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Follicular lymphoma with leukemic phase at diagnosis: A series of seven cases and review of the literature

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ABSTRACT

Follicular lymphoma (FL) is a prevalent type of non-Hodgkin lymphoma in the United States and Europe. Although, FL typically presents with nodal involvement, extranodal sites are less common, and leukemic phase at diagnosis is rare. There is mounting evidence that leukemic presentation portends a worse prognosis in patients with FL. We describe 7 patients with a pathological diagnosis of FL who presented with a leukemic phase. We compared our cases with 24 additional cases reported in the literature. Based on our results, patients who present with leukemic FL tend to have higher risk disease. Leukemic FL also seems to be associated with a worse prognosis; however, larger studies are needed to confirm our findings. A discrepancy with previously reported cases of FL in leukemic phase raises the possibility of differences attributable to geographic regions.

1. Introduction

Follicular lymphoma (FL) is a non-Hodgkin lymphoma (NHL) of follicle center B-cells that grow in a follicular pattern. FL is the second most frequent type of B-cell lymphoma seen in United States (US) and Europe, and accounts for approximately 25–30% of all the cases of NHL in adults [1]. However, FL is less common in Asia and Latin America. In a comparative study, the incidence of FL was 8% in Hong Kong compared to 32% in the Omaha, Nebraska and 28% in London, United Kingdom [2]. In addition, a recent report showed an incidence of 17% in Latin American countries, compared to 34% in North America [3].

FL tends to present with generalized lymph node involvement at diagnosis and is usually asymptomatic or oligosymptomatic, although it can also present with B symptoms, such as fever, drenching night sweats and unintentional weight loss, and autoimmune cytopenias. Follicular lymphoma often involves spleen and bone marrow, and rare circulating neoplastic lymphocytes can be found, but a leukemic phase of FL at the time of diagnosis is rare [4]. In a previous study, there was an indication that although FL is rare in Asia, the rates of leukemic presentation of FL might be higher than in the US and Europe [5].

We present the clinical, pathological and cytogenetic characteristics of seven cases of FL who presented with a leukemic phase at diagnosis, and compare with similar cases reported in the literature.

2. Patients and methods

Medical records from three institutions (Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru; Rhode Island Hospital in Providence, RI, USA, and the Moffitt Cancer Center in Tampa, FL, USA) were reviewed between 2008 and 2010 looking for patients with a pathological diagnosis of FL, an absolute lymphocyte count > 4000/μL and evidence of FL cells in the peripheral blood identified morphologically. The lymphocyte count cutoff was selected based on the current definition of lymphocytosis in adults [6]. Clinical data from all cases were collected from retrospective chart review, and included age, sex, race, absolute lymphocyte count at presentation, FL International Prognostic Index (FLIPI) score, therapeutic regimens received, outcome and overall survival (OS). Cases were reviewed by at least two hematopathologists at the respective center of diagnosis. Cases were diagnosed following criteria defined by the World Health Organization. Routinely stained slides of specimens derived from lymph nodes, bone marrow and Wright Giemsa stained slides of peripheral blood or bone marrow aspirate smears were reviewed. Diagnoses were all confirmed through flow cytometric immunophenotyping and/or through immunohistochemical studies for expression of CD20, bcl2, bcl6 and CD10 as well as proliferation index by Ki-67 expression. Classic cytogenetic analyses and fluorescence *in situ* hybridization (FISH) studies using probes for *BCL2* rearrangements were used in a subset of cases.

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Table 1
Clinical characteristics of 7 patients with leukemic follicular lymphoma.

Case	Age	Sex	Race	Stage	Tumors or LAD?	Lymphocyte count (cells/μL)	Therapy	Survival (months)	Outcome
1	39	M	White	IVB	Yes	36,600	R-bendamustine × 1 R-cyclophosphamide × 5 Maintenance R	20	AWD
2	60	M	White	IVB	Yes	226,950	R-CVP × 6 R-fludarabine × 6 R-bendamustine × 9	33	Dead
3	56	M	Hispanic	IVB	Yes	5000	R-CHOP × 6 R-ICE R-GEMOX	17	Dead
4	76	M	Hispanic	IVB	Yes	11,430	R-CHOP R-CHOP	3	Dead
5	40	M	Hispanic	IVB	Yes	51,840	R-ICE R-ESHAP	15	AWD
6	61	M	White	IVB	No	200,000	R-CHOP ASCT	34	AWOD
7	64	M	Hispanic	IVA	Yes	37,000	R-CHOP	4	AWD

M: male; LAD: lymphadenopathy; CVP: cyclophosphamide, vincristine, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; ICE: ifosfamide, carboplatin, etoposide; GEMOX: gemcitabine, oxaliplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin; ASCT: autologous stem cell transplant; AWD: alive with disease; AWOD: alive without evidence of disease.

