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High-resolution computed tomography patterns and immunopathogenetic findings in drug-induced pneumonitis

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Summary
We tried to determine whether high-resolution computed tomography (HRCT) patterns correlate with the immunopathogenetic findings and whether they could provide helpful information for predicting the outcomes in non-neoplastic drug-induced pneumonitis. The HRCT images were classified as most suggestive of pneumonitis, diffuse alveolar damage (DAD), non-specific interstitial pneumonia, organizing pneumonia (OP), hypersensitivity pneumonitis, and acute eosinophilic pneumonia (AEP) in 34 patients with non-neoplastic drug-induced pneumonitis. The patients were analyzed for the bronchoalveolar lavage (BAL) cell findings and for the circulating levels of interferon-inducible protein 10 (IP-10) and macrophage-derived chemokine (MDC), which were measured by an enzyme-linked immunosorbent assay. The cumulative dose of corticosteroids received by the patients and the day when they required supplemental oxygen were calculated as outcome markers. There were no differences in the circulating chemokine levels and the BAL cell profiles except for the eosinophil percentages among the HRCT patterns. Most of the cases with pulmonary eosinophilia belonged to the OP and AEP groups, and the circulating MDC levels correlated with BAL eosinophil percentages. We could not find any relationship between the BAL cell profiles or the chemokine levels and the outcome markers. In contrast, the HRCT patterns rather predicted the outcomes because larger cumulative dose of steroids and longer oxygen supply were required for the patients in the DAD and OP groups. In

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contrast, all patients with AEP recovered without steroid administration. The present study suggests that HRCT does not predict cellular pathophysiology but it may predict the corticosteroid use in non-neoplastic drug-induced pneumonitis.

Introduction

Although the high-resolution computed tomography (HRCT) findings of lung disease are often non-specific, there are some characteristic HRCT findings for some lung diseases which are based on the pathologic findings.[1–3] Especially in idiopathic interstitial pneumonias (IIPs), which consist of seven histologically distinct subtypes, the HRCT findings reflect the histological patterns, thus predicting the prognosis and determining the most appropriate intervention.[1,4–6] The HRCT classification based on the evidence from IIPs and other diffuse lung diseases could be applied to drug-induced pneumonitis.[7–13] However, the utility of HRCT for predicting the outcome in drug-induced pneumonitis is still controversial. Cleverley et al.[9] reported that the HRCT was of limited value in predicting the histological patterns and prognosis when they examined 20 cases of drug-induced lung disease including 15 cases of neoplastic drug-induced pneumonitis. Another report showed that the HRCT pattern could predict the prognosis in gefitinib-induced pneumonitis, gefitinib being, is a selective inhibitor of the epidermal growth factor receptor tyrosine kinase.[14]

Unlike the pathogenesis of neoplastic drug-induced lung injury in which direct cytotoxic mechanisms are often involved,[15] the immune-mediated mechanisms, particularly the T lymphocyte-mediated specific inflammation induced by causative agents appear to contribute to the pathogenesis of non-neoplastic drug-induced pneumonitis.[16] In such cases, the different types of immune responses may produce the different histological phenotypes, which may also be reflected by the HRCT patterns. In general, the chemokine predominantly attracting T helper type 1 (Th1) or T helper type 2 (Th2) cells participate in generating a specific inflammation.[17–20] The Th1 response is crucial for the granulomatous responses[17] and hypersensitivity pneumonitis,[18] whereas elevated Th2 chemokines levels are found in eosinophilic pneumonia.[19,20] The Th1 chemoattractant, interferon-IP-10, and the Th2 chemoattractant, macrophage-derived chemokine (MDC) are detected in the immune-mediated lung diseases and reflect a Th1/Th2 polarization in the lungs.[17,18,20] However, there have so far only been a few reports measuring Th1/Th2-associated chemokines as they related to the mechanisms of drug-induced pneumonitis.[21]

The aim of this study was to clarify the relationship between the HRCT patterns and the immunopathogenetic findings, such as the bronchoalveolar lavage (BAL) cell profiles and circulating chemokine levels in non-neoplastic drug-induced pneumonitis. We also tried to examine whether the HRCT patterns or the immunopathogenetic findings would be helpful for predicting the outcome as assessed by the cumulative dose of corticosteroids and the duration when the patient was under oxygen inhalation.

