

An unusual presentation of pulmonary lymphoma: When diffuse ground glass opacities can mean anything

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Abstract

Primary lung lymphoma (PLL) is a rare type of lymphoma confined to the lung at the time of diagnosis. Pulmonary diffuse large B cells lymphoma (P-DLBCL) is the second most common type of PLL and it usually appears radiologically as solitary or multiple nodules or areas of consolidation. We present the case of a 63-year-old Caucasian male who developed severe acute respiratory failure and diffuse ground glass opacities (GGO) on chest computerized tomography. Diffuse GGO may be the radiological expression of very different diseases, ranging from infectious processes to interstitial lung diseases (ILDs) and neoplastic diseases. In our case, pneumonia and *de novo* ILD were initially considered given the symptoms and past medical history. However, bronchoscopy with trans-bronchial biopsies demonstrated the presence of P-DLBCL, despite an unusual radiological presentation and negative cytological analyses on bronchoalveolar lavage. In conclusion, P-DLBCL should be considered among the many differential diagnoses of diffuse GGO.

Case Report

A 63-year-old Caucasian male was referred to the intensive care unit (ICU) of our hospital for severe acute respiratory failure and diffuse ground glass opacities.

His past medical history was consistent with a diagnosis of type II diabetes and atrial fibrillation, for which he was on Flecainide and previously on Coumarins. He reported no allergies.

His recent history started with non-productive cough, fever (maximum 39°C) and asthenia that were treated at home with Levofloxacin and subsequently Ciprofloxacin per os without clinical improvement. He was referred to the emergency room where, after performing chest X-ray (showing a parenchymal opacity in the left lower lobe) and arterial blood gas (ABG) (with a PaO₂/FiO₂ = 357) he was diagnosed with left lower lobe pneumonia, and he was admitted to the respiratory unit. After admission patient quickly deteriorated with onset of acute respiratory failure requiring oxygen therapy (ABG with 8 L/min oxygen showed pO₂ 65 mmHg). The only other relevant exam on admission was lymphopenia (180 lymphocytes/ microL, 1.9%) on complete blood cells count, with no evidence of anti-Human Immunodeficiency Virus (HIV) antibodies.

In the hypothesis of a diagnosis of pneumonia in an immunocompromised patient who had failed first line antibiotics, he was started on intravenous (IV) broad-spectrum antibiotics (Linezolid and Meropenem). In the absence of clinical improvement and due to the worsening of respiratory failure, on the 3rd day of hospitalization, patient was transferred to the ICU and later intubated in order to start invasive mechanical ventilation. Upon ICU transfer a chest computerized tomography (CT) and bronchoscopy were performed: the first showed bilateral diffuse ground glass opacities with a few reticular thickenings (Figure 1A), the second demonstrated no evidence of macroscopic lesions of bronchial mucosa and microbiological and cytological analysis on bronchoalveolar lavage (BAL) were performed. Broad-spectrum serological and microbiological tests were also performed, including those for aerobic and anaerobic bacteria, mycobacteria, fungi and respiratory viruses, and the results both on blood and BAL were negative. Complete differential cell count on BAL showed a mixed neutrophilic and lymphocytic alveolitis (macrophages 35%, neutrophils 30%, and lymphocytes 35%), without evidence of neoplastic cells. On transthoracic and transesophageal echocardiography neither cardiac alterations nor endocardial vegetations were detected.

Once the infectious aetiology was reasonably excluded, the hypothesis of an acute exacerbation of *de novo* interstitial lung disease (ILD) was considered. The two most probable diagnoses based on the radiologic pattern and acute onset were acute hypersensitivity pneumonitis and Flecaïnide-induced ILD, however, in the first case no clear history of antigen exposure was found, in the second case the most common presentation of the disease is with organizing pneumonia (OP), usual interstitial pneumonia (UIP), or acute respiratory distress syndrome (ARDS) patterns [1]. A complete autoimmune panel was performed with only a mild positivity of anti-nuclear antibodies (1:160, nucleolar pattern) and patient was started on IV methylprednisolone 1 mg/kg/die, without clinical improvement. On the 16th day of hospitalization, due to the progressive worsening of clinical conditions, patient underwent a

