Case Reports in Oncology

Case Rep Oncol 2018;11:567–572

DOI: 10.1159/000491920
Published online: August 17, 2018

Case Report

Leukoerythroblastosis with Cytopenia as an Initial Presentation of Lung Adenocarcinoma

Rouslan Kotchetkov[a] Robert El-Maraghi[a] Leena Narsinghani[b]

[a]Simcoe Muskoka Regional Cancer Program, Royal Victoria Regional Health Centre, Barrie, ON, Canada; [b]Department of Pathology, Royal Victoria Regional Heath Centre, Barrie, ON, Canada

Keywords
Lung adenocarcinoma · Leukoerythroblastosis · Cytopenia · Bone marrow

Abstract
A 74-year-old male with a history of chronic lymphocytic leukemia (CLL) previously treated with fludarabine/cyclophosphamide/rituximab (FCR) 5 years ago, presented with progressive fatigue, mucocutaneous bleeding, and cytopenias (hemoglobin 51 g/L, platelets 8.0 × 10^9/L, lymphocytes 0.4 × 10^9/L). He had normal respiratory findings, and no lymphadenopathy or hepatosplenomegaly. Further workup revealed a small spiculated lung nodule and multiple sclerotic bony lesions. Due to bleeding/profound thrombocytopenia, lung biopsy was not feasible. Peripheral smear revealed leukoerythroblastosis with few nucleated red blood cells and left shift of granulocytes. Bone marrow (BM) aspirate yielded a dry tap with clusters of extrinsic atypical cells on touch preparations. BM core biopsy showed infiltration and near complete replacement by a population of highly atypical cells with surrounding fibrosis. Cells were positive for cytokeratins CK7 and CK8/18, Napsin A, and thyroid transcription factor-1, specific for a primary poorly differentiated lung adenocarcinoma. Leukoerythroblastosis in association with cytopenia often indicates a BM infiltration and warrants an early BM biopsy to rule out hematological and solid malignancies, particularly in CLL patients treated with FCR. In our case, a diagnosis of a lung adenocarcinoma was established by BM examination, the only clinically feasible diagnostic modality.

KARGER

Rouslan Kotchetkov
Simcoe Muskoka Regional Cancer Program
Royal Victoria Regional Health Centre
201 Georgian Drive, Barrie, ON L4M 6M2 (Canada)
E-Mail Kotchetkovr@rvh.on.ca

Background

Chronic lymphocytic leukemia (CLL) is a hematological neoplasm composed of small mature B-cells and is the most common leukemia of adults in the western countries. Between 30 and 60% of patients, depending on disease stage, have hypogammaglobulinemia, associated with immunodeficiency and predisposition to secondary malignancies [1]. Chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab (FCR) is the most commonly used frontline treatment regimen in fit patients with CLL [2, 3]. Although it produces a high rate of very long-term progression-free survival in certain subgroups of patients [2], therapy with FCR causes an increase in second cancers, in particular acute myeloid leukemia and myelodysplastic syndromes [4].

Case Presentation

A 74-year-old man presented with increasing fatigue and generalized abdominal discomfort over one month associated with occasional joint aches and pains that he attributed to a coincident administration of the flu shot. He was otherwise well with no fevers or chills, nausea or vomiting, mouth sores, or diarrhea and no headaches, dizziness, or double vision. He did not have any new cough, but he had mild dyspnea, and his energy was somewhat reduced. He developed new bleeding from his gums and had bloody blisters in his mouth but had no hemoptysis, hematuria, or hematochezia.

