of a crazy-paving appearance. Ground-glass attenuation was defined as hazy increased attenuation of the lung that did not obscure the underlying vessels. Air-space consolidation was defined as a homogeneous increase in pulmonary parenchymal attenuation that obscured the underlying vessels. A nodule was defined as a focal, rounded opacity less than 3 cm in diameter, which could be either well or poorly defined. When a nodule was located in the center of the lobule or lobular core, it was defined as a centrilobular nodule. Interlobular septal thickening was defined as abnormal widening of interlobular septa. Thickening of bronchovascular bundles was defined as an increase in bronchial wall thickness and an increase in the diameter of pulmonary artery branches caused by thickened peribronchovascular interstitium. Lymph nodes were considered to be enlarged if their short-axis diameter on CT exceeded 10 mm. If a pleural effusion was present, then its distribution (unilateral or bilateral distribution) was also recorded. A crazy-paving appearance was defined as a reticular pattern superimposed on a background of ground-glass attenuation [15,16].

The anatomic distribution was noted to be: central, if the abnormalities were primarily located in the inner third of the lung; peripheral, if the abnormalities were primarily present in the outer third of the lung; and random, if there was no predominant location. Zonal predominance was assessed as being upper, lower, or random. Upper lung zone predominance was present when most of the abnormalities were above the level of the tracheal carina; lower zone predominance was present when most of the abnormalities were below this level.

2.4. Statistical analysis

The frequencies of interobserver agreement for all of the abnormalities noted on CT images including the predominant overall anatomic distribution and the overall zonal predominance, was analyzed with the κ statistic. Interobserver agreement was classified as poor ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), good ($\kappa = 0.61–0.80$), or excellent ($\kappa = 0.81–1.00$).

3. Results

Interobserver agreement for all of the abnormalities noted on CT images was moderate to excellent ($\kappa = 0.41–1.0$) (Table 1). There was fair to moderate interobserver agreement with respect to the predominant overall anatomic distribution ($\kappa = 0.25–0.53$) (Table 1). There was moderate to good interobserver agreement for the overall zonal predominance ($\kappa = 0.41–0.65$) (Table 1).

The frequencies of the various CT findings are summarized in Table 1. All AEP patients presented with bilateral abnormal attenuation; bilateral areas with ground-glass attenuation were found in all AEP patients (Figs. 1–3). In the present study, the crazy-paving appearance was seen in 8 (28%) of 29 patients (Fig. 3). Bilateral areas of air-space consolidation were found in 16 patients (55%) (Figs. 4–6). Nodules were present in 9 patients (31%) (Fig. 7). All cases had poorly defined centrilobular nod-

Table 1
CT findings of 29 patients with acute eosinophilic pneumonia

CT finding	Number of patients	κ
Ground-glass attenuation	29/29 (100)	1.00
Air-space consolidation	16/29 (55)	0.77
Nodules		
Centrilobular	9/29 (31)	0.41
Random	0/29 (0)	1.00
Interlobular septal thickening	26/29 (90)	0.52
Thickening of bronchovascular bundles	19/29 (66)	0.52
Pleural effusion		
Bilateral	22/29 (76)	1.00
Right side	1/29 (3)	1.00
Left side	0/29 (0)	1.00
Cardiomegaly	0/29 (0)	1.00
Lymph node enlargement	13/29 (45)	0.56
Predominant overall anatomic distribution		
Central	2/29 (7)	0.65
Peripheral	9/29 (31)	0.41
Random	18/29 (62)	0.41
Overall zonal predominance		
Upper	4/29 (14)	0.53
Lower	8/29 (28)	0.25
Random	17/29 (58)	0.26

Note: Data in parentheses are percentages. The κ statistic is classified as poor ($\kappa = 0.00$–0.20), fair ($\kappa = 0.21$–0.40), moderate ($\kappa = 0.41$–0.60), good ($\kappa = 0.61$–0.80), or excellent ($\kappa = 0.81$–1.00).

ules. Interlobular septal thickening was found in 26 patients (90%) (Fig. 6). Thickening of bronchovascular bundles was seen in 19 patients (66%) (Figs. 1–3 and 5). Pleural effusions were present in 23 patients (79%): 22 (76%) patients had bilateral pleural effusions; 1 (3%) patient had a right-sided pleural effusion; and no patients had a left-sided pleural effusion. None of the patients had cardiomegaly. Lymph node enlargement was present in 13 patients (45%).

