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Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies

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KEYWORDS
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Introduction

The rare incidence of pulmonary alveolar microlithiasis has not allowed us to describe in detail main characteristics of the disease. However, an overview of the world literature may provide some guidelines relative to the epidemiology, familiarity, clinical and pathological features together with possible therapies.

Epidemiology

Although the first few pulmonary alveolar microlithiasis cases have been reported by Malpighi,[1] the term was first coined by Phur[2] in the 1930s in order to indicate the main feature of the disease. Indeed, the essence of this disorder is the presence in pulmonary alveolus of round shaped little bodies containing concentric calcareous lamellas.

The disease is present in all the continents and does not have any preference for specific races or countries. The incidence is similar in both sexes and it is higher in age brackets between 20 to 50 years. However, Mariani e Lopez[3] reported two cases of microlithiasis at the age of 2 years whereas a case of neonatal microlithiasis occurring in premature twins was reported by Caffrey et al.[4] Finally, a case of this disease occurring at the age of 72 years was described by Barnard and it is the oldest case which has been reported up till now.[5] According to recent data[6] about 300 cases have been published so far. Most of them were reported in Europe then in Asia, North America, Africa and Oceania (Table 1). The country with the highest number of cases is Turkey (56 cases) then Italy (36 cases). In reference to Italian record of cases, 64% of them were found in Southern Italy (Puglia, Campania, Basilicata) as opposed to the remaining 36% which were found in Nothern and Central Italy (Lazio, Abruzzo, Romagna, Piemonte).

Familiarity and possible pathogenetic hypotheses

The analysis of reported cases reveals that the disease is prevalent amongst family units. Familiarity exhibiting horizontal relationship was found amongst 5 sisters by Perosa and Ramunni (family L.A.),[7] amongst 4 sisters by Gomez-Esquerra, amongst 2 brothers by Martinez, [8] amongst 4 sisters by Sosman[9] and amongst 3 sisters by Mariani.[10] One case of familiarity exhibiting vertical relationship with parent-child ratio of 1:1 was described by Mikhailov[11] and another one was reported in

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Table 1 World distribution of pulmonary alveolar microlithiasis.

Europe:	123 cases Italy 36, France 18, Great Britain 16, Germany 14, Spain 12, Yugoslavia 7 Russia 6, Bulgaria 4, Austria 3, Switzerland 3, Czechoslovakia 2, Hungary 2
Asia:	115 cases Turkey 56, Japan 20, Thailand 14, India 13, Saudi Arabia 6, China 2, Pakistan 2, Armenia 1, Israel 1
North America:	30 cases USA 26, Mexico 3, Jamaica 1
South America:	9 cases Colombia 6, Brazil 2, Argentina 1
Africa:	7 cases Egypt 3, Morocco 2, Kenya 1, South Africa 1
Oceania:	2 cases Australia 2

By Castellana G. et al. in: ''La microlitiasi alveolare polmonare: rivisitazione della casistica italiana''. Rass Patol Apparato Respir 1998; 13(6): 405–7.

Bulgaria. Familiarity exhibiting both horizontal and vertical relationship was reported by Perosa and Ramunni[7] in a family unit of 5 people (family Mu): 2 sisters and 3 children of one of the sisters. Therefore, this represents the largest family group as well as the family with the highest parent–child ratio of pulmonary alveolar microlithiasis reported to date in the literature. Also, it provides support for the hypothesis that the disease may be hereditary and related to an underlying autosomal recessive gene disorder. Furthermore more recent reports may support this hypothesis. Indeed, Castellana and coll[12] described a case of microlithiasis in a patient who was related to a family in whom Perosa and Ramunni found the 5 cases of this same rare condition. The case described by Castellana was a cousin of one of the two sisters indicated by Perosa and Ramunni suggesting the hypothesis of a possible hereditary transmission.

