Human Pathology: Case Reports 14 (2018) 85–87

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: www.elsevier.com/locate/ehpc

Case Report

# Pulmonary microlithiasis: A case of forensic autopsy and a brief literature review

Gelsomina Mansueto[a,*], Emanuele Capasso[b], Massimo Niola[b], Mariano Paternoster[b]

[a] Department of Advanced Biomedical Sciences, Legal Medicine Unit-Pathology Unit, University of Naples Federico II, Via Pansini 5, Edificio 20, 1° piano, 80131 Napoli, Italy

[b] Department of Advanced Biomedical Sciences, Legal Medicine Unit, University of Naples Federico II, Via Pansini 5, Edificio 20, 1° piano, 80131 Napoli, Italy

ARTICLE INFO

*Keywords:*
PAM
Alveolar microlithiasis
Forensic autopsy
Pulmonary hypertension

ABSTRACT

*Background:* Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disease with a high penetrance characterized by widespread intra-alveolar accumulation of countless minute calculi called microliths. Patients with PAM may be asymptomatic, and the diagnosis is often an accidental finding during medical imaging performed for other diseases. Otherwise, it can develop into pulmonary fibrosis. In both cases, the disease can lead to respiratory and pulmonary heart failure which, though occurring rarely, may have a fatal outcome.

*Case presentation:* We report the case of a 40-year-old male found dead in the bathroom. In the absence of trauma or other signs of injuries and in absence of a history of previous diseases, forensic autopsy was required to identify the time, cause and means of death. Our final diagnosis was death by right ventricular hypertrophy with initial signs of acute ischemia in a patient with PAM.

*Conclusions:* This case provides insights into a pathology which is not frequent and can lead to death, besides illustrating the importance of histology in solving cases that come within a forensic setting. Therefore histology is fundamental to diagnose the cause of death, supplemented by knowledge of physiology and pathology in the cardiovascular and respiratory.

## 1. Background

PAM was first described by Friedrich in 1856 and then by Harbitz in 1918 [1,2]. It is a rare autosomal recessive disease with a high penetrance, characterized by accumulation of microliths of a compound called calcium phosphate in the small air sacs, and is caused by a mutation of the SLC34A2 gene, encoding the type IIb sodium phosphate co-transporter that is expressed in the alveolar type II cells [3,4]. These deposits eventually cause widespread damage to the alveoli and surrounding lung tissue (interstitial lung disease) which leads to breathing problems. People with this disorder can develop a persistent cough and dyspnea, especially during physical exertion. Affected individuals may also experience chest pain that worsens when coughing, sneezing or taking deep breaths.

The current focus of the scientific literature comprises world epidemiology and the characteristics of PAM, paying particular attention to familial, genetic, clinical, diagnostic, radiological and therapeutic aspects in order to offer insights into this rare disease. A recent review of the literature reported 544 publications that confirm the heterogeneous geographical distribution and autosomal recessive genetic transmission of the disease [5].

## 2. Case presentation

A 40-year-old man was found dead in the bathroom. External examination did not reveal evidence of trauma; no history of previous diseases.

A standard autopsy was performed. Inspection of the neck, chest and abdomen was negative for any outer lesion, with organs and viscera of normal size, without evident macroscopic pathological changes. Toxicology was negative for all drugs.

The lungs were normal in size with a congested surface, cracking to the touch and strident to cut. The heart was preserved and the coronary vessels were not occluded, but the thickness of the right ventricles was increased (1.3 vs 0.3–0.5 cm). Histology of the lungs showed areas of fibrosis, atelectasis and proteinaceous oedema, and congestion as signs

* Corresponding author.
*E-mail addresses:* gelsomina.mansueto@unina.it, mansueto.g@inwind.it (G. Mansueto), emanuele.capasso@unina.it (E. Capasso), massimo.niola@unina.it (M. Niola), mariano.paternoster@unina.it (M. Paternoster).

https://doi.org/10.1016/j.ehpc.2018.09.005
Received 12 June 2018; Received in revised form 12 September 2018; Accepted 27 September 2018

