Pulmonary Alveolar Proteinosis In Israel: Ethnic Clustering

Issahar Ben-Dov MD[1], Yelena Kishinevski MD[5], Judith Roznman MD[2], Alkrinawi Soliman MD[11], Hashem Bishara MD[7], Erika Zelligson MD[9], Joel Grief MD[5], Asher Mazar MD[6], Marina Perelman MD[3], Rafael Vishnizer MD[10] and Daniel Weiler-Ravel MD[8]

[1]Pulmonary Institute and Departments of [2]Radiology and [3]Pathology, Sheba Medical Center, Tel-Hashomer, [4]Pulmonary Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, [5]Department of Anesthesiology, Asaf Harofeh Medical Center, Zerifin, and [6]Pulmonary Institute, Rabin Medical Center, Petah Tiqva (These medical centers are affiliated with the Sackler Faculty of Medicine, Tel Aviv University); [7]Pulmonary Institute, Rambam Medical Center and [8]Pulmonary Institute, Carmel Medical Center, Haifa, and [9]Pulmonary Institute, Ziv Medical Center, Safed (These medical centers are affiliated with the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa); [10]Pulmonary Institute, Kaplan Medical Center (affiliated with the Hebrew University-Hadassah Medical School, Jerusalem); and [11]Department of Pediatrics, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

Key words: alveolar proteinosis, prevalence, incidence, familial and ethnic distribution, radiological presentation

Abstract

Background: Pulmonary alveolar proteinosis is a rare disease in which a surfactant-like phospholipid-rich protein accumulates in the lungs. The disease is amenable to effective therapy by total lung lavage.

Objectives: To investigate the prevalence, ethnic distribution and course of PAP[1] in Israel.

Methods: A countrywide survey was conducted during which pulmonologists were questioned about patients with PAP. The patients were examined and their charts, radiological images, pathological slides and physiological data were reviewed.

Results: The survey yielded 15 patients (8 females) during the period 1976–98 (14 in the last decade), giving a prevalence of 3.7×10^6 and an incidence of 0.36×10^6/year. Mean age of the patients was 33±13 years (range 0.5–46 years). Seven patients were North African (two were siblings), four were from Iraq and two were Arabs; there was only one Ashkenazi Jew (a child). Symptoms at the onset were dyspnea and chest pain. Spontaneous remission occurred in at least 3 patients, and 10 patients required 1–4 bronchoalveolar lavage treatments. The subjective and physiological response was favorable, but there was less consistent radiological improvement.

Conclusion: The prevalence of PAP in Israel is approximately 3.7×10^6. Most cases occurred in Jews who had immigrated from North Africa or Iraq, and two were siblings. The prevalence among the Arab population appears to be similar. This clustering suggests the existence of a genetic predisposition. The course of the disease appears to be similar to that reported elsewhere.

IMAJ 1999;1:75–78

Pulmonary alveolar proteinosis is a rare disease that affects mainly young and middle-aged adults. The mechanism leading to the accumulation of the surfactant-like phospholipid-rich protein in the lung is unknown [1], although a similar pathology may be associated with hematological malignancies and various infections [2]. In many cases the disease is considered idiopathic. In up to a third of the cases the abnormality resolves spontaneously [3], while in the others the alveolar filling material interferes with gas exchange, leading to effort intolerance and eventually to respiratory failure. However, an effective treatment for the disease is total lung lavage, which mechanically removes the proteinaceous material [4,5]. The prevalence of idiopathic PAP is unknown, and although estimated in the United States at between 10 and 40 cases/10^6 [5], no ethnic association has been reported [5]. Based on this estimate it is anticipated that up to several dozen cases may be found in Israel, whose population is approximately 5.5×10^6. The purpose of this survey was to determine the prevalence, the ethnic distribution and the natural course of idiopathic PAP in the multi-ethnic population of Israel.