Materials and methods

Patient selection and sample retrieval

This study was retrospectively done under IRB approval and included 34 consecutive patients with non-neoplastic drug-induced pneumonitis encountered at the Oita University Hospital during the period between January 1996 and July 2007. The diagnosis of drug-induced pneumonitis was made according to a method for estimating the probability of drug reactions by Naranjo et al.,[22] and thus 14 definite cases and 20 probable cases were included.

HRCT scanning method

All patients underwent chest HRCT scanning. The CT scans were obtained with a window setting for lung parenchyma (window width, 1600–1800 HU; window level, −600 to −700 HU) and mediastinum (window width, 300–350 HU; window level, 25–40 HU).

The HRCT images of drug-induced ILD were classified into the following five patterns. The diffuse alveolar damage (DAD) pattern was defined as a pattern of extensive bilateral ground-glass attenuation or consolidations with traction bronchiectasis, such as in acute interstitial pneumonia.[7,9,23] The organizing pneumonia (OP) pattern was defined as a pattern of multifocal areas of air-space consolidation in a predominantly subpleural or peribronchial distribution, such as in cryptogenic OP or chronic eosinophilic pneumonia,[7,9,12] and the hypersensitivity pneumonitis (HP) pattern was defined as a pattern of only non-specific area of ground-glass attenuation without any structural distortion.[7,24] The acute eosinophilic pneumonia (AEP) pattern was defined as a pattern of patchy distribution of areas of ground-glass attenuation accompanied by interlobular septal thickening and pleural effusion.[12,13] The non-specific interstitial pneumonia (NSIP) pattern was defined as a pattern of bilateral linear opacities, such as in idiopathic NSIP.[7,9] Following the initial independent evaluation by three observers, the HRCT patterns were determined based on the agreement of at least two observers.

BAL cell profiles

The time intervals between the BAL and the HRCT study were 0–2 days. After informed consent was obtained from the subjects, we performed BAL and analyzed total cell concentration and cell differentiation as described previously.[19]

Measurement of MDC, IP-10 and KL-6 in serum

Blood samples were obtained from clotted blood following centrifugation at 1500*g* at 4 °C for 10 min, and then were stored at −80 °C until the measurements were performed.

The concentrations of MDC and IP-10 were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, MN, USA). The lower limits of detection for MDC and IP-10 were 62.5 and 1.7 pg/ml, respectively. The levels of KL-6 were measured by a sandwich-type electrochemiluminescence immunoassay kit (Picolumi KL-6; Sanko Junyaku, Tokyo, Japan).

Statistical analysis

The results are presented as median values, with minimum and maximum values as the range. The Kruskal–Wallis test was used to compare the values of the different groups. In cases of a significant difference between the groups, the intergroup comparisons were assessed by the non-parametric methods using the Mann–Whitney *U* test.

The Pearson's correlation coefficient was used to determine any correlations between the variables. Probability values of <0.05 were regarded as significant.

Results

Patient characteristics and clinical parameters

Thirty-four patients consisted of 20 men and 14 women. The average age was 64 years (range, 26–82 years). The causal agents were 9 antibiotics, 7 non-steroidal anti-inflammatory drugs, 6 Chinese medicines, 4 anti-rheumatic drugs, 2 anti-arrhythmic drugs and others. The median value of the PaO_2/FIO_2 ratio (P/F ratio) was 296 (range, 120–445). Fifteen patients were treated with pulsed methylprednisolone followed by oral corticosteroid, 8 with oral corticosteroid, and 2 with pulsed methylprednisolone. No steroids were given to 11 patients who recovered spontaneously by discontinuing the causative drugs. No individuals experienced death during the course of this study.