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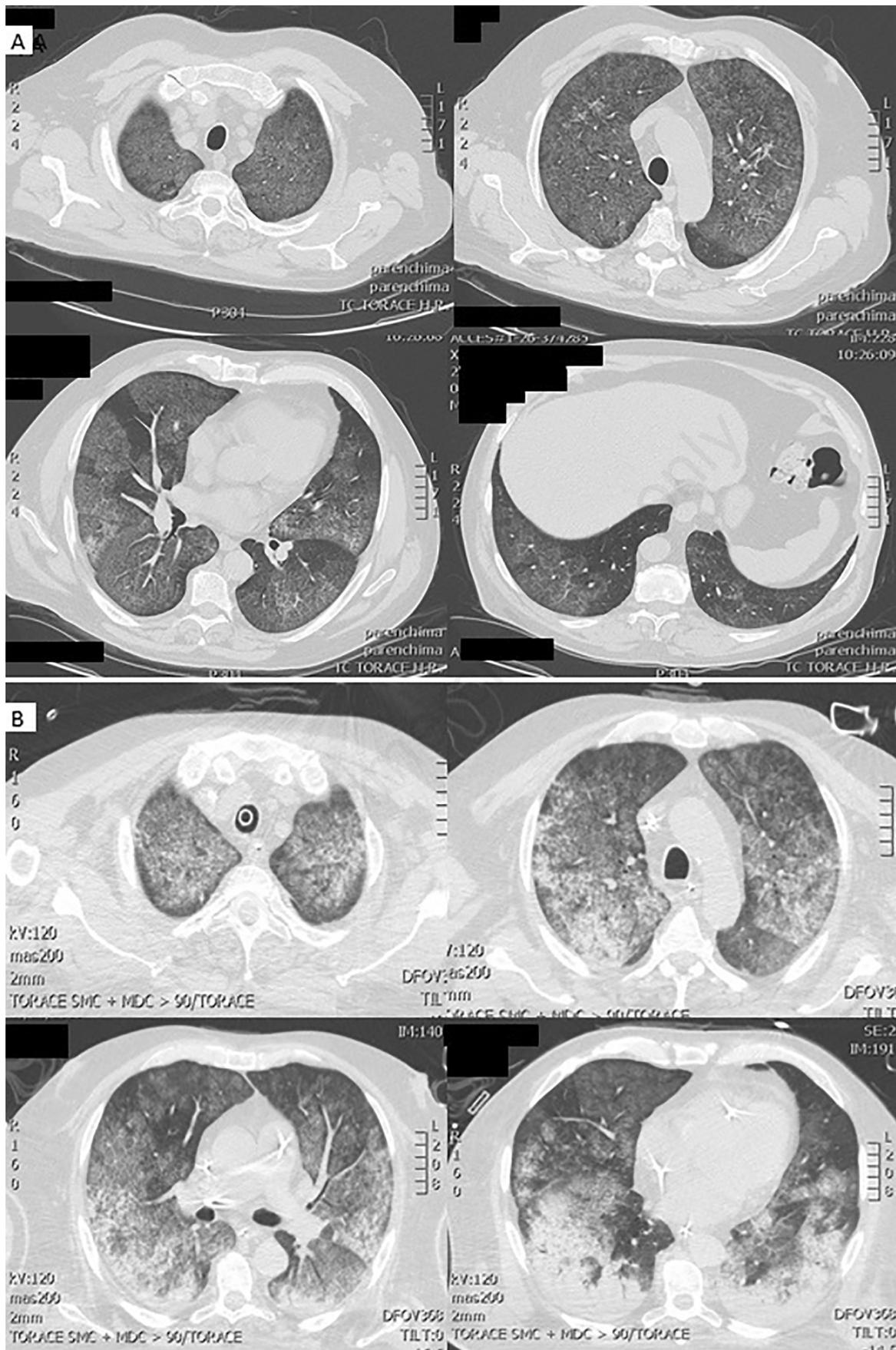


Figure 1. Chest computerized tomography (CT) performed on day 3 (a) and on day 16 (b) after hospitalisation.

total body CT scan, which highlighted the worsening of the pulmonary bilateral ground glass opacities with initial consolidations in the posterior areas of both upper and lower lobes (Figure 1B) and showed, for the first time, the presence of hepatomegaly and splenomegaly. In the hypothesis of a lymphoproliferative disorder patient underwent bone marrow examination (not significant) and a second bronchoscopy with BAL and trans-bronchial biopsies (TBB) in the right upper lobe (ground glass opacities).

The patient eventually died on the 24th day of hospitalization, while BAL microbiological and cytological results from the second bronchoscopy were irrelevant and results from TBB histological examination were available since the day before patient's death.

