Pulmonary Alveolar Proteinosis: A Report of Seven Patients from King Chulalongkorn Memorial Hospital

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From 1983 to 2001, 7 patients with pulmonary alveolar proteinosis were admitted to the King Chulalongkorn Memorial Hospital. Presenting symptoms varied from asymptomatic (1 patient), progressive dyspnea on exertion (4 patients) to respiratory failure (2 patients). Other symptoms included dry cough and weight loss. Gradual onset of dyspnea could be observed by average time to hospital (7 months). Early worsening of dyspnea and high-grade fever suggested a possibility of superimposed infection. Chest radiographs revealed symmetrical infiltration without lobar predominance. 4 of 7 patients were misdiagnosed as pulmonary tuberculosis before diagnosis of PAP was made. Diagnosis was made by bronchoscopic examination with typical lavage fluid or pathological results; only one case need open lung biopsy. 6 of 7 patients required lung lavage to relieve dyspneic symptoms. Coinfection with Nocardia and Mycobacterium tuberculosis was found in one patient. Prognosis was good but recurrence was common.

Keywords: *Alveolar proteinosis, Clinical features, Treatment*

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Pulmonary alveolar proteinosis (PAP) [1,2] is a rare pulmonary disease characterized by excessive accumulation of surfactant proteins and phospholipids within the alveoli and distal bronchioles. The major complaint includes chronic progressive dyspnea with variable degrees of severity. PAP in adults is considered as idiopathic etiology. However, it may be associated with infections, hematologic diseases, immunodeficiency states and silicosis; which worsen the symptoms and make diagnosis more difficult. Unfamiliarity of this rare disease is an important diagnostic problem for general practitioners and pulmonologists.

Although PAP has been reported in Thailand by several authors[3-5], missed diagnosis as pulmonary tuberculosis was clearly noted in the present series. This present report is to alert physicians to this rare chronic pulmonary disease. Diagnostic and therapeutic methods suitable in Thailand were also discussed.

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Material and Method

In the present series, the authors retrospectively described 7 patients diagnosed with pulmonary alveolar proteinosis in adults in King Chulalongkorn Memorial Hospital, a university hospital, between 1983 and 2001. Clinical presentation, past medical history, severity of PAP evaluated by spirometry and arterial oxygen pressure, diagnostic methods and treatment used in each case were collected. All patients were examined on the follow-up visit for at least 3 years to evaluate recurrence of the disease.

Results

Summary of clinical features, diagnostic methods, treatment and outcome are shown in Table 1.

Discussion

Pulmonary alveolar proteinosis (PAP) [1,2] is a rare pulmonary disease. Clinical features of PAP in adult usually presents with insidious onset of exertional dyspnea and cough. Severity of dyspnea varies from mild dyspnea on heavy exercise to severe respiratory failure. Most of the patients have dry cough but some have whitish productive sputum with a few cells on

Table 1. Clinical features, severity, diagnostic methods, associated disease, treatment and outcome of patients diagnosed with pulmonary alveolar proteinosis in King Chulalongkorn Memorial Hospital

Case	Year	Sex	Age	Presenting symptoms	Physical Examination	prior Rx as TB	CXR findings	Time to Dx	Lung function tests	Oxygenation	Diagnostic methods	Associated Disease	Rx	Recur*
1	1983	M	41	DOE, chronic cough	Normal BS	No	Both lower lobes (alveolar)	6 mos	Normal	O2 sat = 98%	TBB	No	No	No
2	1985	M	38	DOE, chronic cough, wt. loss	Normal BS Clubbing of finger	Yes	Diffuse (alveolar)	2 yrs	TLC = 65%	PaO2 = 85 (on O2 canula 3 LPM)	BALF, TBB	No	SL *3	No
3 #	1988	M	36	Dyspnea at rest, cough, fever, wt. loss	Rhonchi BT = 39C	No	Diffuse (interstitial)	3 mos	Can't be performed	RF on respirator FiO2 =0.4	TBB	Nocardiosis TB	SL *3	Yes (3 mos)
4	1992	F	33	DOE, chronic cough, wt. loss	Rales	Yes	Diffuse (interstitial)	1 yr	Can't be performed	PaO2 = 39 RA	BALF, TBB	No	WLL *3	Yes (1 yr)
5	1995	F	72	DOE, chronic cough, wt. loss	Rhonchi + rales	Yes	Diffuse (alveolar)	1 yr	Can't be performed	RF on respirator FiO2 = 1.0	Open lung biopsy	Hx CA cervix	WLL *7	No
6	2000	F	45	DOE, chronic cough, wt. loss	Rales (mild)	No	Diffuse (alveolar)	7 mo	TLC = 56% FVC = 50%	PaO2 = 55 RA	TBB, HRCT	No	WLL *2 (+2)	Yes (2 yrs)
7	2001	F	22	DOE, chronic cough, wt. loss	Rales (mild)	Yes	Diffuse (alveolar)	1.5 yr	FVC = 33.6%	PaO2 = 52 RA	BALF, TBB, HRCT	No	WLL *2	No

BS = breath sound; BALF = bronchoalveolar lavage fluid; CA = carcinoma; DOE = dyspnea on exertion; Dx = diagnosis;
HRCT = high resolution computerized tomography; Rx = treatment; SL = segmental lavage; TB = tuberculosis;
TBB = transbronchial biopsy; TLC = total lung capacity; WLL = whole lung lavage
# dead (1 case)
* recurrence defined by period between each episodes has free symptoms more than 2 months

microscopy. Weight loss is common in cases of severe dyspnea due to overloading respiration. Physical examination is usually minimal when compared with oxygenation impairment and abnormal imaging.