The predominant overall anatomic distribution was central in only 2 (7%) of 29 patients, peripheral in 9 patients (31%), and random in 18 patients (62%). The overall zonal predominance

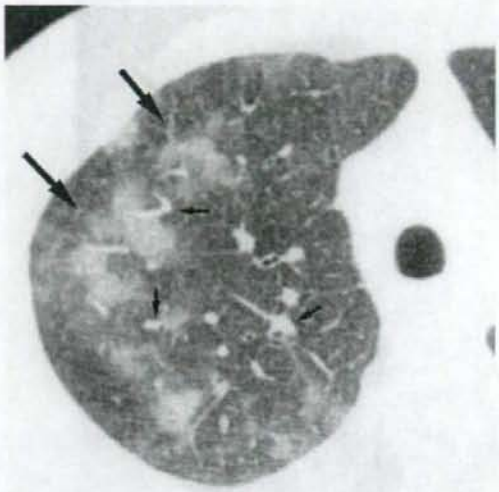

Fig. 2. Acute eosinophilic pneumonia in a 20-year-old woman. Transverse thin section CT (1.5-mm collimation) through the right upper lobe demonstrates patchy areas with ground-glass attenuation (large arrows) and thickened bronchovascular bundles (small arrows).

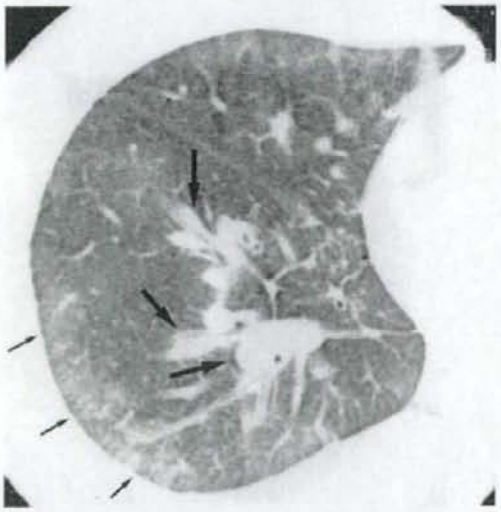

Fig. 1. Acute eosinophilic pneumonia in an 18-year-old woman. Transverse thin section CT (2-mm collimation) through the right lower lobe demonstrates thickened bronchovascular bundles (large arrows) and areas with ground-glass attenuation (small arrows) involving mainly the peripheral lung region.

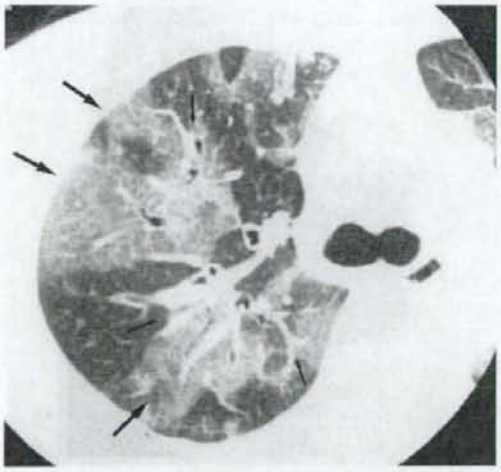

Fig. 3. Acute eosinophilic pneumonia in a 72-year-old woman. Transverse thin section CT (2-mm collimation) at the level of tracheal carina demonstrates the crazy-paving appearance (large arrows). Also note peripheral thickened bronchovascular bundles (small arrows).

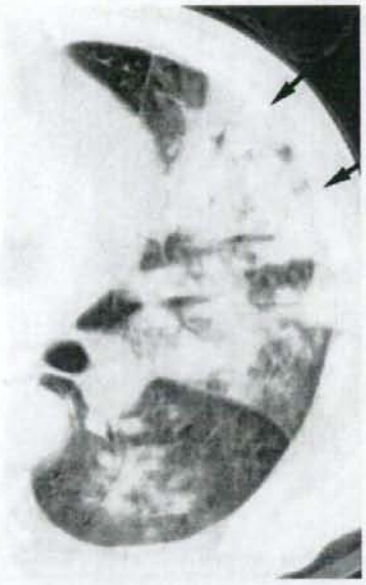

Fig. 4. Acute eosinophilic pneumonia in a 36-year-old man. Transverse thin section CT (1-mm collimation) through the left upper lobe demonstrates extensive diffusely distributed air-space consolidation (large arrows).

