Case Report
Primary pulmonary lymphoma manifesting as diffuse ground glass opacities: a case report and literature review

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Received May 11, 2020; Accepted June 29, 2020; Epub August 1, 2020; Published August 15, 2020

Abstract: Primary pulmonary lymphoma is a rare clinical neoplasm, and its atypical manifestation frequently leads to misdiagnosis. Here, we have reported a rare case of a 55-year-old man who presented with cough, dizziness, and fatigue. His chest computed tomography (CT) revealed diffuse ground glass pulmonary opacities. Bronchoscope lavage demonstrated lymphocyte predominance, while transbronchial biopsy indicated chronic inflammation. The administration of a broad-spectrum antibiotic regime supplemented with a high dosage of methylprednisolone was ineffective in improving the general condition of the patient, and the diffuse ground glass pulmonary opacities continued to worsen. CT-guided percutaneous lung biopsy confirmed the diagnosis of primary pulmonary lymphoma-diffuse large B-cell (PPL-DLBCL) without extrapulmonary involvement. The patient’s general condition improved with the systemic chemotherapy of CHOP. In the context of a systemic review of relevant literature, pulmonary lymphoma should be considered in the differential diagnosis of diffuse ground glass opacities, and bronchoscopy is recommended for pathological diagnosis. Moreover, CT-guided percutaneous lung biopsy should also be adopted whenever necessary.

Keywords: Primary pulmonary lymphoma, diffuse ground glass opacities, diffuse large B-cell lymphoma

Introduction
Primary pulmonary lymphoma (PPL) is a rare clinical disease, accounting for approximately 0.5-1% of all primary pulmonary malignancies [1]. The radiological manifestation of PPL varies from nodules, masses, consolidation to hilar/mediastinal adenopathy, and non-specific symptoms such as dizziness, fever, cough, and dyspnea; these confounding symptoms inevitably lead to misdiagnosis [2]. Here, we have reported a case of PPL that manifested as diffuse ground glass pulmonary opacities. We conducted a systemic review of relevant literature, which indicates the importance of including pulmonary lymphoma in the differential diagnosis when diffuse ground glass opacities are present.

Case report
A 55-year-old man without any remarkable medical history presented to the Emergency Department of The First Affiliated Hospital of Wenzhou Medical University with a 2-week history of dry cough and a 1-week history of dizziness and fatigue. His chest computed tomography (CT) revealed diffuse bilateral ground glass opacities without mediastinal or hilar lymphadenopathy (Figure 1A), while his arterial blood gas (ABG) analysis implicated respiratory alkalosis with pH 7.5, 62 mmHg PaO₂, 32.6 mmHg PaCO₂, and 25.3 mmol/L HCO₃ (under air condition). The patient was accordingly admitted to the Respiratory Department under the suspicion of pulmonary infection. The patient had been a swineherd for several decades, and he acknowledged his recent dust exposure in his pigpen rebuilding activities.

Upon admission, the patient was conscious, oriented, and showed the following vital signs: auricular temperature 38.2°C, pulse rate 68/min, respiratory rate 22/min, and blood pressure 88/48 mmHg. No significant physical examination was performed, expect for emacia-
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Figure 1. Chest CT examination after hospitalization. A. A CT scan of the chest on admission illustrated diffuse bilateral ground glass opacities with granules in both lung fields. B. Chest CT at 10th day illustrated diffuse bilateral ground glass opacities in the upper lobes and masslike areas of consolidations in the lower lobes of both lung fields. C. Chest CT at 30th day illustrated resolution of diffuse bilateral ground glass opacities and shrinkage of masslike areas of consolidations in the lower lobe of both lung fields.

