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Follicular lymphoma with leukemic phase at diagnosis: An aggressive disease. Report of seven cases and review of the literature

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Abstract

Follicular lymphoma (FL) is a prevalent subtype of non-Hodgkin lymphoma in the United States and Europe. Although, FL typically presents with nodal involvement, extranodal involvement has been rarely described. 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 component. We also present data on patients with leukemic FL reported in the literature. Based on our results, leukemic FL seems to be associated with a worse prognosis. However, larger prospective studies are needed to confirm our findings.

Keywords

Follicular lymphoma; leukemic phase

Introduction

Follicular lymphoma (FL) is a lymphoproliferative neoplasm of follicle center B-cells, which have at least a partially identifiable 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 non-Hodgkin lymphomas (NHL) among adults [1]; however, FL is less common in Asia and Latin America. In a comparative study, the incidence of FL in Hong Kong was 8% compared to 32% in the Omaha, NE and 28% in

London, UK [2]. Similarly, a recent report shows an incidence of 17% in Latin American countries, which was lower than the 34% seen 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. FL often involves spleen and bone marrow, 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 a brief review of the literature.

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 and evidence of FL cells in the peripheral blood identified by flow cytometry. 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. All cases were then evaluated by a third hematopathologist (RNM). Pathological characteristics evaluated were grade, expression of CD20, bcl2, bcl6 and CD10, and cytogenetic and fluorescent *in situ* hybridization (FISH) studies looking for t(14;18).

For the literature review, a literature search was performed independently by two authors (BGB, JJC) using Pubmed from January 1990 through December 2011 looking for case reports and series providing data on patients with FL with a leukemic component. Inclusion criteria were age <18 years, pathological diagnosis of FL and absolute lymphocyte count <4,000/uL. Patients with primary cutaneous FL were excluded. Two authors independently gathered pertinent clinical and pathological data (BGB, JJC).

Characteristics will be presented using descriptive statistics. 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).

Results

Clinical characteristics

We identified seven cases of leukemic FL. The median age at presentation was 57 years (range: 39–76 years). All cases were men. Six cases (86%) presented with concurrent lymphadenopathy and one case (14%) had pure leukemic FL. The median absolute lymphocyte count was 81,260/uL (range 5,000–226,950/uL). 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%) have died, 2

(29%) are alive with disease and 2 (29%) are alive without disease. Clinical characteristics are shown in Table 1.

Pathological characteristics

Pathological characteristics are shown in Table 2.

Literature review

We identified 9 studies [5–13] reporting data on 24 cases with leukemic FL for a total of 31 cases, including ours. 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/uL (range: 4,800–560,000/uL). Complete characteristics are shown in Table 3.

Discussion

FL is the second most common type of lymphoma in the 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 that the proportion of FL in Asian and Latin American countries varies between 10–15% [3, 14, 15]. Based on this, it is also likely that the clinical presentation of FL would vary according to race and/or ethnicity. However, additional research is needed to clarify this point.

Although the presentation of FL is typically nodal, cases of extranodal presentation have been reported [16–19]. FL may evolve to or present with a leukemic component. In the leukemic form of FL, a variable proportion of the peripheral blood lymphocytes exhibit a distinct appearance that has been previously described as "notched-nucleus cell" [20]. The lymphocyte count varies from moderately to severely elevated; in the present study, it ranged between 5,000 and <500,000 cells/mm³. The true incidence of such an event is unknown but varies in different series, ranging between 4–23%. A Japanese group reported leukemic phase at presentation in FL patients as high as 45% [5]. However, circulating FL cells can also be identified in patients without lymphocytosis [21], as FL cells are frequently detected in peripheral blood by molecular methods (11a).

Published studies described FL with leukemic phase that could occur in conjunction with other areas of disease (i.e. lymph nodes) or without concurrent tumors or lymphadenopathy. Al-Nawakil et al. described ten patients with FL and leukemic phase at diagnosis [6]. Six of them had concomitant lymph node involvement and four patients had pure FL cell leukemia, which was associated with a more indolent clinical outcome. In our report, the only patient that presented with pure leukemic FL is alive and in a complete remission after receiving chemoimmunotherapy followed by autologous stem cell transplantation. All the other patients have died or are alive with evidence of disease.

Given the indolent nature of FL, it is difficult to establish the true 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 a leukemic presentation, which accounted for 21% of the cases, portends a worse progression-free survival (PFS) in

patients with FL treated with chemoimmunotherapy [22]. More recently, Sarkozy and colleagues identified a leukemic phase in 7% of patients with FL, which was associated with a shorter PFS, independent of the FL international prognostic index (FLIPI) score and beta-2-microglobulin levels [23]. Of note, both studies have been presented solely in abstract form. 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 in patients with FL [24], and has shown to be applicable across a range of clinical settings [25, 26]. In such study, patients with a leukemic component were categorized as having extranodal disease, and were not analyzed separately. More recently, the FLIPI-2 score has been developed [27], which specifically considers bone marrow involvement as an adverse factor. However, leukemic presentation was not evaluated as a prognostic factor.

The introduction of anti-CD20 monoclonal antibodies has resulted in better response and survival rates in patients with FL [28, 29]. However, based on the available data, patients with leukemic phase still have an unsatisfactory prognosis. Several unanswered questions remain: Should leukemic FL be diagnosed based on the solely presence of circulating FL cells? 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 flow cytometry to detect a leukemic component? What is the best regimen to treat patients with leukemic FL? Should we recur to ASCT 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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Table 1

Clinical characteristics of 7 patients with leukemic follicular lymphoma

Case	Age	Sex	Race	Stage	Tumors or LAD?	Lymphocyte count (cells/mm ³)	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	5,000	R-CHOP×6 R-ICE R-GEMOX	17	Dead
4	76	M	Hispanic	IVB	Yes	11,430	R-CHOP	3	Dead
5	40	M	Hispanic	IVB	Yes	51,840	R-CHOP 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

Table 2

Pathological characteristics of 7 patients with leukemic follicular lymphoma

Case	Grade	CD20	CD10	BCL2	BCL6	KI67	Cytogenetics	FISH t(14;18)
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: fluorescent *in situ* hybridization

Table 3

Characteristics of 31 patients with leukemic follicular lymphoma from the literature

Characteristic	Number	Percentage
Age >60 years	15/31	48.4%
Male sex	22/31	71.0%
Region		
Europe	15/31	48.4%
America	8/31	25.8%
Asia	8/31	25.8%
Concurrent tumors	21/26	80.8%
Blood 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/uL	8/27	29.6%
CD10 expression	27/29	93.1%
CD20 expression	31/31	100%
BCL2/IgH gene rearrangement *	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

* By FISH or PCR