# Isolated pulmonary langerhans cell histiocytosis: A diagnostic challenge in oncologic patients

Sir,

Langerhans cell histiocytosis is a rare disorder with unknown aetiology that can involve different organs, rarely just the lungs. Isolated pulmonary involvement (pulmonary langerhans cell histiocytosis [PLCH]) primarily affects young adults (20–40 years) with cigarette smoking habit.[1,2]

We report a case of a 33-year-old man presenting multiple small irregular micronodules and thin-walled cyst at chest computed tomography (CT) undergone for high-grade testicular cancer follow-up [Figure 1a and 1b]. The patient had been treated with bleomycin for 1 year achieving disease stability. Two months before CT, chest radiography was negative for the presence of pulmonary abnormalities. Pulmonary function tests (PFT) including the diffusion capacity for carbon monoxide, routinely monitored during treatment with Bleomycin, showed a slight decrease. First, drug-induced lung toxicity was suspected and the patient immediately interrupted therapy with bleomycin (Grade 1A). Three-month follow-up high-resolution CT (HRCT) examination [Figure 2a and 2b] showed unmodified parenchymal manifestations, with multiple cysts and solid bilateral irregular micronodules, predominantly in middle-to-upper lung lobes, but also present in lower lobes, adjacent to bronchus, surrounded by normal lung parenchyma. According to the oncologic history of the patient and the persistence of pulmonary manifestations, metastatic lung disease was suspected. A video-assisted thoracoscopic surgical biopsy was done to confirm the suspicion: histopathological evaluation revealed the presence of typical CD1a+ S100 Langerhans cells in the lung tissue (haematoxylin–eosin staining and immunohistochemistry), highly suggestive for the diagnosis of PLCH. Accurate revision of HRCT examinations showed a combination of micro-nodules, measuring 1–5 mm in diameter, and thin-walled cysts, around or adjacent to bronchi; in particular, the lesions' distribution was in contrast with a haematogenous pattern, typical of metastatic disease[3,4] [Figure 3a-c]. Notably, in our patient, pulmonary lesions were located both in upper and lower lobes, mimicking diffused lung metastatic disease, even though in metastatic cancers, cysts were larger rather than smaller.[5] The nodule margins were characteristically irregular and smooth with centrilobular, peribronchial or peribronchiolar distribution associated with cysts rarely isolated, mainly located in the upper and middle lung lobes with regression on serial imaging studies.[6] From a clinical point of view, at first CT examination, the patient reported anorexia and weight loss and a positive history for cigarette smoking (20 packs/year) was assessed. The PLCH typical radiological pattern can be diagnostic if correctly evaluated with suggestive clinical features and once established a relevant cigarette smoking attitude.[1,2] HRCT has a pivotal role in PLCH diagnosis because it represents the gold standard in the differential diagnosis of interstitial lung diseases. This is possible because HRCT differential diagnosis was made according to the predominant CT pattern, the distribution of the findings and the additional CT findings.[7]

- Predominant CT pattern: HRCT appearance of PLCH varies from nodular, nodular–cystic, cystic or fibrotic pattern, according to the stage of the disease. Early stages (within 6 months) present a predominant nodular pattern, followed by cavitate nodules, thick-walled cysts, leading to emphysematous appearance, if the disease was present for longer than 3 years.
- Distribution of the findings: PLCH is characterized by centrilobular, peribronchial or peribronchiolar distribution, sometimes forming a stellate nodule, mainly located in the upper and middle lung lobes.
- Additional CT findings: In the late stage of PLCH, often small stellate scars are surrounded by emphysematous spaces. The modification of lung nodules in serial

CT examinations can confirm the evolution of PLCH throughout a combination of bizarre-shaped cysts and nodules up to bullous emphysema-like lesions.

