World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

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Pulmonary alveolar microlithiasis: A case report from Morocco with review of literature

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World Journal of Advanced Research and Reviews, 2022, 15(03), 352–357

Publication history: Received on 17 August 2022; revised on 22 September 2022; accepted on 24 September 2022

Article DOI: https://doi.org/10.30574/wjarr.2022.15.3.0950

Abstract

Background*:* Pulmonary alveolar microlithiasis (PAM) is a rare infiltrative chronic lung disease characterized by deposition of spherical calcium phosphate microliths called calcospherites within the alveoli with predominance in lower and mid zones. Etiology and pathogenesis is not fully understood.

Case presentation: We report a case of 58 year old female patient presenting with progressive shortness of breath and chronic bronchitis over a period of 4 years. Physical examination revealed she had signs of chronic respiratory failure. Chest radiograph showed dense micronodular opacities giving classical sandstorm appearance. High resolution computed tomography showed diffuse microcalcifications, bilateral ground glass attenuation and septal thickening with calcification along the interlobar septa and subpleural regions.

Conclusion: According to our research this is the 15th case of PAM that has been declared in Morocco. Given the rarity of this entity, the purpose of this study was to increase knowledge of this disease among pulmonologists, in order to provide timely diagnosis.

Keywords: Pulmonary Alveolar Microlithiasis; Diagnostic imaging; Solute carrier family 34 member 2; Type IIb Sodium; Dependent phosphate co-transporter; Infiltrative lung disease-Case report

1. Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare and uncommon lung disease characterized by the deposition of calcium phosphate microliths or calcospherites within the alveolar spaces [1] Since the first description of the disease almost 150 years ago, over 1022 cases have been reported in the world literature [2]. Although the etiopathogenesis remains unclear, PAM is considered to be an autosomal recessive disease caused by mutations of the solute carrier family 34 (sodium phosphate), member 2 gene (the SLC34A2 gene), which encodes a sodium phosphate cotransporter [3]. There is a blockade in phosphate reabsorption in PAM, leading to excess alveolar phosphate that binds with calcium to form calcium phosphate crystals [4]. Despite cases of PAM being reported at all ages, patients in the second and third decade were most commonly affected [2]. Most of the time the disease is discovered incidentally on chest imaging, and when symptomatic, the clinical course is generally slowly progressive evolving to respiratory failure [1, 5]. Here we report a case of PAM in a female who presented with severe respiratory distress and hypoxemia.

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2. Case presentation

Our patient was a no smoker 58-year-old female from Morocco whose parents are first cousins; she had a history of pulmonary tuberculosis in 1994 and environmental exposure to pigeon droppings. In the last four years, she has developed a progressive chronic bronchitis associated with chronic dyspnea. Her family history was quite interesting, in fact both her brother and sister suffered from an undocumented pulmonary disease. The patient was initially admitted to the Mohammed VI University Hospital Center Marrakech's emergency for shortness of breath and chest pain and was then later transferred to our Respiratory department for further investigations. Upon admission, she had signs of chronic respiratory failure. Physical examination found a patient with circumoral cyanosis, tachypnea and clubbing of the fingers and toes. She also had bilateral lower limb edema associated to abdominal distension related to ascites. The patient's oxygen saturation was 90% on five liters of oxygen via nasal cannula. Diffuse coarse crackles were also noted.

Chest X-ray showed no evidence of rib fractures but demonstrated bilateral diffuse reticulonodular opacities that had a greater distribution in the middle and lower lung zones. The nodular opacities were fine, well-marginated calcified micronodules that were only millimeters in diameter and described as having the classic "sandstorm-like" appearance. Figure 1