The chest HRCT patterns

The representative HRCT patterns are shown in Figure 1. The DAD pattern was determined in 6 patients, the NSIP pattern in 5 patients, the HP pattern in 7 patients, the OP pattern in 10 patients, and the AEP pattern in 6 patients. The categories of the causal agents showed no particular relationship with the HRCT patterns.

We examined whether the HRCT patterns would reflect the disease severity and the outcome. The DAD group had a significantly lower P/F value (median, 198; range, 120–280), as compared with that of the NSIP group (median, 293; range, 258–439), the HP group (median, 292; range, 225–339), the OP group (median, 318; range, 240–445), and the AEP group (median, 293; range, 213–357) (Figure 2A). For the quantitative assessment, the cumulative doses of steroids received by the patients were expressed following conversion to prednisolone dose. Among each group, the DAD group required the largest cumulative amount of corticosteroid (median, 5240 mg;

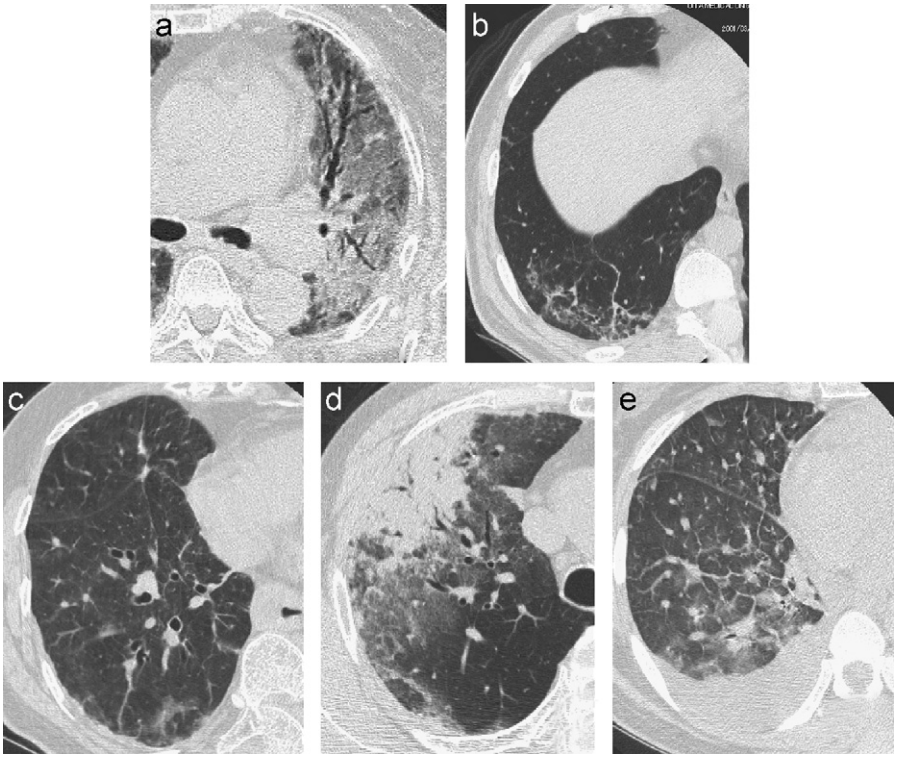

Figure 1 Representative high-resolution computed tomography (HRCT) patterns: (a) diffuse alveolar damage (DAD) pattern, (b) non-specific interstitial pneumonia (NSIP) pattern, (c) hypersensitivity pneumonitis (HP) pattern, (d) organizing pneumonia (OP) pattern, and (e) acute eosinophilic pneumonia (AEP) pattern.