Material and Methods

In order to identify patients with PAP in Israel, a survey of pulmonary units throughout the country was carried out. Only patients with typical clinical and X-ray findings along with biopsy or BAL[2] confirmation were accepted. Excluded were patients in whom PAP was associated with the diagnoses as noted above (secondary PAP). Physical examinations were conducted in all of the patients included in the survey, and their charts, X-rays, results of

[1] PAP = pulmonary alveolar proteinosis

[2] BAL = bronchoalveolar lavage

the pulmonary function testing and the pathological examinations were reviewed.

Results

Fifteen patients identified at eight medical centers were included, 14 of whom had been diagnosed since 1988. Seven of the patients are of North African descent (two of them are siblings), four are from Iraq and two are Arabs; there was only one Ashkenazi Jew, who was also the only child in the group. Based on these findings the prevalence and incidence of PAP in Israel is $3.7x10^6$ and $0.36x10^6$/year respectively. Eleven patients were lifetime nonsmokers. The mean age was 33±13 years (range 0.5–46). Common symptoms at the onset were dyspnea, recurrent febrile episodes, and chest pain. The interval between presentation to diagnosis varied from 1 month to 18 years. However, the two patients with the longest delay experienced a prolonged (more than a decade) spontaneous remission after the initial presentation (see below).

The diagnosis was based on open lung biopsy in eight patients, trans-bronchial biopsy in five, and BAL cytology and electron microscopy in two. Lung function at presentation [Figure 1] revealed vital capacity 48–81% of predicted, forced expiratory volume/sec 43–81%, and single-breath diffusion capacity 21–61%. Resting oxyhemoglobin saturation ranged between 70 and 98%, while saturation during exercise declined to 87–90%.

Bronchoalveolar lavage

Ten of the patients underwent between one and four BAL treatments due to progressive dyspnea and/or hypoxemia, as described elsewhere [5]. In the adult patients each lung was lavaged with 9–21 L of normal saline (0.5 L for the infant), with 3 days to 6 weeks interval between lavaging the two sides. No severe hypoxemia had been reported during the procedures. The anesthetic time lasted from 3 to 5.5 hours per session, and most patients were extubated within an hour. Throat pain, hoarseness, muscle soreness with elevation of creatine phosphokinase, and prolonged (2 weeks) intubation were reported, each in one patient. Following the lavage all the patients experienced marked subjective improvement, although lung function improvement was moderate, 0–20% [Figure 1].

The radiological findings during the course of the disease and following lavage are summarized in Table 1. The findings were similar in 14 of the 15 patients — all had bilateral diffuse interstitial and alveolar opacities. Computerized tomography, with or without thin cuts, was available in 12 patients. A common finding was the combination of augmented interstitial markings, crossing areas of ground-glass attenuation in a patchy distribution that resembles crazy paving or frost flowers. These subsegmental-sized opacities were separated from the normal lung mostly by sharp borders. The opacities often spared the apices or subpleural lung field (rim sparing), mainly at the lung bases. This probably results from central displacement of the sediment away from areas where lung movement with respiration is maximal. A unique pattern of predominant posterior nonsegmental opacities was found in the infant, which may have resulted from his predominant supine posture. Spontaneous partial clearing and/or fluctuation of the opacities were common, but in only four cases was a marked or complete spontaneous radiological improvement noted.

Table 1. Radiological findings during the course of the disease among 15 patients with idiopathic pulmonary alveolar proteinosis in Israel, 1976-97

Opacity	Common*	Less common**	Absent
Type and shape	Alveolar, interstitial, ground glass, sharp or hazy border	Air bronchogram, nodules, cavities, bronchiectasis	Pleural disease, adenopathy
Distribution	Diffuse, patchy, bilateral, peribronchial, perihilar, apical or peripheral, rim sparing	Apical, costophrenic, dependent zone predominance	
Spontaneous dynamic changes	Fluctuations in density and in location	Complete remission	
Changes following lavage	Mild improvement	Marked improvement or resolution	

* Common = found in most but at least 30% of patients
** Less common = found in less than 30% of patients

