BRIEF REPORT

Concurrent Pleural Infiltration by Chronic Lymphocytic Leukemia and Adenocarcinoma of Unknown Primary Site Diagnosed by Effusion Cytology

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Synchronous malignancies in a pleural effusion are rare. A case of concurrent pleural infiltration by adenocarcinoma of unknown primary site and chronic lymphocytic leukemia (CLL) is presented in this case study, which was diagnosed by effusion cytology. Pleural effusion is not an uncommon complication in patients with B-CLL. Even in a pleural effusion rich in monoclonal lymphocytes, the presence of a second cancer must be excluded because this can be the main cause of mortality. The role of cytology in such cases is of paramount importance. Diagn. Cytopathol. 2012;00:000–000.

Key Words: adenocarcinoma; B-CLL; pleural effusion; synchronous; unknown primary

Pulmonary complications are common in patients with chronic lymphocytic leukemia (CLL), resulting in significant morbidity and mortality. Pulmonary infiltrates due to infection or leukemia, drug-related toxicity, alveolar hemorrhage, pulmonary embolism, secondary malignancy, or leukostasis are commonly encountered in CLL patients. Airway obstruction from hilar and mediastinal lymphadenopathy, atelectasis, and pleural effusion of diverse etiologies may also be encountered.[1]

The coexistence of two malignancies in the pleura[2] or in pleural effusion[3,4] is a rare phenomenon. Even more exceptional is the synchronous pleural involvement of CLL and cancer.[3] In this report, we present a case of adenocarcinoma of unknown primary site, which was diagnosed by effusion cytology in a patient with a history of B-CLL.

Case Report

An 81-year-old male presented with dyspnea and cough that had gradually developed over the previous 2 weeks. He had a history of B-CLL for 20 years without previous treatment. His past medical history was remarkable for a cholecystectomy and right colon polypectomy, and suffered from coronary artery disease, inflammatory bowel disease, and dementia.

Upon physical examination, tachypnea, signs of pleural effusion of the right hemithorax, splenomegaly, right cervical and bilateral axillary lymphadenopathy, and a subcutaneous left breast induration with a maximum diameter of 4 cm over the left breast were noticed.

A routine blood count revealed lymphocytosis (white blood cells 36,380/mm^3—91% lymphocytes) while the rest of the exams were within normal range. Thoracic imaging revealed a massive right-sided pleural effusion.

Diagnostic and therapeutic thoracocentesis was performed. The pleural fluid was determined to be a hemorrhagic exudate with lymphocytic infiltration (WBC count

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of 3,600/mm^3—77% lymphocytes). The fluid culture tested negative, while cytomorphological examination revealed numerous small lymphocytes and malignant cells suggestive of adenocarcinoma.

