



## Case report

## Direct pulmonary infiltrates as an initial manifestation of chronic lymphocytic leukemia

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## ABSTRACT

An 85-year-old man who did not have any hematological or respiratory disorders was transferred to our hospital because of progressive dyspnea. Computed tomography (CT) findings showed ground-glass opacities with a centrilobular distribution and centrilobular micronodules with a “tree-in-bud” pattern. A biopsy of the lungs showed lymphocytic infiltrations in the parenchyma and these were positive for B cell markers. A diagnosis of chronic lymphocytic leukemia (CLL) was made and direct pulmonary involvement of CLL was confirmed simultaneously. One month after initiation of chemotherapy, his symptoms improved and a chest CT scan showed marked resolution. Pulmonary infiltrates of CLL should be included in the differential diagnosis when these signs are encountered on CT.

### 1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, and pulmonary involvement of CLL is found up to 40% of cases at autopsy [1]. However, pulmonary infiltrates of CLL are seldom diagnosed during life [2]. Recently, some patients with pulmonary infiltrates due to CLL were reported, but pulmonary involvement mainly developed several years after diagnosis of CLL [3–6]. We describe a case of direct pulmonary infiltrates of CLL. Interestingly, pulmonary infiltrates of CLL were an initial manifestation and the diagnosis of direct pulmonary involvement and CLL were made concomitantly in this case.

### 2. Case report

An 85-year-old man was referred to our hospital with a 1-month history of progressive dyspnea. He was a former smoker and did not

have any hematological or respiratory disorders. His performance status was ECOG 3. On a physical examination, fine crackles were audible bilaterally on auscultation, and lymph nodes were not palpable on the body surface. Arterial blood gas analysis showed a PaO<sub>2</sub> of 76.7 mmHg in room air. A chest radiograph showed bilateral ground-glass opacities in the lower lung fields (Fig. 1).

Computed tomography (CT) of the chest showed ground-glass opacities with a centrilobular distribution and centrilobular micronodules with a “tree-in-bud” pattern (Fig. 2). A laboratory examination showed a white blood cell count of 12,200 cells/μL with 67% lymphocytes (absolute count: 8174/μL). The hemoglobin level was 11.7g/dL, platelet count was 21.6 × 10<sup>4</sup>/μL, lactate dehydrogenase level was 264 IU/L, C-reactive protein level was 0.06 mg/mL, KL-6 level was 1050 U/mL, soluble interleukin-2 receptor level was 2290 U/mL, and β-D-glucan level was < 2.6 pg/mL. At that time, hypersensitivity pneumonitis, atypical pneumonia, mycobacterium infection, and lympho-

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### Abbreviations list

CLL	Chronic lymphocytic leukemia
CT	Computed tomography

proliferative disorder were considered in the differential diagnosis. Bronchoscopy was performed for the diagnosis. Bronchoalveolar lavage fluid demonstrated an increase in lymphocytes by 53%. Bacteria and mycobacterium were not cultured in the bronchoalveolar lavage fluid. A transbronchial lung biopsy showed lymphocytic infiltrations in the parenchyma, which were positive for CD5, CD20, and CD23 on immunohistochemical staining (Fig. 3). Infectious causes were ruled out by blood and bronchoalveolar lavage fluid samples. Flow cytometric immunophenotyping of peripheral blood and a bone marrow biopsy with immunohistochemical staining showed monotypic B cells that were positive for CD5, CD20, CD19, IgD, and CD23, and negative for CD10 and cyclin D1 (Fig. 4).

On the basis of these findings, the diagnosis of CLL was made and direct pulmonary involvement of CLL was confirmed simultaneously. Although CLL staging was Binet A (low risk), the patient's performance status was 3. Therefore, chemotherapy with fludarabine was started. One month after initiation of chemotherapy, his symptoms improved and a chest CT scan showed marked resolution of the ground-glass opacities and micronodules (Fig. 5). Watchful waiting was chosen after receiving two courses of fludarabine monotherapy. CT findings and the patient's symptoms did not worsen, and peripheral blood lymphocytes were not increased 1 year after chemotherapy.

### 3. Discussion

Pulmonary complications are common in patients with CLL, and are a common and crucial cause of admission to hospital. Khanijo et al. reported that the majority of patients with CLL and thoracic complications had a high disease activity of CLL and had received previous treatment for CLL [7]. They also found that in-hospital mortality was 24.9% among patients with CLL with hospital admission due to thoracic complications. In a previous report, radiological pulmonary infiltrations that were observed in patients with CLL were due to infections, hemorrhage, edema, transfusion-related lung injury, or drug-induced pulmonary damage [5]. Among them, infectious causes are the most



Fig. 1. Chest radiograph on admission showing ground-glass opacities in the lower lung fields.

