Clinico-Epidemiological Features of Pulmonary Histiocytosis X

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Abstract

Objective To define the clinico-epidemiological features of pulmonary histiocytosis X in Japan.

Methods A nationwide survey was carried out in 1997 using two questionnaires.

Results The first questionnaire, which attempted to determine the number of patients during 1996, revealed that the number of patients treated at hospitals with 200 or more beds during the one-year period was estimated to be 160 (95% confidence interval: 140–180). The estimated crude prevalence among those aged 16 to 70 years was calculated as 0.27 and 0.07 per 100,000 population in males and females, respectively. The second questionnaire was concerned with the clinico-epidemiological features of the disease. Seventy-three histologically diagnosed patients were evaluated. It primarily afflicted younger adults, between the ages of 20 and 50, and showed a male predominance. Over 90% of the patients were smokers or ex-smokers and over 50% started smoking before 20 years of age, suggesting a strong association with cigarette smoking. Steroid therapy was applicable to 34% of the patients. In the patients who received steroid therapy, regression and stabilization were observed in 28% and deterioration in 36%. As for the patients for whom steroids were not required, remission occurred in 63% and progression in 10%. The ratio of remissions plus stabilization was higher in the patients who were not treated with steroids compared with those who required steroid therapy (p<0.05).

Conclusion In patients with pulmonary histiocytosis X therapeutic results obtained with steroids seemed not to be encouraging, although steroids are thought to be the most plausible treatment.

Key words: pulmonary eosinophilic granuloma, pneumothorax, steroid

Introduction

In 1953 Lichtenstein (1) proposed the term histiocytosis X to identify an all-inclusive syndromes that included pulmonary histiocytosis X (also termed eosinophilic granuloma of the lung or Langerhans’ cell granulomatosis), Letterer-Siwe and Hand-Schüller-Christian diseases, and was characterized by Langerhans’ cell infiltration. This term is being used worldwide, although these three pathologies differ in the age at onset, clinical features, histological findings and prognosis (2, 3). Therefore, these are currently recognized as clinically and pathologically different diseases.

Pulmonary histiocytosis X is characterized by the proliferation of Langerhans’ cells predominantly in the lungs. Because most of the patients are adult smokers, the etiology is considered to differ from that of the other two diseases. No survey regarding pulmonary histiocytosis X and involving a large population has been undertaken in Japan. In 1997 the Epidemiology of Intractable Disease Research Committee and the Respiratory Failure Research Committee supported by the Ministry of Health and Welfare, conducted a nationwide survey on this disease to elicit details concerning its clinico-epidemiological features. In this report, we present the clinico-epidemiologic features from 73 pathologically diagnosed patients, and we focus on the responsiveness to steroid therapy.

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Materials and Methods

In this survey, two questionnaires were distributed to the departments of internal medicine of all university hospitals and randomly selected general hospitals having more than 200 beds through stratified sampling throughout Japan (4, 5), since most of the patients with pulmonary histiocytosis X were assumed to be treated at those departments in Japan. We stratified the hospitals according to the type (general or university) and the number of beds. The sampling was conducted using the regis-
try of all the hospitals in Japan, which was obtained from the Ministry of Health and Welfare with permission.

The first questionnaire simply inquired about the number of patients with pulmonary histiocytosis X who satisfied the diagnostic criteria. To be eligible for the present survey, the patient was to have visited the department and treated in 1996. This questionnaire was directly mailed to the heads of the departments of internal medicine in January 1997, together with the diagnostic criteria.

In the second questionnaire, detailed clinico-epidemiological information on individual patients was surveyed. This form covered the diagnostic criteria of pulmonary histiocytosis X so as to verify the proportion of patients who actually satisfied the criteria. The second questionnaire was forwarded to the heads of the departments, who reported the patients in the first questionnaire.

Then, we assessed whether a patient met the diagnostic criteria according to the clinical data provided on the second questionnaire. When no sufficient information was available for this judgment, more detailed information on the patient was obtained from the attending doctor. Patients who did not satisfy the criteria were excluded from the study.

The annual number of patients treated for pulmonary histiocytosis X was estimated, based on the assumption that the response from departments was independent of the number of patients treated there.