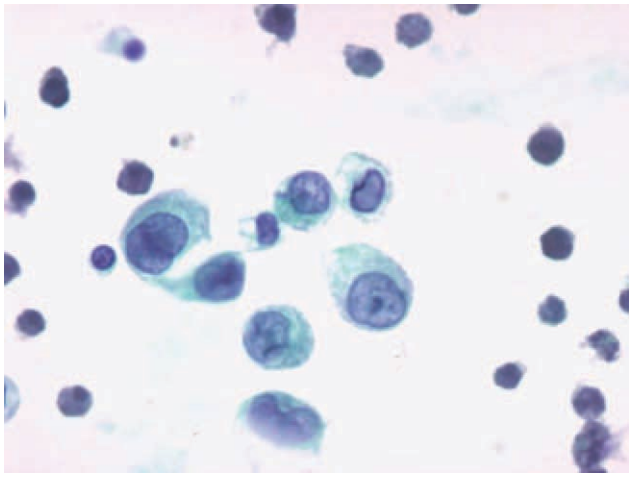

Fig. 1. Papanicolaou-stained smear from pleural effusion showing malignant epithelial cells with cytological abnormalities admixed with irregularly outlined lymphocytes (ThinPrep, ×400). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Cytological examination of pleural effusion revealed both loose groups and isolated malignant epithelial cells with prominent nucleoli and a variable amount of vacuolated cytoplasm admixed with numerous lymphocytes of medium size and irregularly outlined and poorly defined nuclei (Fig. 1). Immunocytochemical analysis using Thin Prep prepared smears showed that the carcinomatous cells were thyroid transcription factor-1 (TTF-1) -, HBME1 -, Calretinin -, Wilms tumor protein (WT-1) -, MOC-31 +, BerEP4 +, carcinoembryonic antigen (CEA) +, cytokeratin 7 (CK7) +, and cytokeratn 20 (CK20) -, while the lymphoid cells expressed only the lambda light chain, as determined using anti-kappa and anti-lambda antibodies (Figs. 2a–d).

Immunophenotyping analysis of lymphoid cells by flow cytometry identified an elevated percentage of B lymphocytes (69% of total lymphocytes) that expressed CD19. Further immunophenotyping of the CD19+ cells revealed clonal expression of Ig-Lambda chains as well as positivity for CD5, CD20, CD22, CD23, and CD45 and lack of expression of CD10 and FCM7 (Fig. 3).

Fine needle aspiration cytology of the subcutaneous palpable mass of the anterior thoracic wall showed infiltration by a monotonous population of lymphoid cells of B-cell origin as indicated by PCR analysis (Fig. 4).

