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LETTER TO THE EDITOR

Title:

ACUTE LEUKEMIA IN PATIENTS WITH UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA. A REPORT OF TWO CASES WITH REMARKABLY SIMILAR TIME CLUSTER.

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Running title:

Bilineal leukemia

The association of chronic lymphocytic leukemia (CLL) and acute leukemia (AL) is rare. [1]. In most cases, AL develops after treatment of CLL, thus, previous chemotherapy or radiotherapy is usually considered as a leukemogenic event [2].

We report two cases of acute leukemia occurring in patients with untreated chronic lymphocytic leukemia with remarkably similar time cluster. Those two ALs had the same morphological but distinct immunophenotypic features.

The first patient was a 55-year-old woman. The diagnosis of CLL was made in 1998 when a hematologic work-up was consistent with B-cell CLL, Rai stage 1 [3], and a low tumor burden by TTM classification [4]. Clinical course was stable, and the patient was observed with no therapy. She was admitted to University Hospital "Merkur" in June, 2002 for the evaluation of a newly developed leukocytosis. Laboratory studies revealed a white blood cell (WBC) count of 127 x 10^9/L (myeloblasts 49%, promyelocytes 19%, lymphocytes 18%, monocytes 9%, promonocytes 5%), hemoglobin of 77 g/L, platelet count of 86 x 10^9/L, lactate dehydrogenase of 1013 U/L. The cytological bone marrow smear revealed approximately 10% of atypical blasts type I, approximately 80% blasts type II and III, with numerous granules, somewhere basophile-like, and with some Auer rods (Figure 1.a). Two cell populations were found by flow cytometric analysis; one with phenotypic characteristics of B-cell CLL: CD5/CD19+, CD5/CD23+, monoclonal CD19/kappa+ (with a weak expression of light chains) and blasts population: MPO+, CD2+, CD13+, CD33+, CD117+, HLA D/DR-/+, CD 34-. The results were consistent with mixed cell population within lymphocyte gate (Table 1). Approximately 20% of the cells in the lymphocyte "window" had the immunophenotypic characteristics of B-cell CLL, (CD19/kappa+ versus CD19/lambda+ showing imbalance and supporting clonality) while about 80% of the cells in that gate had characteristics of blasts (MPO+), and most probably corresponded to a subpopulation of smaller blasts that fitted the window. On the contrary, all the cells in the blasts "window" had

the immunophenotypic characteristics of acute leukemia blasts, while the B-cell CLL clone was not present (Table 1). The cytogenetic analysis from the bone marrow sample did not show any chromosomal abnormalities, and the karyotype was: 46, XX [10].

The second patient was a 59-year-old woman. The previous diagnosis of B-CLL was also made in 1998 with a stable clinical course, and was observed without therapy. She referred to University Hospital "Merkur" in May 2002 for the evaluation of a progressive leukocytosis. WBC count was 104,5 x 10^9/L (atypical blasts 45%, promyelocytes 9%, band neutrophiles 1%, lymphocytes 41%, prolymphocytes 3%, and plasma cells 1%), hemoglobin 50,6 g/L, platelet count 24 x 10^9/L. The cytological smear of bone marrow revealed approximately 71% of atypical blasts type I and II, and approximately 25% lymphocytes (Figure 1.b). The flow cytometric analysis demonstrated a population with distinct immunophenotypic features corresponding to B-CLL lymphocytes: CD5/CD19+, CD5/CD23+, monoclonal CD19/kappa+ (with a weak expression of light chains), HLA D/DR+, CD 79α+. The population of blasts co-expressed myeloid lineage markers (MPO+, CD13+, CD33+ CD34+, HLA D/DR+), and B lymphoid lineage (CD19+, CD79α+, TdT+). (Table1) Cytogenetic analysis revealed the following karyotype: 45, XX, inv (3) (q21q26), -7[20]/46XX [5].