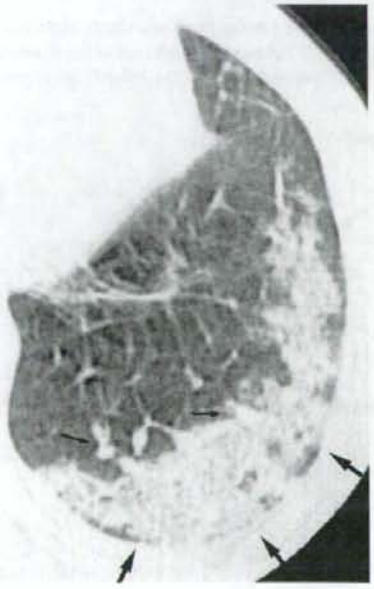

Fig. 5. Acute eosinophilic pneumonia in a 58-year-old woman. Transverse thin section CT (1.5-mm collimation) through the left lower lobe demonstrates areas of air-space consolidation (large arrows) involving mainly the peripheral lung region and thickened bronchovascular bundles (small arrows).

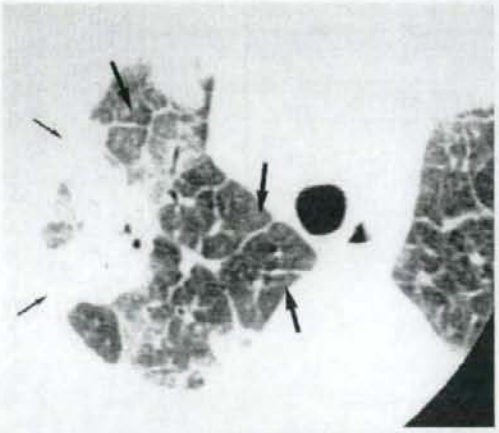

Fig. 6. Acute eosinophilic pneumonia in a 53-year-old woman. Transverse thin section CT (2-mm collimation) through the apical segments of the right upper lobe demonstrates diffusely distributed thickening of interlobular septa (large arrows), extensive areas of air-space consolidation (small arrows).

was upper in 4 patients (14%), lower in 8 patients (28%), and random in 17 patients (58%).

The frequencies for the anatomic distribution of each CT finding are listed in Table 2. Ground-glass attenuation had a central predominance in 3 (10%) of 29 patients, peripheral predominance in 15 patients (52%), and was randomly distributed in 11 patients (38%). Air-space consolidation had central predominance in 2 (13%) of 16 patients, peripheral predominance in 8 patients (50%), and was randomly distributed in 6 patients (37%). Centrilobular nodules had a peripheral predominance in 7 (78%) of 9 patients and were randomly distributed in 2 patients (22%).

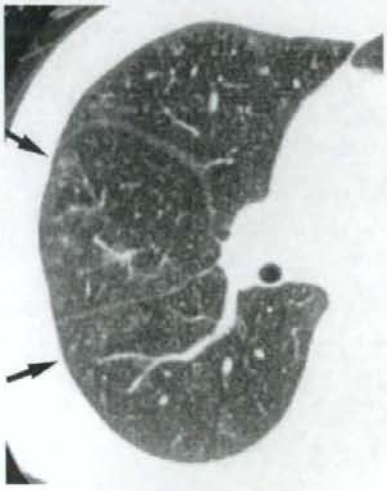

Fig. 7. Acute eosinophilic pneumonia in a 50-year-old woman. Transverse thin section CT (2-mm collimation) at the level of the right inferior pulmonary vein demonstrates poorly defined centrilobular nodules (large arrows).

Table 2
Predominant anatomic distribution of each CT findings of acute eosinophilic pneumonia

CT findings	Number of patients
Ground-glass attenuation	
Central predominance	3/29 (10)
Peripheral predominance	15/29 (52)
Random	11/29 (38)
Air-space consolidation	
Central predominance	2/16 (13)
Peripheral predominance	8/16 (50)
Random	6/16 (37)
Centrilobular nodules	
Central predominance	0/9 (0)
Peripheral predominance	7/9 (78)
Random	2/9 (22)

Note: Data in parentheses are percentages. Data are based on the total numbers of consensual findings by two observers.

4. Discussion

Previous studies have reported the general chest radiographic findings of AEP as bilateral diffuse infiltration with a non-segmental distribution [11–14]. In the present study, bilateral areas with ground-glass attenuation were observed in all AEP patients on thin-section CT; this was the most common finding. Interlobular septal thickening was found in 26 (90%) of 29 patients and was the second most common finding. Furthermore, bilateral areas of air-space consolidation and thickening of bronchovascular bundles were also seen in more than half of the AEP cases. Thus, these findings are also very important in AEP.

No previously published studies have detailed the characteristic anatomic distribution and zonal predominance of abnormal shadows in AEP patients. Johkoh et al. [14] reported that the anatomic distribution and zonal predominance was predominantly random on thin-section CT in AEP patients. In the present study, the predominant overall anatomic distribution and the overall zonal predominance on thin-section CT was random in more than half of AEP patients. However, the anatomic distribution of each CT findings including areas with ground-glass attenuation and areas of air-space consolidation, had a peripheral predominance in almost half of the cases.