No spontaneous pneumothorax occurred in this case; however, cystic changes developed emphysema-like lesions in upper lobes, characteristic for progressed PLCH,[5] [Figure 4] but also suggestive for *Pneumocystis jiroveci* acute pneumonia or respiratory distress syndrome, sometimes indistinguishable.[8] Lymphangioleiomyomatosis (LAM), sarcoidosis, silicosis and tuberculosis should also be taken in consideration as alternative diagnoses of PLCH: however, LAM occurs quite exclusively in women with diffuse lung involvement while for sarcoidosis, silicosis and tuberculosis, nodule distribution typically follows a perilymphatic diffusion pattern.[9,10]

Once diagnosis of PLCH was made, the patient was advised to quit smoking and scheduled for disease-specific follow-up. Current therapies for unifocal PLCH establish the use of local therapies, while the first-line treatment for single pulmonary involvement is smoking cessation. In cases of patients unresponsive to these treatments or with multisystem disease, systemic treatments are recommended (cladribine or cytarabine), with the emerging role of targeted (BRAF and MEK inhibitor) therapies. Persistent symptoms such as pain, fatigue and mood disorders should be managed separately if persistent.[11] In our case, at 6-month follow-up after smoking cessation, HRCT scan showed complete reabsorption of the nodules and high-grade reduction of cyst with an associated reduction in cysts wall thickening [Figure 5a and 5b]. Clinical status improved as well, with a significant reduction of anorexia and weight gain. The patient underwent periodical (every 3 months) clinical and respiratory functional assessment and HRCT (6 months), to follow-up PLCH recrudescence, with no evidence of disease or recurrent nodule formation. Dyspnea was never reported by the patient. In fact, dyspnea is one of the most common symptoms of drug-induced lung disease, due to the potential development of interstitial lung disorder.[12] Bleomycin is a chemotherapeutic agent known to be a potential causative agent of pulmonary fibrosis: however,

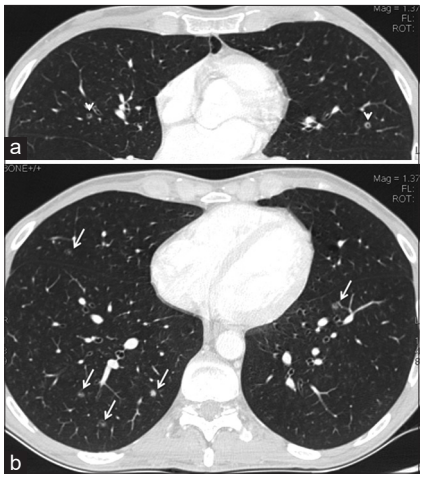


**Figure 1:** (a and b) New evidence of multiple small irregular micronodules (arrow) and thin-walled cyst (arrowhead) at chest-computed tomography (CT) underwent for high-grade testicular cancer follow-up

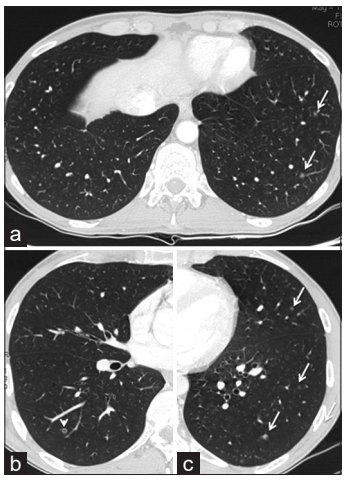


**Figure 3:** (a-c) HRCT examinations show a combination of micro-nodules (arrows) and thin-walled cysts (arrowhead), around or adjacent to bronchi