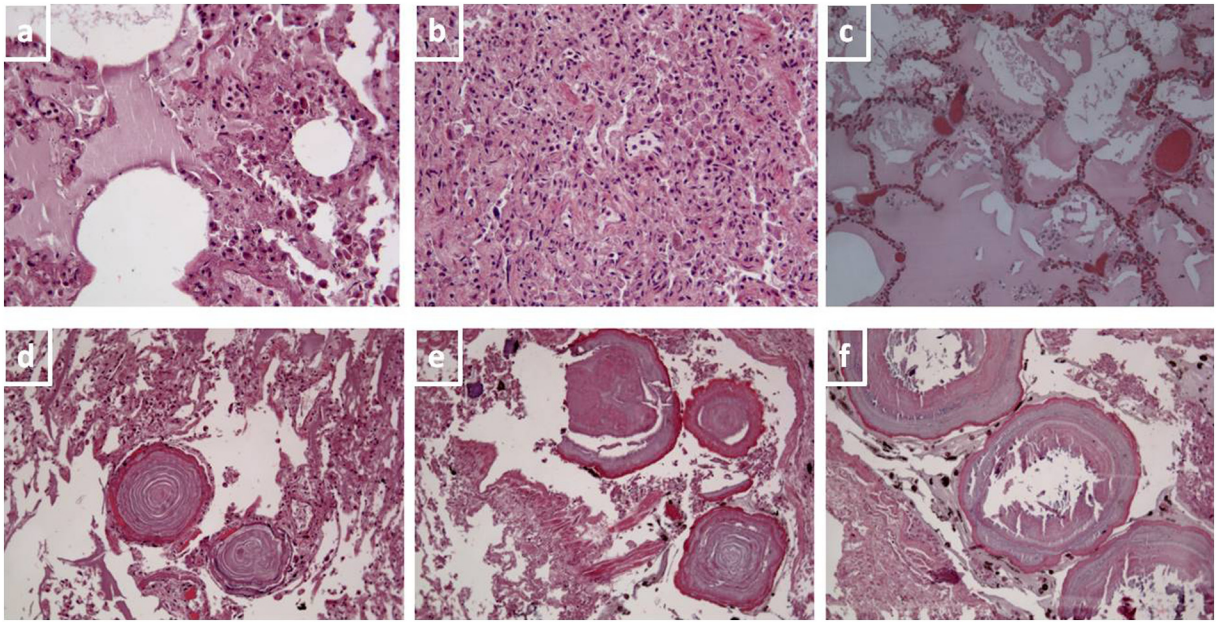


**Fig. 1.** a. The proteinaceous oedema with the presence of hyaline membranes, and with an exfoliation of cellular elements and macrophage (H&E ×20); b. Areas of fibrosis and pulmonary atelectasis (H&E ×20); c. The oedema (H&E ×10); d-e-f. Round shaped little bodies with classical concentric lamellar structure (H&E ×20 in d, ×20 in e, ×40 in f).

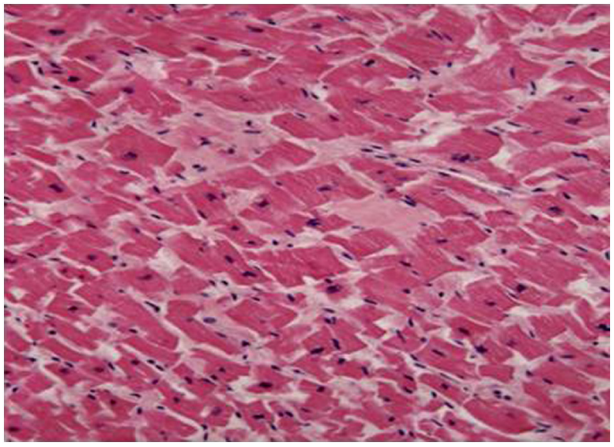

**Fig. 2.** A detail of the myocardial disarrangement in the hypertrophy of the right ventricle (H&E ×20).

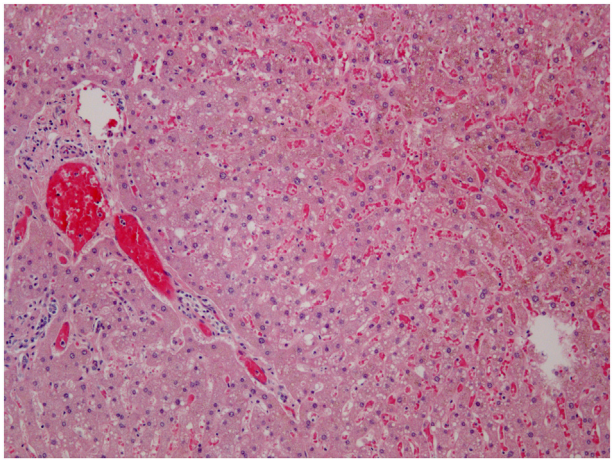

**Fig. 3.** Hepatic congestion (H&E ×10).

of hypertension (Fig.1a–c. H&E, Hematoxylin and eosin stain); multiple diffuse areas with round shaped little bodies containing concentric calcareous lamellas were observed (Fig.1d–f, H&E). Histology of the right ventricle showed hypertrophy and initial signs of acute damage (Fig. 2 H&E). Multiorgan oedema and hyperaemia were detected, especially in the liver, as occurs in the congestion related to right heart disease (Fig.3). The death was determined by cor pulmonale (pulmonary heart disease).

## 3. Discussion and conclusion

PAM is a rare chronic lung disease characterized by deposition of calcium and phosphate in the pulmonary bilateral parenchyma with a predominance in the lower and medium areas [6]. It can be diagnosed at any age. The literature reports a higher number of cases from birth to 40 years of age, but also reports cases that are diagnosed at around 80 years of age and, albeit rare, even deaths with autopsy diagnosis. It is both a familial and sporadic disease, and without particular predilection for female or male subjects. It seems that mutations in the SLC34A2 gene, encoding a co-transporter sodium phosphate in type II pneumocytes, are responsible for production of surfactant and play an important role in the formation and accumulation of microliths [7]. Mutations that result in gene function loss cause a decrease in phosphate cellular absorption, leading to the formation of intra-alveolar microliths due to the presence of phosphate-chelating calcium in extracellular fluid [7]. This is the mechanism of alveolar damage and the result is primary pulmonary hypertension.

