Pulmonary Alveolar Microlithiasis

A Report of Two Youngest Cases in a Family

SZE-PIAO YANG, M.D., F.G.G.P. AND CHI-CHUNG LIN, M.D.*
Taipei, Taiwan, China

PULMONARY ALVEOLAR MICROLITHIASIS is a rare disease; not more than 60 cases have been reported in the world literature. The essential features of this disease are: (1) a characteristic radiologic appearance of miliary disseminated lesions caused by innumerable intra-alveolar concrements throughout the lungs; (2) extremely few clinical symptoms until the late stage of disease, in contrast to the pronounced degree of radiologic and pathologic changes, and (3) frequent occurrence of more than one case in a single family. There seems no sexual predominance and most patients have been found between 30 and 50 years of age.

The etiology of this condition remains obscure, although many acquired or environmental factors, as well as hereditary congenital predisposition, have been suggested.

We have recently encountered two cases of pulmonary alveolar microlithiasis in a family. It is worthwhile adding these cases to the world literature in view of the fact they are siblings and are the youngest cases so far reported. One was eight years of age at the time of diagnosis, but a chest x-ray film taken at two years and ten months has, in retrospect, been recognized as showing the same characteristic pattern, although to a much lesser degree. The other, his younger sister and found by family examination, was four years and four months of age. In our opinion, these cases cannot be ignored whenever the etiology of this disease is to be discussed.

CASE REPORT

CASE 1

K. S. T., an eight-year-old school boy, was referred to us on October 12, 1961, from Taipei Tuberculosis Control Center because of miliary disseminated lesions in his lungs found by mass chest x-ray survey in April, 1961 and not responding to antituberculosis treatment. His past history revealed that he had episodes of "bronnchopneumonia" at eight months, two years and ten months, and four years of age and that he was hospitalized each time in the Provincial Taipei Hospital for 12, 12 and eight days, respectively. He was inoculated with BCG in October, 1953, but his tuberculin test remained negative in January, 1954 as well as in May, 1959. Re-inoculation was made in early 1961, but the tuberculin test still remained negative in May, 1961.

In spite of the extensive lesions throughout his lungs, he had been entirely symptom free and had been physically able to keep pace with his classmates.

When first seen by us, his physical and mental development were normal and no abnormal physical sign was elicited. Subsequent routine laboratory examinations including blood count, urine, stool, sputum and ECG were all within normal limits. Blood chemistry including total protein, A/G ratio, calcium, phosphorous, alkaline phosphatase were also normal.

Chest x-ray film taken on October 12, 1961 (Fig. 1) revealed extensive uniform, bilateral sand-like miliary densities of both lungs obscuring the cardiac outlines and the diaphragm, most marked in both hilar regions and fading out toward the apices and peripheral portions of the lungs. The minor fissure was thickened. These findings were identical with those of previous films taken in April, May and September, 1961 at the Tuberculosis Control Center. Bone study of both hands revealed no abnormality.

For a child eight years old, we first considered sarcoidosis or primary hemosiderosis as a possible diagnosis. Triamcinolone (Kenacort), 8 mg. daily was tried for six weeks. Subsequent chest x-ray film taken on January 11, 1962, however, showed no improvement.

Needle biopsy was finally carried out on February 23, 1962 in order to reach a definitive diagnosis. Microscopically the specimen revealed numerous concentrically laminated (onion-skin) microliths in fairly normal alveoli. The alveolar walls were of normal appearance; neither inflammatory nor fibrotic changes may be seen (Fig. 2).
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2A: (upper) Histologic appearance of needle biopsy specimen of the lung in Case I. Nuert.ius concentrically laminated microliths in most of the alveoli (120 X). Figure 2B: (lower) An onion-like calcified body in fairly normal alveolus (480 X).

Pulmonary function tests made after the diagnosis were within normal limits.

Confirming the diagnosis as "pulmonary alveolar microlithiasis," we had made every effort to trace back his previous films taken during his admission in Taipei Provincial Hospital and to study his family and environmental background. Only one chest x-ray film which was taken at two years and ten months of age could be traced. It revealed the same pattern of abnormality of much lesser degree; the miliary nodulations were less disseminated and less dense. Heart and diaphragm were clearly defined (Fig. 3). All other members of the family were also called up and examined, and this led to the discovery of the second case in the family.