Five years prior to presentation, the patient was diagnosed with CLL, treated with FCR. He achieved complete remission and had been on active surveillance since. Other past medical history was significant for type 2 diabetes, hyperlipidemia, and hypertension for which he was on appropriate medications. In addition, he was a previous smoker of 40 pack-years, but managed to quit 10 years ago. Investigations showed new onset of anemia (hemoglobin of 51 g/L) with an inappropriately normal reticulocyte count (80.3), circulating nucleated red blood cells (Fig. 1a, white arrows) as well as thrombocytopenia (platelet count of 8,000 × 10^9/L). White blood cell count was preserved at 5.58 × 10^9/L, but he had left shift with 0.5 × 10^9/L metamyelocytes and 0.06 × 10^9/L myelocytes (Fig. 1a, blue arrow), and lymphopenia (0.4 × 10^9/L). Lactate dehydrogenase and ferritin were elevated at 843 U/L and 1,450 μg/L, respectively. Liver enzymes, creatinine, and sodium were normal.

He was admitted to hospital for transfusion support and further investigations. This initially included a chest X-ray, which reported clear lung fields as well as no abnormalities in the bones and soft tissues. Ultrasound of the abdomen demonstrated splenic enlargement measuring 18.9 cm associated with a lobulated area of decreased echogenicity measuring up to 5.6 cm. There was also a well-circumscribed echogenic mass measuring up to 2 cm in the mid to lower pole of the kidney on the right side, whereas the left kidney was normal in appearance. It was hypothesized that the splenic changes might have been representative of previous infarction, but the mass in the kidney was new since his previous evaluation. Given these findings, a CT scan was performed. This demonstrated two small lung nodules including an irregular-appearing right middle lobe lesion measuring 9 × 14 mm (Fig. 2a) and an ill-defined spiculated nodule in the lingula measuring 12 × 15 mm (Fig. 2b) as well as a benign-appearing granuloma in the left lower lobe. There was evidence of subpleural emphysema at the lung apices with no pulmonary edema or pneumonia. The liver appeared normal; the spleen was enlarged measuring 20 cm in length with some peripheral wedge-shaped areas possibly representative of subacute splenic infarcts. The right adrenal gland had a round nodule that was

felt to represent a benign adenoma. The kidneys were normal in length and cortical thickening. There was a peripheral wedge-shaped hypoenhancing area in the upper pole of the right kidney and posterior aspect of the left kidney, which were typical of renal infarcts with no renal stone, mass, or obstruction present. In addition, there was evidence of widespread sclerotic bony lesions throughout all the visualized bony structures, with no signs of fracture.

Lung cancer with concomitant myelodysplasia/acute myeloid leukemia/CLL relapse was suspected, but due to bleeding and profound thrombocytopenia, biopsy of one of the lung nodules was not feasible. Bone marrow (BM) investigation was performed in order to further investigate the leukoerythroblastosis and cytopenia. Aspirate yielded a dry tap with clusters of extrinsic atypical cells on touch preparations. BM core biopsy showed infiltration and near complete replacement (Fig. 1b) by a population of highly atypical cells with surrounding fibrosis (Fig. 1c). Cells were positive for thyroid transcription factor-1 (Fig. 1d), cytokeratins CK8/18, CK7, and Napsin A (Fig. 1e), an immunohistochemical profile that is consistent with a primary poorly differentiated lung adenocarcinoma.

