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Case report / *Caso clinico*

Pulmonary alveolar microlithiasis: an Italian case diagnosed by transbronchial cryobiopsy

Microlitiasi alveolare polmonare: un caso italiano diagnosticato con criobiopsia transbronchiale

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Summary

Pulmonary alveolar microlithiasis is a rare autosomal-recessive disorder caused by a mutation of the SLC43A2 gene which determines the accumulation of calcium phosphate microliths (calcospherites) in the alveolar spaces. Italy is the country after Turkey with the major cases reported so far. Most of the cases come from Puglia and particularly in a geographical area between Monopoli and Castellana di Grotte. Patients are usually 30 to 50 years of age, and both genders are affected.

Here, we have reported the case of a 44-year-old woman, who was born in Castellana di Grotte, to whose diagnosis of pulmonary alveolar microlithiasis was confirmed by transbronchial lung cryobiopsy.

Key words: pulmonary alveolar microlithiasis, microliths, transbronchial cryobiopsy

Riassunto

La microlitiasi alveolare polmonare è una rara patologia autosomica recessiva, causata dalla mutazione del gene SLC43A2, che determina l'accumulo alveolare di microliti di fosfato di calcio (calciosferiti). L'Italia dopo la Turchia, è il Paese con il maggior numero dei casi registrati provenienti perlopiù dalla Puglia e in particolare dalla zona geografica compresa tra Monopoli e Castellana di Grotte. La patologia esordisce tra i 30 e i 50 anni e interessa entrambi i sessi. Qui descriviamo il caso di una paziente di 40 anni, originaria di Castellana di Grotte, a cui la diagnosi di microlitiasi alveolare polmonare è stata confermata dalla criobiopsia polmonare.

***Parole chiave**: microlitiasi alveolare polmonare, microliti, criobiopsia transbronchiale*

Case presentation

A 44-year-old woman, housewife, non-smoker, from Puglia, was referred to G.B Morgagni Hospital (Thoracic Disease Department) for an interstitial lung disease not better specified.

Patient started to complain for dyspnea and dry cough only a few months before admission in the Morgagni Hospital. Past medical history was not relevant except two miscarriages. Laboratory data showed only normocytic normochromic anemia and a monoclonal gammopathy. Parathyroid hormone levels were in the normal range.

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Conflict of interest statement
The Authors declare no conflict of interest.

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Physical examination was normal. The pulmonary function tests showed only a slight decrease of the carbon monoxide diffusing capacity (D_{LCO}: 72% of predicted). The six-minute walking test was normal (540 meters, with no desaturation). CT scan of the chest showed severe and diffuse interlobular and intralobular septal thickening with bilateral distribution and lower lobe predominance, associated with "crazy paving" areas and ground glass opacities (Figs. 1, 2). The mediastinum window showed millimeter punctiform calcifications along the interlobular and intralobular septa and in the mediastinal pleura predominant in the lower lobes and in the cardiofrenic angles (Fig. 3). A diagnostic work-up including bronchoalveolar lavage (BAL) and transbronchial lung cryobiopsy was carried out.

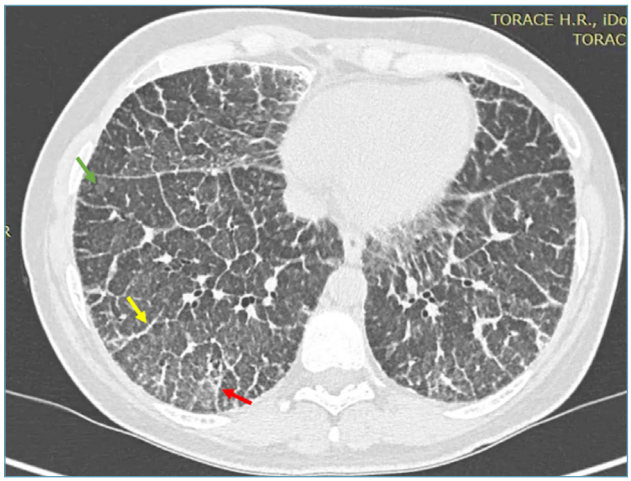

Figure 1. Axial CT shows: thickening septa (yellow arrow), ground glass opacity (green arrow) and crazy paving (red arrow).