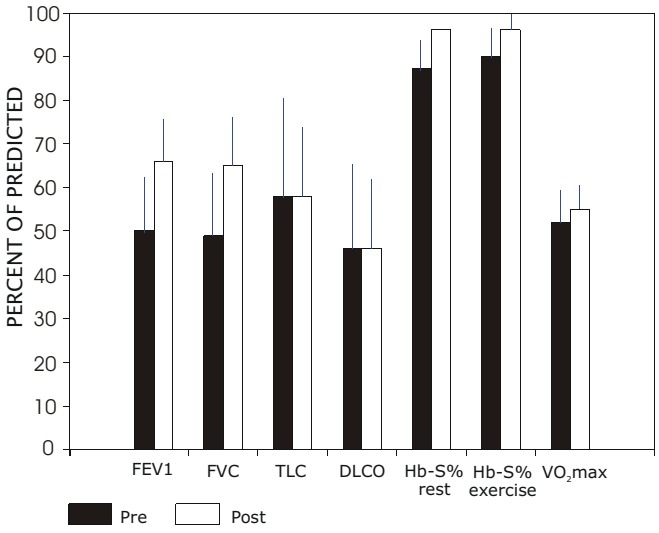

Figure 1. Mean values of lung function and exercise parameters in seven patients before and 1–3 months after bilateral lung lavage. Values are shown as percent of predicted. Oxyhemoglobin saturation is shown as absolute values. The SD for each of the parameters before and after lavage are: FEV_1 13 and 12%; forced vital capacity (FVC) 13 and 15%; total lung capacity (TLC) 19 and 9%; single-breath diffusion capacity (DLCO) 16 and 14%; oxyhemoglobin saturation (Hb-O_2 S%) at rest 8 and 2%; Hb-O_2 S% during exercise 6%; and maximum oxygen uptake 6%.

The pathological abnormalities are summarized in Table 2. Present in all patients was alveolar amorphous, granular, periodic acid-Schiff-positive, eosinophilic material with cholesterol clefts and various degrees of alveolar epithelium proliferation. In some cases the eosinophilic material spilled into the bronchioles. Focal mild inflammatory infiltrate or focal areas of fibroblast proliferation were found in some. In none of the patients was there evidence

Table 2. Histological findings (light microscopy) at diagnosis among 12 patients with idiopathic pulmonary alveolar proteinosis in Israel, 1976–97

Location of abnormality	Common*	Less common**	Absent
Alveolar space	Eosinophilic material in the alveoli, cholesterol clefts, ghost cells, eosinophilic bodies	Alveolar epithelial hyperplasia, large macrophages	Widespread fibrosis
Bronchioles		Eosinophilic material in the bronchioli	
Alveolar septa		Mild focal inflammation, focal fibroblast proliferation	

* Common = found in most but at least 30% of patients

** Less common = found in less than 30% of patients

of infection, and no stains for fungi, acid-fast organisms, pneumocystis carinii cysts or inorganic dust were detected.

Illustrative case

In this 36-year-old aluminum worker, bilateral upper lobe lung opacities had been found on routine chest X-ray when he was 18. PPD was interpreted as negative, no serological markers were detected, and cultures were sterile. Trans-bronchial lung biopsy was interpreted as nondiagnostic. The opacities resolved spontaneously. During the subsequent 18 years the patient was lost to follow-up until he noticed progressive dyspnea. Resting oxyhemoglobin saturation was 90%, which decreased to 87% with exercise. Lung function tests showed severe restriction (TLC[3] 53% of predicted). Trans-bronchial biopsy was not adequate but an open biopsy was diagnostic for PAP. In retrospect, the trans-bronchial biopsy from 18 years previously showed patchy involvement with PAP. Following therapeutic BAL, lung function, peak exercise O_2 uptake, and the anaerobic threshold improved markedly, the latter two by 24 and 44% respectively. The chest X-ray, however, remained largely unchanged. Clinical improvement has persisted throughout the 5 years of follow-up.