Final histological findings from TBB were consistent with fragments of lung parenchyma with presence of solid proliferation of large sized elements with hyperchromatic nucleus, high nucleus-cytoplasm ratio and severe cytological atypia (Figure 2). Immunohistochemical staining for

leukocyte common antigen (LCA), a major membrane glycoprotein restricted to leukocytes, CD20, a marker of mature B cells (Figure 2C), B-cell lymphoma 2 (BCL-2), an anti-apoptosis protein expressed by virtually all lymphoid proliferations, and BCL-6, a transcriptional regulator expressed by germinal center B cells, were all positive with occasional positivity of CD30, a cell membrane protein of the tumor necrosis factor receptor family expressed by activated T- and B-cells. Cytokeratin pool, p40, synaptophysin, CD3 (a T-cells marker), cyclin-D1, Transcription Termination Factor-1 (TTF1) and tdT were all negative. This histological pattern was representative of lung diffuse large B-cells lymphoma (DLBCL).

Discussion

Primary lung lymphoma (PLL) is a rare disease that comprises <0.5% of all primary lung tumors, <1% of all lymphomas, and approxi-

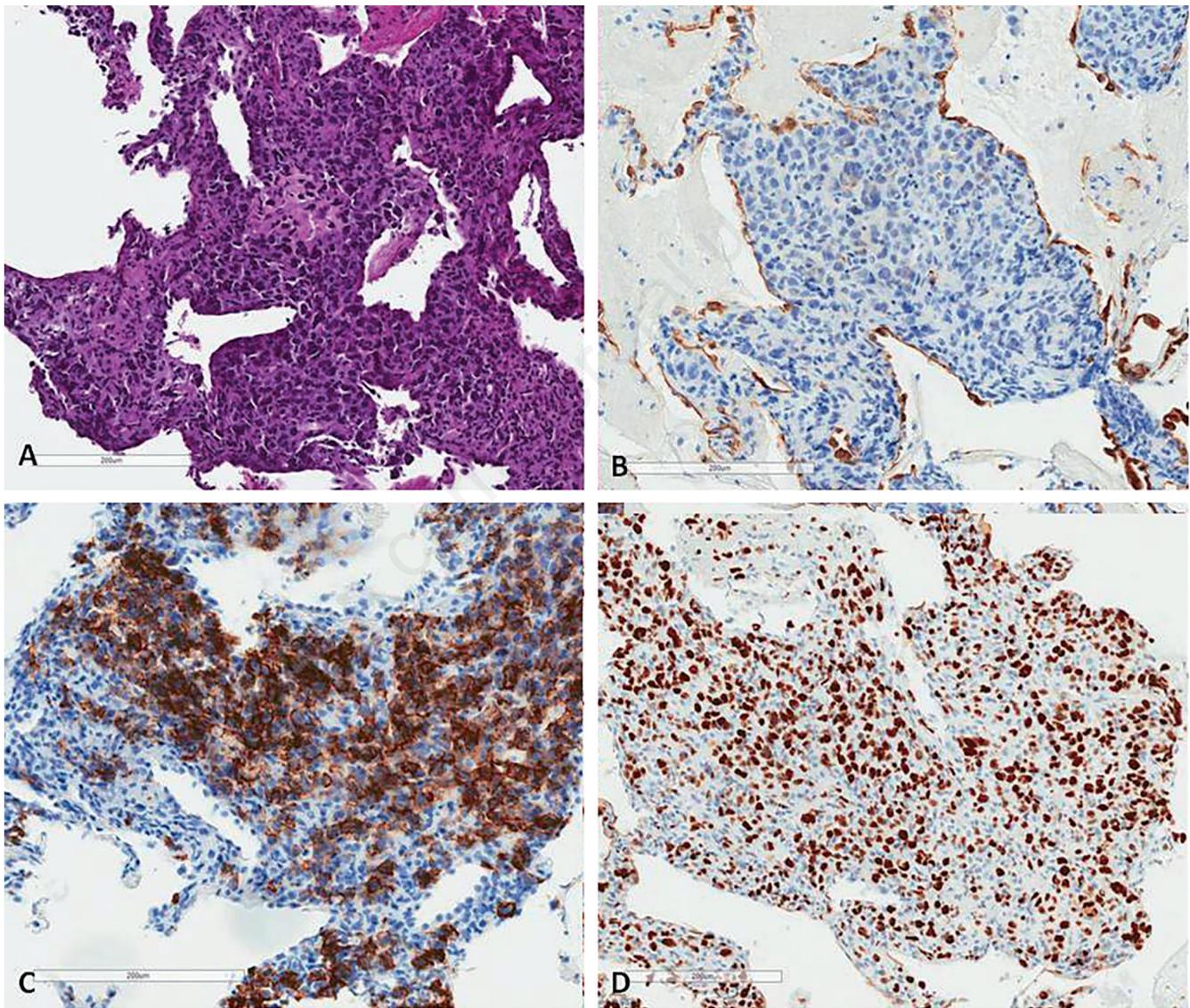


Figure 2. Specimen detail of transbronchial biopsy. A) Hematoxylin-Eosin, alveolar septum is filled by medium to large sized cells with indistinct border, hyperchromatic nuclei and diffuse growth. B) Immunohistochemical stain for pancytokeratin highlights native alveolar lining pneumocytes (in brown) but not neoplastic cells. C) Immunohistochemical stain for CD20 highlights neoplastic cells (in brown); neoplastic cells proliferation does not invade the alveolar lining epithelium, thus, neoplastic cells are not observed in the alveolar space. D) Immunohistochemical stain shows high proliferative index Ki67. No tumor cells proliferation was observed within blood vessels.

mately 3% to 4% of extra-nodal lymphomas [2]. It is defined as a lymphoma confined to the lung with or without hilar lymph node involvement at the time of diagnosis or up to 3 months thereafter [3]. PLL arises from bronchus-associated lymphoid tissue (BALT), which is a component of the pulmonary lymphatic system.

The most common type of PPL is the low-grade marginal zone B-cell lymphoma of MALT type, which represents between 60% and 80% of all cases [4]. Primary pulmonary-DLBCL (P-DLBCL) is the second most common type of PLL (10% to 20% of all cases) [5].

From a histological point of view, DLBCL presents with sheets of atypical lymphocytes that form solid lesions, which subvert the normal alveolar architecture; areas of necrosis may also be found [4]. At radiological imaging, DLBCL can present with solitary or multiple nodules or areas of consolidation; cavitations and/or areas of necrosis may also be a common feature [5].