Discussion

CLL is associated with immunodeficiency and predisposition to secondary malignancies, including lung cancer. One study reviewed 12,373 CLL patients in Denmark for the occurrence of secondary cancers with particular emphasis on lung cancer and its major subtypes. The relative risk was expressed as the standardized incidence ratio (SIR), i.e., the ratio of observed to expected number of cancers, based on incidence rates for the Danish population. Lung cancer occurred in 141 patients (SIR = 1.61 [1.37–1.90]). Elevated risks were observed for adenocarcinoma (SIR = 2.20 [1.57–3.08]) and squamous cell carcinoma (SIR = 1.52 [1.06–2.17]) of the lung [5]. Immune dysregulation contributing to malignancy may be either a result of the disease itself or secondary to the treatment with purine analogues [1]. Chemoimmunotherapy with FCR is the most commonly used frontline treatment modality in physically fit patients with CLL [2, 3]. However, a landmark study showed that CLL patients after frontline FCR-based therapy have a 2.38 times higher risk of second cancers than the general population. In particular, the incidence of acute myeloid leukemia and myelodysplastic syndromes was significantly higher after FCR with a crude rate of 5.1% during the follow-up period of 4.4 years (95% CI, 3.7–5.0) [4]. This study did not show an increase in non-hematological cancers, however. The updated results of the CLL8 study with the median observation time of 5.9 years reported 136 cases of secondary malignancies observed in 122 (15.3%) patients. It included 40.4% solid tumors (including melanoma; 55 cases), 27.9% Richter's transformation (38 cases), 17.6% hematological neoplasias (24 cases), and 14% other skin cancers like squamous cell carcinoma (19 cases) [6]. In our case, the clinical and laboratory picture was not consistent with CLL relapse, but rather therapy-related myelodysplasia or acute myeloid leukemia. Complicating matters, the patient had a smoking history, a new small lung mass, and sclerotic lesions that could be consistent with primary lung malignancy. Therefore, in view of the leukoerythroblastosis and the clinical picture, we suspected this patient had concomitant hematological and non-hematological malignancies.

Leukoerythroblastosis, as defined by Wintrobe, is the presence of immature cells of the myeloid series and nucleated red cells in the circulating blood, with or without anemia and is not seen exclusively in malignancies [7]. An earlier report showed that approximately one-half of the leukoerythroblastosis cases series had infiltrative disease of the BM. Chronic and acute leukemias accounted for nearly one-half of the patients, but one-third of these had a

complicating disorder which might have produced leukoerythroblastosis [7]. Lymphoma is not usually a cause of leukoerythroblastosis, and in a series of 112 cases of Hodgkin's disease with available autopsy, 4.46% had myeloid metaplasia, but only 1 of the 6 cases with this finding had normoblasts in the blood [8, 9]. However, in another study, BM infiltration due to lymphoma was found in 6 out of 47 patients suggesting that lymphoma may be a more frequent cause than previously suspected [7]. To our knowledge, there are no more recent publications on this topic.

Isolated leukoerythroblastosis resembling leukemia may also be seen in severe infections [10]. However, leukoerythroblastosis with cytopenias (usually bi- and pancytopenias) is often indicative of BM infiltration and is more frequently an initial presentation of solid malignancies, like gastric adenocarcinoma [11], or signet ring cell poorly differentiated carcinoma [12]. In such circumstances, a diagnosis of non-hematological malignancy may be achieved through analysis of a BM biopsy, such as has been described in a case of metastatic lobular breast cancer by our group and others [13, 14]. Similarly, in the present case, the diagnosis of poorly differentiated lung adenocarcinoma was ultimately established on BM biopsy given that this was the only clinically feasible diagnostic tool.

BM infiltration by solid tumors is an important prognostic factor and often affects therapy decisions. A clinical study of 19 patients with non-hematological malignancies who initially had a diagnosis determined from BM demonstrated that the prognosis of such patients was very poor with survival times generally limited to a few days or weeks. The authors concluded that anemia, thrombocytopenia, elevated red cell distribution width, and hypoproteinemia formed a uniform tetrad in patients with disseminated tumors that were diagnosed via BM examination [15]. Similarly, in our case, no palliative chemotherapy was feasible due to poor BM capacity. The prognosis was communicated with the patient and family and the decision was to proceed with palliative treatment and end-of-life supportive care. The patient was comfortable and ultimately survived five days from the time the BM biopsy results became available.

Conclusion

A leukoerythroblastosis with cytopenia warrants an early BM biopsy to rule out both hematological and solid malignancies, particularly in patients with CLL previously treated with FCR. Furthermore, BM infiltration by solid tumors is an adverse prognostic factor and may help clinicians and patients to make informed management decisions.

Acknowledgement

R. Kotchetkov wrote and reviewed the manuscript; R. El-Maraghi and L. Narsinghani prepared images and reviewed the manuscript.

Statement of Ethics

Informed consent was gained from the patient for publication of this case report and the accompanying images.