Comment

Although PAP has been described in aluminum workers, in this man the disease began prior to any exposure. His sister had a similar course. She initially presented with fluctuating alveolar opacities and was treated for apparent tuberculosis with no response, but later had a prolonged spontaneous (>10 years) clinical and radiological remission. A third sibling underwent splenectomy for anemia during childhood, but no details are available. It is not clear whether or not a genetic, environmental factor(s) or both contributed to the evolution, the spontaneous remission and the late recurrence of the disease in these siblings. At presentation they shared the same environment, but they lived in different households at the time of the later exacerbation. These siblings were born in Morocco, as were almost half of our patients.

Discussion

The current survey revealed that 15 patients with PAP were diagnosed in Israel since 1976, 14 of them during the last decade. The estimated prevalence of PAP in Israel — about 3.7×10^6 with an incidence of 0.36×10^6/year — is lower than that estimated for the USA [5]. We believe that these 15 patients constitute the vast majority of cases of PAP in Israel. This is based on the assumption that the common incapacitating symptoms, which occur mainly during the productive and reproductive years, together with the strikingly abnormal X-ray findings are not likely to be overlooked in a country whose medical care is easily accessible to the general population. Nonetheless, it is possible that since the disease may be mild or focal and may resolve spontaneously, cases may have been overlooked.

Ethnic distribution

The disease has been described in most industrial countries and is more common in males, but no ethnic predominance has been reported [5]. In our series the ethnic and familial clustering and the rarity of cases among Ashkenazi Jews suggest a genetic predisposition. Alveolar macrophage dysfunction has been suggested in PAP [3,5] and may be the common pathway. A recent finding emphasizes the crucial role of macrophages of a similar process in mice that lack granulocyte-macrophage colony-stimulating factor [6]. The occurrence of PAP in siblings has been previously reported, however most of these cases were infants in whom the disease may have been different from the adult disease [7].

Clinical course

Spontaneous remissions, and more commonly spontaneous fluctuations of the symptoms and of the radiological findings (density and location), were common [5,8]. In one of the patients the disease worsened during a normal pregnancy and improved postpartum

Response to therapeutic lavage

Despite the small number of patients, therapeutic lavage using a tracheal divider tube was successfully performed in several centers. Following the lavage all patients had marked subjective improvement. Objectively, resting hemoglobin saturation improved in all (up to 19%), FEV_1[4] and forced vital capacity consistently improved (13–17%) but total lung capacity and the diffusion capacity showed less consistent improvement [Figure 1]. Exercise capacity improved in some but not all subjects. However, given the long period of deconditioning, the lack of immediate improvement is not unexpected. Radiological findings changed very little after lavage [Table 1], which is in con-

[3] TLC = total lung capacity

[4] FEV_1 = forced expiratory volume/sec

trast to the apparent normalization of the X-ray following BAL reported elsewhere [5]. The reason for the lack of radiological normalization in our patients is not clear. It cannot be attributed to the longer delay in reaching the diagnosis, to a delayed initiation of the lavage, or to the presence of lung fibrosis [Table 2].

Radiological findings [Table 1]

In previous studies in which the authors described the radiological findings [8–10], they discussed the apparent absurdity of the existence of interstitial abnormalities in a disease, which is the hallmark of an alveolar filling process [10]. Despite previous suggestions that CT scan findings may be diagnostic [9], we and others [10,11] believe that no abnormality is pathognomonic for PAP. However, the patchy distribution of ground glass attenuation with increased interstitial markings (frost flowers), and/or patchy basilar rim sparing were highly suggestive. The spontaneous fluctuation in the density and location of the opacities is also characteristic. In our experience, however, BAL induced a radiological improvement that was less than expected. Although radiological findings are an important aid to the diagnosis, they are not sensitive enough to detect fluctuations (either spontaneous or BAL induced) in their disease severity.