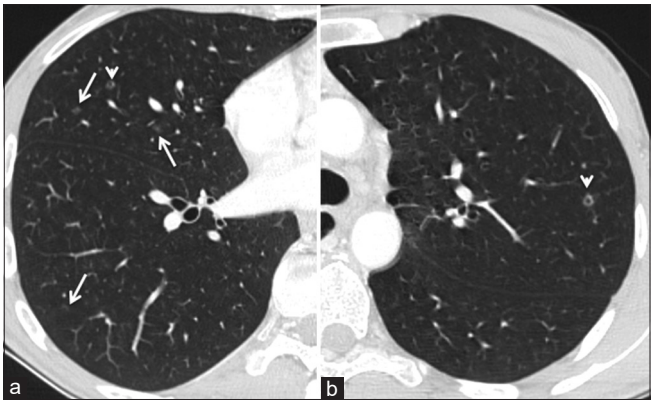


**Figure 2:** (a and b) Chest CT images with multiple cysts (arrowhead) and solid bilateral irregular micronodules (arrows), predominantly in middle-to-upper lung lobes, but present also in lower lobes, adjacent to bronchus, surrounded by normal lung parenchyma

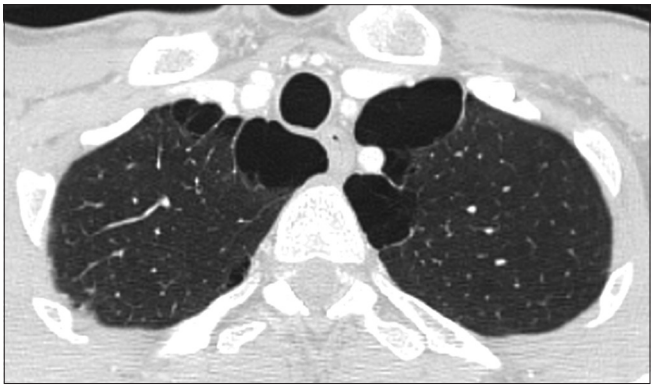

**Figure 4:** Axial CT image shows the presence of cystic changes in the upper segments of both upper lobes with characteristic emphysema-like lesions

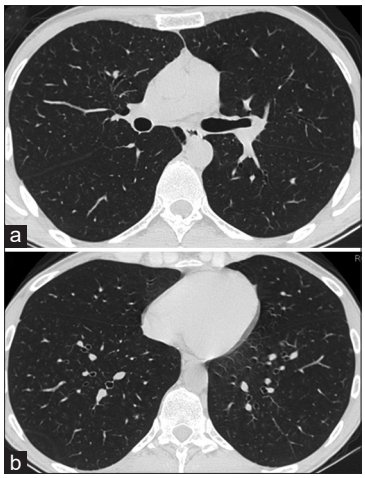


**Figure 5:** (a and b) Six-month HRCT follow-up examination showed complete reabsorption of the nodules and high-grade reduction of cyst with restoration of the normal parenchyma

in this patient, no pulmonary toxicity signs were observed during imaging follow-up and PFTs remain negative for functional worsening. Pulmonary involvement usually reveals subacute or chronic interstitial pneumonitis, sometimes complicated by idiopathic pulmonary fibrosis, or bronchiolitis obliterans with organizing pneumonia and eosinophilic hypersensitivity.[13] Honeycomb cysts are characterized by lower and subpleural distribution with a decrease in lung volume. Moreover, in this patient, we did not observe any of the characteristic bleomycin toxicity clinical manifestations, such as nonproductive cough, fever and pleural pain. Different pathologies can mimic nodular and cystic distribution such as reported above; however, lung biopsy is no longer required to make the diagnosis of PLCH, excluding cases suspected for metastatic lung involvement, as in our case. In selected patients, bronchoalveolar lavage (BAL) can be helpful to exclude pulmonary infections or sarcoidosis and to further support PLCH diagnosis through the identification of CD1A + S100 cells in BAL fluid. However, in most cases, the association with smoking and PLCH typical radiological pattern is sufficient to make the diagnosis. For this reason, an HRCT examination of the lungs performed with a slice thickness no greater than 1.00 mm is ideal to achieve the best parenchymal resolution, essential to correctly address the lesions to the right diagnosis. HRCT can be also helpful in scoring pulmonary alterations according to functional decline, supporting its potential value for prognostic purposes.[14]

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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