Family and Environmental History:

A thorough survey of his family and environmental history was made. His grandparents died during the 2nd World War on the China mainland, both being over 40 years of age. His father, who is a government employee, was married to his mother on the mainland in 1946 and came to Taiwan in the same year. The economic condition of the family has been fair.

He has six siblings, two older sisters, ages 14 and 12, and three younger sisters, ages four years, 3 years, and five months respectively. They all were born and brought up in Taipei, the capital city of Taiwan. Chest x-ray survey of all these
family members was made, and one of his younger sisters, the next to him, had the same pattern of chest x-ray abnormalities which will be reported. The rest of the family all had normal chest x-ray findings. The relatives of the maternal side are all living on the China mainland and information on their physical condition cannot be obtained.

CASE 2

Y. H. T., a girl aged four years and four months, the next younger sister of Case 1. Typical chest x-ray pattern of pulmonary alveolar microlithiasis was found during the family survey on March 7, 1962 (Fig. 4) after the first case was correctly diagnosed. Her mother suffered from Asian influenza in the first trimester of pregnancy in 1957. She was spontaneously delivered on November 5, 1957 and the baby was of 6.5 lb. body weight. She was said to have congenital heart disease by several doctors at three months of age when she was first brought to a doctor for a "cold." There were neither complaints nor cyanosis. No chest x-ray film had been taken previously. Tuberculin test in May, 1960 was negative and subsequently BCG was inoculated.

She was a moderately developed and nourished girl. Neither clubbing of the fingers nor cyanosis could be seen. No abnormal physical sign could be detected except a grade III harsh systolic ejection murmur audible at the third intercostal space along the left sternal border. Laboratory examinations including hemogram, urine, stool, sputum, blood chemistry, daily urinary excretion of calcium and phosphorous were all within the normal limits. An electrocardiogram was also negative. Roentgenogram of the chest was strikingly similar to her brother's, revealing the classic snowstorm appearance throughout both lungs. The heart was slightly enlarged to both sides and the contour was like a narrow bottle, defined by fine subpleural calcific deposits. Diaphragm and lower thoracic cage were blurred, and thickening.
of the minor fissure was more prominent (Fig. 4). Together with auscultatory findings, phonocardiogram with amyl nitrate tests, a ventricular septal defect was considered to be the most probable diagnosis of her congenital heart condition.

Because the roentgenogram was so characteristic of pulmonary alveolar microlithiasis, needle biopsy was not attempted.

**DISCUSSION**

Although the condition of pulmonary alveolar microlithiasis was first described by Harbitz' in 1918, it was Sosman' and his collaborator who provoked the general interest of medical circles by reviewing and discussing 24 cases in their collection and another 22 previously reported cases. Thereafter, five more cases were reported in the literature'" and more in the unavailable literature, making a total of about 60 cases reported throughout the world. There seems no sexual predominance. The majority of cases have been between 30 and 50 years of age when this condition was first, and most frequently, accidentally found. The youngest case so far is a child aged six reported by Sato' in 1955. The family tendency of the disease was first recognized by Mikhailov' in 1954, three in one family, and others follow.'" Up to the present, eight instances of familial occurrence have been found.

The reader is referred to Sosman's excellent article' which summarizes our present knowledge, and we do not attempt, in this paper, to discuss the whole story of the disease. Instead, with the two youngest cases in one family in hand, the discussion will be limited to the etiology of this condition which is still obscure.

Before the familial tendency of this disease was recognized, acquired factors such as chronic bronchitis,' emphysema,' fungi,' repeated pneumonitis,' and dust' had been suggested as the causative agents. In discussing the etiology, Kent, Gilbert and Meyer' emphasized that the laminated appearance of the calculi suggests the presence of a general stimulus occurring in successive stage and assumed, by analyzing the previously reported 14 cases and their own case, that it is the result of a peculiar pulmonary exudate, probably hyperimmune in nature, and due to a variety of insults including pneumonias and rheumatic fever. They apparently did not pay too much attention to the until then, single report of familial occurrence in their etiologic consideration.