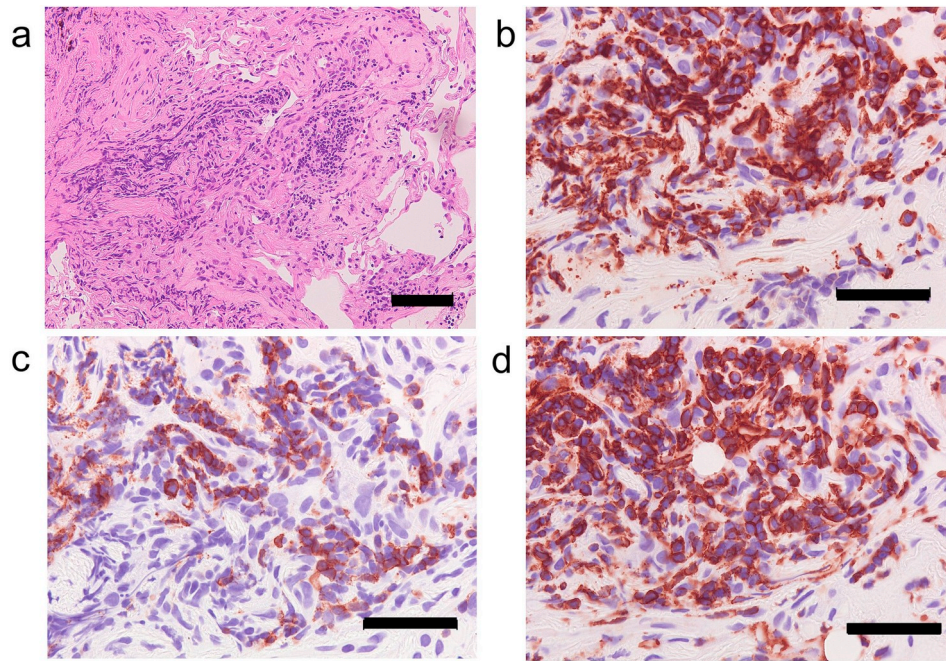


Fig. 2. High-resolution computed tomography images showing the presence of centrilobular micronodules, with a “tree-in-bud” pattern and perivascular ground-glass opacities that are predominant in the lower lobes.

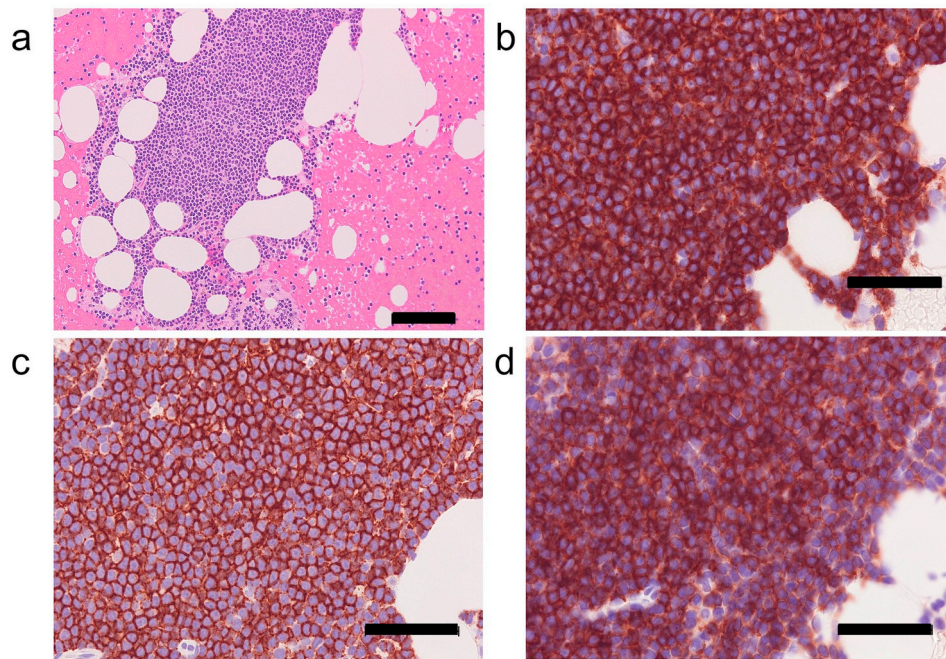
common pulmonary complications in patients with CLL. Ahmed et al. reported that pneumonia comprised 75% of pulmonary complications in patients with CLL [8]. However, direct pulmonary infiltrates of CLL were found only in 2.1% of the patients who were admitted to hospital.