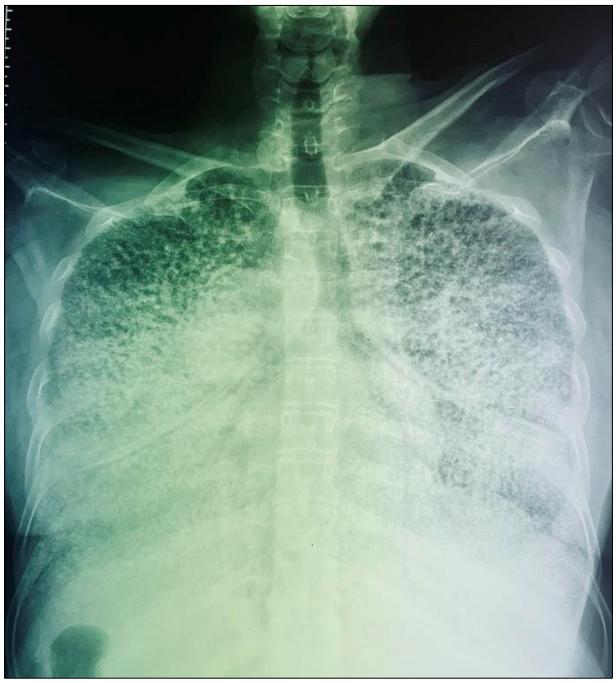

Figure 1 Chest X-ray showing bilateral calcified micronodules described as "sandstorm-like" appearance

High resolution computed tomography (HRCT) revealed widespread micro-calcifications throughout the lungs concentrated in the middle to lower zones. Diffuse ground-glass opacities were bilateral, with striking interlobular septal thickening and pleural calcification. Multiple small subpleural cysts also were present associated to mild bilateral posterobasal traction bronchiectasis. Besides a thin layer of pericardial effusion CT scan revealed peritoneal effusion with dilation of central hepatic veins indicating a chronic right-sided heart-failure. Figure 2.

Routine blood biochemistry showed a slight increase in white blood cell count associated to hepatic cytolysis with an elevation in serum transaminase levels > *2* × upper limit of normal, abdominal ultrasound was then performed revealing signs of congested liver. Arterial blood gas analysis on room air found a chronic respiratory alkalosis combined to severe hypoxemia with pH: 7.46, PaCO2: 46 mmHg, PaO2: 59, 8 mmHg and HCO3-: 22 mmol/l. Echocardiograph revealed enlargement with systolic dysfunction of the right ventricle and severe pulmonary hypertension (pulmonary systolic pressure to 100 mmHg). Because the patient was uncooperative for pulmonary function test (PFT), respiratory function couldn't truly be evaluated. Since the patient had a history of pulmonary tuberculosis a full assessment was made; the sputum was negative for acid-alcohol resistant bacillus and human immunodeficiency virus testing was negative as well. We initially attempted to perform a bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy but it was intolerable by the patient given her respiratory status.