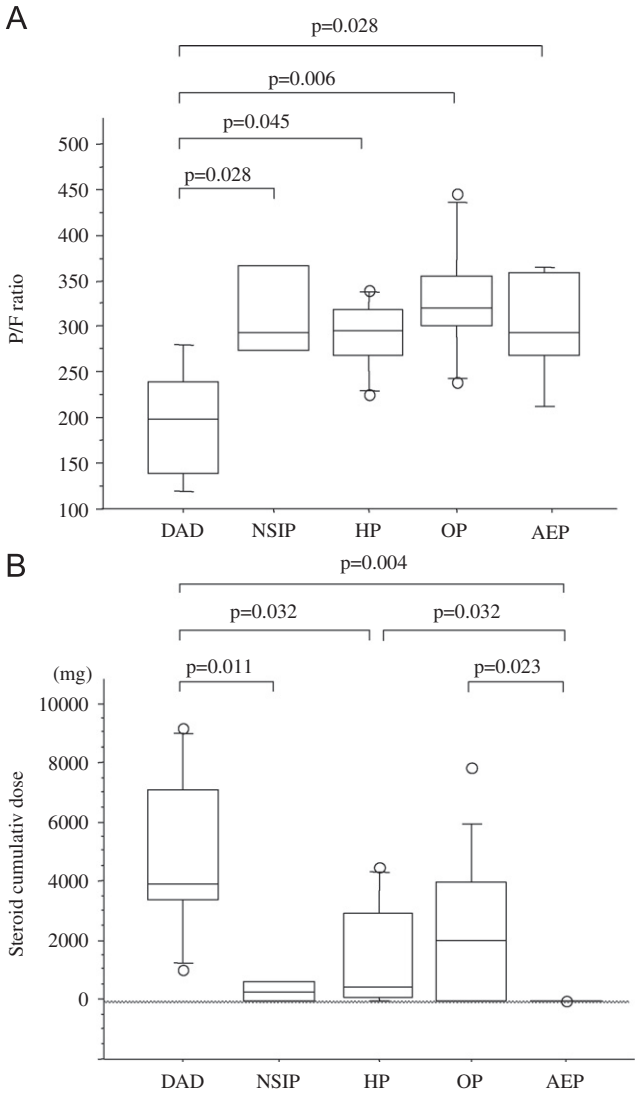

Figure 2 The P/F ratios at admission (A) and the cumulative doses of steroids received by the patients (B) among the groups of HRCT patterns. Data are presented as the median (ranges).

range, 1000–9195 mg), which was higher as compared with the NSIP group (median, 264 mg; range, 0–735 mg), the HP group (median, 415 mg; range, 0–4470 mg) and the OP group (median, 2722 mg; range, 0–7835 mg) (Figure 2B) and the AEP group. None of the 6 patients in the AEP group received steroid treatment. We also examined every HRCT finding in association with the cumulative steroid doses. As a consequence, the patients with air-space consolidation on HRCT required a larger amount of steroid (Figure 3A).

The cumulative doses of corticosteroids correlated negatively with the P/F ratios (Figure 3B), thus indicating the steroid doses to be prescribed by the disease severity at the initial presentation. We therefore calculated how long the patients required oxygen therapy, which also reflected long-term outcome, thus resulting in a similar tendency to that of the cumulative doses of steroids. When examined in all patients, the days under oxygen therapy correlated well with the cumulative doses of steroids (Figure 3C).

BAL cell profiles

We summarized the BAL cell profile in each group of HRCT pattern in Table 1. It was interesting to note that the DAD group exhibited a similar BAL cell profile as the 4 other groups; increased percentages of lymphocyte in all cases and increased eosinophil levels in 2 cases, thus suggesting immune-mediated mechanisms. Among the different groups of the HRCT patterns, there were no differences in the total cell concentrations and in the percentages of lymphocyte and neutrophil. Prominent BAL eosinophilia (eosinophils $>20\%$) was observed in 10 cases, most of which belonged to the groups with the OP and the AEP patterns. In another expression, 5 of 10 patients in the OP group and 4 of 6 patients in the AEP group had BAL eosinophilia. We did not find any case with prominent eosinophilia in the NSIP and HP groups.