The crazy-paving appearance is defined as areas with ground-glass attenuation with superimposed intralobular reticular opacities [15,16]. At first, this pattern was considered to be highly suggestive of alveolar proteinosis [17]. However, the crazy-paving appearance has since been recognized as a nonspecific finding that is seen in a variety of interstitial and airspace lung diseases [15,16]. In the present study, the crazy-paving appearance was seen in 8 (28%) of 29 patients (Fig. 3). Thus, AEP should be considered in the differential diagnosis of cases with a crazy-paving appearance.

Cheon et al. [11] reported that poorly defined nodules were seen in only one of six AEP patients. However, Johkoh et al. [14] reported that nodules are uncommon findings in AEP. In the present study, nodules were present in 9 (31%) of 29 patients and were, thus, not uncommon findings (Fig. 7). All of these cases had poorly defined centrilobular nodules. Abe et al. [18] reported that 1 case with an early stage of AEP had fine nodules on high resolution computed tomography (HRCT); they thought that the presence of a fine nodular shadow might be a useful finding in establishing the diagnosis of AEP, especially in the early stage. Remy-Jardin et al. [19] reported that poorly defined micronodules were seen in smoking-induced lung on thin-section CT, and were not seen in ex-smokers. In the present study, all of the patients with nodular shadow were current smokers, and it was considered that their cigarette smoking had provoked the AEP. Therefore, in patients with AEP, nodular shadows may be the result of smoking.

In previous studies of AEP patients, Cheon et al. [11] reported that pleural effusions were observed in 4 (67%) (bilateral = 2, unilateral = 2) of 6 patients, Pope-Harman et al. [12] reported that pleural effusions were observed in 9 (60%) (bilateral = 8, unilateral = 1) of 15 patients, and King et al. [13] reported that pleural effusions were observed in 7 (58%) (bilateral = 5, unilateral = 2) of 12 patients. In the present study, pleural effusions were seen in 23 (79%) of 29 patients and were almost always bilateral. Given these results, pleural effusions are common in AEP.

The eosinophilic lung diseases are a diverse group of pulmonary disorders linked by the common findings of peripheral or tissue eosinophilia. AEP is one of the idiopathic eosinophilic lung diseases that include simple pulmonary eosinophilia and chronic eosinophilic pneumonia. Simple pulmonary eosinophilia, also known as Loeffler's syndrome, is clinically characterized by minimal or no pulmonary symptom, increased peripheral blood eosinophils and typically spontaneous resolution within one month. The radiographic abnormalities are characterized by transient and migratory infiltration. On CT, simple pulmonary eosinophilia generally has a peripheral predominance [2,14]. Interlobular septal thickening, thickening of bronchovascular bundles and pleural effusions that are common findings in AEP patients are almost never seen findings in patients with simple pulmonary eosinophilia [14] and very helpful in differential diagnosis from AEP. Clinically, patients with chronic eosinophilic pneumonia preset frequently with progressive respiratory symptoms for more than 3 months or longer. Chronic eosinophilic pneumonia is usually associated with increased peripheral blood eosinophils and presents prompt response to the steroid therapy. The radiographic abnormalities are characterized by the presence of homogeneous peripheral airspace consolidation, "the photographic negative of pulmonary edema" [14,20,21]. On CT, interlobular septal thickening, thickening of bronchovascular bundles and pleural effusions that are common findings in AEP patients are uncommon findings in patients with chronic eosinophilic pneumonia [14] and also helpful in differential diagnosis from AEP.

Our study has three major limitations. First, the number of patients in this study was relatively small. However, previous studies had even fewer patients. Second, this was a retrospective study. Therefore, a prospective study is needed to confirm the results of this study. Finally, CT images used in this study were obtained with different CT scanners and protocols. Thus,

the details of each finding could be evaluated only to a limited degree. However, the main purpose of this study was to evaluate the anatomical distribution of the CT findings of AEP; we believe that the CT images used in the present study were adequate for this purpose.

In conclusion, CT findings in AEP patients consisted mainly of bilateral areas of ground-glass attenuation, interlobular septal thickening, thickening of bronchovascular bundles, and the presence of a pleural effusion without cardiomegaly. The most common overall anatomic distribution and zonal predominance of the abnormal CT findings were random. Using the characteristic CT findings, AEP can be differentiated from the other eosinophilic lung diseases using thin-section CT; however, the CT findings must be carefully correlated with the clinical features to make a definitive diagnosis.

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