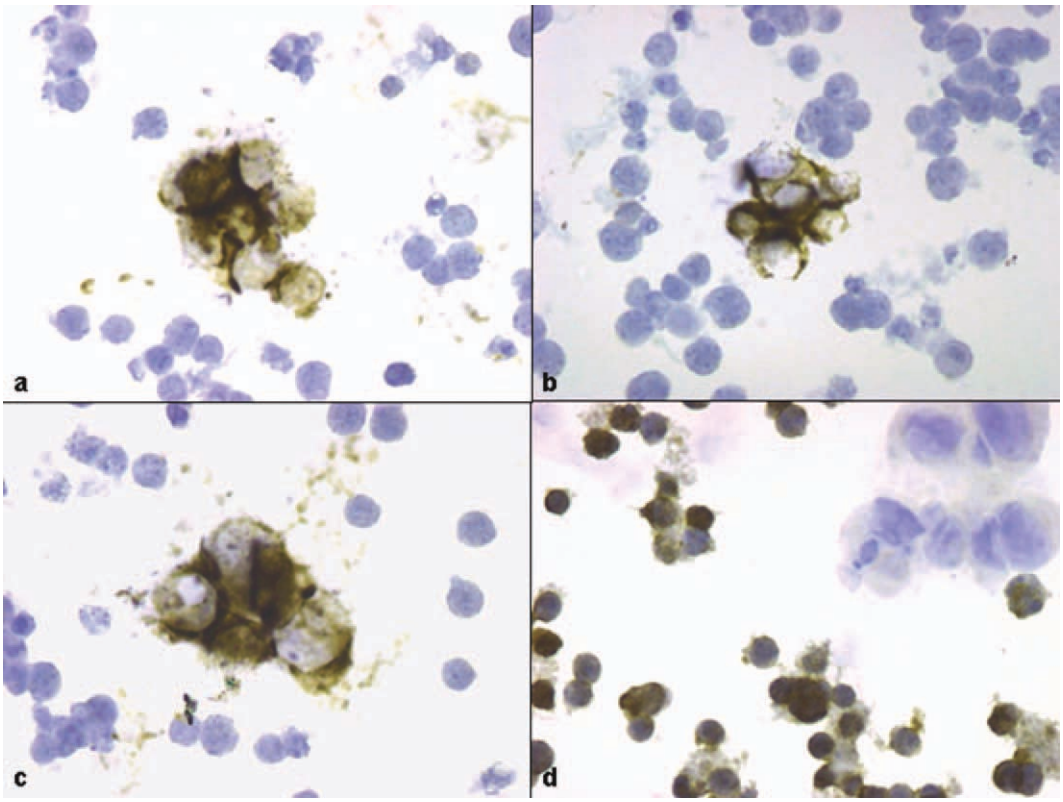

Fig. 2. Immunocytochemical stain on a ThiPrep slides from a pleural effusion. Strong immunoreactivity of metastatic carcinoma cells for MOC-31 (**a**: ×400), Ber-EP4 (**b**: ×400), and CK7 (**c**: ×400). Lymphoid cells stain for lambda light chain (**d**: ×400). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