The percentages and numbers of eosinophil as well as lymphocytes or neutrophils did not correlate with the P/F ratios, the cumulative steroid doses, the days under oxygen therapy, or the circulating KL-6 levels.

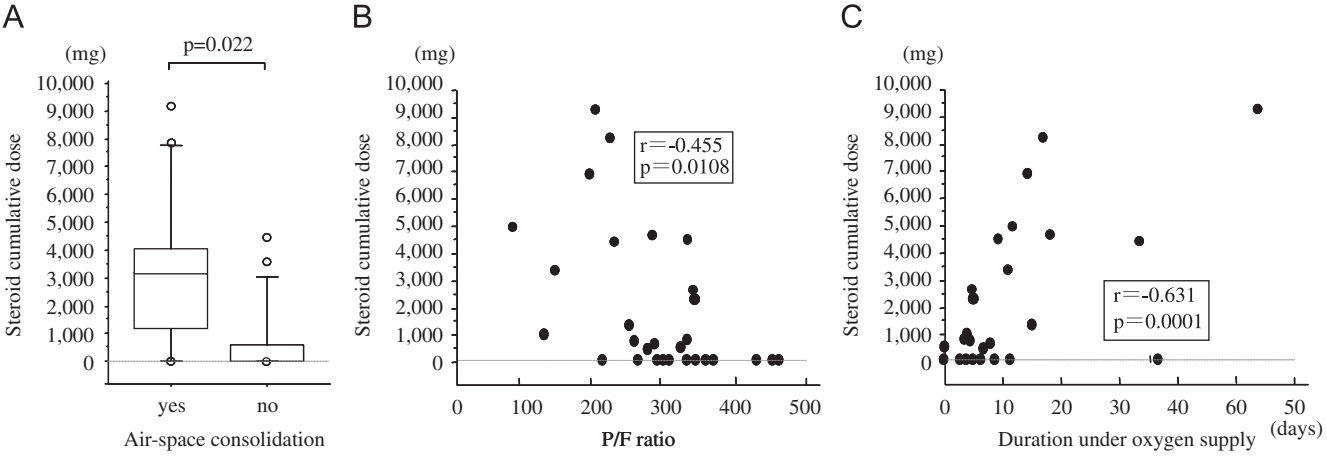

Figure 3 Relationship between the cumulative doses of steroids received by the patients and the presence of air-space consolidation on high-resolution computed tomography (HRCT) (A), the P/F ratios at admission (B), and the days when patients required supplemental oxygen (C).

Table 1 Findings of bronchoalveolar lavage and the circulating levels of IP-10, MDC and KL-6 in the groups of the distinct HRCT patterns.

	Number	T.C.C. (cells/ml)	Lymphocyte (%)	Neutrophil (%)	Eosinophil (%)	IP-10 (pg/ml)	MDC (pg/ml)	KL-6 (U/ml)
DAD	6	4.2 (1.9–5.0)	15.8 (10.7–19.1)	9.6 (0–41.5)	9.7 (0–32.1)	1799 (251–3313)	342 (157–1622)	1200 (154–3490)
NSIP	5	2.3 (0.7–4.3)	17.0 (12.0–40.3)	7.3 (0–10.6)	3.0 (0.3–6.0)	273 (62–1233)	522 (288–796)	1425* (287–4180)
HP	7	5.7 (3.0–21.0)	54.0 (13.0–86.0)	6.6 (0–64.0)	7.0 (0–14.4)	1825 (138–2864)	753 (160–1333)	571 (215–2530)
OP	10	4.3 (1.5–20.0)	31.0 (3.0–66.4)	12.0 (0–44.0)	21.0* (0.2–40.0)	2158 (288–17,042)	1464 (185–5247)	328 (142–896)
AEP	6	3.7 (1.8–6.5)	20.4 (5.2–27.7)	11.4 (0–33.0)	26.4 (1.3–45.0)	217 (81–2251)	698 (304–2861)	271 (98–4180)
Total	34	4.2 (0.7–21.0)	21.2 (3.0–86.0)	7.8 (0–64.0)	9.0 (0–45.0)	678** (62–17,042)	726** (157–5,247)	465 (98–4180)
HV	34	N.D.	N.D.	N.D.	N.D.	144 (110–259)	514 (229–723)	N.D.