Laboratory investigations of his serum sample revealed white blood cell count of 11.54×10^9/L (3.5-9.5×10^9/L), C-reactive protein (CRP) 41.4 mg/L (0-8 mg/L), procalcitonin (PCT) 0.222 ng/mL (0.000-0.500 ng/mL), 1,3-β-D glucan assay (G assay): <10 pg/mL (<100.5 pg/mL), and negative galactomannan assay (GM assay). The hepatorenal function was normal, while the lactate dehydrogenase (LDH) level was markedly elevated to 760 U/L (0-247 U/L) together with 2.78 µg/mL β2 microglobulin (0.9-2.7 µg/mL). The levels of T-lymphocyte subsets and immunoglobulin classes were found to be within the normal reference ranges. Human immunodeficiency virus (HIV) tested as negative. A rare pulmonary infection as well as extrinsic allergic alveolitis was suspected based on the clinical characteristics and auxiliary examination findings. The patient was accordingly started on intravenous empiric antibiotic treatment (moxifloxacin 0.4 g, once daily, and piperacillin 4.5 g, every 8 h) and glucocorticoid (methylprednisolone 40 mg, once daily). On the 4th day of admission, the patient received bronchalveolar lavage (BAL) of the upper lobe of the right lung and transbronchial lung biopsy (TBLB) of the upper lobe of the left lung. The cytological classification of BAL detected 24% neutrophils, 52% lymphocytes, and 24% macrophages, which indicated lymphocyte predominance. On the other hand, the Metagenomics Next-generation Sequencing (mNGS) did not detect any pathogen. The histopathologic examinations of TBLB revealed sporadic monocytes and lymphocytes in the pulmonary interstitium, which was suggestive of chronic inflammatory lesions. A broader spectrum of antibiotic regime was hence adopted (constituting moxifloxacin 0.4 g, once daily; meropenem 1 g, every 8 h; and voriconazole 0.2 g, 12 h), and the dosage of glucocorticoid was doubled (methylprednisolone 40 mg, 12
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h). However, the combination therapy was found to be ineffective. The presenting clinical conditions continued to worsen, especially progressive respiratory failure. Therefore, the method of oxygen supplementation was switched from venturi mask (FiO₂ 35%, 45%, and 50%) to high-flow nasal cannula (High flow 60 L/min, FiO₂ 60%). Consistently, the ABG demonstrated a decline in the PaO₂/FiO₂ level from 450 to 150, which is a sensitive indicator of blood-gas exchange. The serum laboratory examinations revealed that the LDH level constantly increased from 760 U/L to 1152 U/L during the clinical course. Accordingly, the patient was examined with a second chest CT at the 10th day of admission, which highlighted the diffuse bilateral ground glass pulmonary opacities with consolidations (Figure 1B).

Considering the negative result of mNGS and the ineffectiveness of the administered antibiotic regime, pulmonary infection was reasonably excluded. The limited effect of glucocorticoids eliminated the chances of an interstitial lung disease. In view of the worsening general conditions, especially progressive respiratory failure, it is urgent to clarify the diagnosis of this disease. CT-guided percutaneous lung biopsy of the upper lobe of the left lung was conducted on the 12th day of admission. While awaiting the pathology report, the patient was transferred to the respiratory intensive care unit (RICU), and noninvasive ventilation with bi-level positive airway pressure (BiPAP) was initiated. Eventually, the CT-guided biopsy revealed the presence of large-sized polygonal atypical lymphoid cells in widened alveolar interstitium and alveolar space, with a diffuse growth pattern, which were positive for CD20 (Figure 2B), PAX-5 (Figure 2C), and MUM-1, while negative for CD3, CD30, CK (Figure 2D), TTF-1 (Figure 2E) on immunohistochemical examination; these observations were suggestive of diffuse large B-cell lymphoma (DLBCL). The mean Ki-67 proliferation rate was 80% (Figure 2F), indicative of progressive phenotype. Fluorescence in situ hybridization (FISH) excluded the rearrangement of MYC, BCL2, and BCL6. Simultaneously, the bone marrow examination did not reveal any abnormality, which was indicative of PPL. The patient was accordingly started on systemic chemotherapy with CHOP (constituting rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). Gradually, the patient’s general condition improved under 90% oxygen saturation. The third chest CT was conducted before hospital discharge on the 30th showed partial resolution of the multiple areas of con-