The symptoms of pulmonary infiltrates of CLL are nonspecific, such as dry cough, progressive dyspnea, chest pain, and hemoptysis. The radiological appearance of pulmonary leukemic infiltrates is interlobular septal thickening and irregular thickening of the bronchovascular bundle and prominent peripheral pulmonary arteries [9,10]. Heyneman et al. reported that interlobular septal thickening was observed in all patients with pulmonary leukemic infiltrates [9]. This CT finding reflects the predilection of leukemic cells infiltrated into lymphatic roots [11]. Another feature of pulmonary leukemic infiltrates is consolidation, ground-glass opacities, and numerous centrilobular nodules with a tree-in-bud appearance [3,4]. CT findings of previous reports are shown in Table 1. Consolidations, centrilobular nodules with a tree-in-bud pattern, and ground-glass opacities are frequently observed in patients with pulmonary infiltrates of CLL [3–6]. In our patient, centrilobular micronodules, with a tree-in-bud pattern, and perivascular ground-glass opacities were observed in his CT images. These findings are non-specific and have a wide range of differential diagnoses, including atypical pneumonia, mycobacterium infection, and hypersensitivity pneumonitis. Infectious causes were firmly excluded using blood and bronchoalveolar lavage fluid samples in our patient. Symptoms and imaging findings were unchanged and the KL-6 level was not decreased 2 weeks after hospitalization. Therefore, hypersensitivity pneumonitis was excluded.

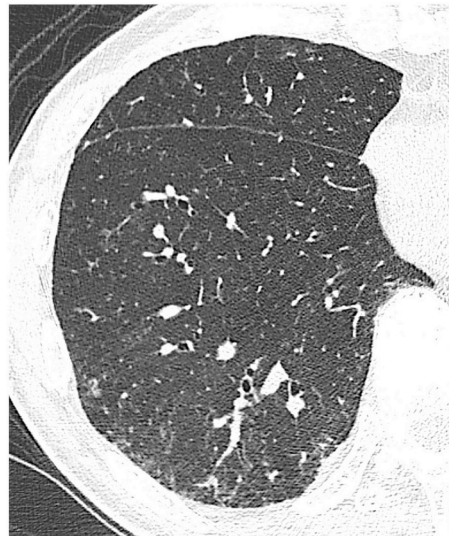
Finally, the diagnosis of CLL was confirmed in our patient using flow cytometric immunophenotyping of peripheral blood and a bone marrow biopsy. Direct pulmonary involvement of CLL was determined by pathological and immunohistochemical findings of a transbronchial lung biopsy concomitantly. Carmier et al. reported six patients with symptomatic pulmonary infiltrates of CLL [4]. The diagnosis of CLL preceded pulmonary infiltration in these patients by 3–14 years. Interestingly, direct pulmonary infiltrates were an initial manifestation in our patient. Pulmonary infiltrates of CLL should be included in the differential diagnosis when ground-glass opacities with a centrilobular distribution and centrilobular micronodules with a tree-in-bud pattern are found on CT.



**Fig. 3.** Transbronchial lung biopsy showing (a) infiltration of small lymphocytes in the lung parenchyma (hematoxylin–eosin staining, scale bar: 200  $\mu$ m). Lymphocytes show immunoreactivity for (b) CD5, (c) CD20, and (d) CD23 (scale bar: 100  $\mu$ m).



**Fig. 4.** Bone marrow biopsy showing (a) infiltration of small- and intermediate-sized lymphocytes into the bone marrow (hematoxylin–eosin staining, scale bar: 200  $\mu$ m). Lymphocytes were immunohistochemically stained for (b) CD5, (c) CD20, and (d) CD23 (scale bar: 100  $\mu$ m).



**Fig. 5.** High-resolution computed tomography image that was acquired 1 month after initiating fludarabine chemotherapy showing diminution of ground-glass opacities.

**Table 1**  
Clinical information and CT findings of patients with CLL with pulmonary leukemic infiltration.

Case no.	Reference no.	Age (years)	Sex	Timing of pulmonary infiltration	Lymphocytes (/μl)	CT findings		
						Consolidations	Centrilobular nodules with a tree-in-bud pattern	Ground-glass opacities
1	Our case	85	Male	At the same time of diagnosis of CLL	8174	–	+	+
2	3	80	Female	Eleven years after diagnosis of CLL	9600	–	+	–
3	4	63	Male	After diagnosis of CLL	127,000	–	+	+
4	4	74	Male	After diagnosis of CLL	50,000	+	+	+
5	4	72	Male	After diagnosis of CLL	48,000	+	+	+
6	4	64	Male	After diagnosis of CLL	1000	+	+	+
7	4	68	Male	After diagnosis of CLL	6000	–	–	+
8	4	73	Male	After diagnosis of CLL	700	+	+	+
9	5	68	Male	After diagnosis of CLL	3900	–	+	+
10	6	61	Male	Five years after diagnosis of CLL	19,024	+	–	–

CT = Computed tomography; CLL = Chronic lymphocytic leukemia.

**Declarations of interest**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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