Definition of abbreviations: AEP, acute eosinophilic pneumonia; DAD, diffuse alveolar damage; HP, hypersensitivity pneumonitis; HV, healthy volunteer; IP-10, interferon-inducible protein-10; MDC, macrophage-derived chemokine; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; T.C.C., total cell concentration. Data are presented as the median (ranges).

*$p<0.05$, compared with the HP group (Mann–Whitney *U* test).

**$p<0.05$, compared with the HV group (Mann–Whitney *U* test).

The KL-6 and the circulating chemokine levels

We employed serum KL-6 as a marker of alveolar epithelial cell damage and the KL-6 value is shown in Table 1. The serum KL-6 of DAD and NSIP groups tended to be high and when the cut-off value was determined to be 500 U/ml, the KL-6 positive ratios were varied among the HRCT groups with 83% in DAD, 75% in NSIP, 43% in HP, 30% in OP, and 17% in the AEP group. The KL-6 levels did not correlate with the cumulative steroid doses or the days under oxygen therapy.

We examined an association between the circulating chemokines levels and the HRCT patterns (Table 1). The circulating levels of IP-10 and MDC of the disease group were significantly higher when compared with those of age-matched healthy volunteers (HV). The circulating IP-10 levels were preferentially high in the DAD, HP, and OP groups although they were not statistically significant among the HRCT groups. We did not find any correlation between the serum IP-10 levels and the clinical parameters including the P/F ratio, cumulative dose of steroid, the circulating KL-6 level or BAL cell profile.

The MDC levels tended to be high in the OP group, 50% of which exhibited pulmonary eosinophilia. Interestingly, we found a positive correlation between the circulating MDC level and the eosinophil percentages in the BAL fluids, but not in the serum (Figure 4). The circulating MDC levels did not correlate with the P/F ratio, the steroid cumulative dose, or the KL-6 level.

Discussion

We hypothesized that the HRCT patterns may be associated with cellular pathophysiology in the inflamed lungs and chemokine expression patterns in non-neoplastic drug-induced pneumonitis. As a consequence, our study only disclosed the fact that the pulmonary eosinophilia was

Figure 4 Correlation between the serum concentrations of macrophage-derived chemokine (MDC) and the percentage of eosinophil in bronchoalveolar lavage (BAL) fluid.

preferentially found in the OP and AEP groups, which could have a similar cellular pathophysiology as shown previously by Silva and Müller.[25] It was common that the patients demonstrating the same HRCT pattern had different BAL cell profiles and chemokine expressions, indicating that HRCT does not precisely predict the cellular pathophysiology in drug-induced pneumonitis.

There have so far been few studies performed regarding the chemokine levels in drug-induced pneumonitis. We found increased serum levels of Th1 chemokine IP-10 and Th2 chemokine MDC in the patients; however, there were no uniform trends toward Th1 or Th2 polarization among the different HRCT groups. A recent paper suggests that elevated serum IP-10 might be involved in drug-induced DAD[21]; however, the present study disclosed that this phenomenon of the IP-10 elevation was not specific for the DAD pattern. Moreover, unlikely to previous studies showing the circulating levels of IP-10 to correlate with the severity of Th1-associated diseases,[26–28] the serum IP-10 levels did not correlate with the disease severity or the outcome assessed by the P/F ratios, the cumulative steroid doses, or the days under oxygen therapy in our patients with non-neoplastic drug-induced pneumonitis. The results of correlation with the disease severity or the outcome were similar in the serum MDC levels. As an interesting finding, the present study showed a positive correlation between the serum MDC levels and pulmonary eosinophilia regardless of the HRCT findings. This indicates that the serum MDC levels could therefore be more useful to predict BAL eosinophilia than did the HRCT.

