

ASSOCIATED CHRONIC LYMPHOCYTIC LEUKEMIA AND ACUTE MYELOID LEUKEMIA. CASE REPORT

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Abstract: An increased incidence of different malignancies associated to chronic lymphocytic leukemia (CLL) has been reported and it is considered a complication of this disease. The association of CLL and acute leukemia is a rare event described in <1% of CLL, the acute leukemia has been of both the myeloblastic and lymphoblastic types. The coexistence of acute myeloid leukemia (AML) and CLL in the same patient has been occasionally reported. Most of these cases have been associated with the administration of chemotherapy or radioterapy for CLL, suggesting that the former may be a secondary leukemia. On the other hand, CLL could precede, but could also be diagnosed at the same, or delayed time as AML, suggesting the presence of other leukemogenic factors. We describe the development of AML in a patient with previously diagnosed CLL.

Cuvinte cheie: leucemie limfatică cronică, leucemie acută mieloidă, chimioterapie, imunosupresie

Rezumat: Asocierea leucemiei limfatice cronice (LLC) cu diferite afecțiuni maligne are o incidență în creștere și este considerată o complicație a acestei boli. Asocierea dintre LLC și leucemie acută este un eveniment rar, descris la <1% din LLC, leucemia acută putând fi deopotrivă limfoidă sau mieloidă. Coexistența leucemiei mieloidă acută (LAM) și LLC la același pacient a fost raportată ocazional. Cele mai multe dintre aceste cazuri au fost asociate cu administrarea de chimioterapice sau radioterapie în LLC, sugerând a fi o leucemie secundară. În altă ordine de idei, LLC poate preceda, poate fi diagnosticat în același timp sau ulterior față de LAM, sugerând prezența altor factori leucemogeni. Vom prezenta apariția LAM la un pacient diagnosticat anterior cu LLC.

INTRODUCTION

The possibility that patients with B-cell chronic lymphocytic leukemia (CLL) may suffer from second primary cancers is well known (1). The association of CLL and acute leukemia has been infrequently described. The type of acute leukemia being either from the lymphoid or more often from the myeloid lineage. The lymphoblastic variety usually occurs well into the course of the CLL. It most likely represents natural progression of the disease to a more acute phase rather than a separate occurrence (2). In most cases, AML arises after treatment of CLL with chemotherapy and/or radiotherapy, suggesting that it may be a secondary leukemia. In other cases, however, both disorders have been diagnosed simultaneously in untreated patients, appearing as two distinct and unrelated malignancies (3). We hereby describe the development of an AML in a CLL patient, after Hidroxiuree treatment for 1 year.

CASE REPORT

A 75-year-old woman who were registered in Medias with a possible chronic lymphoproliferative syndrome, for which has followed treatment with hydroxyurea for about 1 year, presented in 01/25/2011 into Hematology Department of Emergency County Clinical Hospital, Sibiu, accusing asthenia, dizziness and impaired general condition. Past medical history was remarkable for: hypertension, diabetes mellitus type II, CIC.

On admission, physical examination showed the presence of petechiae on the legs and oral mucosa, bruising on the left shoulder (after subcutaneous administration), pale skin, minimal lymphadenopathy (bilateral cervical 1 cm, left axillary <2 cm), splenomegaly (2 cm below rebord). Laboratory

investigations including blood counts: leucocyte-34.500/μl, RBC-3.05 million / μl; hemoglobin-9,7g/dl, hematocrit to 31,9%, platelets 60.000 / ml and the peripheral blood differential count showed: 0.1% myelocytes; 34% segmented neutrophils, 1% eosinophils, 0% basophils, 62% lymphocytes (small lymphocytes, mature-looking. Gumprecht nuclear shadows), 3% monocytes. Coombs test was negative.

Figure no. 1. Peripheral blood smear, May-Grünwald-Giemsa stain (700x). It shows a segmented neutrophil, 2 lymphocytes and 1Gumprecht nuclear shadows.



Peripheral blood immunophenotyping (lymphocyte population 82%, 76% was CD19 + with the following

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phenotype: CD5 +, CD20 +, CD23 +, CD10 negative, negative FCM7) supports the diagnosis of lymphoproliferative B line syndrome.