In the present series, the patients seem to have more severe disease at the time of diagnosis when compared with others. The authors found only one case that had persistente alveolar infiltration with very mild symptoms (patient 1) and had spontaneous remission; the rate which was lower than previously described (25%) [6]. On the first visit, 2 of 7 patients had respiratory failure (patient 3 and 5); 3 of 7 had moderate to severe hypoxemia at rest (patient 4, 6, 7). Time to diagnosis was approximately 11 months, which may depend on several factors including gradual progression of the disease, individual perception of disease and/or delayed diagnosis due to physicians' unfamiliarity. Typical chest radiographs show diffuse bilateral alveolar infiltrates [1]. Although up to 20% of cases have reported an asymmetrical pattern and some with isolated lobar involvement [7], all patients in the present series revealed symmetrical infiltration.

Patients with PAP are susceptible to opportunistic pulmonary infections such as Nocardia species, Mycobacterium species, Cryptococcus neoformans, Histoplasma capsulatum, Pneumocystic carinii, Aspergillus species, and viruses due to alveolar macrophage dysfunction [8, 9]. High fever, which is unlikely in PAP and suggests superimposed infection, was observed in patient 3 who was infected with nocardia and *M. tuberculosis*. Furthermore, progression of dyspnea and hypoxemia was more rapid in this patient (time to respiratory failure within 3 months). The authors proposed that rapid deterioration of dyspneic symptoms may be also used as a clue for superimposed infection.

In patient 5, history of cervical cancer was noted without any evidence of recurrence at the time of diagnosis of PAP. The patient has course and presentation and recovery of disease as usually found in idiopathic PAP. So it is likely that history of cervical cancer in this patient was only a coincidental finding. Although Dejsomritrutai et al reported secondary alveolar proteinosis in acute leukemia in Thailand since 1992 [4]; however, the authors did not fund such associated disease in the present series.

Because of rarity, nonspecific symptoms and variability in severity and course of PAP, diagnosis can be easily missed. In the present report, 4 of 7 patients (57.14%) were misdiagnosed and mistreated as pulmonary tuberculosis before diagnoses of PAP were made. Although tuberculosis is much more common than PAP in Thailand and have some clinical features in common such as weight loss, fatigue, and chronic cough; they are different in several aspects as shown in Table 2. Therapeutic trial by antituberculous drugs can be used in high tuberculosis prevalence countries; however, there should be caution in patients prone to severe side effects from antituberculous drugs. Other diagnosis should be considered if no favorable response after 2 months of antituberculous treatment.

Definite diagnoses were made by bronchoscopy in 6 of 7 patients (85.71%). Bronchoalveolar lavage fluid had characteristic milky gross appearance with extracellular granular material but few cellular

Table 2. Differentiating PAP and TB lung by clinical features and basic laboratory findings

Differentiating features	Pulmonary alveolar proteinosis (PAP)	Pulmonary Tuberculosis
Clinical presentation	Dyspnea, dry cough,wt.loss, no fever	Fever, dry cough, wt.loss, fatigue,
Onset of disease	More gradualTime to hospital (avr.) = 7 mo [2]	Time to hospital (avr.) = 6-8 wks [20]
Radiographic findings	Diffuse, symmetrical fine Interstitial/ alveolar infiltrates Proximal > Distal No predominant lobe No pleural effusion	Cavitation, Reticulonodular infiltrates, Fibrotic change, Tuberculoma, Lobar predominant. Diffuse: Miliary pattern (1.3-5.8%) [19,20] With extrapulmonary involvement: pleural effusion/ adenopathy (9%) [19]
Oxygenation	Hypoxemia	Hypoxemia is uncommon
Sputum examination	Negative	PositiveResponse
Response to antiTB drugs	No response	

components including overfed foamy macrophages and inflammatory cells on microscopy as previously described [1,10]. Transbronchial biopsy increased diagnostic yield in 3 cases (patient 1, 3, 6). The material appears basophilic with Giemsa, eosinophilic with H&E, and positive with PAS with diastase resistant. Open lung biopsy was required in only one case in the present study (patient 5). High-resolution computerized tomography (HRCT) of the thorax in PAP typically shows a "crazy paving" pattern described as geographic ground-glass opacities with networks of reticular opacities within the affected lung [11]. However, this finding is non-specific [12,13] and can be seen in many lung diseases such as ARDS, pulmonary hemorrhage, cardiogenic pulmonary edema, mucinous bronchoalveolar carcinoma, lipoid pneumonia, etc. Although HRCT combined with clinical features can increase specificity, definite diagnosis needs pathological examination. HRCT were performed in last 2 cases without changes in diagnosis and treatment. Severity of disease could be best assessed and followed by symptoms and basic investigation such as chest radiographs, spirometry and oxygen saturation. Therefore, the authors concluded that HRCT is not necessary in PAP.