In this series, six patients were determined to have the AEP pattern on HRCT. In four patients, the BAL harvested numerous eosinophils greater than 20%, whereas we could not obtain the evidence of pulmonary eosinophilia from the other two patients. These results prove that different immunological mechanisms produce similar HRCT patterns. Importantly, however, all six cases showed homogeneous outcomes revealing spontaneous improvement without steroid therapy. This suggests that the AEP pattern in HRCT is self-limited regardless of the presence of pulmonary eosinophilia.

Given that the immunopathogenetic findings did not predict the disease severity or clinical outcome, we then explored whether the HRCT pattern would predict the degree of hypoxemia, the steroid requirement and prolonged clinical course. We adopted the cumulative doses of steroid and the days under oxygen therapy as clinical outcome markers because no death was observed among our patients. We also measured the serum KL-6, which reflects alveolar epithelial cell damage[29] and correlates with the extent of lung injury in drug-induced pneumonitis.[7] In this regard, the DAD pattern referred to the most severe injury of the lung parenchyma because of lower P/F ratios and higher steroid cumulative doses and prolonged oxygen supply received by the patients, which is consistent with the previous observation.[9–11] However, unlike to the previous reports for neoplastic drug-induced pneumonitis,[9–11,30] death was not observed during the course of our DAD patients. This indicates that there may be some substantial differences in the immunological or pathological features between neoplastic and non-neoplastic drug-induced pneumonitis. We analyzed the BAL cell profiles in our patients with non-neoplastic drug-induced DAD, which disclosed an increased percentage of lymphocytes in all cases and increased eosinophil levels in two cases. Moreover, the patients had elevated levels of IP-10 in their sera. These results suggest immune-mediated mechanisms in our DAD patients.

In general, patients with OP can easily achieve a complete recovery after corticosteroid therapy.[4,5] In this series of non-neoplastic drug-induced pneumonitis, the cumulative doses of steroids received by the patients with OP were comparable to those with DAD. The results may be explained by the association between larger cumulative doses of steroids and the presence of air-space consolidation on the HRCT scans. Alternatively, because DAD and OP often shares similar chest HRCT findings such as areas with ground-glass attenuation, air-space consolidation and architectural distortion,[31] it might occasionally be difficult to differentiate between DAD and OP. Although the different levels of serum MDC and KL-6 between the two groups probably indicate a distinct immunopathogenesis in the two groups, and we thus expected a large amount of steroids to be required when air-space consolidation is found.

This study has several limitations. First, most of our patients are probable cases. In order to give a definite diagnosis, symptom re-appearance by re-administration should be proved[22]; however, a re-challenge test is not always acceptable in our country. All cases enrolled in this study were carefully examined for other etiologies to cause acute lung injury, especially infectious causes by using BAL fluids. When there were some doubts regarding the diagnosis, then such cases were excluded. Second, this was retrospectively done in a single institution to study relatively small number of cases. To resolve the problem, a prospective and multi-center work should be conducted in the future.

In conclusion, we herein showed that HRCT did not precisely predict cellular pathophysiology. The circulating MDC levels correlate with BAL eosinophilia regardless of the HRCT findings. We also demonstrated that an assessment of the HRCT patterns was more beneficial for predicting the disease severity and cumulative steroid dose required to cure lung disease than was a measurement of the immunopathogenetic findings, such as the BAL cell profiles or circulating chemokine levels. The presence of air-space consolidation in the DAD and OP patterns as well as lower P/F ratios may let the clinicians expect larger amount of steroid use and prolonged oxygen supply in cases of non-neoplastic drug-induced pneumonitis.

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