Clinical course was evaluated according to changes in clinical, laboratory and radiographic findings and lung function by the physicians in charge. To identify the characteristic features associated with deterioration of the disease, 1) gender, 2) age at diagnosis, 3) smoking history including Brinkman’s index and the age at which they started smoking, 4) whether the initial detection of the disease was due to subjective symptoms or not, 5) pulmonary function variables, 6) whether there were complications such as pneumothorax, bone lesions, liver dysfunction, diabetes insipidus, skin lesions and renal dysfunction, and 7) whether steroid therapy was adopted or not, were compared between those who showed deterioration of the disease and those whose clinical conditions remained unchanged or improved. Because the patients who died and were cured were only a few (n=3 and n=1, respectively), these patients were excluded from the analysis.

Grading score was defined as 1 or 0 in the values of %VC, PaO2, and %DLco, occurrence of pneumothorax [Pneumothorax] and requirement of steroid therapy [Steroid] as follows: Grade 1: %VC<80%, PaO2<70 Torr, %DLco<70%, pneumothorax (+), and steroid therapy (+). Grade 0: %VC≥80%, PaO2≥70 Torr, %DLco≥70%, pneumothorax (−), and steroid therapy (−). All variables, which achieved statistical significance (p<0.05) in the chi-squared test for independence and with Fisher’s exact test when appropriate, were subsequently included in the multiple logistic analysis to establish an individual factor that influenced the clinical course (6).

Results

The number of patients

Of the 3,461 departments of internal medicine to which we sent the first questionnaire, 1,873 (54.1%) replied, and 123 patients were reported. In response to the second questionnaire, 76 cases (61.8% of the patients reported in the first survey) were reported from 53 hospitals. Among them, there was no “duplicate” case. There were three cases suspected of having pulmonary histiocytosis X but without typical pathological findings (inappropriate cases). In this study, these three cases were excluded. Taking the proportion of cases excluded into account, the total annual number of patients treated in 1996 throughout Japan, was estimated to be 160 (95% confidence interval: 140–180). Then the estimated crude prevalence among those aged 16 to 70 years was calculated as 0.27 and 0.07 per 100,000 population in males and females, respectively.

Establishment of Diagnosis

Seventy-three patients with pathologically-confirmed pulmonary histiocytosis X were analyzed to examine the clinico-epidemiological features. The pathological diagnosis was mainly made by light-microscopic examination of a specimen obtained by open-chest biopsy in 38 cases, thoracoscopic lung biopsy in 21 cases, transbronchial lung biopsy in 10 cases and bone biopsy in 2 cases. The biopsy demonstrated destructive granulomatous lesions containing Langerhans’ cells. When applicable, immuno-histochemical staining of Langerhans’ cells was positive with antibodies to S-100 protein, and electron microscopy analysis revealed Birbeck granules within Langerhans’ cells. Rather than a pathological diagnosis, cellular analysis of broncho-alveolar lavage fluid (BALF) was performed in 2 subjects. Such diagnosis was considered when BALF was contained Langerhans’ cells in excess of 5% of the total cell

Figure 1. Age at diagnosis of pulmonary histiocytosis X (n=73). The peak incidence was found in the third decade.
Clinical findings

Our series consists of 56 men and 17 women, showing a male predominance (male: female = 3:1). Their age at diagnosis ranged from 17 to 70 years with a peak incidence in the third decade, as shown in Fig. 1. Only one patient had a family history of pulmonary histiocytosis X (brother). The mean duration of observation before 1996 was 4.1±0.5 year (range: 0 to 20 years).

Ninety-three percent of the patients were smokers or ex-smokers; smoking varied from 1.5 to 97.5 pack-years. Fifty-six percent started smoking before 20 years of age. Sixty-two percent had already quit smoking at the time of this study. At the time of diagnosis, only 38 patients (52%) showed symptoms like productive or non-productive cough, dyspnea, chest pain, fever or general malaise. Pneumothorax was noted in 18 patients (25%) between the time of diagnosis and this study. Extrapulmonary manifestations or complications were observed in 18 patients (25%); 7 (10%) with bone lesions, 11 with diabetes insipidus, 4 with skin lesions, 4 with liver dysfunction and 3 with renal dysfunction (Fig. 2).

Radiographic findings

The upper zone was involved in 96% of the cases as revealed by chest computed tomography (CT), whereas in 3 cases (4%) the upper zone appeared free from lesions. All lung zones were involved in 55% of the patients. All categories of reticular, micronodular and ring figures were found. All lung zones were involved in 67% (12/18) of patients with pneumothorax as a complication, and 45% (25/55) of patients without pneumothorax (p=NS by chi-squared test).