Disclosure Statement

The authors disclose no conflict of interest.

References

1 Reda G, Fattizzo B, Cassin R, Orofino N, Flospergher E, Iurlo A et al. Secondary Malignancies in Chronic Lymphocytic Leukemia: A Single Centre Retrospective Analysis of 514 Cases. Blood. 2015;126:5279.
2 Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J et al.; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010 Oct;376(9747):1164–74.
3 Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008 Aug;112(4):975–80.
4 Benjamini O, Jain P, Trinh L, Qiao W, Strom SS, Lerner S et al. Second cancers in patients with Chronic Lymphocytic Leukemia who received frontline FCR therapy - Distribution and clinical outcomes. Leuk Lymphoma. 2015 Jun;56(6):1643–50.
5 Schöllkopf C, Rosendahl D, Rostgaard K, Pipper C, Hjalgrim H. Risk of second cancer after chronic lymphocytic leukemia. Int J Cancer. 2007 Jul;121(1):151–6.
6 Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016 Jan;127(2):208–15.
7 Burkett LL, Cox ML, Fields ML. Leukoerythroblastosis in the adult. Am J Clin Pathol. 1965 Nov;44(5):494–8.
8 Hazard GW, Porter PJ, Ingall D. Case records of the Massachusetts General Hospital. N Engl J Med. 1964 Aug;271:363–71.
9 Levitan R, Diamond HD, Craver LF. Myeloid metaplasia in Hodgkin's disease. N Y State J Med. 1959 Jun;59(12):2376–8.
10 Canbolat Ayhan A, Timur C, Ayhan Y, Kes G. Leukoerythroblastosis Mimicking Leukemia: A case report. Iran J Pediatr. 2014 Jun;24(3):332–3.
11 Takayasu V, Goto EH, Casagrande MZ, Miranda PG, Diniz GB, Monteiro MF et al. Bicytopenia and leukoerythroblastosis: a rare initial presentation of signet ring cell gastric adenocarcinoma. Autops Case Rep. 2017 Jun;7(2):55–60.
12 Pinheiro NC, Rodrigues J, Pereira J, Silva AM. Signet ring cell carcinoma's myelophthisis. BMJ Case Rep. 2014 Mar;2014 mar12 1:bcr2014203662.
13 Kotchetkov R, Ellison E. Metastatic lobular breast carcinoma mimicking multiple myeloma. Blood. 2014;124(14):2313.
14 Mahdi EJ, Mahdi AJ. Leucoerythroblastosis and thrombocytopenia as clues to metastatic malignancy. BMJ Case Rep. 2014 Jan;2014 jan30 2:bcr2013202612.
15 Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T, Ozan U, Ozturk H et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. BMC Cancer. 2005 Nov;5(5):144.