Pathological findings [Table 2]

If other alveolar filling disorders and certain organisms can be excluded by auxiliary methods, the histological diagnosis can be easily established [1]. Since the distribution of PAP is patchy, it can be missed by trans-bronchial biopsy. If the fluid obtained from a diagnostic BAL has a milky appearance, the diagnosis is strongly suggested, although the return of the first aliquot(s) may not have that appearance. Cytology and electron microscopy are helpful and are considered diagnostic [12]. Despite reports that PAP may be associated with inorganic dust exposure [13], we found no inorganic particles in our patients. Moreover, despite the limited radiological improvement following therapeutic BAL, we found no unusual pathological features such as prominent septal fibrosis or inflammation that could have accounted for the persistent radiologic abnormalities. The only histological marker that could have suggested a more severe disease [5] was the presence of eosinophilic material in the bronchioli that was seen in some patients.

Conclusion

The prevalence of PAP in Israel is approximately 3.7×10^6. Most cases were Jews who immigrated from North Africa or from Iraq, and two were siblings. The prevalence among the Arab population appears to be similar. This clustering suggests the existence of a genetic predisposition. The course of the disease and the response to therapeutic lavage appears to be similar to experience reported in the USA and Europe.

References

1. Rosen SH, Castelman B, Liebow AA. Pulmonary alveolar proteinosis. *N Engl J Med* 1958;252:1123–42.
2. Bedrossian CWM, Luna MA, Conklin RH, Miller WC. Alveolar proteinosis as a consequence of immunosuppression: a hypothesis based on clinical and pathological observations. *Hum Pathol* 1980;11(Suppl):527–35.
3. Larson RK, Gordnier R. Pulmonary alveolar proteinosis: report of six cases, review of the literature and formulation of a new theory. *Ann Intern Med* 1965;62:292–312.
4. Ramirez-R J, Kieffer RF, Ball D. Bronchopulmonary lavage in man. *Ann Intern Med* 1965;63:819–28.
5. Wasserman K, Masson GR. Pulmonary alveolar proteinosis. In: Murry JF, Nadel JA, eds. Textbook of Respiratory Medicine. Vol 2, Philadelphia: W.B. Saunders Co., 1994:1933–47.
6. Drannof G, Crawford AD, Sadelain M, Ream B, Rhashid A, Bronson RT, Dickersin RG, Bachurski CJ, Mark EL, Whitsett JA. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. *Science* 1994;264:713–16.
7. Teja K, Cooper PH, Squires JE, Schnatterly MS. Pulmonary alveolar proteinosis in four siblings. *N Engl J Med* 1981;305:1390–2.
8. Prakash UBS, Barham SS, Carpenter HA, Dines DE, Marsh HM. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. *Mayo Clin Proc* 1987;62:499–518.
9. *Murch CR, Carr DH.* Computed tomography appearances of pulmonary alveolar proteinosis. *Clin* Radiol 1980;40:240–3.
10. Goodwin D, Muller NL, Takasugi JE. Pulmonary alveolar proteinosis: CT findings. *Radiology* 1988;169:609–13.
11. Tan RT, Kuzo RS. High resolution CT findings of mucinous bronchoalveolar carcinoma: A case of pseudopulmonary alveolar proteinosis. *Am J Radiol* 1997;168:99–100.
12. Burkhalter A, Silverman JF, Hopkins III MB, Geisinger KR. Bronchoalveolar lavage cytology in pulmonary alveolar proteinosis. *Am J Clin Pathol* 1996;106:504–10.
13. Miller RR, Churg AM, Hutcheon M, Lam S. Case reoorts: pulmonary alveolar proteinosis and aluminum dust exposure. *Am Rev Respir Dis* 1984;130:312–15.

Correspondence: Dr. I. Ben-Dov, Pulmonary Institute, Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel: (972-3) 530 2735; Fax: (972-3-) 535 4993; email: bendovi@post.tau.ac.il

My doctor has always told me to smoke. He even explains himself: "Smoke, my friend. Otherwise someone else will smoke in your place".

Erik Satie (1866–1925), French composer.
Me'moires d'un amne'sique (1924).