Lung cysts in chronic paracoccidioidomycosis*

Cistos pulmonares na paracoccidioidomicose crônica

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Abstract

On HRCT scans, lung cysts are characterized by rounded areas of low attenuation in the lung parenchyma and a well-defined interface with the normal adjacent lung. The most common cystic lung diseases are lymphangioleiomyomatosis, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonia. In a retrospective analysis of the HRCT findings in 50 patients diagnosed with chronic paracoccidioidomycosis, we found lung cysts in 5 cases (10%), indicating that patients with paracoccidioidomycosis can present with lung cysts on HRCT scans. Therefore, paracoccidioidomycosis should be included in the differential diagnosis of cystic lung diseases.

Keywords: Paracoccidioidomycosis; Cysts; Multidetector computed tomography.

Resumo

Os cistos pulmonares na TCAR são caracterizados por áreas arredondadas de baixo coeficiente de atenuação no parênquima pulmonar com uma interface bem definida com o pulmão adjacente normal. As doenças pulmonares císticas mais comuns são linfangioleiomiomatose, histiocitose de células de Langerhans e pneumonia intersticial linfocítica. Em uma análise retrospectiva de achados de TCAR em 50 pacientes com diagnóstico de paracoccidioidomicose crônica residual, observou-se a presença de cistos pulmonares em 5 casos (10%), mostrando que pacientes com paracoccidioidomicose podem apresentar cistos pulmonares na TCAR. Portanto, essa infecção deve entrar no diagnóstico diferencial das doenças císticas pulmonares.

Descritores: Paracoccidioidomicose; Cistos; Tomografia computadorizada multidetectores.

Lung cysts are rounded, well-circumscribed spaces surrounded by an epithelial or fibrous wall. On HRCT scans, lung cysts are characterized by rounded areas of low attenuation (air content) in the lung parenchyma and a well-defined interface with the normal adjacent lung.[1] The most common cystic lung diseases are lymphangioleiomyomatosis, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonia.[1-3] Paracoccidioidomycosis, however, does not currently feature on the list of differential diagnoses of cystic parenchymal lung diseases.

Paracoccidioidomycosis primarily affects the lung and is the most common systemic mycosis in Brazil.[4-6] Caused by the dimorphic fungus *Paracoccidioides brasiliensis*, chronic paracoccidioidomycosis affects mainly males in their economically productive years (30-60 years of age).[6] Similarly to tuberculosis and histoplasmosis, paracoccidioidomycosis is acquired by inhalation of viable propagules that undergo reactivation in adults, causing the chronic form of the disease, the primary target of which is the respiratory system.[4,7] In infected tissues of immunocompetent individuals, innate immunity induces a granulomatous inflammatory reaction in an attempt to inhibit the proliferation of the fungus and prevent its dissemination to other organs.[8] Tuder et al. described, in addition to the presence of granulomas, dense fibrosis and reticulin fiber proliferation even in areas where there were no granulomas in chronically injured lungs.[9] The chronic form of lung involvement is progressive and typically manifests as a bilateral, diffuse reticulomicronodular interstitial infiltrate on X-rays, correlating with the pathophysiology

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of the disease, which begins in the mediastinal lymph nodes and disseminates to the periphery of the lung via the lymphatic vessels.[4,6,7] Residual parenchymal scarring might be present in more than half of the individuals after antifungal treatment.[10,11] However, to our knowledge, no studies have described the incidence of lung cysts in this condition.

The chest X-ray abnormalities in patients with chronic paracoccidioidomycosis are often multiple and nonspecific, the most common patterns being linear and reticular opacities, nodules of different sizes, ill-defined opacities, air-space consolidation, and cavities.[12,13] In endemic areas, the finding of a "butterfly wing" pattern, with symmetrical opacities in the middle lung regions, associated with emphysema, should suggest that diagnosis.[13] In chronic paracoccidioidomycosis, architectural distortion, paracicatricial emphysema, and bronchiectasis are also common manifestations that reflect the residual fibrotic changes of this disease.[7,10]