Figure 2. Complications and extrapulmonary manifestations in pulmonary histiocytosis X. Pneumothorax was the most frequently observed among them.

Figure 3. Steroid therapy and the course of the disease. The ratio of remissions plus stabilization was higher in the patients who were not treated with steroids compared with the patients who required steroid therapy.
Pulmonary Histiocytosis X

**Pulmonary function data**

Restrictive and obstructive lung disorders, defined as %VC≤80% and FEV1.0%≤70% were observed in 16 (24%) and 6 cases (9%), respectively. Decrease in diffusion capacity defined as %DLco≤70% was observed in 25 cases (45%). Hypoxemia (PaO2≤60 Torr) and hypercapnia (PaCO2≥45 Torr) were observed in 2 (3%) and 17 cases (26%), respectively.

**Clinical course**

Steroid therapy was given to 34% of the patients. In the patients who received steroid therapy, regression and stabilization were observed in 28% of the patients by evaluating the radiographic course of the disease. In 36% of the patients the disease worsened and 8% (2 patients) of them died due to respiratory failure. In these death cases, respiratory failure had developed for 8 and 9 years after the diagnosis of the disease (the age at diagnosis was 17 and 32 years, respectively).

As for the patients in whom steroids were not required, spontaneous remission occurred in 63% of them and 27% remained stable, although in 10% of the subjects the disease progressed. One patient (53 years) died of rupture of an abdominal aortic aneurysm one year after the diagnosis that may not have been caused by pulmonary histiocytosis X. The ratio of remissions plus stabilization was higher in the patients who were not treated with steroids compared with the patients who required steroid therapy (p<0.05 by chi-squared test) (Fig. 3).

The patients who had pneumothorax as a complication had a lower ratio of remissions plus stabilization than the patients who did not have pneumothorax (p<0.05 by chi-squared test) (Fig. 4). In addition, a higher proportion of these patients received steroid therapy (13/18 patients) compared with the patients who did not develop pneumothorax (12/55 patients) (p<0.05 by chi-squared test).

In patients without smoking history (n=5) neither death nor regression was observed, although 80% received steroid therapy and 40% experienced pneumothorax.

Among several demographic and respiratory variables, %VC (p=0.01, odds ratio 5.69), the occurrence of pneumothorax (p=0.009, odds ratio 5.39) and steroid treatment (p=0.0004, odds ratio 9.23) differed significantly between those who showed deterioration of the disease and those whose clinical conditions remained unchanged or improved. PaO2 (p=0.06, odds ratio 3.90) and %DLco (p=0.09, odds ratio 3.57) tended to differ between the subgroups. Other variables such as gender, age, smoking history and subjective symptoms did not differ between the subgroups.

The logistic regression equation was;

\[
\ln \left( \frac{P}{1-P} \right) = -0.23 \times [\%VC] + 0.51 \times [\text{Pneumothorax}] + 1.69 \times [\text{Steroid}],
\]

where \( \ln \) denoted natural logarithm; \( P \) represented the probability of deterioration, numbers in parentheses were grading scores of each variable. When the backward method was applied to seek the most explanatory variable to deterioration, the steroid therapy was came in at last.

![Figure 4](image)

**Figure 4.** Pneumothorax and the course of the disease. The patients who had pneumothorax as a complication had a lower ratio of remissions plus stabilization than the patients who had not had pneumothorax.
Discussion

This is the first epidemiological survey of pulmonary histiocytosis X in Japan. Because this disease is rare, large-scale studies like ours are essential to elucidate the clinico-epidemiological features of this disease. No epidemiological survey has been conducted in the world to estimate the prevalence of this disease. This implies that the secular trend in its prevalence could not be discussed.

One limitation of our survey might be that only the patients treated in hospitals (with 200 or more beds) were surveyed, ignoring those treated in clinics (with less than 20 beds or without beds) and hospitals with less than 200 beds. It would be, however, unlikely that in Japan many patients with adult pulmonary histiocytosis X are diagnosed and treated only in clinics, since its diagnosis and treatment is rather difficult for general practitioners.