Both patients with previously untreated CLL followed by AL were female of a similar age, with a four-year history of clinically indolent CLL without therapy. Both were referred because of the newly developed leukocytosis. The cytological analysis revealed two separate processes: B-CLL and AML, confirming the diagnosis of bilineal leukemia. Both ALs had the same morphological features consistent with AML M2 by FAB classification. The two ALs had different immunophenotypic features. In the first case, the blasts expressed typical myeloid markers, while in the second case, the blast shared myeloid and lymphoid lineage markers. According to Matutes E. and al., this leukemia could have been considered

biphenotypic [5]. Also, the co-expression of CD19 and CD13 antigens supports the diagnosis of the biphenotypic leukemia.

Our results support the other authors' suggestions that the use of full panel of monoclonal antibodies for immunophenotyping is recommended to provide the information about cell heterogeneity, as well as the information of an unexpected second malignancy presence [6, 7]. Although CLL/AML mixed leukemia is considered very rare, it is possible that the routine use of flow cytometric studies nowadays could affect or modify the epidemiological data. It is possible that CLL, which can initially be asymptomatic, was not diagnosed in more cases presenting with acute leukemia then conventionally expected. Newly developed blast clone could have overgrown previously present CLL clone and relatively reduce lymphocyte mass. Therefore, reduced lymphocyte population could be considered as non-neoplastic in routine morphological analysis, or in flow cytometry focused on acute leukemia panel. It is possible that the routine use of flow cytometric studies and broad panel of monoclonal antibodies against mature and immature myeloid and lymphoid markers could reveal higher incidence of diagnosis of CLL/AL concomitant leukemia than is believed today.

The etiology of CLL/AL mixed leukemia is not clear [8, 9]. The development of a second acute leukemia in patients with stable CLL suggests the appearance of a new leukemogenic factor. The common characteristics of our patients were the time cluster and the fact that they had both lived at the border of the war area under air strikes. They have been potentially exposed to various toxic agents associated with the military activity in the region. It is known that depleted uranium (DU) has been used in the Balkan War. The potential radiotoxic properties of DU are the subject of controversy. DU has been identified as an oncogene-inducing factor by in vitro studies, as well as in animal models [10, 11]. On the contrary, the epidemiological studies among the Gulf War veterans and UN soldiers did not confirm its cancerogenic potential [12, 13]. Although the hematopoetic system is very sensitive to

radiation exposure, the conducted studies have not found an increased incidence of hematologic malignancies among the children or soldiers potentially exposed to DU [12, 14]. Our patients suffering from a rare leukemia shared a few important epidemiological characteristics, among them the possible exposure to DU. We hope that this fact could add to recent debates on the possible role of depleted uranium (DU) in leukemogenesis.

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Table 1. Immunophenotypic features of bone marrow lymphocytes and blast population of patients

	Patient 1		**Patient 2**	
	Cellular population (%)			
cellular antigen	lymphocytes (12 %)	blasts (80 %)	lymphocytes (30 %)	blasts (53 %)
CD5	45.3	3.0	34.8	18.6
CD19	19.5	1.0	83.9	56.9
CD23	52.4	4.4	68.4	11.0
TdT	0.1	0.3	5.6	19.7
CD13	50.6	86.0	22.4	60.0
CD33	32.6	85.4	25.6	35.8
CD5/CD23	36.1	1.4	26.8	7.2
KAPPA+ CD19+ «weak»	18.9	0.3	73.7	12.2
LAMBDA+ CD19+ «weak»	0.6	0.1	1.9	2.1
CD5/CD19	34.4	0.6	31.3	14.6
HLA D/DR	49.3	13.9	91.3	89.4
CD34	0.8	3.0	5.3	71.7
MPO	78.5	95.8	4.2	20.3
CD 79α	18.9	0.4	59.5	23.3
CD117	3.4	38.9	-	-
CD 15	2.7	16.4	-	-
CD19/CD13	-	-	2.0	33.7
CD19/CD33	-	-	21.6	18.7

Legends to figure:

Figure 1. The cytological smear of bone marrow (May Grünwald Giemsa, 1000x) 1.a: patient 1; 1.b: patient 2.