The patient was a 74-year-old white man with a history of stage IV chronic lymphocytic leukemia (CLL) diagnosed 6 years previously. The last cycle of chemotherapy that he received was fludarabine 14 months prior to admission. Additional history was significant for bouts of recurrent bronchitis over the previous 6 months. One month prior to admission, the patient presented with a persistent cough, and he was noted to have a decreased hematocrit and platelet count. Chest CT done at that time demonstrated increased subcarinal, mediastinal, and hilar adenopathy. Therefore, a decision was made to restart fludarabine treatment. The patient presented to the clinic 1 day after initiation of fludarabine with complaints of severe cough that was productive of greenish-yellow, blood-tinged sputum. He also complained of increased shortness of breath, shaking chills, and fever to 38.8°C.

**Physical Examination**

The patient was an ill-appearing white man in no acute distress. His temperature was 37.2°C and pulse was 94 beats/min. His BP was 153/64 mm Hg and respirations were 20 breaths/min. There was pronounced cervical and axillary adenopathy. A chest examination demonstrated diffuse rhonchi and expiratory wheezes. A cardiovascular examination was significant for an unchanged II/VI systolic murmur. The abdomen was soft without tenderness or hepatosplenomegaly.

**Laboratory Findings**

Laboratory values were as follows: WBC count, $26.3 \times 10^3/\mu L$; 3% neutrophils; 95% lymphocytes, 1% eosinophils; hematocrit, 26%; platelets, $34 \times 10^5/\mu L$; and lactate dehydrogenase, 541 IU/L (range, 313 to 618 IU/L).

Chest radiograph (Fig 1) showed left mid-lung zone peripheral mass, hilar and mediastinal adenopathy, cardiomegaly, and bilateral pleural thickening.

Chest CT (Fig 2) showed bilateral pleural effusions, mediastinal adenopathy, and a dense parenchymal mass. Other CT images (not shown) revealed cervical, axillary, and hilar adenopathy. Other discrete pulmonary nodules were noted in the right lung.

What procedure would you recommend next?

What is your diagnosis?
Figure 1. Chest radiograph showing left mid-lung zone peripheral mass, hilar and mediastinal adenopathy, cardiomegaly, and bilateral pleural thickening.

Figure 2. Chest CT showing bilateral pleural effusions, mediastinal adenopathy, and a dense parenchymal mass.
Diagnosis: Pulmonary involvement with CLL/small lymphocytic lymphoma (SLL).

CLL can have varying pulmonary manifestations that are often difficult to distinguish from other pulmonary disorders on clinical grounds. Pulmonary infiltrates, pleural effusion, and hilar and mediastinal adenopathy are common radiographic findings. Infectious causes account for the majority of pulmonary infiltrates seen in patients with CLL. Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus, as well as Legionella and Nocardia spp are frequent bacterial pathogens that cause pneumonia in CLL. Opportunistic infections such as Pneumocystis carinii, fungi, viruses, and mycobacteria are also seen in CLL patients, most commonly in those being treated with corticosteroids and/or fludarabine.

Pulmonary infiltrates may also represent pulmonary toxicity from therapeutic agents used in the treatment of CLL. Respiratory complications in patients treated with fludarabine are almost always due to infection. This is presumably the result of the effect that the drug has on the CD4 count, which can be suppressed for extended periods of time following therapy. A less common respiratory complication is a hypersensitivity reaction to fludarabine, with resultant interstitial pneumonitis.

The alkylating agent chlorambucil is frequently used in the treatment of CLL. Although reports of chlorambucil-induced pulmonary fibrosis are rare in comparison to other alkylating agents such as busulfan and cyclophosphamide, it does occur. The symptoms are nonspecific (cough, dyspnea, fever, anorexia), and the chest radiograph usually shows a diffuse reticulonodular pattern with relative sparing of the apices. Pulmonary function tests show a restrictive defect with a decreased diffusion capacity. Chlorambucil-induced pulmonary fibrosis cannot be distinguished pathologically from other causes of drug-induced pulmonary fibrosis.

Pulmonary infiltrates in CLL may be the result of alveolar hemorrhage, especially in thrombocytopenic patients. Infiltrates can also be seen as a result of pulmonary leukostasis, although less commonly in CLL than in other leukemias.

Patients with CLL are at higher risk for the development of secondary neoplasms, the most common of which is lung cancer. Approximately 5% of CLL patients develop a diffuse large cell lymphoma at some point during their disease course. The histologic progression of CLL to diffuse large cell lymphoma, termed Richter’s syndrome, is associated with an aggressive disease course and an average survival of only 5 months.

Direct pulmonary infiltration by leukemic cells occurs more frequently in CLL than in other types of leukemia. Approximately 17% of pulmonary infiltrates seen in CLL are secondary to direct pulmonary extension, whereas only 10% of infiltrates seen in other types of leukemia represent direct tumor involvement. Pathologically, pulmonary infiltration of CLL reveals small mature-appearing lymphocytes (somewhat larger than normal lymphocytes) with condensed chromatin and rounded nuclei. Histologically, these findings are identical in both CLL and SLL, a low-grade malignant lymphoma. Therefore, SLL is considered to be the tissue counterpart of CLL. Clinically, these two entities are similar as well.

Common presenting symptoms of pulmonary CLL/SLL include dry cough, low-grade fever, and progressive dyspnea. Either diffuse or localized infiltrates may be seen on chest radiograph, as well as intrathoracic adenopathy. Pleural effusions are less common. Most cases of pulmonary CLL/SLL have been diagnosed with open lung biopsy; however, at least one report has shown that both transbronchial biopsy and BAL may also be used effectively to make the diagnosis. Both CLL and SLL are treated using the same chemotherapeutic agents, usually 5-day cycles of fludarabine given at 4-week intervals.

The patient was admitted to the hospital, antibiotic therapy was begun for suspected community-acquired pneumonia, and further fludarabine therapy was withheld. Despite treatment, his clinical status did not improve. He subsequently underwent CT-guided biopsy of the pleural mass seen in Figure 2, and the results were consistent with SLL. The patient had demonstrated prior intolerance to full-dose fludarabine therapy, and the new biopsy results confirmed disease progression despite dose-reduced therapy. Therefore, the decision was made to initiate therapy with rituximab, a monoclonal antibody used in patients with CLL refractory to more established therapeutic agents. He tolerated the therapy without difficulty, his symptoms resolved, and subsequent CT scans have demonstrated a marked reduction in disease.

**PEARLS**

1. The majority of infiltrates seen in patients with CLL are secondary to infectious causes. Opportunistic infections are uncommon, except in patients being treated with fludarabine and/or corticosteroids.

2. Other less common causes of pulmonary infiltrates in CLL include alveolar hemorrhage and pulmonary leukostasis, as well as therapy-related...
pulmonary drug toxicity effects causing pulmonary fibrosis or interstitial pneumonitis.

3. SLL is the tissue counterpart of CLL and should be considered in the differential diagnosis of a patient with CLL and pulmonary infiltrates on chest radiograph.

4. Most cases of pulmonary SLL have been diagnosed by open lung biopsy, although recent literature suggests that the diagnosis can be made using transbronchial biopsy, BAL, or transthoracic needle biopsy.

Suggested Reading