For the literature review, a literature search was performed independently by two authors (BEB, JJC) using Pubmed from January 1990 through December 2011 looking for case reports and series providing data on patients with FL with a leukemic phase. Inclusion criteria were age > 18 years, pathological diagnosis of FL and absolute lymphocyte count > 4000/μL. Patients with primary cutaneous FL were excluded. Two authors independently gathered pertinent clinical and pathological data (BEB, JJC).

Characteristics will be presented using descriptive statistics. Overall survival (OS) was calculated as the time elapsed from diagnosis to death or last follow-up. All graphs and calculations were obtained using Medcalc (Mariakereke, Belgium).

3. Results

We identified seven cases of leukemic FL in the 3-year period. The median age at presentation was 57 years (range: 39–76 years). All patients were men. Six patients (86%) presented with concurrent lymphadenopathy and one case (14%) had pure leukemic FL. The median absolute lymphocyte count was 81,260/μL (range 5000–226,950/μL). All cases presented with high-risk FLIPI score; 4 cases (67%) had a score of 4 and 2 cases (33%) had a score of 5. All cases were treated with rituximab-containing therapies. Three patients (43%) died, 2 (29%) are alive with disease and 2 (29%) are alive without disease. Clinical characteristics are shown in Table 1. Pathological characteristics are shown in Table 2. A typical presentation of a patient with lymph node, bone marrow and peripheral blood involvement is shown in Figure 1.

3.1. Literature review

We identified 9 studies [5,7–14] reporting data on 24 patients with leukemic FL, that coupled with our cases, total 31 patients. The median age at presentation was 60 years (range: 30–89 years). There was a male predominance (ratio 2.4:1). The median WBC count was 37,000/μL (range: 4800–560,000/μL). A summary of selected clinical and laboratory findings are shown in Table 3.

Table 3
Characteristics of 31 patients with leukemic follicular lymphoma (7 from the present study and 24 from the literature).

Characteristic	Number	Percentage
Age > 60 years	15/31	48.4%
Male gender	22/31	71.0%
Geographic region		
Europe	15/31	48.4%
America	8/31	25.8%
Asia	8/31	25.8%
Nodal or extranodal involvement	21/26	80.8%
Leukemic phase only	5/26	19.2%
B symptoms	6/15	40.0%
FLIPI		
Low (0–2 points)	8/17	47.1%
High (3–5 points)	9/17	52.9%
WBC count > 100,000/μL	8/27	29.6%
CD10 expression	27/29	93.1%
CD20 expression	31/31	100%
BCL2/IgH gene rearrangement[a]	19/22	86.4%
Therapy		
R-chemotherapy	17/24	70.8%
Chemotherapy	6/24	25.0%
None	1/24	4.2
Outcome		
Alive	22/26	84.6%
Dead	4/26	15.4%

FLIPI: follicular lymphoma international prognostic index; WBC: white blood cell; IgH: immunoglobulin heavy chain.
[a] By FISH or PCR.

4. Discussion

Follicular lymphoma is the second most common type of lymphoma in United States and Europe, accounting for approximately 20% of all NHL the cases [1]. However, the distribution of FL in other regions of the world appears different. Recent studies have shown

Table 2
Pathologic, immunophenotypic, and cytogenetic characteristics of 7 patients with leukemic follicular lymphoma.

Case	Grade	CD20	CD10	BCL2	BCL6	KI67	Cytogenetics	FISH t(14;18)-*BCL2-IgH*
1	2	+	+	+	+	ND	inv(3)(q12q27), del(10)(q24q26), t(14;18)(q32;q21)	ND
2	1	+	+	+	ND	ND	4p+, 5q-, 6q+, 14q+, 18−, 22p+	+
3	2	+	+	+	+	40%	ND	+
4	1	+	+	+	+	20%	ND	+
5	1	+	+	+	+	60%	ND	ND
6	1	+	+	+	+	20%	ND	+
7	3a	+	+	+	+	20%	ND	ND

ND: not done; FISH: fluorescence *in situ* hybridization.

