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The Clinical Characteristics of Pulmonary Alveolar Proteinosis : Experience at Seoul National University Hospital, and Review of the Literature

Pulmonary alveolar proteinosis is such an extremely rare disease in Korea, that only a few cases have been reported. Meanwhile five cases were experienced at Seoul National University Hospital over ten years since 1987. We summarized the clinical characteristics and courses of them. Seven cases reported in the literature were included to add data about clinical characteristics and courses although only a few case reports mentioned patient's course. Middle aged male patients were mainly affected. No association with particular environmental or occupational exposure was identified. Dyspnea on exertion was the main symptom. Bilateral crackles were consistent, and bilateral parahilar hazy infiltrations on plain chest radiograph and ground glass opacity on high-resolution CT were characteristic. Superimposed infection was not identified in any patient at the time of diagnosis. Decreased diffusing capacity and hypoxia were present in almost every case. Whole lung lavage proved to be an effective therapeutic measure. The response to treatment was good. Long-term course of the disease, e.g. recurrence rate, is not yet known.

Key Words : *Pulmonary alveolar proteinosis*

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INTRODUCTION

Pulmonary alveolar proteinosis is a rare disease of unknown etiology first described by Rosen and colleagues in 1958 (1).

This disease is characterized by accumulation in the bronchioles and alveoli of amorphous lipoproteinaceous material rich in phospholipids, which results in impaired gas exchange. Though it is thought that defects in the process of normal turnover of surfactant material are responsible for the development of the disease (2), exact pathogenesis is not clear. Whole lung lavage, since the first introduction by Ramirez et al. in 1963 (3), remains to be the only effective therapeutic measure. It is extremely rare in Korea, where only a few cases have been reported since 1987, and clinical characteristics and course of pulmonary alveolar proteinosis cases in Korea are not known.

Meanwhile five cases were experienced at Seoul National University Hospital over ten years since 1987. We retrospectively reviewed the clinical characteristics and courses of them. As the number of cases was so small, seven other Korean cases reported in the literature were added to utilize as data supplementing our own. Unfortunately, however, most of these case reports did not mention courses.

METHODS

A total of twelve cases were analyzed; five of these had been diagnosed at Seoul National University Hospital (SNUH) since 1987, at which time the first case in Korea was reported (4). The remaining seven cases were collected from the literature after a search of the Korean Index Medicus (5-9). We retrospectively reviewed the medical records of the five SNUH cases; for the other seven, we were obliged to rely on the literature.

RESULTS

Age and sex distribution

Age ranged from 30 to 66 (median, 45.5) years. Three of twelve cases were females. The male to female ratio was 3:1 (Fig. 1).

Smoking and occupation history

In one case, smoking history was not available, but other-

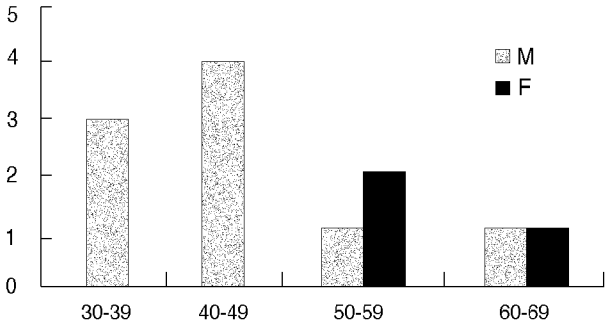

Fig. 1. Age and sex distribution of pulmonary alveolar proteinosis patients. The abscissa represents age in years at the time of diagnosis; the ordinate represents the number of cases. M: male; F: female

wise all the male patients were smokers. All female patients, on the other hand, were non-smokers. In two cases, occupation was not stated. Among the remaining ten, there were three clerks, two farmers, one seaman, and one mechanic. All three female patients were housewives.

Symptoms and signs (Table 1)

The main symptoms were dyspnea on exertion and cough, occurring in 100 % and 50 % of patients, respectively. Sputum, weight loss, and fever were each present in only one case. The time interval from onset of subjective symptoms to diagnosis ranged from one month to over ten months; in eight of twelve cases it was four to six months. Crackles in the both lower lung areas were audible in every case except one. Cyanosis and clubbing were found in two cases and one, respectively.