Because HRCT allows a more detailed evaluation of the type of lesion, disease extent, and therapeutic response, it has gained popularity in the evaluation of patients with paracoccidioidomycosis.[14] Abnormal HRCT findings occur in more than 90% of patients with chronic paracoccidioidomycosis, and ground-glass opacities, consolidations, nodules, masses, cavities, septal thickening, reversed halo sign, emphysema, and fibrotic changes are reported to be the most prevalent findings. However, despite the epidemiological significance of paracoccidioidomycosis in Latin America, few studies have attempted to describe the chest HRCT findings of this disease.[7,15,16]

According to Funari et al., who studied 42 patients with chronic paracoccidioidomycosis (with or without a history of antifungal treatment), the most common CT findings are interlobular septal thickening (in 88%), nodules (in 83%), traction bronchiectasis (in 83%), peribronchovascular interstitial thickening (in 78%), paracicatricial emphysema (in 68%), centrilobular opacities (in 63%), and intralobular lines (in 59%). These changes are often seen in combination, tend to be bilateral and symmetrical, and involve all lung zones.[7] Gasparetto et al., reviewing 148 HRCT scans from patients with paracoccidioidomycosis, reported the presence of the reversed halo sign in 10% of the patients with active infection with *P. brasiliensis*.[17] Souza et al. evaluated 77 untreated patients and found ground-glass opacities (in 58.4%), centrilobular nodules (in 45.5%), nodules (in 41.6%), parenchymal bands (in 33.8%), cicatricial emphysema (in 33.8%), interlobular septal thickening (in 31.2%), and architectural distortion (in 29.9%). The findings were distributed predominantly in the peripheral region (in 53%) and in posterior regions (in 88%), involving all lung zones.[15] Extrapulmonary findings in the thorax are uncommon and include tracheal, pleural, lymph node, and osseous involvement.[18]

Our study, conducted in the outpatient clinics of the departments of pulmonology and infectious diseases of the University of São Paulo School of Medicine *Hospital das Clínicas*, showed that lung cysts are another possible CT pattern related to paracoccidioidomycosis.

The study was a reanalysis of 50 CT scans from patients who had previously been evaluated from the radiological and functional standpoint.[19] In this reevaluation, the presence of lung cysts, a CT change that had not been described previously, was of note. We studied patients diagnosed with chronic paracoccidioidomycosis and treated for more than six months in whom the skin lesions resolved, microbiological test results were negative, and anti-*P. brasiliensis* antibody titers, as determined by counterimmunoelectrophoresis, were low (< 1:4 or a drop of at least 4 dilutions).[5] Patients with lung cancer or respiratory coinfections (tuberculosis or other chronic infections) were excluded. Of the 50 patients studied, 47 were male and 3 were female. Ages ranged from 33 to 73 years (mean, 56.9 ± 9.7 years). In all patients, the diagnosis was confirmed by microbiological analysis (direct visualization or culture of the lesions) or by histopathology. The study and the content of the consent form were approved by the Ethics Committee for the Analysis of Research Projects of the Clinical Board of the University of São Paulo School of Medicine *Hospital das Clínicas* (Protocol no. 870/06). All study participants gave written informed consent.

The HRCT scans were obtained with a Philips Brilliance CT 40 multislice scanner (Philips Medical Systems, Cleveland, OH, USA) by using the following parameters: collimation, 8 × 3; increment, 1.6 mm; rotation time, 0.75; voltage, 120 Kv; amperage, 150 mAs/image; and a 7.5-mm reconstruction interval with 7.5-mm increments. Fifty-seven 7.5-mm CT slices and two hundred and ten

3.3-mm slices were obtained. Image slices at maximum inhalation and maximum exhalation were obtained for all patients. The changes were classified in accordance with the latest Brazilian Thoracic Association guidelines.[1] All analyses were independently performed by a radiologist specializing in chest CT and by a pulmonologist specializing in interstitial diseases, both of whom were blinded to the clinical data of the patients. In cases of disagreement, the final results were obtained by consensus.

Lung cysts were found in 5 cases (10% of the patients): in 1 of the cases, there was a single cyst in the right lower lobe; and in the other 4, there were two or more parenchymal cysts with no preferential location (Figure 1).

The clinical and demographic characteristics, as well as the number of lung cysts, of the 5 patients are shown in Table 1.

