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Pulmonary Alveolar Microlithiasis: About Two Cases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Alveolar microlithiasis (AML) is a rare condition characterized by the accumulation of calcium concretions in the pulmonary alveolar lumen. We report two cases of AML, suspected on chest radiography and confirmed by chest CT scan with pathognomonic appearance and transbronchial lung biopsy. ALM is often asymptomatic in contrast to the importance of the characteristic radiological lesions. The etiology of this pathology is unknown, but a genetic origin with the autosomal recessive transmission is suspected with mutation of the SLC34A2 gene.

Keywords: Alveolar microlithiasis; calcospheritis; imaging; pulmonary calcifications; SLC34A2 gene.

1. INTRODUCTION

Pulmonary alveolar microlithiasis is a rare inherited disease. It is characterized by the formation and deposition of phosphocalcium in the alveolar spaces. It remains asymptomatic for a long time, and the disease is often discovered by chance during a systematic radiological examination [1]. It is an autosomal recessive disease in which the SLC34A2 gene mutation has been identified [2,3]. Pulmonary Alveolar Microlithiasis is seen all over the world with no particular affinity for geographical location or ethnicity. Turkey, Italy, and the US have reported the largest number of cases. Previously, there seemed to be a slight male predominance but with the increasing number of cases published, the gender distribution is now the same between

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males and females [4-6]. We report two observations of pulmonary alveolar microlithiasis with a review of the literature.

Recently, the abnormality of the gene responsible for the disease has been identified.

1.1 Patients and Observations

Observation 1

42-year-old female patient with no toxic habits and no particular pathological history. She was hospitalized at the age of 18 years for dyspnea of progressive aggravation with cyanosis of the lips and extremities and a digital hippocratism probably related to an undiagnosed microlithiasis. The reason for consultation on 07/2017 was worsening dyspnea in front of the slightest effort. The pulmonary auscultation found bilateral crackling rales. Chest radiography showed a very fine-grained miliary appearance of calcium density outlining the pleura and obliterating the edges of the heart (Fig. 1). The thoracic CT scan showed diffuse calcified micronodules confluent in places with pseudocondensations predominating at the bases with a circumferential calcified parapleural line extending over the entire height of the thorax. This appearance was very suggestive of alveolar microlithiasis (AML). Flexible bronchoscopy showed a normal endoscopic appearance. The search for microliths in the bronchioloalveolar lavage was not performed due to the lack of a specialized laboratory. Tuberculosis workup: GeneXpert MTB and direct examination and culture for BAAR in the bronchial aspirate fluid were negative. Transbronchial lung biopsy showed the presence of microliths in the form of spherical elements with a concentric lamellar onion bulb structure located in the alveolar lumen confirming MLA (Fig. 3). The family investigation revealed another case in the siblings. The treatment was symptomatic with short courses of corticosteroids and antibiotic therapy in case of superinfection with pneumococcal and influenza vaccinations and against COVID 19. Evolution was marked by the aggravation of dyspnea in front of stage 4 mMRC . The six-minute walk test showed a desaturation of 70% after five minutes of walking. The functional respiratory exploration showed a severe mixed syndrome with an obstructive component of 49% of the theoretical value and a forced vital capacity (FVC) of 44%. The arterial gasometry showed hypoxia at 45 mmHg and normocapnia. The current chest radiograph showed the same appearance as the previous radiographs. The recent chest CT scan showed an aggravation of the previously described lesions. Cardiac ultrasound showed pulmonary hypertension (PH) at 50mmHg. The patient was put on long-term oxygen therapy (LTO) associated with diuretics. She died after 7 months of evolution

Observation 2

Patient aged 38 years, exposed to passive smoking for 9 years, with no particular pathological history. Admitted to the department on 11/2019 for the diagnosis of pulmonary alveolar microlithiasis retained during a family screening following the death of a brother 4 months ago in acute respiratory distress. The interrogation did not reveal any respiratory symptoms. The clinical examination was unremarkable. The thoracic imaging revealed micronodular calcifications in the parenchymal, septal, and subpleural areas in favor of pulmonary alveolar microlithiasis (Fig. 2). The diagnosis was confirmed by trans-bronchial biopsies with the presence of intra-alveolar calcifications compatible with alveolar microlithiasis. The tuberculosis work-up was negative. Respiratory function tests were borderline normal. Treatment was symptomatic with pneumococcal and influenza vaccinations and COVID 19. The patient is still being followed at our training facility. Lung transplantation is scheduled in this patient.

2. DISCUSSION

Alveolar microlithiasis was first described by Malpighi in 1686 and by Harbitz in 1918 [1]. Less than 600 cases have been reported in the literature. The frequency is high in Mediterranean countries, especially in Turkey and Italy, with a definite familial character in 50%, suggesting an autosomal recessive mode of transmission [1,2]. The etiopathogenesis is unknown but a genetic origin with the autosomal recessive transmission is suspected. A homozygous loss-of-function mutation in the SLC34A2 gene encoding a sodium/phosphate co-transporter channel expressed by type II pneumocytes has been described in patients of Japanese origin [3]. The dysfunction of this protein, by reducing the clearance of phosphates produced by the degradation of surfactant phospholipids, could lead to the formation of calcospherites [7]. However, environmental factors could also be involved. MLA can be found at any age from infancy to late life and about 25% of cases occur in children under 18 years of age [2]. The