Laboratory and pulmonary function test findings

There were few laboratory findings showing the evidence of infection or inflammation. Among cases in which data were available, leukocytosis over 10,000/μL was present in only three of eleven cases (27%); a high erythrocyte sedimentation rate, i.e., over 15 mm/hr, was found in only two of eight cases (25%). Among five cases in which data for C-reactive protein (CRP) were available, none was CRP-positive, either qualitatively, or quantitatively over 1.0 mg/dL. On the other hand, elevation of lactic dehydrogenase (LDH) and especially, carcinoembryonic antigen (CEA) was characteristic. LDH data were available in eight cases; in five of these, levels were elevated (> 225 IU/L). In all three cases in which serum CEA levels were known, these were elevated (> 2.5 ng/mL), being remarkably high (55.4 and 66.3 ng/mL) in two. CEA level in bronchoalveolar lavage fluid checked in one case, was markedly elevated (299 ng/mL). Data for forced vital capacity (FVC) were available in ten cases, and among these, restrictive impairment (i.e., FVC < 80% of predicted value) was found in six. Mean FVC was 77% of predicted value. In eight of nine cases in which data for diffusing capacity were available, this had decreased (i.e., DLCO /V_A < 80% of predicted value); this capacity was severely impaired. Mean DLCO/V_A of these nine cases was 51% of predicted value. Arterial blood gas data was available in every case but one; none was free of hypoxemia, and the mean value was 66 mmHg.

Table 1. Symptoms and physical findings in 12 patients

Symptoms or physical findings		Number of cases
Symptoms	Dyspnea on exertion	12
	Cough	6
	Sputum	1
	Weight loss	1
	Febrile sense	1
Physical findings	Crackles	11
	Cyanosis	1
	Clubbing	1

Radiologic findings

As seen on plain chest radiographs (Fig. 2), bilateral lung involvement was consistently characteristic. In ten of 12 cases, infiltration was diffuse and hazy, and in the remainder, infiltration was patchy. In 11 cases, predominant parahilar mid- and lower lung distribution was seen, and in another case, exceptional peripheral predominance in distribution was noted. Eight patients underwent high-resolution computed tomography (HRCT); ground glass opacity was seen in seven, and thickening of the interlobular septum in six.

Diagnosis

In certain cases, pulmonary alveolar proteinosis was suspected on the basis of history and radiologic findings, but all were confirmed by pathologic examination. For this, specimens were obtained by transbronchial lung biopsy in five cases, by thoracoscopic lung biopsy in two, and by open lung biopsy in five. In all cases, light microscopy revealed characteristic periodic acid-Schiff (PAS)-positive materials in alveoli, with an intact alveolar structure. In seven cases, the records included notes regarding electron microscopy findings, and electron-dense lamellar bodies were seen in every case.

Treatment

Three of the 12 cases were untreated. One of these untreated patients (Case 2 of Table 2) died of acute respiratory failure seven years after initial diagnosis. Since he was not followed up during that period, it is not clear whether pulmonary