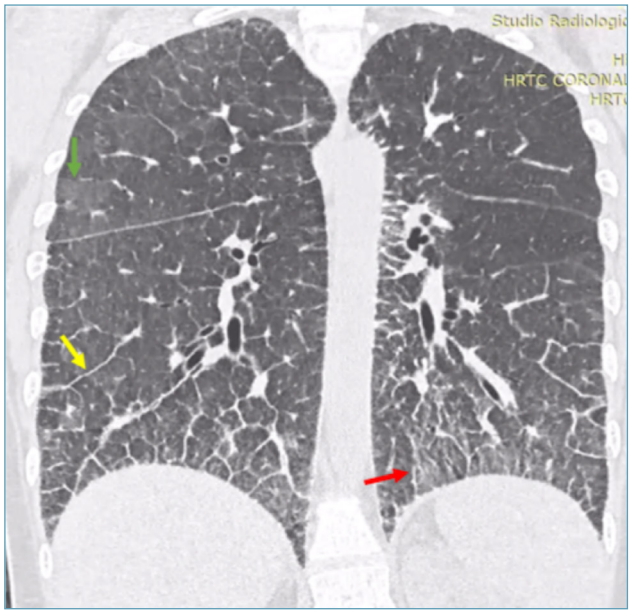

Figure 2. Coronal view CT shows: thickening septa (yellow arrow), ground glass opacity (green arrow) and crazy paving (red arrow). Note the bilateral distribution and lower lobe predominance.

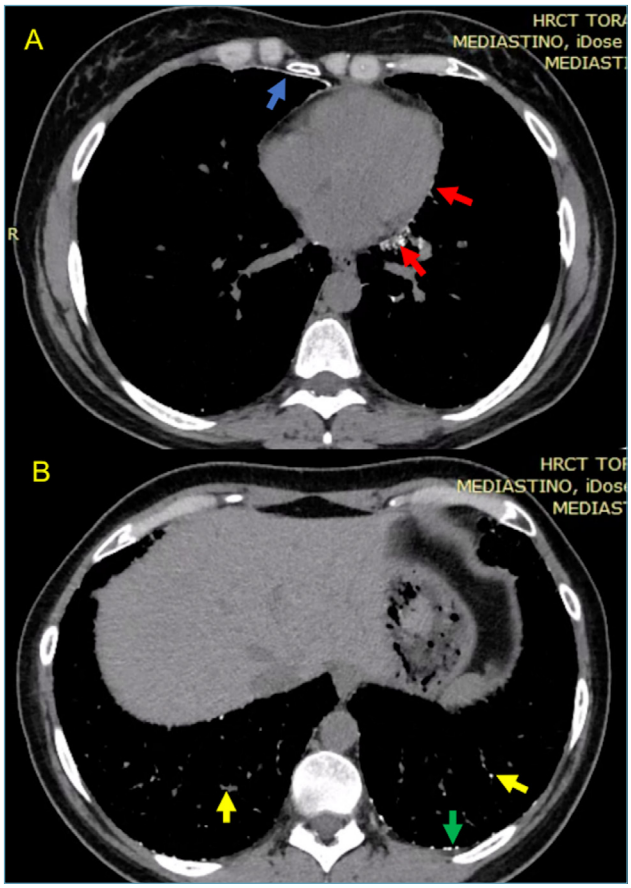

Figure 3. Axial CT mediastinal window scan show in A: calcifications along the heart borders (red arrow), subpleural linear calcifications (blue arrow); B: confluent and diffuse calcified nodules (green arrow), millimeter punctiform calcifications along the interlobular and intralobular septa predominant in the lower lobe (yellow arrow).

Patient underwent deep sedation using propophol and remiphentanyl. She was intubated with a rigid Storz tracheoscope [1]. Bronchoalveolar lavage with 150 ml of saline was done in the posterior segment of the right lower lobe. Transbronchial cryobiopsies were obtained using a 1.7 probe. The freezing time was 8 seconds for each biopsy. Two samples from the posterior and two form the lateral segment of the right lower lobe were carried out. BAL cellular profile was normal (macrophages 94%; lymphocytes 1%; neutrophils 5%). Microbiological investigations including culture for mycobacteria resulted to be negative; microliths were not found. Histopathologic analysis showed numerous calcified spherules in the alveoli and in the walls of some bronchioles. Scattered foci of bone metaplasia were also detected (Fig. 4 A-B). The final diagnosis was therefore pulmonary alveolar microlithiasis.

