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Journal

ISSN

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Publication Date

DOI

Copyright Information

Peer reviewed

Original contribution

Benign lymphoid aggregates in the bone marrow: distribution patterns of B and T lymphocytes

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Summary Benign lymphoid aggregates are seen in only a minority of bone marrow specimens, but their distinction from non–Hodgkin lymphoma, particularly B-cell lymphomas, can represent a diagnostic challenge. Although criteria have been proposed to help distinguish between benign and malignant aggregates, a detailed description of the distribution patterns of B and T lymphocytes within benign lymphoid aggregates has not been investigated. One hundred thirty-seven cases of bone marrow specimens containing benign aggregates were studied with a panel of immunostains. A subset of these cases was also examined for immunoglobulin gene rearrangements by polymerase chain reaction. The aggregates were categorized based on size, location (paratrabecular or random), presence of infiltrating edges, and distribution of lymphoid cell populations. In addition, we examined 40 cases of bone marrow biopsies with documented malignant lymphoid aggregates for comparison purposes. We report that the distribution of B and T lymphocytes within lymphoid aggregates may serve as a useful criterion to aid in the separation between benign and malignant aggregates. When aggregates exhibit a predominance of T cells, consist of a central core of T cells surrounded by a rim of B cells, or have a mixed distribution of B and T cells, they are more likely to be benign. On the other hand, an increased likelihood of malignancy occurs when aggregates exhibit a predominance of B cells or consist of a central core of B cells surrounded by a rim of T cells (excluding germinal center formation), and assessing other features worrisome of malignancy (large aggregate size, presence of infiltrative edges, cellular atypia, and paratrabecular location, among others) is warranted.
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1. Introduction

Lymphoid aggregates, whether benign or malignant, are a relatively uncommon finding in bone marrow biopsy specimens. In many cases, identifying the neoplastic nature of the aggregates by morphology can be easily achieved; however, in instances when multiple aggregates are identified with no documented history of lymphoma, such distinction may be difficult to achieve with certainty. Morphologic and immunophenotypic criteria have been proposed to help distinguish between benign and malignant lymphoid aggregates. Benign lymphoid aggregates (BLAs) are typically small (<600 μm), have distinct borders without interstitial spillage of lymphoid cells, and have a nonparatrabecular location [1-3]. On the other hand, variation in the size of the

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lymphoid aggregates, paratrabecular location, inclusion of fat cells, and location surrounding large sinuses are all features that have been reported to be worrisome for malignancy [2,3].

BLAs have been reported to be associated with a variety of conditions including aging, autoimmune diseases, inflammatory conditions, and infectious disorders [1]. They have also been reported to be commonly identified in patients with chronic myeloproliferative neoplasms, especially primary myelofibrosis [4] and, rarely, in association with myelodysplastic syndromes [5]. Moreover, an increased incidence of benign aggregates in lymphoma patients who have been treated with rituximab has recently been reported [6,7]. These aggregates are often found in postchemotherapy bone marrow specimens and can mimic residual lymphoma [7,8]. BLAs have also been rarely reported in association with tobacco use and certain medications [9,10].

The use of immunohistochemical stains to assist in distinguishing between benign and malignant aggregates has been investigated before, although in a relatively limited fashion [2,9,11]. Previous studies have focused on conventional stains but have only used a limited antibody panel, or have only investigated the distinction between BLAs and follicular lymphoma (FL) [8,12,13]. Moreover, no detailed description of the distribution of B and T lymphocytes within BLA and the significance of that distribution has been reported. In this study, we examined BLA and associated clinical conditions; however, our primary goal was to study the distribution of lymphocyte populations within the aggregates and to determine if distribution patterns can aid in the distinction of neoplastic from benign aggregates.