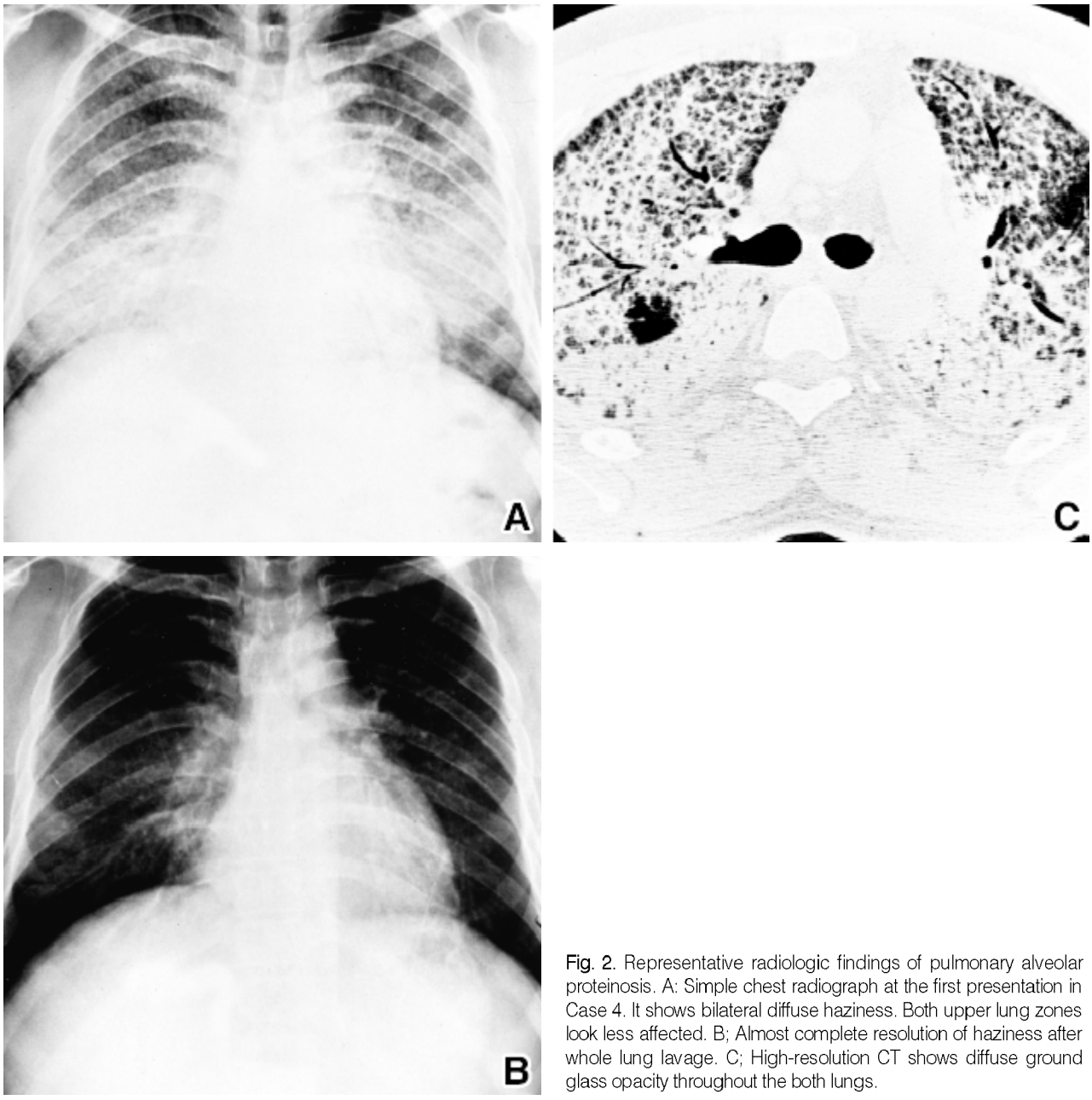

Fig. 2. Representative radiologic findings of pulmonary alveolar proteinosis. A: Simple chest radiograph at the first presentation in Case 4. It shows bilateral diffuse haziness. Both upper lung zones look less affected. B; Almost complete resolution of haziness after whole lung lavage. C; High-resolution CT shows diffuse ground glass opacity throughout the both lungs.

alveolar proteinosis was directly responsible. Another (Case 5) recovered spontaneously and is being followed up, while the third patient (Case 1) died of *Nocardia* infection one year after diagnosis. Whole lung lavage was performed in six cases and lobar lavage in three. Pulmonary function test and arterial blood gas results before and after treatment are shown in Table 3. One patient (Case 11) died from immediate complications, namely brain edema due to hyponatremia, arising after whole lung lavage in one lung; this complication has not been reported in the literature. No other significant complication occurred, and the responses to whole lung lavage were dramatic. In four of six cases in which this was performed, data for arterial blood gases taken both immediately before and after the procedure were available; changes in PaO_2 are shown in Table 4.

Clinical course

Among seven cases described in the literature, clinical courses after diagnosis were mentioned briefly in only two cases,

Table 2. Age and sex, diagnostic procedure, treatment, courses of 12 patients

Case	Age	Sex	Diagnosis	Treatment	Course
1	50	F	OLB*	None	Expired of *Nocardia* infection one years after diagnosis
2	30	M	TBLB†	None	Expired of acute hypoxic respiratory failure six years after diagnosis
3	66	F	OLB	Whole lung lavage	Being followed up for sixteen months without relapse
4	43	M	OLB	Whole lung lavage	Being followed up for 34 months. Relapsed twice after whole lung lavage
5	41	M	VATS‡	None	Spontaneous improvement being followed up for eight months
6	53	M	OLB	Whole lung lavage	Followed up for six months without relapse
7	52	M	TBLB	Repeated lobar lavage	Duration of follow up is not mentioned
8	47	M	OLB	Repeated lobar lavage	Duration of follow up is not mentioned
9	31	M	TBLB	Repeated lobar lavage	Followed up for nine months
10	59	F	VATS	Whole lung lavage	Not mentioned
11	44	M	TBLB	Whole lung lavage	Expired of brain edema 11 days after the whole lung lavage
12	39	M	TBLB	Whole lung lavage	Not mentioned