Figure 2. Histopathologic features of percutaneous lung biopsy specimens. (A) Diffuse proliferation of large atypical lymphoid cells with hyperchromatic nucleus expand alveolar septa and partially destroy lung architecture. There are no neoplastic cells within the vascular lumina (hematoxylin-eosin staining, original ×100). The neoplastic cells are positive for CD20 (B) and Pax5 (C) (both are B-cell markers), supporting the diagnosis of DLBCL (immunohistochemical staining, original ×100). The neoplastic cells are negative for pan-cytokeratin (D) and TTF-1 (E). Both markers highlight residual alveolar lining epithelium (immunohistochemical staining, original ×100). (F) The Ki67 proliferative index is high (immunohistochemical staining, original ×100).
solidation and ground glass opacities (Figure 1C). However, the patient died from multiple organ failure at the second cycle of systemic chemotherapy.

Discussion

PPL is a lymphoma that is confined to the lungs without or with hilar lymph node involvement at the time of diagnosis or up to 3 months thereafter [3]. In the present case, PPL was diagnosed based on the exclusion of extrapulmonary involvement including bone marrow biopsy, even when the patient did not live up to the subsequent 3 months from diagnosis. The typical radiologic manifestations of PPL are single or multiple nodules and masses or mass-like consolidations [4, 5], with rare cases of diffuse ground glass opacities. It was believed that the diffuse ground glass opacities may indicate a rapid progressive clinical course and a relatively poor prognosis in pulmonary lymphoma [6-8]. In parallel with previously reported cases, the present case patient developed progressive respiratory failure with continual consolidation of ground glass opacities. His histologic examination confirmed DLBCL, which is the second-most common histologic patterns of PPL. Generally, the DLBCL frequently develops in immunocompromised individuals; however, the patient tested HIV negative and his CD4+ count in the peripheral blood was >400/µL. Overall, the non-specific symptoms and the rare radiologic manifestation collectively delayed the diagnosis, taking up a total of 20 days to clarify the diagnosis of PPL-DLBCL. Fortunately, the general conditions improved when the systemic chemotherapy was initiated.

The lessons derived from the clinical practice relative to the present case are as follows: First, the differential diagnosis of diffuse ground glass pulmonary opacities is limited on admission. *Pneumocystis carinii* pneumonia was considered in this case with reference to the diffuse ground glass opacities and the elevated serum LDH level. Simultaneously, extrinsic allergic alveolitis was also considered based on the history of dust exposure. However, neoplastic diseases and pulmonary interstitial diseases such as bronchoalveolar carcinoma and lymphocytic interstitial pneumonia were neglected. Second, it is pivotal to obtain specimens to clarify the diagnosis when diffuse ground glass opacities are present. In that scenario, bronchoscopy is the first option, as BAL and TBLB may provide sufficient specimens. With regard to the present case, the cytopathologic examination by BAL was conducted without any evidence of malignant cells, while the cytological classification demonstrated lymphocyte predominance, which retrospectively indicated lymphoma. Unfortunately, flow cytometric immunophenotyping of lymphocyte subpopulation could not be adopted. Contrary to the positive finding of TBLB in previously reported cases [8, 9], the histopathologic examination of TBLB revealed sporadic monocytes and lymphocytes in the pulmonary interstitium with preserved lung architecture in this case, which was indicative of chronic inflammation. It was hence speculated that the degree of lymphoma infiltration was confined when the TBLB was performed. CT-guided percutaneous lung biopsy and thoracoscopic lung biopsy were then considered as the alternative invasive approaches. CT-guided percutaneous lung biopsy was subsequently adopted considering the tolerance under hypoxemia. If the bronchoscopy and CT-guided percutaneous lung biopsy failed to provide sufficient specimens, then thoracoscopic lung biopsy may be considered.