In this study, the response rate for the first questionnaire was 54%. The rate was not low, as compared with response rates of around 50% reported for other nationwide surveys of intractable diseases which have been performed in Japan (7). Japanese hospitals with more than 200 beds have both a sufficient number of trained personnel and the medical equipment required for the diagnosis of pulmonary histiocytosis X. In response to the second questionnaire, 62% of the patients identified in the first survey were reported. This may have affected our results. It would be possible that physicians who are more interested in pulmonary histiocytosis X were likely to reply, with accurate diagnosis, to the second questionnaire. If this is the case, our proportion of inappropriate cases would be underestimated, which might result in an overestimation of the annual number of the patients. In contrast, if some expert physicians for this disease might tend not to respond to the second survey, the proportion of inappropriate cases would be overestimated and the quality of the clinical information would be decreased. Nevertheless, the inappropriate cases were only three and they might have been this disease if the clinical and radiographic findings were taken into account. Therefore the sampling bias may have not been so large.

No effective therapy has been developed for pulmonary histiocytosis X, except for discontinuance of smoking (8). Discontinuance of smoking is likely to be the key treatment, resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator resulting in clinical improvement in about one-third of the patients.

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Although no reliable criteria for steroid administration has been proposed for this disease, steroid therapy may be indicated for the patients with a higher activity of the disease, because pulmonary histiocytosis X is predominantly an interstitial lesion characterized by the presence of stellate nodules containing a polymorphic inflammatory infiltrate. Inasmuch as no other treatments, except steroid, alkylating cytostatics, antimetabolites and vinca alkaloids, have been available to date, steroid therapy was chosen for most patients in the present study. The overall results of the outcome of steroid treatment were not encouraging in this study (Fig. 3). However, it seems important that some patients may have responded to corticosteroids, resulting in remission or stabilization of the disease. Considering the possibility of steroid therapy, it may be justified to carry out a controlled study to provide further reliable information regarding the indication of this therapy (13). In the present study it is likely that when the patients had more advanced or active disease, they were place on steroids and as a result patients with pneumothorax had a higher ratio of steroid therapy.

This clinico-epidemiological study revealed the high incidence of pneumothorax (25%) as one of the complications and high deterioration ratio of the patients who had had pneumothorax. However, how many times pneumothorax recurred was not examined in this study. The present study indicated that a higher proportion of patients with pneumothorax had experienced or had received steroid therapy compared to patients without pneumothorax. This suggests that pneumothorax may be one of the factors that influence the clinical course. Repeated episodes of pneumothorax may carry a bad prognosis, although it has not been confirmed by all studies (14, 15). All lung zones were involved in 67% of patients with pneumothorax as a complication, and 45% of patients without pneumothorax, respectively (p=NS). This suggests no correlation between the radiographic extent of disease and the occurrence of pneumothorax as a complication. The greater frequency of pneumothorax could not be simply explained by more extensive disease.

Previous reports indicated that the rate of pneumothorax was about 4–5% of patients (10, 11). In the present study the occurrence of pneumothorax seemed to be considerably high. The higher rate of pneumothorax may suggest the involvement of parenchymal lesions nearby the pleura, although the mechanisms of spontaneous pneumothorax in this disease are still unclear. It is unclear whether patients with pneumothorax continue to smoke and are therefore at greater risk. Familiar coincidence of this disease could suggest a possible genetic predisposition (12). However, only one case was found to have a family history of this disease in the present study.

More than 90 percent of the cases reported in response to the second questionnaire were diagnosed by CT, although the radiographic appearances per se are not diagnostically. With re-
gard to the distribution of the lesions on chest radiographs, it is widely believed that the lesions are predominant in the upper lung fields. Our results were generally in agreement with that, because over 90% of the patients showed the lesions in the upper fields. However, it should be noted that all lung zones were involved in about half of the subjects, although the radiographic appearances per se are not diagnostic.

Previous reports found male (2), female (16) or equal preponderance (11). In the present study, a strong male predominance was found, which may suggest an ethnic difference. Otherwise, it could be that the greater incidence of males is explained by gender differences in smoking prevalence or the extent of smoking in Japan.

In conclusion, this nationwide survey of pulmonary histiocytosis X documents a cross-sectional clinico-epidemiological feature in our country. Therapeutic results obtained with steroids seemed to be unpromising, although steroids are thought to be a most plausible treatment. Further prospective studies are needed to shed light on the long-term survival and prognostic factors.

Acknowledgement: We wish to thank the support of the members of the Epidemiology of Intractable Disease Research Committee, especially Dr. Takashi Kawamura and Yoshiyuki Ohno, Department of Preventive Medicine, Nagoya University School of Medicine, Japan.

This study was supported by a research grant for The Respiratory Failure Research from the Ministry of Health and Welfare of Japan.

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References