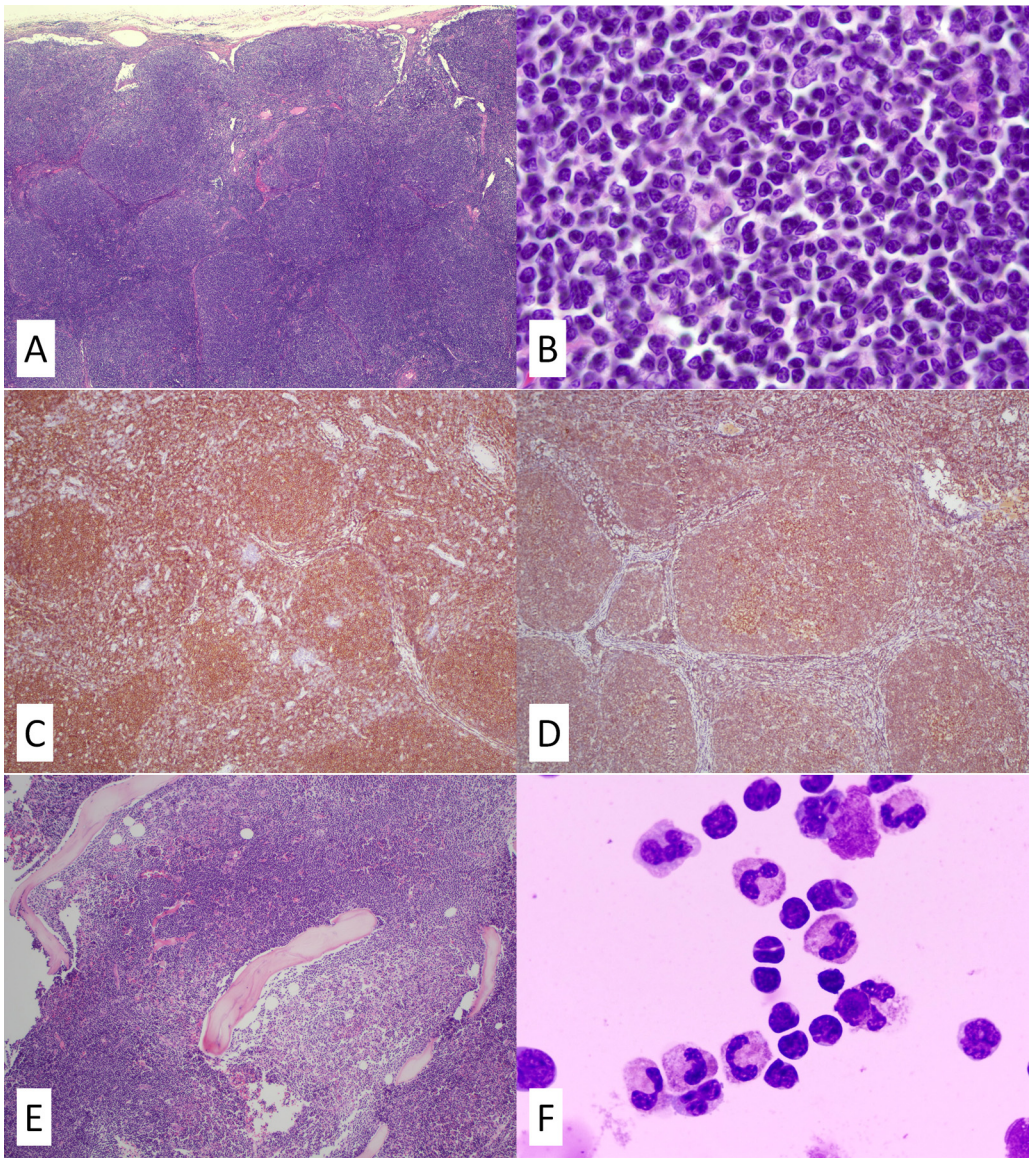

Fig. 1. (A) Lymph node. Low magnification of a lymph node with complete effacement of the architecture due to numerous neoplastic follicles with ill-defined outlines (40×); (B) lymph node. High magnification of a neoplastic follicle in a lymph node shows that most lymphocytes are small with irregular nuclear contours, consistent with small centrocytes (1000×); (C) lymph node. Immunohistochemistry for the germinal center cell marker CD10 shows that most lymphocytes are positive (100×); (D) lymph node. Immunohistochemistry for the germinal center cell marker BCL6 shows that most lymphocytes are positive (100×); (E) bone marrow is characterized by a paratrabecular aggregate of lymphocytes. A fragment of bone trabecula is noted in the center of the field, where the top side is occupied by a large lymphoid aggregate, while the lower side shows residual hematopoiesis (100×); (F) peripheral blood. This high magnification shows numerous small lymphocytes with hyperchromatic nuclei and markedly irregular nuclear contours (1000×).

that the proportion of FL in Asian and Latin American countries varies between 10 and 15% [3,15,16]. Thus, some researchers have suggested that the clinical presentation of FL would vary according to race and/or ethnicity in different geographic areas.