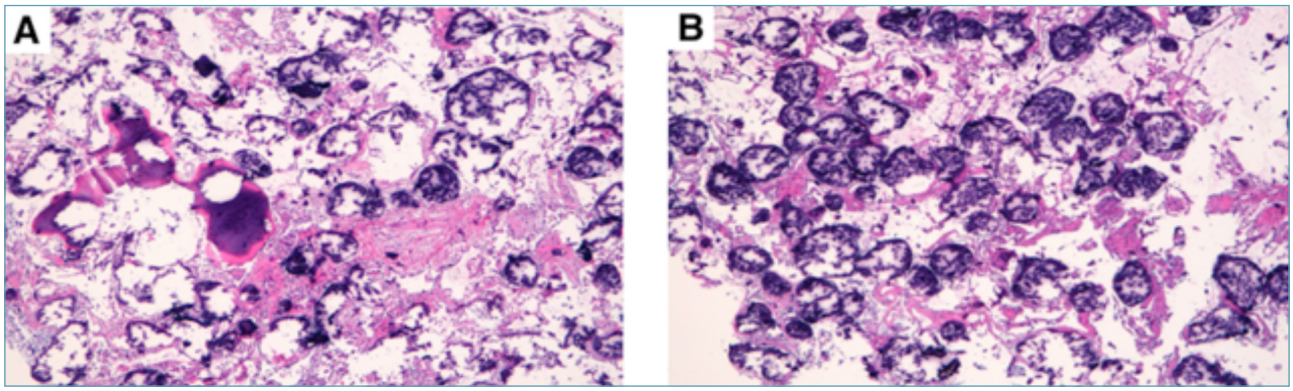

Figure 4 (A-B). Lung transbronchial cryobiopsies showing numerous intraalveolar rounded calcified bodies and ossification (A) (H&E, 20X).

Discussion

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive lung disease characterized by the accumulation of calcium phosphate deposits (calcospherites or microliths) in the alveoli despite normal serum calcium and phosphorus, and absence of any systemic disease of calcium metabolism [2].

In etiopathogenetic terms, a genetic predisposition has been recognised associated with the SLC34A2 gene mutation located on chromosome 4. It encodes a sodium phosphate co-transporter (Npt2b) expressed in type II alveolar epithelium cells in the lungs that is involved in the metabolism of alveolar phosphorus. A loss of function of Npt2b brings to ineffective removal of phosphorus from the alveoli that breaks down calcium to form microliths [2].

Npt2b is also expressed in the gut, breast, liver, testes, prostate, kidney, ovary and aortic valve and this may explain the extrapulmonary manifestations of the disorder [3-7].

Patients often complain of dyspnea on exertion, dry cough (whit occasional microlith expectoration), chest pain. The disease may also rarely manifest with hemoptysis and pneumothorax. The physical examination is usually not relevant [3]. Normal or mild restrictive respiratory physiology occurs at onset, with deterioration in the last part of the disease course [2].

Chest radiograph show diffuse and bilateral micronodular opacity ("sand storm") more evident in the middle and lower areas. High Resolution Computed Tomography (HRCT) scan findings are diffuse ground-glass opacities and septal thickening throughout both lungs, associated with calcified nodules along the interlobar septa e subpleural regions predominantly in the lower zones. Crazy paving features and thin-walled subpleural cysts have also been reported [8-10]. The association of microliths in the BAL and HRTC has been proposed as the best diagnostic procedure for PAM [11].

However, when we cannot find microliths in the BAL, the radiological features are aspecific to make diagnosis alone and lung biopsy is necessary.

In this contest transbronchial lung cryobiosy (TBLC) is a safe and minimally invasive technique that could be used in order to obtain histological information [1].

In most of case the diagnosis of PAM was confirmed through transbronchial biopsy or open lung biopsy [12,13], only one case of TBLC is reported [14].

For several years, surgical lung biopsy has been the gold standard in ILD and an alternative method in case of transbronchial biopsy (TBB) failure [15].