Although clinical features of this disease have been well described, the mechanism which may induce microliths to form is unknown. Inhalation of specific powders was thought to be involved in the origin of microliths as some patients lived in the same rural district and worked on the same farmlands.[7] Nevertheless, the analysis of chemical composition of the land (characteristic ''red land'' containing silica, iron, aluminium, titanium) together with the absence of microlithiasis in other areas provided with land exhibiting the same chemical composition had not confirmed this hypothesis. Furthermore, structural affinities which have been found in microliths and in ''corpora amilacea'' hypothesized that the origin of both compounds could be similar. Therefore, a possible condensation of alveolar mucus was thought to be involved in the formation of microliths as the origin of ''corpora amilacea'' had been hypothesized to be connected to this mechanism. On the other hand, the condensation of alveolar mucus could require the presence of an excess of this substance in pulmonary alveolus. This excess might be related to a reflux of mucus in alveolus connected to reduced activity of bronchial ciliated epithelium. In accordance to this hypothesis, some studies were performed in order to evaluate the lung mucociliary function in patients with microlithiasis. D'Addabbo et al.[13] reported that in patients with microlithiasis the clearance of inhaled radiogold particles was shown to be significantly slower as compared with controls. In addition, the pattern of serial scans clearly indicated that the lung mucociliary function was impaired in patients with microlithiasis. This may suggest that slowing of the clearance may represent a pathogenetic factor capable of favouring the formation of alveolar microliths. Results obtained by Chinacoti et al.[14] in patients who were accustomed to smoke ''snuff'' (a particular mixture of tobacco and oriental gum) seems to be in favour of this hypothesis. Indeed, 9 cases of pulmonary alveolar microlithiasis were described among these smokers and experimental results demonstrated the ability of the above-mentioned mixture to inhibit the activity exerted by bronchial ciliated epithelium. Furthermore, results coming from other experimental studies suggested the possibility either of an alveolar thesaurotic process[15] or an alveolar congenital enzymatic defect. This last abnormality could induce the development of a far too alkaline alveolar microenvironment which may lead to precipitation of calcium salts with following formation of microliths.

Finally, cases of pulmonary alveolar microlithiasis secondary to lung cancer, tubercular remains and pleural mesothelioma have been reported too.[16]

Pathological features

Pulmonary alveolar microlithiasis-related pathological features may appear either confined to particular areas of the lung or widespread. In the

widespread form, lungs exhibit increased weight (about 5 kg) and consistency as well. External surface of lungs may appear granular because of protrusion of microliths under visceral pleura. Furthermore, areas of bullous emphysema may be found both on the anterior margin and at the apex of lungs. In the confined form, microliths are present in restricted areas of lungs only exhibiting the same pathological features as those of the widespread form. The diameter of microliths is about of 0.2 μ and, in this case, microliths may fill the pulmonary alveolus whose wall and septums may appear to be pressed. In the case of smaller sizes a space between alveolus wall and microliths may occur; it may be filled by macrophages. Microliths are not uniformly distributed in lungs as there are very few at the upper regions as opposed to the lower ones where they are more numerous. In reference to histology, microliths consist of calcareous concentric lamellas which are placed around a central nucleus exhibiting an amorphous or granular aspect. Chemically, microliths consist of large amounts of calcium and phosphorus which are mixed to small amounts of magnesium and aluminium. Tinctorial properties indicate that microliths are Pas-positive.

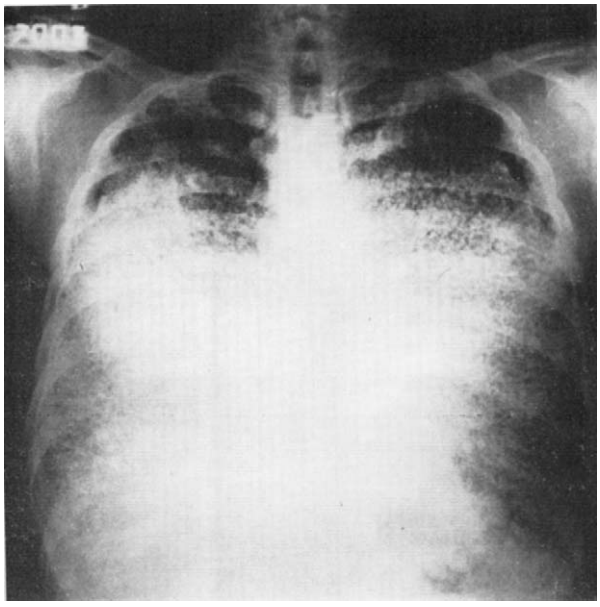

Figure 1 Pulmonary alveolar microlithiasis: X-ray pattern of lungs. By Lauta V.M.: "La funzione undulopodica dell'epitelio bronchiale nella microlitiasi endoalveolare del polmone studiata con curve di eliminazione di particelle di Au^{198} e con scintigrafie polmonari". Atti Ac Pugl Sci 1980; 18: 13–44.