Whole lung lavage is an effective method for relieving symptoms in PAP. Because some PAP patients can resolve spontaneously and whole lung lavage is for symptomatic relief only, timing for lavage depends on limitation of patient's activities and progression of disease. In patient 1 who faced very mild symptoms, therefore, the authors decided to reassure the patient and close follow-up. Therapeutic multiple segmental lavages were done by fiberoptic bronchoscopy in 2 cases (patient 2, 3) in Chulalongkorn hospital since 1985 and showed beneficial results. Considering of small amounts of fluid used in the procedure and severity of disease, resolution of symptoms could not be explained by removal of surfactant or antibody itself. In ex vivo study, mechanical fluid flow can activate human macrophage and alveolar epithelial fluid clearance rapidly improved after lung lavage in pulmonary alveolar proteinosis; may be another hypothesis working on effector cells [14,15]. Multiple segmental lavage needs to be validated in two distinct situations: mild disease as an out-patient based treatment and severe respiratory failure cases who can not tolerate whole lung lavage [16,17]. Infection can worsen the symptoms and response to lung lavage as observed in patient 3. Because macrophage function can recover after removal of surfactants [18], the authors recommended that whole lung lavage and appropriate antibiotics in PAP patients with infection should be started as early as possible.

During the last decades, GM-CSF has been used as another treatment for PAP [1,2]. Treatment response is gradual and in some cases is ineffective. This drug is not available in Thailand nowadays. Use of G-CSF in treatment of PAP has limited data in only few a cases.

In conclusion, the authors have described a variety of PAP cases with different clinical presentations and courses. Missed and delayed diagnosis could be avoided by physicians' awareness of this disease. Bronchoscopy is an important diagnostic tool in PAP and also provides therapeutic implication in particular cases. The authors suggested that whole lung lavage is the most suitable treatment for PAP in Thailand.

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โรคพัลโมนารี แอลวีโอล่าร์ โปรตีนโนซิส รายงานผู้ป่วย 7 รายจากโรงพยาบาลจุฬาลงกรณ์

กมล แก้วกิติณรงค์, ฉันชาย สิทธิพันธ์, สมเกียรติ วงษ์ทิม, วิศิษฏ์ อุดมพาณิชย์

จาก พ. ศ. 2526 ถึง พ.ศ. 2544 พบผู้ป่วยโรคแอลวีโอล่าร์โปรตีนโนซิส ในโรงพยาบาลจุฬาลงกรณ์ 7 ราย อาการนำของผู้ป่วยพบได้ตั้งแต่ไม่มีอาการเลย (1 ราย) เหนื่อยขณะออกแรง (4 ราย) จนเกิดภาวะหายใจวาย (2 ราย) อาการอื่นที่พบได้เช่น อาการไอแห้ง และ น้ำหนักลด มีอาการเหนื่อยขณะออกแรงและเป็นมานาน ค่อยๆ เพิ่มขึ้นเรื่อยๆ ทีละน้อย อาการเหนื่อยที่ค่อยเป็นทีละน้อยสังเกตได้จากระยะเวลาตั้งแต่เริ่มป่วยจนมาถึงโรงพยาบาลเฉลี่ยซึ่งเฉลี่ยเท่ากับ 7 เดือน การทรุดลงของอาการเหนื่อยที่เร็วกว่าปกติและอาการไข้สูง ถ้าพบควรนึกถึงว่ามีการติดเชื้อร่วมด้วย ภาพรังสีปอดพบเงาทึบกระจายทั้ง 2 ข้างแบบสมมาตร ผู้ป่วย 4 ใน 7 รายได้รับการวินิจฉัยผิดเป็นวัณโรคมาก่อน การวินิจฉัยสามารถทำได้โดยการส่องกล้องตรวจหลอดลมโดยมีลักษณะทางพยาธิวิทยาที่เฉพาะจากสารน้ำและชิ้นเนื้อปอด มีเพียงหนึ่งรายที่ต้องทำการผ่าตัดเปิดทรวงอกเพื่อตัดชิ้นเนื้อ ผู้ป่วย 6 ใน 7 รายต้องได้รับการรักษาโดยการล้างปอดเพื่อบรรเทาอาการเหนื่อย การติดเชื้อโนคาร์เดียและวัณโรคพบร่วมในผู้ป่วย 1 ราย โดยทั่วไปการพยากรณ์โรคดีแต่มีโอกาสเป็นซ้ำได้บ่อย