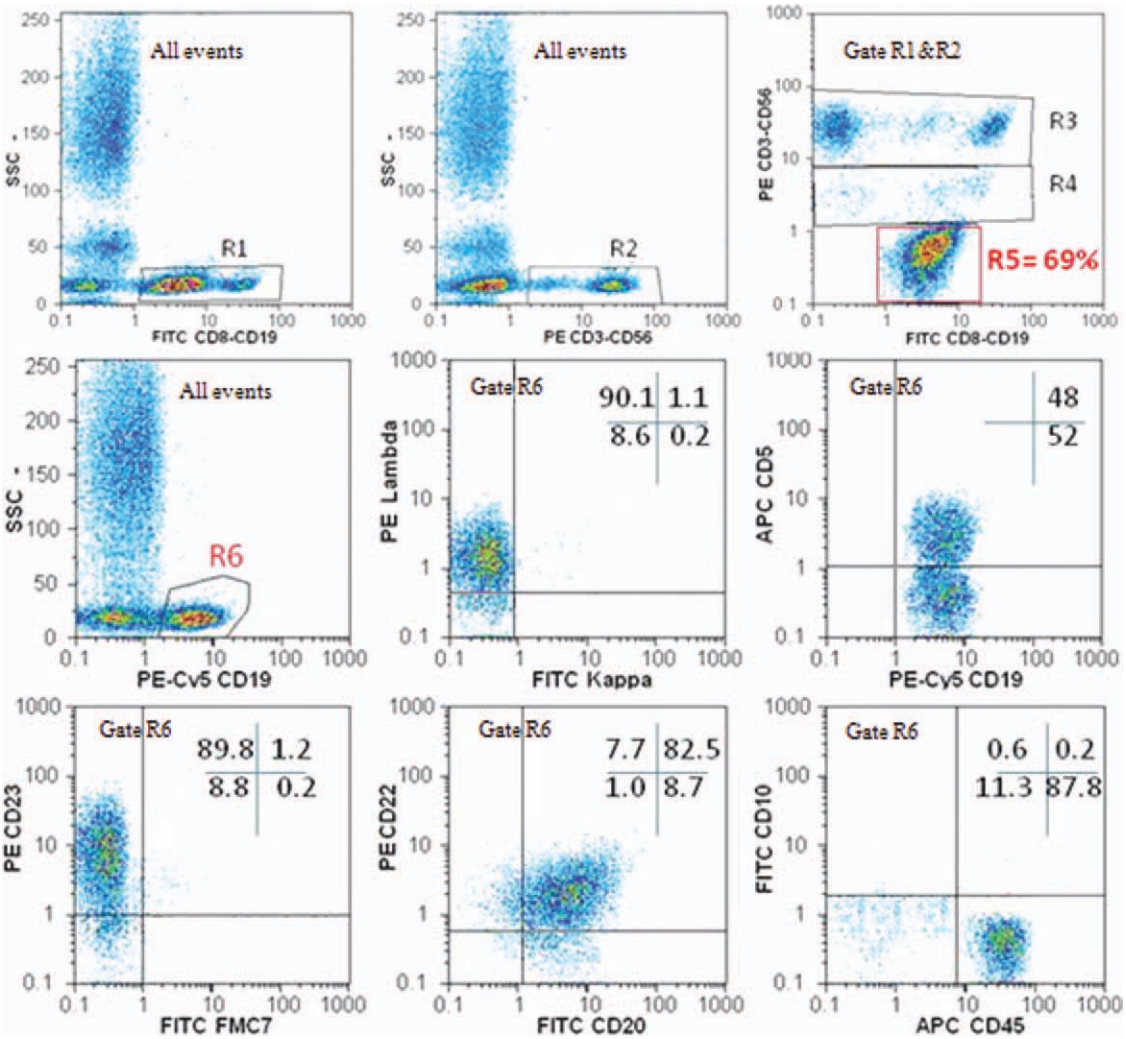

Fig. 3. Flow cytometric analysis: An elevated percentage of B lymphocytes (69%) was recognized using a screening tube. B cells were enumerated on the basis of low side-scatter (SSC) positivity for the CD19-CD8 cocktail and absence of CD3, CD4, and CD56. Further immunophenotyping was performed using additional staining tubes and a gate for B-cells based on SSC-low/CD19+ (plot 4, R6). Clonal expression of surface Ig-Lambda chains (plot 5) and positivity for CD5 (48%, plot 6), CD23 (~90%, plot 7), CD22 and CD20 (~90%, plot 8) was identified. B cells also lack the expression of CD10 (plot 9, <99%) and FCM7 (plot 7, 0.2%). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Repeated CT scan of the thorax after the thoracocentesis failed to reveal any parenchymal mass, but a pleural thickening with a locally nodular appearance was observed (Fig. 5). Mediastinal and axillary adenopathy as well as multiple subcutaneous nodules of the anterior thoracic wall were also demonstrated. CT scan and sonographic examination of the abdomen revealed splenomegaly with multiple infiltrations as well as para-aortic, iliac, inguinal, femoral, and mesenteric lymph nodes.

Gastroscopy and colonoscopy were negative for the presence of a neoplasm. The patient died of septic shock before a biopsy of pleura could be obtained.

Discussion

Pleural effusion is frequently encountered in patients with CLL. In the differential diagnosis, infection, primary pleural involvement, central lymphatic obstruction, pleural infiltration by second malignancies, and postirradiation and/or postchemotherapy changes should be included.[5]

Patients reported to have pleural involvement with CLL are known to have the disease for several years before the development of effusion.[6] Malignant pleural effusion due to CLL was confirmed in 7% of hospitalized CLL-patients.[1] The pleural fluid can be either hemorrhagic due to pleural involvement with B-CLL[6,7] or chylous (chylothorax).[8,9] In addition to B cells, "reactive" T cells may also be seen in pleural involvement.[10] In other cases, carcinoma development[10] or the coexistence of two malignancies[3] may also be observed.

Flow cytometry is useful in the evaluation of lymphoid cells in pleural fluid because it can detect cell surface antigens in cytological material.[11] In this study, immuno-

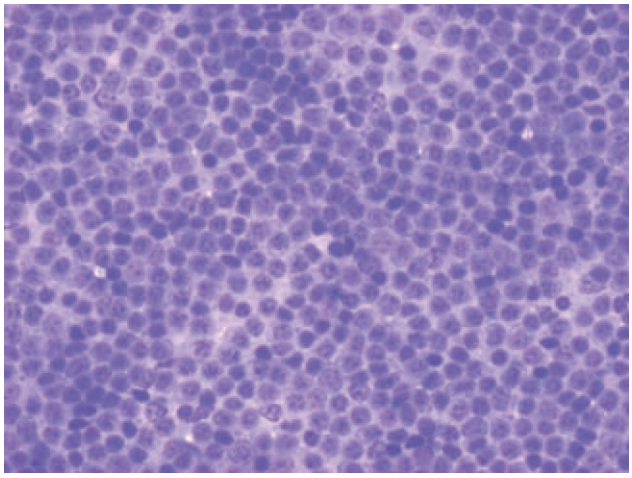

Fig. 4. FNAC of subcutaneous thoracic wall nodule showing monotonus population of lymphoid cells (×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