The present study is, to our knowledge, the first to describe the presence of parenchymal cysts in patients with chronic paracoccidioidomycosis.

Multiple mechanisms can explain the formation of cysts in various lung diseases. These mechanisms would include vascular occlusion followed by ischemia and necrosis, bronchial dilatation, smooth muscle cell proliferation, and even a check-valve mechanism in small airways, which, because of inflammatory cell infiltration and subsequent centrilobular fibrosis, would lead to bronchial obstruction and dilatation downstream of the lesion.[2,3,20] It can be speculated that, in paracoccidioidomycosis, centrilobular fibrosis, with involvement of the small airways and small vessels[9,16] would cause bronchial obstruction and distal airway dilatation, similarly to the check-valve mechanism identified in bronchiolitis.[21] Another possible explanation would be the presence of peribronchial nodules or granulomas associated with mycosis, promoting dilatation of a small airway, with the consequent formation of lung cysts, similarly to what is observed in Langerhans cell histiocytosis.[2,3] Another plausible explanation would be that the cysts or pneumatoceles would result from an inflammatory process leading to central necrosis and elastic recoil of the adjacent lung tissue, with localized air expansion, whether in the airways or in the lung interstitium, as occurs in other infectious diseases, such as staphylococcal pneumonia.[3]

Finally, we must consider the high level of smoking in the study population, which would

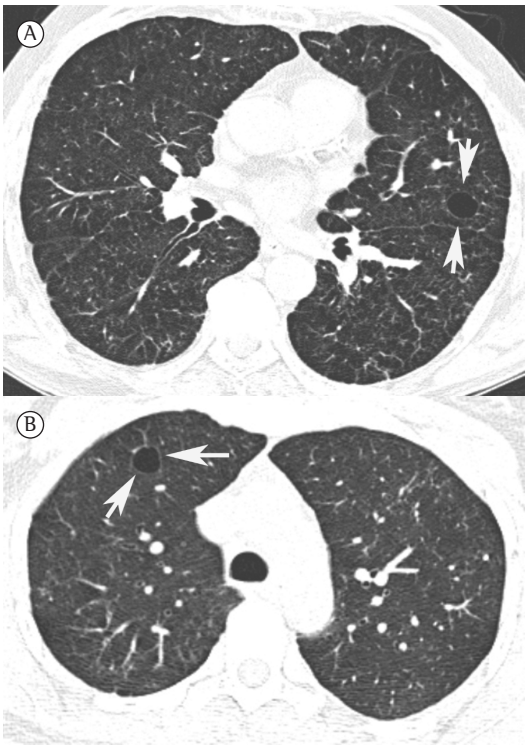

Figure 1 - HRCT scans. In A, HRCT scan slice at the level of the aortic arch showing a thin-walled cyst in the right lung of a 41-year-old female patient (arrows). Also note faint reticular and nodular opacities in the lung, which are probably residual in nature. In B, HRCT scan slice at the level of the lower lobes showing a thin-walled cyst in the left lung of a 68-year-old male patient (arrows). Note the presence of faint reticular opacities predominantly in the posterior regions.

Table 1 - Clinical and demographic characteristics, as well as number of lung cysts, of the patients studied.[a]

Variable	Result
Age, years	55.0 ± 9.2
Body mass index, kg/m^2	23.9 ± 3.6
Current or former smoking[b]	5 (100)
Active smokers[b]	3 (60)
Smoking history, pack-years	46.6 ± 30.9
Treatment duration, months	16.7 ± 8.5
CIE, titration[c]	1:2 (0-1:4)
Lung cysts, n	
Patient 1	2
Patient 2	3
Patient 3	1
Patient 4	multiple
Patient 5	multiple

CIE: serology with counterimmunoelectrophoresis. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%). [c]Value expressed as median (interquartile range).

make it possible to attribute the formation of the cysts to a smoking-related disease, such as Langerhans cell histiocytosis and desquamative interstitial pneumonia. However, no other characteristics related to the cysts and suggesting those diagnoses were found on the HRCT scans from those 5 patients.

In conclusion, patients with chronic paracoccidioidomycosis can present with lung cysts on HRCT scans. Therefore, paracoccidioidomycosis should be included in the differential diagnosis of cystic lung lesions.

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