Indeed, primary pulmonary hypertension is due to direct damage to the alveolar wall with increased extravascular compartment resistance. When this occurs, characteristic morphological signs are represented by protein oedema passing through the alveolar spaces of the liquid part and the corpuscular part and by erythrocyte extravasations due to direct damage to the alveolar segment vessel walls. Obviously, this all results in an increase in blood flow resistance to pulmonary arteries, resulting in right ventricular overload, right atrium stasis and peripheral circulatory hypertension whose congestion and blood extravasations are morphologic and histological manifestations. The severity of cardiac hypertrophy depends on the lung failure.

The diagnosis of PAN is often incidental during imaging carried out

for other diseases in an asymptomatic subject. In some cases, it can develop into pulmonary fibrosis and thus be symptomatic, ultimately leading to respiratory and pulmonary heart failure and a possible fatal outcome [8,9]. In our case, the pulmonary data were of the hypertensive type even if severe fibrosis had not yet occurred. However, the thickness and histology of the right ventricle were indicative of ventricular hypertrophy as in cor pulmonale (pulmonary heart disease),-with peripheral congestion as stasis.

Patients with PAM have a restrictive syndrome which then evolves into the disease and is responsible for an increase in the right parietal thickness as in the case we described. Indeed, the right ventricular hypertrophy generally associates with cor pulmonale. As stated above, PAM patients often have very mild symptoms or none at all and when diagnosis is performed using RX imaging and biopsy, they generally have an unfavourable prognosis. The cardiac hypertrophy that develops is not necessarily important in terms of parietal thickness; it is capable of changing functionally and with secondary ischemic events. Our case is the first of sudden death by PAM not diagnosed while the patient was alive.

The scarce and unspecific clinical manifestations, together with the scarcity of appreciable macroscopic alterations detected at autopsy in PAM, with the exception of cor pulmonale, do not allow an immediate diagnostic definition of the cause of death, regardless of the result of anatomic and histological investigations.

In the present case, the most important element was represented by pulmonary microlithiasis, which led to an increase in pulmonary resistance and a decrease in ventilation with an increase in the thickness of the heart walls in response to the excessive work.

To our knowledge, this is the first case of PAM death and our autopsy diagnosis was important to resolve the legal setting.

## Authors' contributions

GM[*,1] & MP[4] conceived and drafted the manuscript.

EC[2] and MN[3] have been involved in drafting the manuscript and revising it critically for important intellectual content.

## Ethics approval and consent to participate

We present anonymous data from histological findings in a case of death. No ethics approval and consent are required.

## Consent for publication

We present histological findings. Is not necessary the consent for publication. The data is anonymous.

## Availability of data and material

Data are available by request

## Competing interests

The authors report no conflict of interest.

## Funding

This study had no funding source.

## Authors' information

The authors are working in an University medical post graduate institute.

## Double blind

Yes

## Acknowledgements

We are particularly grateful to Sara Pignatiello for cutting and staining histological slides.

## References

[1] N. Friedrich, Corpora amylacea in den Lungen, Virchows Arch. A Pathol. Anat. Histopathol. 9 (1856) 613–618.
[2] F. Harbitz, Extensive calcifications of the lungs as distinct disease, Arch. Intern. Med. 21 (1918) 139–146.
[3] A. Corut, A. Senyiğit, S.A. Ugur, et al., Mutations in SLC34A2 cause pulmonary alveolar microlithiasis and are possibly associated with testicular microlithiasis, Am. J. Hum. Genet. 79 (2006) 650–656.
[4] F.A. Ferreira Francisco, J.L. Pereira E Silva, B. Hochhegger, et al., Pulmonary alveolar microlithiasis. State-of-the-art review, Respir. Med. 107 (2013) 1–9.
[5] G. Castellana, G. Castellana, M. Gentile, R. Castellana, O. Resta, Pulmonary alveolar microlithiasis: review of the 1022 cases reported worldwide, Eur. Respir. Rev. 24 (2015) 607–620.
[6] S.M. Khaladkar, S.K. Kondapavuluri, A. Kamal, R. Kalra, R. Kube, Pulmonary alveolar microlithiasis - Clinical and radiological dissociation - a case report with radiological review, J. Radiol. Case Rep. 10 (1) (2016) 14–16.
[7] A. Stamatopoulos, D. Patrini, S. Mitsos, R. Khiroya, E. Borg, M. Hayward, D. Lawrence, N. Panagiotopoulos, An unusual late onset of pulmonary alveolar microlithiasis: a case report and literature review, Respir. Med. Case Rep. 22 (2017) 24–27.
[8] T. Terada, Pulmonary alveolar microlithiasis with cor pulmonale: an autopsy case demonstrating a marked decrease in pulmonary vascular beds, Respir. Med. 103 (11) (2009) 1768–1771.
[9] K. Khalid Mahmood, M. Ubaid, A. Mahmood, Pulmonary microlithiasis – a case report, Respir. Med. Case Rep. 19 (2016) 112–114.