Although FL is a lymph node-based lymphoma, it commonly involves extranodal sites as part of disseminated disease. However primary FL of extranodal sites is uncommon [17–20], and rare cases of FL may evolve to or present with a leukemic phase. In the leukemic phase of FL, a variable proportion of the peripheral blood lymphocytes exhibit a distinct appearance that has been previously described as "notched-nucleus cell" [21]. The lymphocyte count varies from moderately to markedly elevated; and in the current study, it ranged between 5000 and >500,000 cells/μL. Small numbers of circulating FL cells are commonly identified in patients with FL, either morphologically or immunophenotypically, and apparently are not associated with clinical outcomes [22]. However, absolute neoplastic lymphocytosis > 4000/μL in FL is uncommon and probably of clinical significance. The incidence of absolute neoplastic lymphocytosis in FL is not clearly defined, but some studies suggest that 4–23% of FL cases associate with lymphocytosis. Chubachi et al. from Japan reported that 45% of patients with FL present with leukemic phase [5].

Published cases of FL with leukemic phase usually had concomitant FL involving other areas (*i.e.* lymph nodes), but a subset did not have concurrent nodal or extranodal involvement. Al-Nawakil et al. described ten patients with FL and leukemic phase at diagnosis [7]. Six of them had concomitant lymph node involvement, while 4 patients had leukemic phase only, and these latter cases had a more indolent clinical course. In our report, the only patient that presented with pure leukemic FL is alive and in a complete remission after receiving chemo-immunotherapy followed by autologous stem cell transplantation. All the other patients died or are alive with evidence of disease.

Given the overall indolent course of FL at presentation, it is difficult to determine the aggressiveness of leukemic presentations and its potential prognostic value. There are mounting data, however, associating a leukemic presentation with an adverse outcome in patients with FL. In a recent report from Japan, Kodaira and colleagues showed that FL with leukemic presentation accounted for 21% of patients, and portends a worse progression-free survival (PFS) in patients with FL treated with chemo-immunotherapy [23]. More recently, Sarkozy and colleagues presented in abstract form a study in which leukemic phase occurs in 7% of patients with FL and it associates with a shorter PFS, independent of the FL international prognostic index (FLIPI) score and beta-2-microglobulin levels [24]. Therefore, leukemic FL might be considered to have a distinct biological behavior and could influence the prognosis of these patients.

Currently, the FLIPI score is arguably the most commonly used prognostic tool for patients with FL [25], and has shown to be applicable across a range of clinical settings [26,27]. In the seminal FLIPI study, patients with a leukemic component were categorized as having extranodal disease, and were not analyzed separately. More recently, the FLIPI-2 score system has been developed [28], which specifically considers bone marrow involvement as an adverse factor. However, leukemic presentation was not evaluated as a prognostic factor.

The use of immunotherapy such as anti-CD20 monoclonal antibodies has resulted in better response and survival rates in patients with FL [29,30]. However, based on the available data, patients with leukemic phase still have an unsatisfactory response. Several unanswered questions remain: Should leukemic FL be diagnosed based on the solely presence of circulating FL cells without considering absolute lymphocyte counts? Or should a diagnosis of leukemic FL be rendered based on an actual number of circulating FL cells? Should all patients with a clinical diagnosis of FL undergo morphologic or flow cytometry immunophenotype to detect a leukemic component? What is the best regimen to treat patients with leukemic FL? Should we recur to autologous stem cell transplant in specific cases? Future prospective studies are necessary to evaluate the role of leukemic phase in the prognosis of FL, and to improve our current therapies in these patients.

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Conflict of interest

The authors have no conflict of interest to disclose.

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The authors are the sole responsible for the design and interpretation of the study, and the manuscript writing.

Contributions. BEB and JJC conceptualized and designed the study. Acquisition, analysis and interpretation of data were done by BEB, JJC, PQ, DM, JCA, RNM, GL, BDS and EMS. The manuscript was written by BEB, RNM and JJC. Final approval of the manuscript was given by BEB, JJC, PQ, DM, JCA, RNM, GL, BDS and EMS.

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