Clinical features

The dissociation between definite X-ray pattern of lungs and relative poor clinical symptoms is one of the most common characteristics of the disease. The family anamnesis does not report significant elements. Patients may report previous recurrent bronchopneumonias which are not known to have been favourite in their onset from the preexisting pneumopathy or to assume the role of predisposing factor in the appearance of alveolar microlithiasis. Clinical symptoms are often absent and, in this case, diagnosis of the disease may be sustained by a specific X-ray pattern of lungs only. In other cases, patients may report a certain degree of dyspnea with a productive cough, sporadic hemoptysis with thoracic pains; rales may be found at lung bases by physical examination of the chest. X-ray pattern of lungs consists of dissemination of nodules of almost equal sizes among them. They are as radioopaque as tissues containing calcium as well as they are widespread in all the pulmonary regions so much that lungs appear to be sprinkled with sand (Figs. 1 and 2).[17,18] However, the distribution of nodules may be irregular; at times, they are mainly distributed at lung bases and disappear into the apexes; at times, they may be more evident at

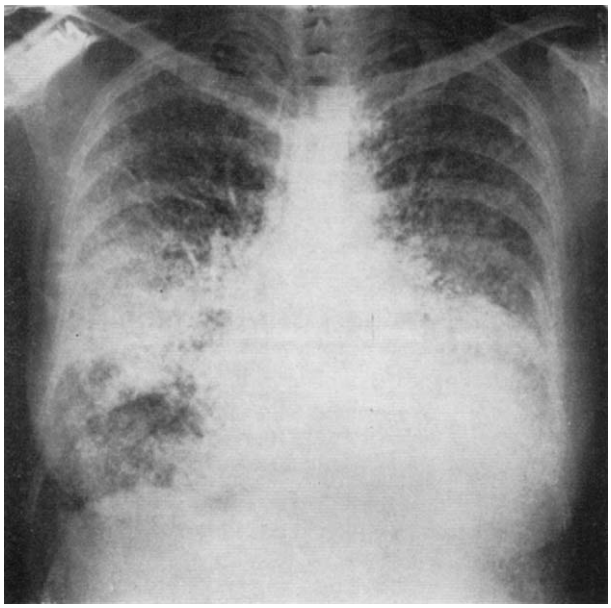

Figure 2 Pulmonary alveolar microlithiasis: X-ray pattern of lungs. By Lauta V.M.: "La funzione undulopodica dell'epitelio bronchiale nella microlitiasi endoalveolare del polmone studiata con curve di eliminazione di particelle di Au^{198} e con scintigrafie polmonari". Atti Ac Pugl Sci 1980; 18: 13–44.

hilum and disappear into the peripheral areas of lungs; at times, they are mainly distributed along bronchuses and vases. The computerized axial

tomography of the chest performed with high resolution technique provides evidence of numerous and tiny alveolar calcareous microcorpuscles with areas of bullous emphysema at the upper lobes of lungs.[19]

Laboratory data

Routine tests (ESR, blood nitrogen, glycemia, urinalysis) exhibit normal values except for a certain tendency to polycythemia at the hemogram. Usually, no microliths is possible to be detected in the sputum whereas they may be found in the broncho-alveolar lavage fluid by chemical examination.[20,21] Pulmonary function tests exhibit a proportional reduction of FEV_1 (forced expiratory volume in 1 s) and VC (vital capacity) values together with a decrease of FRC (functional residual capacity), RV (residual volume) and TLC (total lung capacity) values. The alveolocapillary diffusion is normal as opposed to a mild increase of plethysmography resistance values. The evolutive course of the disease leads to pulmonary insufficiency which is related to the increase of microliths number in several areas of the lungs. Usually, the exitus occurs by 10–15 years from the diagnosis, even if Castellana and coll[6] point out a pulmonary alveolar microlithiasis case revisited after 44 years from the diagnosis. Authors report that this is the longest living case in world literature, attesting this disease is not very evolutive in any cases.