To better understand the clinicopathologic features of pulmonary lymphoma that manifest as diffuse ground glass opacities, relevant case reports were searched in PUBMED using the keywords “pulmonary”, “lymphoma”, and “diffuse ground glass opacities”. In addition, a manual search was adopted to compensate for the defect of artificial search mentioned earlier. The comprehensive literature review suggested that the intravascular large B-cell lymphoma (IVBBL)-which is a specific variant of DLBCL [10] characterized by the selective growth of lymphoma cells within the vascular lumina-commonly manifests as diffuse ground glass pulmonary opacities. The pathophysiology of diffuse ground glass opacities is either selective growth of lymphoma cells within the vascular lumina, or within the pulmonary interstitium and alveolar space. CT-guided percutaneous biopsy in this study showed diffuse proliferation of large atypical lymphoid cells within alveolar septa and alveolar spaces, confirming he diagnosis of DLBCL, but not the subtype of IVBCL. This finding indicated an entity of DLBCL characterized by the selective growth of lymphoma cells within the pulmonary interstitium. The clinicopathologic features of this new entity of DLBCL are given in Table 1.
## Table 1. Review of relevant literature regarding DLBCL except subtype of IVBCL

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Specimen</th>
<th>Diagnosis</th>
<th>Therapy</th>
<th>Prognosis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, fever, and asthenia</td>
<td>TBLB</td>
<td>PPL-DLBCL (not IVBCL subtype)</td>
<td>No</td>
<td>Died</td>
<td>[6]</td>
</tr>
<tr>
<td>Fever and dyspnea</td>
<td>TBLB</td>
<td>SPL-DLBCL (not IVBCL subtype)</td>
<td>R-CHOP</td>
<td>Remission</td>
<td>[9]</td>
</tr>
<tr>
<td>Fever, night sweats, and dyspnea</td>
<td>TBLB and liver biopsy</td>
<td>SPL-DLBCL (not IVBCL subtype)</td>
<td>R-CHOP</td>
<td>Remission</td>
<td>[8]</td>
</tr>
<tr>
<td>Cough and dyspnea</td>
<td>Thoracoscopic lung biopsy</td>
<td>PPL-MALT</td>
<td>No</td>
<td>Remission</td>
<td>[12]</td>
</tr>
<tr>
<td>Breathlessness and cough</td>
<td>A video-assisted thoracoscopic lung biopsy</td>
<td>PPL-DLBCL (not IVBCL subtype)</td>
<td>R-CHOP</td>
<td>Remission</td>
<td>[13]</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>TBLB</td>
<td>PPL-DLBCL (not IVBCL subtype)</td>
<td>R-CHOP</td>
<td>Remission</td>
<td>[7]</td>
</tr>
<tr>
<td>Cough and fever</td>
<td>TBLB</td>
<td>SPL-DLBCL (not IVBCL subtype)</td>
<td>No</td>
<td>Died</td>
<td>[7]</td>
</tr>
<tr>
<td>General fatigue</td>
<td>A right inguinal lymph node biopsy</td>
<td>SPL-DLBCL (not IVBCL subtype)</td>
<td>No</td>
<td>Died</td>
<td>[14]</td>
</tr>
</tbody>
</table>
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A systemic review of the relevant literature clearly emphasizes the importance of considering pulmonary lymphoma in the differential diagnosis of diffuse ground glass opacities. For histologic classification, the most common was found to be DLBCL. In addition to IVBCL, a new entity of DLBCL identified in this case should be focused on. Bronchoscopy should be preferentially adopted when diffuse ground glass opacities is presented. CT-guided percutaneous lung biopsy may be considered when routine bronchoscopy does not work.

Acknowledgements

We would like to thank HYX and DZ from Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Wenzhou Medical University, for the careful revision of the manuscript.

Written informed consent for publication of the clinical details was obtained from the patient.

Disclosure of conflict of interest

None.

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