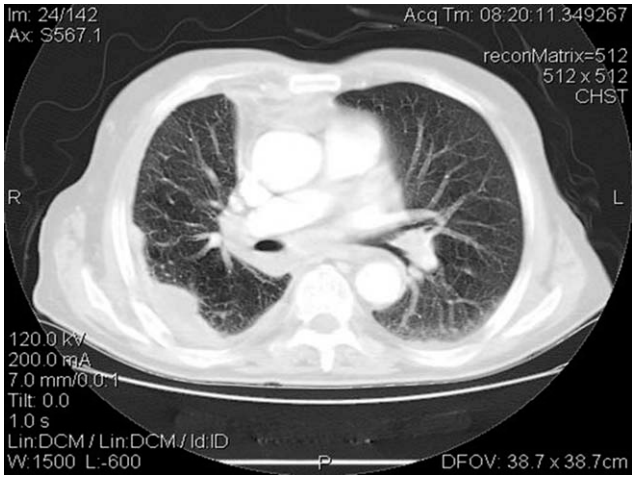

Fig. 5. CT of the thorax after thoracocentesis.

phenotyping was performed by flow cytometry and the lymphocytes were positive for CD19, CD5 (43%), CD20, CD22, CD23, and CD45, and were negative for CD10 and FCM7. A clonal lambda light chain was also detected. The lack of uniform CD5 expression in CD19+ CLL cells is often observed, especially when they progress to aggressive forms.

It has also been shown that CLL patients are at a high risk for developing a second or a third non-lymphoid malignancy.[12] The development of secondary malignancies was equally probable in a population that did receive chemotherapy as well as in those who received no treatment for their disease.[12,13] The most frequent second neoplasms in patients with CLL are melanoma, soft tissue sarcoma, colorectal carcinoma, and lung cancer,[6] with ~2.5% of CLL patients developing lung cancer.[1,13,14]

Lung cancer (36%), mesothelioma (21%), and carcinoma of unknown primary site (18%) are the most frequent malignancies presenting with pleural effusion,[15] and adenocarcinoma is the most common histological type.[16] Cytologic examination has 70% sensitivity in establishing the diagnosis of cases with pleural effusion due to metastatic adenocarcinoma. Nevertheless, cytology is less efficient in cases of mesothelioma, squamous cell carcinoma, lymphoma, or sarcoma involving the pleura, with sensitivities for detection of 10, 20, 25–50, and 25%, respectively.[17] It is also important to note that adenocarcinoma of the lung often invades the pleura because of its peripheral location.[18]

Parekh et al.[14] reviewed the records of 26 patients who were diagnosed with both CLL and lung carcinoma. In that study, lung carcinoma was diagnosed a decade after CLL, and 10 patients had a third malignancy. Moreover, in the patients with secondary malignancies, lung carcinoma was the cause of death, and not CLL or other solid tumors.

As previously noted, patients with CLL often develop disease-related pleural infiltration and lung cancer. Nevertheless, the concurrent pleural infiltration of CLL and lung cancer is an exceptional complication. The diagnosis of two synchronous malignancies by effusion cytology has only been previously reported twice.[3,4] One case was synchronous CLL and lung adenocarcinoma,[3] and the other case was breast and colon carcinoma.[4] Nevertheless, in our case, no primary site could be identified, although the CT imaging analysis raised doubts of mesothelioma. To distinguish mesothelioma from metastatic adenocarcinoma, we used a panel of monoclonal antibodies, and the immunocytochemical findings showed that the tumor cells were negative for mesothelial cell markers against HBME1, Calretinin, and WT-1, but were positive for epithelial cell markers MOC-31, BerEP4, and CEA. To prove or to exclude pulmonary origin of adenocarcinoma, an anti-TTF-1 antibody was used. Cancer cells were negative for TTF-1, so it is unlikely that the metastatic carcinoma primarily occurred in the lung. In addition, to rule out any possible metastasis from the gastrointestinal tract, anti-CK7 and anti-CK20 antibodies were used. The cancer cells were positive for CK7 and negative for CK20, and therefore it was unlikely that the tumor had originated in the gastrointestinal tract. To the best of our knowledge, this is only the second reported case in the English literature of synchronous pleural infiltration by CLL and adenocarcinoma being diagnosed by effusion cytology.