Since the recognition of its familial predisposition, there seems no doubt about the existence of some hereditary factors in the development of the disease, although some environmental or acquired factors such as dust' or other irritants'" and diet,' have been stressed as playing an important role, reasoning from the fact that most cases were found between 30 and 50 years of age, that exposure history to some kind of dust or irritant'" was detected in some cases, and that a certain number of family members living in the same environment had the disease while the rest of the same family living in different environments did not develop the disease.' These statements cannot be warranted, however, because nearly all cases so far reported were accidentally found by survey chest x-ray film and this condition may last years without symptoms, so that strictly speaking we still cannot identify the real beginning and the mode of development of this condition by a study of the previously reported cases.

Based on the present cases and a review of the literature, we may note the following facts as important in considering etiology.

1. There are increasing instances of familial occurrence.

2. The condition may begin to develop soon after birth and before any environmental or acquired factors may come into operation.

3. It may take at least several years to develop from the early phase of x-ray finding to the fully developed classic chest x-ray abnormalities.

4. The early phase of chest x-ray abnormalities reveals that miliary nodulation is less disseminated and less dense in appearance indicating that the lesions are not only sparsely scattered, but also are not well calcified.

5. The pathologic change of microlithiasis is limited to the lumen of the alveoli. The alveolar wall is usually normal except
in the late stage. This may explain the lack of clinical symptoms as well as respiratory insufficiency for years.

6. The predominant elements of the calculi are calcium and phosphorus. Calculi are undoubtedly gradually formed by deposit of calcium phosphate and carbonate in alveolar exudate.

7. No definite unified environmental or exogenous factors can be elicited as stimulating agents.

Knowing these facts we may conclude that an inherited abnormality plays a fundamental role in the development of this condition and that environmental factors, if any, may merely play a rather unimportant and a nonspecific role. We personally strongly favor Sosman's theory that the origin of this condition could be an inborn error of respiratory metabolism at the alveolar interface, possibly due to an abnormality affecting carbonic anhydrase which may result in the deposit of calcium phosphate and carbonate.

Close follow-up study of the entire family would be very valuable for further clarification.

Summary

1. The two cases of pulmonary alveolar microlithiasis reported in a family are the youngest so far recorded in the literature. One had an early phase of roentgenologic abnormalities at two years and ten months of age and developed the characteristic findings by the age of eight years when diagnosis was made by needle biopsy. The second is four years of age, and already has fully developed classic chest x-ray abnormalities, as well as congenital heart disease.

2. Regarding etiology of this condition, we are strongly in favor of the theory of an inborn error of respiratory metabolism.

Resumen

1. Los dos casos de microlítidas alveolar relatados en una familia son los más jóvenes hasta hoy publicados. Uno de ellos tuvo una etapa en la que hubo anormalidades roentgenológicas a los dos años y diez meses de edad y presentó las características de la enfermedad a los 8 años, siendo entonces verificado el diagnóstico por la biopsia por punción pulmonar. El segundo tiene 4 años de edad y ya ha presentado el cuadro clásico completo a los rayos X, y enfermedad cardíaca congénita.

2. Con respecto a la etiología de esta afección nos inclinamos mucho hacia la teoría de un error innato en el metabolismo respiratorio.

Zusammenfassung

1. Die beiden Fälle von pulmonaler alveolärer Mikrolithiasis aus einer Familie, über die berichtet wird, sind die jüngsten bisher in der Literatur mitgeteilten. Der eine hatte eine frühe Phase von röntgenologischen Veränderungen mit 2 Jahren und 10 Monaten und es entwickelten sich bei ihm die charakteristischen Merkmale im Alter von 8 Jahren, als die Diagnose gestellt wurde aufgrund der Lungen-Nabel-Biopsie. Der zweite Fall ist 4 Jahre alt, und bei ihm haben sich bereits die klassischen röntgenologischen Thoraxveränderungen entwickelt sowie ein angeborenes Herzleiden herausgestellt.

2. Was die Ätiologie dieser Erkrankung angeht, spricht nach unserer Meinung sehr vieles zu Gunsten der Theorie einer angeborenen Störung des Lungenstoffwechsels.

References


For reprints, please write Dr. Yang at National Taiwan University Hospital, Taipei, Taiwan.