*OLB; open lung biopsy, †TBLB; transbronchial lung biopsy, ‡VATS; video-aided thoracoscopic surgery, Case 1-5; SNUH cases, Case 6-12; previously reported cases

except the case of one patient who died immediately after whole lung lavage. One patient (Case 6) was followed up for six months without relapse after whole lung lavage, the other (Case 9) was followed up for nine months after repeated lobar lavage without symptoms. The clinical courses of the five SNUH cases are known; two patients died and three were followed up. As mentioned previously, one (Case 2) died of acute respiratory failure; in the other case (Case 1), the cause of death was *Nocardia* pulmonary infection one year after diagnosis. Either case was not treated by whole lung lavage. Among three cases followed up, one (Case 4) recurred twice after whole lung lavage; the first relapse occurred six months after the first lavage. And two years after the second procedure, there was a further relapse. After the third lavage, this patient was followed up for four months. In the second case (Case 3), pulmonary alveolar proteinosis was suspected after routine plain chest radiogragh and subsequent high-resolution CT at the other hospital three years

Table 3. Pulmonary function test (PFT) and results of arterial blood gas analysis (ABGA) before and after treatment

Case	Treatment	Pre-treatment PFT or ABGA	Post-treatment PFT or ABGA
1	None	FVC 1.8 (76%), FEV_1/FVC 84%, DLCO/VA 3.1 (75%), PaO_2 69 mmHg (room air)	—
2	None	FVC 3.9 (97%), FEV_1/FVC 93%, DLCO/VA 2.98 (54%), PaO_2 77 mmHg (room air)	—
3	WLL*	FVC 1.34 (57%), FEV_1/FVC 93%, DLCO/VA 1.73 (47%), PaO_2 58 mmHg (room air)	FVC 1.68 (71%), FEV_1/FVC 87%, DLCO/VA 3.06 (81%), PaO_2 81 mmHg (room air)
4	WLL	PaO_2 37 mmHg (FiO_2 0.4)	FVC 3.00 (77%), FEV_1/FVC 81%, DLCO/VA 3.10 (71%), PaO_2 111 mmHg (FiO_2 0.5)
5	None	FVC 3.29 (70%), FEV_1/FVC 90%, DLCO/VA 3.99 (93%), PaO_2 69 mmHg (room air)	—
6	WLL	FVC 2.31 (80%), FEV_1/FVC 91%, PaO_2 56 mmHg (room air)	FVC 2.75 (96%), FEV_1/FVC 87%, PaO_2 75 mmHg (room air)
7	RLL†	FVC (70%), FEV_1/FVC 103%, DLCO/VA (49%), PaO_2 60 mmHg (room air)	Not mentioned
8	RLL	FVC (81%), FEV_1/FVC 95%, DLCO/VA (46%), PaO_2 50 mmHg (room air)	Not mentioned
9	RLL	FVC (76%), FEV_1/FVC 99%, DLCO/VA (33%), PaO_2 55 mmHg (room air)	FVC (102%), FEV_1/FVC 98%, DLCO/VA (72%), PaO_2 85 mmHg (room air)
10	WLL	Not mentioned	Not mentioned
11	WLL	FVC 2.92 (63%), FEV_1/FVC 84%, DLCO/VA 3.65 (35%), PaO_2 44 mmHg (room air)	—
12	WLL	FVC 2.65 (78%), FEV_1/FVC 100%, DLCO/VA 2.33 (32%), PaO_2 54 mmHg (room air)	FVC 3.22 (95%), FEV_1/FVC 89%, DLCO/VA 4.05 (55%), PaO_2 69 mmHg (room air)