Now the use of cryobiopsy in the diagnosis of ILD is acquiring increasing evidence. The procedure is performed by a team of interventional pulmonologist with anesthesiology assistance. Patient is intubated with a rigid Storz tracheoscope under deep sedation and keeping spontaneous breathing. The target zone is choice according the most affected lung areas on HRTC of the chest. Subsequently an endobronchial Fogarty balloon is placed in order to ensure a ready hemostasis in case of bleeding (Fig. 5B). Under fluoroscopic guide, the probe takes the biopsy sample at about 1 cm from the pleura (Fig. 5 A-C). A size of 5 mm is appropriate for histological evaluation [15].

Taking samples from different segment of the same lobe is recommended for increase the diagnostic yield. As reported in our case, the cryoprobe was freezing for 8 s and we obtained respectively two samples of 6.94 x 4.02 mm and 5.32 x 4.14 from the posterior segment and two samples of 5.51 x 4.23 mm and 5.35 x 3.62 mm from lateral segment of the right lower lobe.

According to recent literature, TBLC would be a good compromise between TBB and SLB.

Compared to TBB, cryobiopsy has got a better diagnostic accuracy for larger pieces of tissue extracted by cryoprobe with the freeze-thaw cycle. Samples' size is

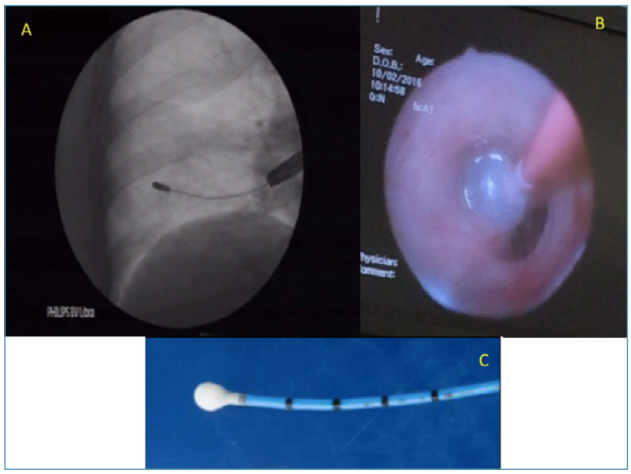

Figure 5. A: Fluoroscopic guide. B: Fogarty balloon. C: Cryoprobe.

up to 64 mm^2 and includes peripheral structures of the secondary pulmonary lobules [15]. TBLC could be also a viable alternative to SLB. Ravaglia et al. compared the diagnostic yield and safety of TBLC to SLB in a cohort of 447 patients. SLB has a slightly higher diagnostic yield, and higher mortality and cost than TBLC as well [16].

Tomassetti et al. reported the impact of TBLC on diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis compared to SLB. The study shows how both methods similarly increase IPF diagnostic confidence: from 29 to 63% for TBLC group and from 30 to 65% for SLB group [17].

These results were confirmed by COLDICE study that described a cohort of patients who underwent to sequential TBLC and SLB. Results showed a high level of agreement between TBLC and SLB in histopathological interpretation and multidisciplinary discussion [18].

Histology is an important step as part of multidisciplinary settings. In our case, we have not found microliths in the BAL and the patient underwent transbronchial lung cryobiopsy breaking the limits of conventional TBB. The importance of a definitive early diagnosis avoids exposing the patient to inappropriate therapies with the possibility to include him-her in the transplant list as soon as possible.

PAM has indeed poor prognosis and lung transplant is the only way to increase life expectancy [19].

Conclusions

PAM is a rare disease, which attacks primarily the lungs becoming site of accumulation of calcium phosphate deposits. The symptomatology and the radiologic patterns are aspecific, so PAM could be confused with other diseases such us amyloidosis, silicosis, sarcoidosis, metastatic calcification, pulmonary alveolar proteinosis and pulmonary hemosiderosis [3]. When there is some doubt, the histology is necessary for a definitive diagnosis. The aim of this case report is to suggest cryobiopsy as part of the diagnostic algorithm for PAM when the BAL is not pathognomic and genetic studies are missing. Before this description only one case of TBLC in PAM was reported [14]; both cases had no complications. Future studies may confirm the role of cryobiopsy in the diagnostic process for PAM.

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