majority of patients with ALM remain asymptomatic for a long time, with the disease being discovered incidentally on a chest X-ray or during the family investigation. But the evolution towards respiratory failure is inevitable with dyspnea, cyanosis, digital hippocrasis and then right heart repercussions. This is the case of our patient who had consulted for minimal symptoms contrasting with the importance of the pulmonary lesions and whose progressive evolution for 23 years has led to chronic respiratory failure with chronic pulmonary heart. Thoracic imaging is crucial and often allows to the discovery of the disease. The typical appearance is represented by diffuse, bilateral, regular, micronodular opacities with sandy calcium density, predominantly at the bases and in the hilar regions, creating a "sandstorm" appearance, blurring the edges of the heart and the diaphragmatic domes. Pleural thickening may be seen, but a characteristic sign of MLA is the presence of a peripheral clear line called the parapleural line [8]. Chest computed tomography (CT) confirms the chest X-ray data. It is useful for early diagnosis and for monitoring the progress of patients. However, it allows for a more precise appearance and distribution of parenchymal calcifications and sometimes shows pleural and/or pericardial calcifications. High-resolution CT (HR-CT) shows the preferential subpleural and peribronchovascular accumulation of lung calcifications and specifies their distribution [8,9]. The scannographic appearance in our patient was consistent with that described in the literature. Technetium 99m methyl diphosphonate (Tc 99m MDP) scintigraphy showed abnormally high levels of calcium in the lung, predominantly at the bases. Positron emission tomography (PET scan) with 18FDG could be of diagnostic interest by showing pulmonary hyperfixation [10]. The association with extrapulmonary calcifications, notably renal, prostatic or gonadal, has been reported [11]. Functional respiratory exploration allows to establish an initial functional assessment and following the evolution of the disease. Typically, ALM results in a restrictive ventilatory disorder. The study of bronchoalveolar lavage fluid (BALF) may reveal microliths. Transbronchial lung biopsy with microscopic examination currently seems to be a reliable means of diagnosis because it allows collecting of fragments of sufficient size and affirms the diagnosis of MLA by the presence of microliths in the form of a spherical element with a concentric lamellar onion bulb structure located in the alveolar lumen [1,2]. In our two patients, it was transbronchial lung biopsy that confirmed the diagnosis. Surgical lung biopsy remains a more aggressive procedure and there is no specific effective treatment for this disease [12].

The therapeutic possibilities are limited. Corticosteroid therapy and disodium etidronate have been tried in combination with sodium sulfate and a low phosphate diet [2] and only lung transplantation can improve survival. The identification of the gene responsible for pulmonary alveolar microlithiasis could constitute a therapeutic hope, in particular through the development of gene therapy, as well as an early genetic diagnosis of familial forms.

The evolution is slow: an Italian survivor has been reported 50 years after diagnosis [9,10]. A recent review by Deniz et al [4] showed a correlation between the profusion of micronodules and the alteration of the lung parenchyma, as well as of the respiratory function. Nevertheless, the evolution is not uniform and not predictable. Respiratory function impairment is more rapid in smokers [3]. Death occurs 10 to 15 years after diagnosis, most often with chronic respiratory failure and pulmonary hypertension [8,9], secondary to chronic hypoxia.

3. CONCLUSION

ALM is a very rare condition, often asymptomatic and with a very slow evolution. Health professionals should be aware of a striking radiological appearance in contrast to poor or absent clinical signs. High-resolution CT scans and transbronchial lung biopsy are of great diagnostic value. Today, lung transplantation remains the only and last therapeutic option for this disease [14,15].

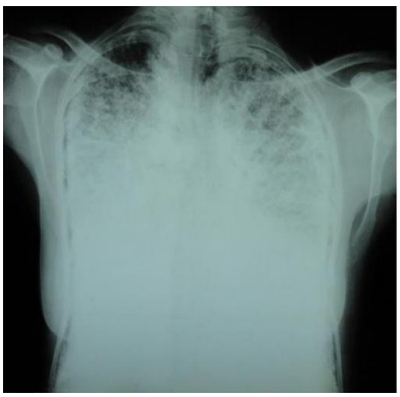

Fig. 1. Frontal chest X-ray showing reticulo-micronodular opacities, with calcium density drawing the pleura and erasing the edges of the heart

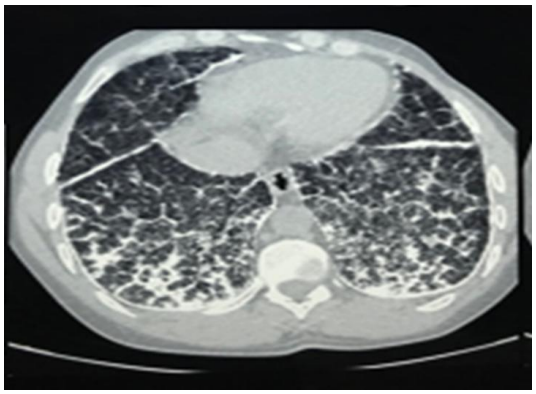

Fig. 2. Cross-sectional chest CT scan showing diffuse confluent calcified micronodules in places, predominantly at the bases with a circumferential calcified para pleural line

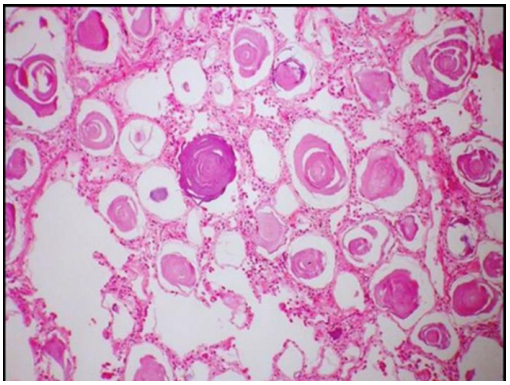

Fig. 3. Pulmonary biopsy, presence of calcospherites at the pulmonary alveolar level

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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