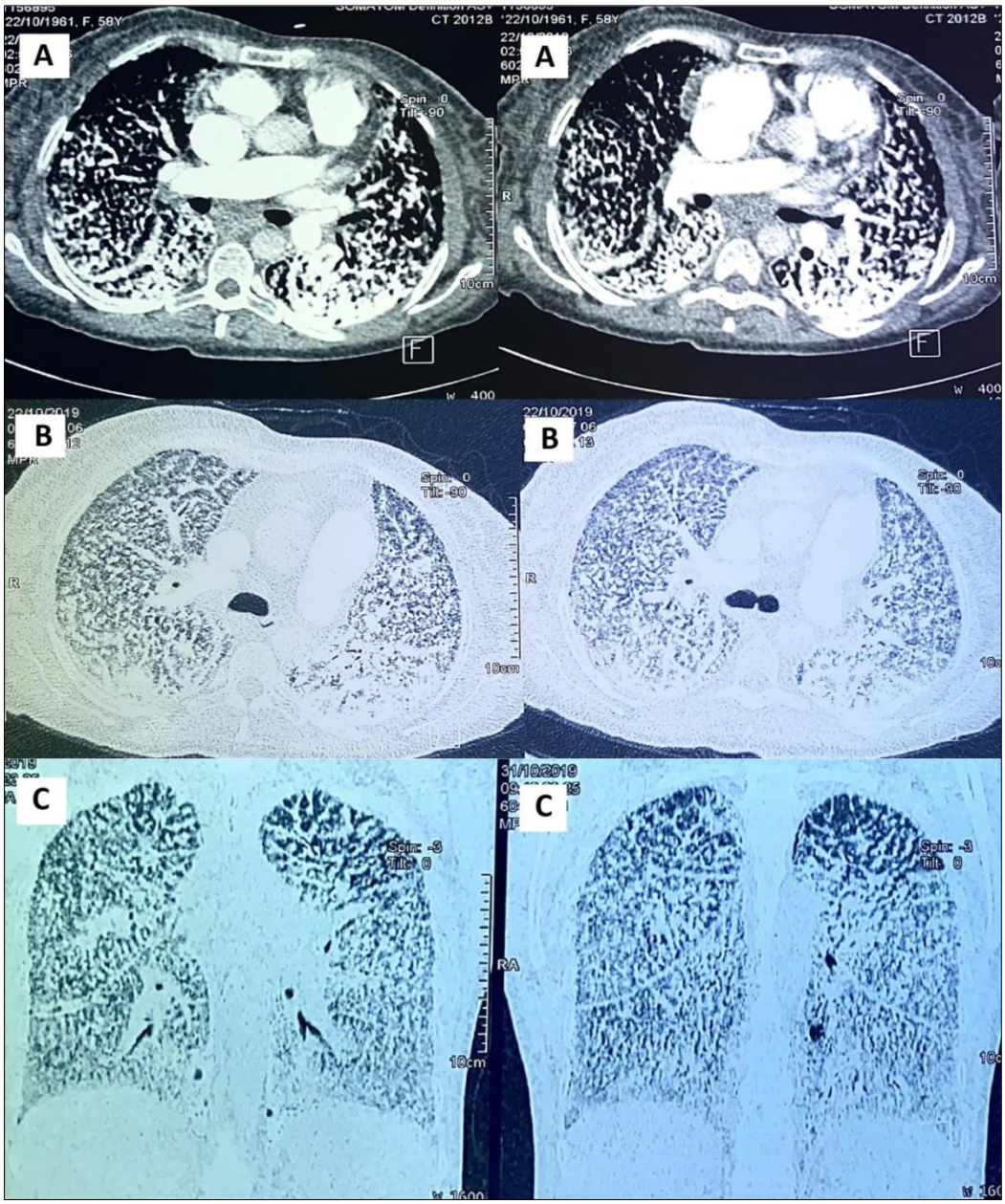

Figure 2 A/B/C HRCT at parenchymal and mediastinal windows demonstrates widespread micro-calcifications throughout the lungs. Diffuse ground-glass bilateral opacities, interlobular septal thickening and pleural calcification. Multiple small subpleural cysts

After excluding other differential diagnoses such as sarcoidosis, silicosis, amyloidosis and pulmonary alveolar proteinosis; we eventually retained the diagnosis of pulmonary alveolar microlithiasis following the patient's family history, clinical presentation and the characteristic imaging in favor of PAM. Due to PAM's family history and known familial nature of this disease, genetic testing was recommended but has not been completed at the time of this publication.

During her hospitalization, the patient was put on antibiotic and diuretic treatment with good clinical and biological evolution. She was then discharged from the hospital under oxygen therapy at home with regular follow-up consultation. Unfortunately, months later she was reported out of sight. Before her checkout informed consent was obtained. The patient understands that her name and initials will not be published and has given her consent for clinical information to be reported in a case report.

3. Discussion

PAM is a rare autosomal recessive disease affecting the lung; it was first described in 1868 by Marcello Malpighi but it was not until 1918 that Harbitz more accurately described the radiologic findings. The current name, mikrolithiasis alveolaris pulmonum, was provided by Ludwig Puhr in 1933 [6]. Since then over a 1000 cases have been reported worldwide on almost every continent but the majority of them have been from Asia (56.3%) and Europe (27.8%) with predominance in a few countries, particularly Turkey, Italy and the USA [7]. According to our research this is the 15th case of PAM that has been declared in Morocco. Despite the fact that sporadic cases occur, the disorder is autosomal recessive, and study results have shown a substantial familial occurrence with familial cases accounting 30–50% of the reported cases [8]. In addition, a history of consanguineous marriage has been identified in a large number of parents of affected individuals, with the disease frequently involving siblings, which is the case for our patient [9]. Although no male or female predominance has been identified in the familial cases, the sporadic cases have occurred more commonly in male individuals [6].