There was performed bone marrow aspirate and biopsy. Microscopic examination of bone marrow aspirate (MO) revealed hypercellularity, areas with lymphocytic predominance (with a 70% diffuse infiltration by small lymphocytes, adult type, and ~10% blasts) and blast predominantly area between 16-34% (ungranulated round or polygonal blasts, with hyperbasophilic cytoplasm, nucleus showing 1-3 nucleoli). Cytochemical stains on smears of bone marrow shows 24% peroxidase positive blasts and a decreased FAL (leukocyte alkaline phosphatase) score (FAL = 14). Myelogram conclusion: MO- with hypercellularity in appearance chronic lymphoproliferative syndrome (CLL) associated with acute myeloid leukemia.

Figure no. 2. Bone marrow smear, May-Grünwald-Giemsa stain (700x). The area with blast cells predominance, recognized by hyperbasophilic cytoplasm, voluminous nucleus with fine chromatin and 1-3 nucleoli, characterize AML.

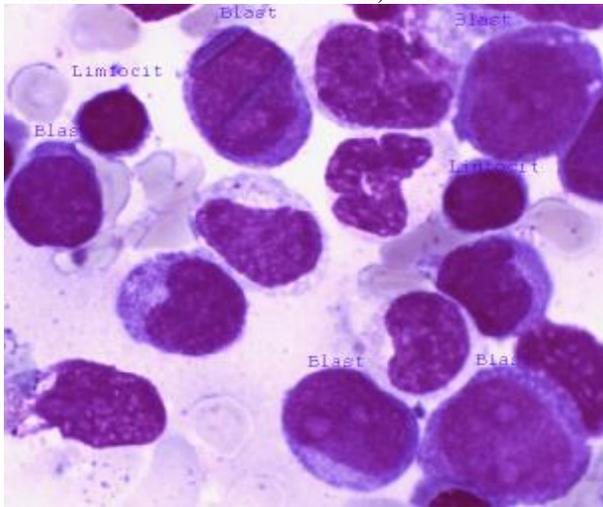
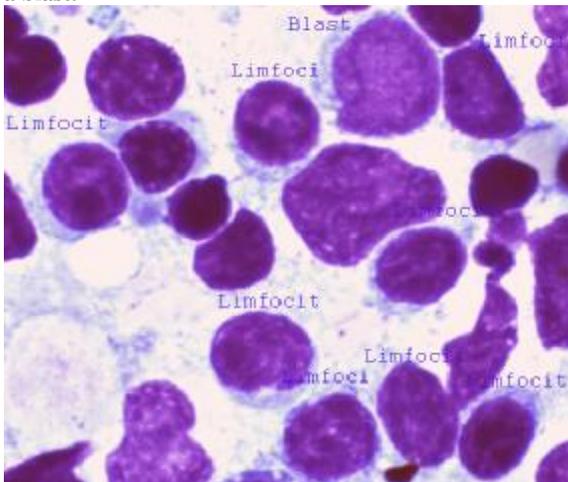


Figure no. 3. Bone marrow smear, May-Grünwald-Giemsa stain (700x). Small, apparently mature lymphocyte predominance area, feature to LLC. It notes the presence of a blast.



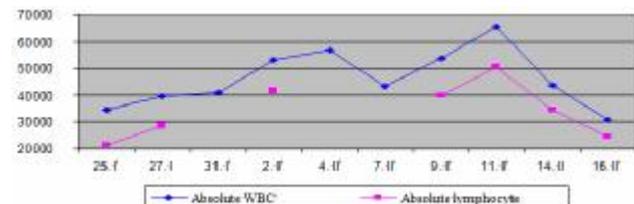
Histopathology revealed hypercellularity, a myeloid: erythroid increased report (10:1) conferring on acute myeloid leukemia appearance and focal-nodular and para-trabecular

infiltration with small atypical B lymphocytes in chronic lymphoproliferative process.

BCR-ABL protein was harvested because of suspicion on exacerbation of chronic myeloproliferative diseases, but because of patient death the analysis was not performed. In contrast, molecular typing reveals that JAK 2 gene was negative, which decreases the possibility of another classic myeloproliferative disease exacerbation, in addition to chronic granulocytic leukemia.