Diagnosis

The diagnosis of pulmonary alveolar microlithiasis is based mainly on the already mentioned dissociation between definite X-ray pattern of lungs and relative poor clinical symptoms.

However, a differential diagnosis must be performed in reference to similar X-ray patterns occurring in other pneumopathies. Indeed, the sarcoidosis is characterized by a similar dissociation between clinical and radiological elements. Nevertheless, lung nodules exhibit more stable sizes together with a higher radiopacity in patient with microlithiasis than in those with sarcoidosis. In addition, epithelioid cells as well as Langhan's giant cells are possible to be detected in the broncho-alveolar lavage fluid by cytologic examination in patients with sarcoidosis who may also exhibit positivity for the Kweim test. Furthermore, the stable sizes and the higher radiopacity expressed by lung nodules in microlithiasis may also allow the differential diagnosis between this pneumopathy and miliary tuberculosis. Common involvement of hilar lymph nodes during the development of lung tuberculosis may be an additional element in this differential diagnosis. Idiopathic and secondary pulmonary emosiderosis may be taken into consideration for a possible differential diagnosis with microlithiasis. The coexistence of some clinical symptoms such as hemoptysis, anemia, latent jaundice are in favour of idiopathic pulmonary emosiderosis whereas heart trouble inducing hypertension of pulmonary circulation sustain the diagnosis of secondary pulmonary emosiderosis. Finally, the dissociation between radiological and clinical factors may also be found in some pneumoconiosis such as the anthracosis and silicosis. In this case, previous inhalation of relative mineral particles related to a specific working activity may make differential diagnosis with microlithiasis easier.

Therapy

The inability to identify clear etiological and pathogenetic elements makes the therapeutic approach difficult. In any rate, it is palliative and unrealistc as well. Gocmen and coll[22] proposed the use of diphosphonate in order to reduce calcium phosphate precipitation in pulmonary alveolus. This treatment would have induced a little improvement of lungs' X-ray pattern only without any involvement of evolutive course of the disease. The use of steroids proved to be ineffective whereas therapeutic broncho-alveolar lavage fluid (BAL) gave rise to controversial opinions. The use of BAL for a therapeutic aim is based on the intake of physiological salt solution in pulmonary airways with the following drainage of an identical amount of liquid in order to remove the majority of microliths from alveolus. Although the theoretical principle seems to be sound as well as results coming from some clinical studies report valid collections of microliths, according to some Authors the evolutive course of the disease does not seem to be involved.[19,20,23] However, other results which indicate the possibility of a control of the course of the disease by this therapeutic method have been reported.[21]

In conclusion, these elements indicate more and more the requirement that new fields of research are necessary in order to identify more specific ways of treatment.[24,25]

Summary

Pulmonary alveolar microlithiasis is characterized by the presence in pulmonary alveolus of round shaped little bodies containing concentric calcareous lamellas. The incidence is similar in all continents, in both sexes and it is higher in age brackets between 20 and 50 years. The disease is prevalent among family units. Clinical reports may suggest the hypothesis that the disease may be hereditary. Pathogenetic hypotheses may indicate that a reduced lung mucociliary function leading to an excess of alveolar mucus may induce the formation of alveolar microliths by mucus condensation.

Microliths may appear either confined in particular areas of the lung or widespread. Chemically, microliths consist of large amounts of calcium and phosphorus and, in reference to histology, they consist of calcareous concentric lamellas which are placed around an amorphous or granular central nucleus. The dissociation between definite X-ray pattern of lungs and relative poor clinical symptoms is the most common characteristics of the disease. However, a certain degree of dyspnea with a productive cough may occur together with a sporadic hemoptysis and thoracic pains. X-ray pattern of the lung reveals dissemination of radioopaque nodules which may make lungs appear to be sprinkled with sand.

The evolutive course of the disease leads to pulmonary insufficiency which is related to the increase of number of microliths in several areas of lungs.

The inability to identify clear etiological and pathogenetic elements makes difficult therapeutic approach which is palliative such as the use of diphosphonate, steroids and therapeutic BAL.

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