PAM is a rare disease with poorly defined etiology and pathogenesis. It appears to be an autosomal recessive inheritance due to mutations of SLC34A2 gene which was identified in a DNA segment on chromosome 4p15 by a Japanese group performing genome-wide high-density single-nucleotide polymorphism-based homozygosity mapping in six patients from five families [10]. The SLC34A2 gene comprises 13 exons of which 12 encode the type IIb sodium-dependent co-transporter called NPT2b [11, 12].NPT2b is most abundantly expressed in the lung and small intestine, with the highest levels of expression in the alveolar epithelium and ileal epithelium, respectively. In the lung, expression of the NPT2b appears to be most abundant in alveolar type II cells, where it is thought to be required for export of phosphate generated by alveolar macrophage-mediated catabolism of surfactant phospholipids [7]. Loss of function of the gene due to mutation leads to decreased cell uptake of phosphate which is responsible of intra-alveolar microliths formation as a result of phosphate chelating calcium in extracellular fluid [5].

The disease is usually discovered from birth up to 40 yrs of age. PAM's clinical presentation is highly variable, with most patients being asymptomatic in the early stages of the disease with an insidious onset and slow progression over decades [13, 14]. Symptomatic patients develop dyspnea on exertion and dry cough as the disease progresses, but these symptoms are often less pronounced than chest radiographs would suggest, a phenomenon that has been called clinical–radiological dissociation. Less-common symptoms including chest pain; cyanosis and haemoptysis are more likely associated with a severe form of the disease eventually leading to respiratory failure [7].

Chest radiographs show fine, sand like micronodular calcifications throughout both lungs, an appearance classically described as "sandstorm lung" [5]. The middle and lower zones of the lungs are more prominently involved, possibly because of the greater vascular blood supply to these regions. Multiple adjacent subpleural cysts can be seen resulting in a dark pleural line between the lung periphery and either the ribs or the mediastinum called the "black pleura" sign [5, 15]. As the disease progresses, the density of the lung parenchyma may obscure the cardiac borders, diaphragms, costophrenic sinuses and cardiophrenic sulci resulting in the radiographic manifestation described as the "vanishing heart phenomenon" [7]. The chest radiographs of our patient showed a diffuse symmetric lung lesion with dense micronodular aspect, corroborating the pattern described in the literature.

High-resolution CT is the preferred imaging modality for evaluating possible findings of PAM owing to its increased sensitivity in depicting subtle parenchymal changes. HRCT shows characteristic finding of innumerable microliths involving both lungs with predisposition for anterior segments of upper lobes and posterior segments of lower lobes. Microliths are also seen along subpleural and peribronchovascular interstitium with resultant thickened micronodular appearance of these structures. Microliths with diameter of less than 1mm produce ground glass opacities which with appropriate windowing are seen as discrete calcifications [15]. Ground glass opacities with interlobular septal thickening due to microliths resemble crazy paving pattern seen in pulmonary alveolar proteinosis. Appropriate window settings visualize microcalcification which helps in differentiating between the two types. Multiple small thin walled subpleural cysts are also seen which cause dark pleural line on HRCT. Other CT features include calcifications along the interlobular septa, fissures, and pleura and dense areas of consolidation [15]. Bronchiectasis may result from fibrosis, but it is often peripheral and mild. It is essential to differentiate PAM from other diseases with similar radiographic appearances, including miliary tuberculosis, fungal infection, pneumonia, sarcoidosis, amyloidosis, pulmonary alveolar proteinosis, pulmonary hemosiderosis, metastatic calcification, and pneumoconiosis [14]. In this case, associated CT findings and clinical features should always be correlated, since these diseases have different kinds of presentation and evolution [11]. These findings correlate with the CT scan description of our patient.