*WLL; whole lung lavage, †RLL: repeated lobar lavage

Table 4. Improvements in PaO_2 (mmHg) immediately after whole lung lavage

Case	Before	After
Case 3	58	81
Case 4	37	76
Case 6	56	75
Case 12	54	69

before visiting SNUH. Because of the absence of symptoms, the patient had not, however, sought further treatment. About two years later, she experienced dyspnea on exertion and cough, and visited another hospital. After open lung biopsy, pulmonary alveolar proteinosis was again diagnosed. Because her condition improved after a course of antibiotic treatment alone, she did not undergo whole lung lavage. Fourteen months later, however, due to progressive dyspnea on exertion and cough, the patient finally visited our hospital, where whole lung lavage was performed. After sixteen month's follow up, there was no recurrence. In the third case (Case 5), whole lung lavage was planned. However it was not undertaken because hypoxia, dyspnea, and radiologic findings improved spontaneously during hospitalization. During eight months of the follow up, this patient was free of symptoms.

DISCUSSION

Pulmonary alveolar proteinosis is so rare in Korea that no analysis of the clinical characteristics and courses of cases have yet been available. That analysis was our purpose. But there may be cases not reported and therefore not included in our study. Furthermore important details of each case we included are also missing. In spite of these limitations, we hope that this study provides at least an outline.

In general, the clinical characteristics of cases were not much different from those described in the literature (10). The pathogenesis of the disease is not clearly understood, though it is believed that material accumulating in the alveoli is closely related to surfactant (11). The constituents of surfactant are thought to accumulate because of overproduction or defective clearance, though the exact mechanism or evoking factor of derangement of surfactant homeostasis is not fully understood. The inhalation of certain particles has been linked to being one of the causes (12-14), though this study demonstrated no association with inhalation of particular materials, or occupational exposure.

In these cases of pulmonary alveolar proteinosis, there was significant increase of CEA levels in serum and bronchoalveolar lavage (BAL) fluid. However the number of cases in which CEA levels was checked was small. Increased CEA level in serum and BAL fluid in pulmonary alveolar proteinosis patients has been reported in the literature (15-19). Asamoto et al. reported that as many as 63% of 68 patients had abnormally high serum CEA levels (17). Nakajima et al. reported a case in which CEA and other tumor markers in serum and BAL fluid were elevated (18). They demonstrated positive immunohistochemical staining for CEA in alveolar epithelium. Similar results were provided by Hamamatsu et al. (19). So it seems that alveolar epithelial cells secrete CEA. However it is not clear how the material is implicated in the disorder. But we can get some hints from the observation that serum CEA values correlate to disease activity (15).

Our data do not indicate that superinfection, particularly nocardiosis, is prevalent. Superinfection at the time of diagnosis or during the course of the illness was identified in only one patient, who died of the infection. The rarity of superinfection is supported by the prospective study of Kariman et al. (20), which contradicted the findings of previous reports (21).

Although over half of all cases were diagnosed by invasive biopsy procedures, it seems that less invasive transbronchial biopsy would suffice. Five of 12 cases were diagnosed in this way, and the specimens obtained were sufficient for histologic diagnosis. One of five cases diagnosed by open lung biopsy had in fact been previously diagnosed by transbronchial biopsy; lack of experience was the reason for depending on a more invasive open lung or thoracoscopic biopsy in order to rule other interstitial lung diseases out.

Since it was first used by Ramirez (3) in 1965, whole lung lavage remains to be the only effective and safe therapy for pulmonary alveolar proteinosis; its effectiveness has been proved again by its successful use in Korean patients. Unfortunately, one of these died of hyponatremia followed by brain edema after the procedure. But hyponatremia as a complication of whole lung lavage has not been reported in the literature. It may be prudent to check the electrolyte before as well as during and immediately after the procedure. In the remaining cases, whole lung lavage was successful and did not lead to complications.

Spontaneous remission occurred in two cases, though in one of these, whole lung lavage was eventually required. Spontaneous remission has also been described in the literature (10). Among cases in which the clinical courses were known, two of the three patients, not treated with whole lung lavage, died.

Pulmonary alveolar proteinosis is very rare in Korea; it has been only ten years since the first case was diagnosed, and the cumulative number of cases is still very small; long-term prognosis should therefore be determined after more cases have been diagnosed and subjected to long-term follow-up. Since the clinical manifestations are fairly characteristic, diagnosis is not difficult once the disease is suspected. Furthermore, the therapeutic measure available can lead to dramatic improvement in a patient's condition.

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