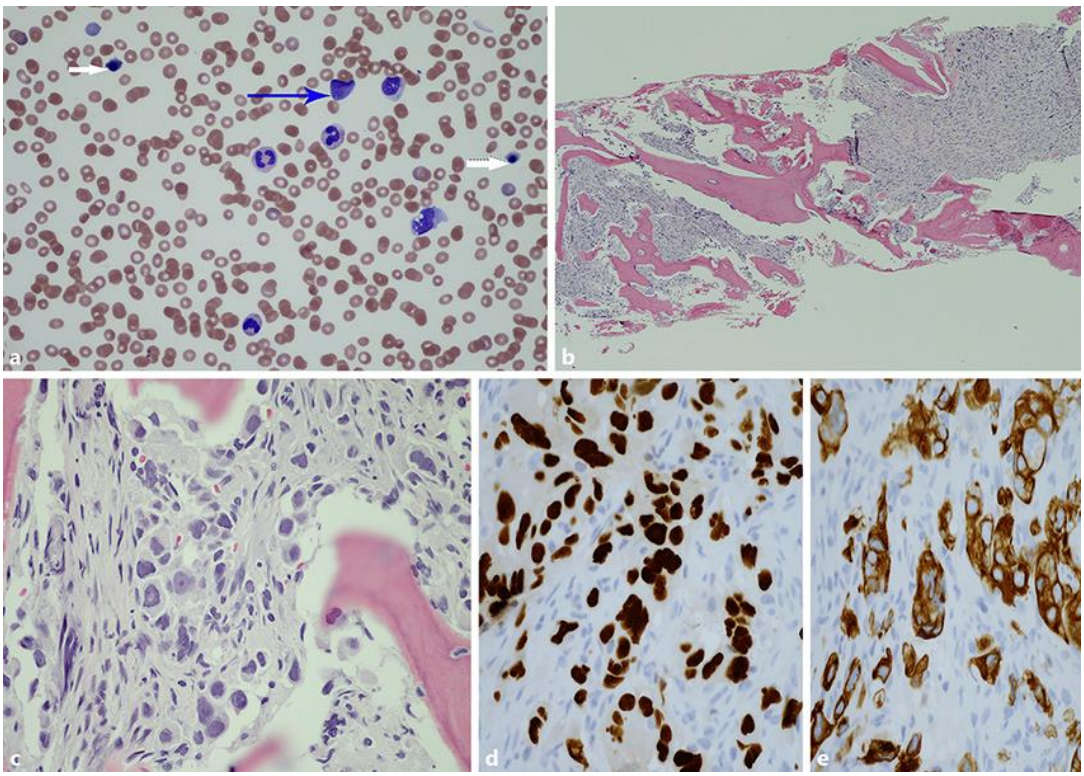

Fig. 1. **a** Leukoerythroblastosis on peripheral blood smear. Solid white arrows show nucleated red blood cells; blue arrow shows early myeloid progenitor cell. Giemsa stain. ×10. **b** Bone marrow core biopsy showing near complete replacement of marrow space by malignant epithelial cells: metastatic poorly differentiated adenocarcinoma. Hematoxylin-eosin. ×20. **c** Malignant epithelial cells are highly atypical with large irregular nuclei, increased nuclear to cytoplasmic ratio, nuclear pleomorphism, and prominent nucleoli. ×40. **d**, **e** Immunostaining of malignant epithelial cells. ×40. **d** Nuclei are positive for thyroid transcription factor-1. **e** Positive staining with (cytoplasmic distribution) cytokeratin 7.

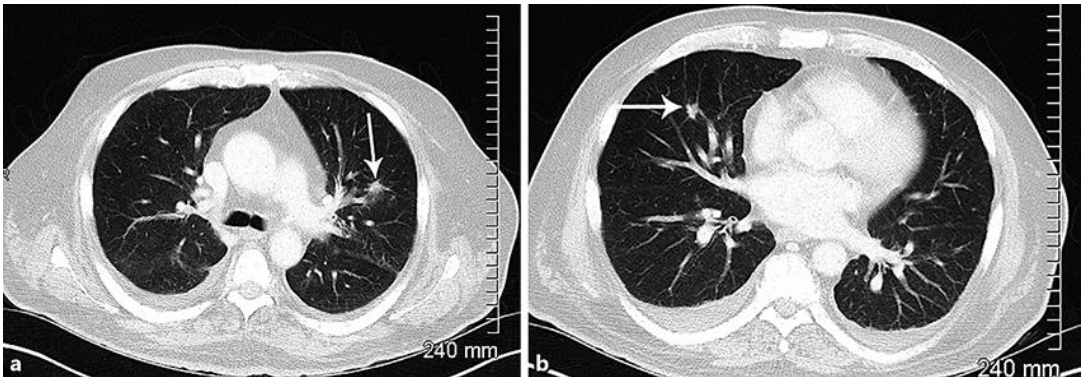

Fig. 2. Chest CT showing a 9 × 14 mm irregular nodule in the right middle lobe (arrow) (**a**) and an ill-defined, spiculated nodule measuring 12 × 15 mm located in the lingua of the left lung (arrow) (**b**).