Conclusion

In patients with CLL and a pleural effusion rich in monoclonal lymphocytes, the presence of a second cancer must be excluded, since this can be the main cause of mortality.

References

1. Ahmed S, Siddiqui AK, Rossoff L, et al. Pulmonary complications in chronic lymphocytic leukaemia. Cancer 2003;98:1912–1917.
2. Hatzibougias D, Bobos M, Karayannopoulou G, et al. A rare tumoral combination, synchronous lung adenocarcinoma and mantle cell lymphoma of the pleura. World J Surg Oncol 2008;6:137.
3. Sur N, Silverman JF. Synchronous malignancies detected by effusion cytology. Diagn Cytopathol 1998;18:184–187.
4. Stopyra GA, Warhol MJ, Multhaupt HA. Utility of CK7 and CK20 immunohistochemistry in the detection of synchronous breast and colon carcinoma in a pleural effusion: A case report and supporting survey of archival material. Diagn Cytopathol 2001;25:54–58.
5. Alexandrakis MG, Passam FH, Kyriakou DS, et al. Pleural effusions in hematologic malignancies. Chest 2004;125:1546–1555.
6. Van den Berge M, Tinga CJ, Bieger RA. 73-year-old man with chronic lymphocytic leukaemia and a haemorrhagic pleural effusion. Ann Hematol 2001;80:183–186.
7. Dhodapkar M, Yale SH, Hoagland HC. Hemorrhagic pleural effusion and pleural thickening as a complication of chronic lymphocytic leukemia. Am J Hematol 1993;42:221–224.
8. Ampil FL, Burton GV, Hardjasudarma M, et al. Chylous effusion complicating chronic lymphocytic leukemia. Leuk Lymphoma 1993;10:507–510.
9. Aranda EA, Aguinaco R. Chylothorax complicating chronic lymphocytic leukemia. Neth J Med 2001;58:223–224.
10. Atanackovic D, Brettner S, Hegewisch-Becker S. Pleural effusion of a second neoplasm in a patient with B-CLL: Two immunological compartments. Am J Hematol 2003;73:184–189.
11. Czader M, Ali SZ. Flow cytometry as an adjunct to cytomorphologic analysis of serous effusions. Diagn Cytopathol 2003;29:74–78.
12. Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, Strom S, Freireich EJ, Medeiros LJ, Kantarjian HM, Keating MJ. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 2009;27:904–910.
13. Hisada M, Biggar RJ, Greene MH, Fraumeni JF Jr, Travis LB. Solid tumors after chronic lymphocytic leukemia. Blood 2001;98:1979–1981.
14. Parekh K, Rusch V, Kris M. The clinical course of lung carcinoma in patients with chronic lymphocytic leukemia. Cancer 1999;86:1720–1723.
15. Cellerin L, Marcq M, Sagan C, Chailleux E. Malignant pleural effusion as the presenting site of cancer: Comparison with metastatic pleural effusions from known cancers. Rev Mal Respir 2008;25:1104–1109.
16. Monte SA, Ehya H, Lang WR. Positive effusion cytology as the initial presentation of malignancy. Acta Cytol 1987;31:448–52.
17. Light RW. Clinical practice. Pleural effusion. N Engl J Med. 2002;346:1971–1977.
18. Litzky LA. The pathology of non-small cell lung carcinoma. In: Fishman AP, et al, Fishman's pulmonary diseases and disorders. McGraw-Hill, New York, 1997, p. 1743.