This case is of some interest for several reasons: firstly, we report an unusual radiological appearance of DLBCL with diffuse bilateral ground glass opacities; as discussed above, the most common radiological patterns for Non-Hodgkin lymphoma B are nodules and consolidation. The second reason is that, despite a final diagnosis of lymphoma, cytological analyses for the detection of neoplastic cells on BAL were negative in both bronchoscopies. This finding can be explained by the histological analysis of TBB samples that showed thickening of inter-alveolar septa due to the presence of neoplastic cells with preservation of the alveolar lining epithelium (Figure 2). The intact alveolar epithelium prevented the exfoliation of neoplastic cells in the alveolar spaces and their finding in BAL. Finally, the diffuse ground glass opacities may have many differential diagnosis, including both infectious, neoplastic causes and ILDs, that were all considered with different timing in our case [6]. Our first line diagnostic approach was with bronchoscopy and BAL to perform both cytological and microbiological analyses, however none of them proved to be useful. TBB were not initially considered given the high suspicion for an infectious etiology and due to the severity of the respiratory failure, which made the risk of procedural complications, such as pneumothorax, life-threatening. Nevertheless, once reasonably excluded the infectious etiology, TBB were performed. In patients with diffuse bilateral GGO, TBB should be considered precociously in the diagnostic approach.

To the best of our knowledge, there are only a few observations of histologically proved DLBCL with GGO as unique radiographic presentation. A recent case report by Inaty *et al.* described a patient with DLBCL that, differently from our case, had a secondary lung involvement [7]. Similarly to our case, TBB proved to be effective in providing a definitive diagnosis. Higashiyama *et al.* recently reported a case of pulmonary DLBCL recurrence after chemotherapy that at CT scan revealed bilateral diffuse GGO despite the CT scan at the time of initial diagnosis presented only nodular alterations [8].

Another rare variant of DLBCL that resides in the lumen of blood vessels, intravascular large B-cell lymphoma, may present as ILD, in-

cluding interstitial thickening and GGO, as reported by Nishii-Ito *et al.* and other case reports [9-11], however, pathologic findings in our case excluded the presence of tumor cells within blood vessels.

Conclusions

Although it is a rare entity, DLBCL must be considered among the possible differential diagnosis of diffuse ground glass opacities. In these peculiar cases, bronchoscopy with BAL might not be sufficient for the diagnosis and a histological sample might be required.

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