It were administered CYTOSAR in small doses (initially 20mg/zi then 40mg/zi, 12 days), Solumedrol 70mg/zi 15 days, Idarubicin 5mg/zi 2 days, as gastric and anti-emetic protection, repeated red cells transfusions and platelet concentrated with slowly favorably haematological evolving. figure no. 4. CBC counts evolution during hospitalization

Figure no. 4. Leukocytes and lymphocytes number evolution



Bacteriological examination on admission shows *E. coli* in urine, *Enterobacter* in the pharynx and following administration of antibiotic therapy according to antibiogram (AmoxiPlus-1, 2g). During the evolution, the patient develops cough and sputum and identify *E. coli* in the sputum. It amend antibiotics treatment (Ciprinol-100mg/10ml; Lyzolin-1g). Throughout hospitalization followed prophylactic antifungal therapy.

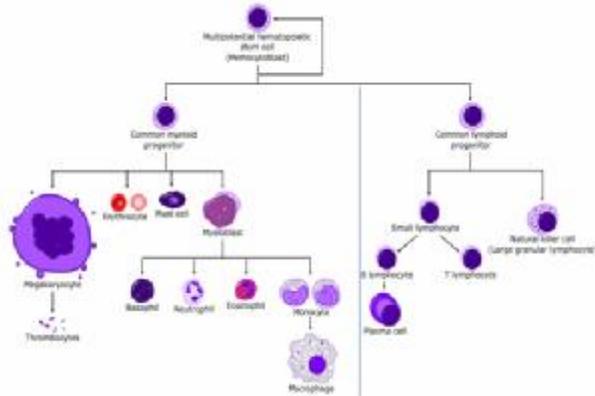
In the 2/18/2011 afternoon, the patient has a seizure cropped after administration of diazepam, then she dies following the brain bleeding.

We have reported a patient who presented with concomitant CLL and AML. Since the admission, the patient had anemia and severe thrombocytopenia, which signifies an advanced CLL disease stage, on discrepancy with minimal splenomegaly and lymphadenopathy. The presence of two populations of leukemic cells was verified by morphology, cytochemical and cellular markers study. Bone marrow contained two distinct cells populations. One cells population had the morphological characteristics of small lymphocytes and flow cytometry proved that were B lymphocytes, the other cells population, are morphologically myeloblasts, peroxidase-positive. Bone marrow examination was surprised by blast cells, because their presence was not betrayed by peripheral blood examination.

There are a variety of possible explanations for the observance of concomitant CLL and AML. In those patients who have received cytotoxic therapy, it have referred to the known leukemogenic effects of alkylating agents and other chemotherapeutic or radiologic treatments. In reports of patients developing acute leukemia following CLL, with or without treatment, frequent reference is made to the high incidence of secondary malignancies due to reduced immune competence (4). The onset of the more aggressive AML may call attention to an indolent, clinically asymptomatic CLL. Many workers propose the concept of a common stem cell defect, perhaps some aberration of a common pluripotent progenitor cell that develops along two different pathways (5). Emergence of different malignant clones for AML and not an evolution of the initial clone of LLC would be another hypothesis.

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Figure no. 5. Haematopoiesis - developing cell lines



Alternatively, there may be some common stimulus or leukemogenic factor that affects more than one cell line (6). It is also possible that multiple primary neoplasms could be due to a genetic susceptibility in certain individuals. A final, although somewhat unlikely hypothesis observes the incidence of concomitant disease to the chance occurrence of two diseases more commonly seen in the elderly (7).

It's hard to believe that lymphocytosis may be reactive to the presence of LAM because the patient had clinical signs of CLL (lymphadenopathy and splenomegaly). However, it is interesting that leukocytosis, respectively lymphocytosis began to reverse after low-dose chemotherapy.

CONCLUSION

The increased risk of developing other malignancies, really represents one of the most severe complications for CLL patients, particularly if heavily treated, as a consequence of the disease and the treatment related immunosuppression. Thus, if such patients show a clinical picture of difficult interpretation, the possibility of a second neoplasia must always be taken into account. It noted the usefulness of flow cytometry in the characterization of two different types of leukemia cell populations.

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