Although pulmonary function tests (PFTs) are often normal in early disease, a restrictive defect with a reduction in diffusion capacity for carbon monoxide is most typical over time [7]. 6-minute walk testing may demonstrate reduced

exercise capacity and exercise-induced desaturation before resting hypoxia becomes evident.Routine blood tests are usually normal in patients with PAM. Surfactant protein (SP)-D, produced exclusively in the lungs by club cells and alveolar type II cells, seems to be elevated in the serum of patients with PAM and further increases with progression of illness [14]. However, SP-D can be elevated in the serum of patients with idiopathic pulmonary fibrosis and pulmonary alveolar proteinosis, with increased values suggestive of progressive disease [7].MCP-1 was recently reported as another potential biomarker based on mouse models. Although MCP-1 and SP-D have been suggested to be useful serum markers in monitoring the disease activity and progression, they will not likely have diagnostic utility for PAM as they can be elevated in other pulmonary diseases [11].

PAM's definitive diagnosis lies on typical radiographic findings plus genetic testing or, in the absence of testing, radiography with tissue diagnosis [11]. In fact characteristic radiographic and CT findings are adequate for establishing the diagnosis; however, histopathologic confirmation achieved by using transbronchial, CT-guided, or surgical biopsy is often required [7]. Bronchoalveolar lavage can help recover microliths but is otherwise unremarkable and not used for diagnosis [9]. Histologic features typical of PAM are intra-alveolar, spherical, lamellated, calcium-phosphate crystals usually <10 mm but can be up to 5.0 mm [14]. In advanced cases, microliths are seen in interlobular septa, bronchovascular bundles and subpleural space where fibrosis and ossification are often observed [2]. Unfortunately, given her respiratory status no bronchoscopy or lung biopsy could have been performed.

To date there is no known effective medical or gene therapy treatment for PAM no capable of reducing disease progression, with the exception of lung transplantation. Systemic corticosteroids, calcium-chelating agents and serial bronchopulmonary lavage have been shown to be ineffective and are used as palliative treatments, however only few studies have reported some discordant results [7]. The use of diphosphonates has also been proposed to reduce calcium phosphate precipitation in PAM but this therapy remains controversial given the limited number of reports in the literature [14]. In severe PAM with respiratory failure and hypoxia, palliative treatment with oxygen improves subjective daytime function and oxygenation [7].

Since the first bilateral lung transplant in a patient with PAM described in 1992 in France, a lot of similar case reports determined its efficiency; indicating that lung transplantation remains the only possible treatment for end-stage disease. Nonetheless, guidelines for the decision as to when transplantation should be undertaken are not available due to the lack of well-defined prognostic indices and the insidious nature of PAM [14].

The prognosis of PAM remains unclear and only few longitudinal studies explored prognosis in patients with PAM. In a long-term follow-up study of 53 Japanese patients, respiratory failure was the most common cause of death in 34.1% of patients within 10–20 years of diagnosis, and of those surviving, an additional 42.9% within 20– 49 years of diagnosis with a mean survival overall of 46.2 years [7]. These results suggest a poor long-term prognosis for patients with PAM, including patients discovered to have asymptomatic disease in childhood.

4. Conclusion

PAM is a rare disease that can affect young patients, with chronic and deteriorating evolution. Clinicians should be aware of it existence and the radiological features associated. The micronodular pattern seen in chest radiography can sometimes be misdiagnosed as miliary tuberculosis or other diseases that present with this pattern. In this way, HRCT should always be performed since it can reveal characteristic patterns of alveolar microlithiasis, reserving lung biopsy for atypical and inconclusive cases.

Compliance with ethical standards

Acknowledgments

Pr. AMRO, Dr.SAIDI and Pr. AIT BATAHAR participated in design and development of the case report, managing and treating the patient, writing of the case report and final approval of the submitted version after critical review, Dr BOUGADOUM and Dr HINDI participated in managing, treating the patient and development of the case report.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

All the authors: Imane SAIDI, Meryem BOUGADOUM, Maryem HINDI, Salma AIT BATAHAR and Lamyae AMRO report no conflict of interest in relation to the subject matter.

Statement of informed consent

Informed consent was obtained. The patient understands that her name and initials will not be published and has given her consent for clinical information to be reported in a case report.

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