2. Materials and methods

A search of the pathology files at the University of California Irvine Medical Center from 1993 to 2011 identified 151 bone marrow biopsy cases with reported BLA. All cases were formalin fixed and included both the trephine and clot biopsy sections. Of these, 14 cases showed loss of the aggregates in deeper sections. On the remaining 137 cases, clinical data were examined for correlation with the presence of benign aggregates. The variables included age, sex, race, history of infectious diseases, and immunologic disorders. Forty bone marrow biopsy specimens with malignant lymphoid aggregates were selected for comparison purposes. These included 9 cases of chronic lymphocytic leukemia (CLL), 10 cases of FL, 4 cases of lymphoplasmacytic lymphoma (LPL), 3 cases of mantle cell lymphoma (MCL), 7 cases of marginal zone lymphoma (MZL), 6 cases of diffuse large B-cell lymphoma (DLBCL) with nodular aggregates, and 1 case of peripheral T-cell lymphoma (PTCL) with nodular aggregates. Follow-up information was available on 61 patients (45%), with a variable follow-up duration that consisted of 17 cases (≤1 year), 23 cases (1-3 years), 13 cases (3-5 years), and 8 cases (>5 years). To investigate the possible association of age with lymphocyte

distribution patterns in lymphoid aggregates, we divided the patients into age groups of less than 25, 25 to 44, 45 to 64, and 65 years and above.

A panel of immunostains that included CD3 (polyclonal 1:200; DAKO, Carpinteria, CA) and CD20 (L26, 1:400; DAKO) was performed on all cases. In addition, bcl-6 (PG-B6p, 1:20; DAKO), CD23 (MHM6, 1:200; DAKO), PD-1 (MRQ-22, 1:100; Cell Marque, Rocklin, CA), and Ki-67 (MIB-1, 1:1000; DAKO) were performed on most cases (88 cases). These stains could not be performed on all cases because the aggregates significantly decreased in size or were lost in deeper sections after performing the CD3 and CD20 stains. CD23 and bcl-6 were used to identify germinal center–associated cells including follicular dendritic cells, centrocytes, and centroblasts. Additional immunostains were performed on select cases with features suspicious of malignancy. These included the following: CD79a (JCB117, 1:200; DAKO), CD43 (DF-T1, 1:400; DAKO), Kappa (polyclonal, 1:50 000; DAKO), Lambda (polyclonal, 1:40 000; DAKO), CD10 (56C6, 1:150; Leica Microsystems, Buffalo Grove, IL), and bcl-2 (124, 1:200; DAKO). We analyzed the staining pattern of the BLA with regard to the relative distribution pattern of the lymphoid populations. In addition, 20 BLA cases with different distribution patterns and corresponding flow cytometry and/or immunohistochemistry data were identified, and B-cell receptor gene rearrangement studies were performed. We were successful in obtaining data in 12 of the 20 cases.

For the B-cell gene rearrangement studies, aggregates were identified on hematoxylin and eosin–stained sections obtained from formalin-fixed clot biopsy sections and macrodissected before DNA extraction. Polymerase chain

Table 1 Immunostaining patterns of BLAs and selected clinical features associated with BLAs

	Total cases	T-cell patterns (mostly T cells, mixed B and T cells, or a central core of T cells)	B-cell patterns [a] (mostly B cells or a central core of B cells)
Total cases	137	102 (74%)	>35 (26%)
Age (y)			
<25	3	>2 (67%)	>1 (33%)
25-44	33	>27 (82%)	>6 (18%)
45-64	49	>37 (76%)	>12 (24%)
≥65	52	>35 (67%)	>17 (33%)
Male	65	>43 (66%)	>18 (34%)
Female	72	>53 (74%)	>16 (26%)
Tobacco	46	>36 (78%)	>10 (22%)
Alcohol	18	>13 (72%)	>5 (28%)
Chronic anemia	25	>20 (80%)	>5 (20%)
Immunologic disorders	24	>16 (67%)	>8 (33%)
HIV	8	>6 (75%)	>2 (25%)

[a] Including cases with germinal center formation.

Table 2 Comparison of the different morphologic features of bone marrow aggregates

	Total cases	T-cell patterns (mostly T cells, mixed B and T cells, or a central core of T cells)		B-cell patterns [a] (mostly B cells or a central core of B cells)		Malignant cases selected for comparison purposes [c]
		All cases	Cases proven to be malignant upon follow-up [b]	All cases	Cases proven to be malignant upon follow-up [b]	
Total cases	137	102	>3 (3%)	35	>5 (14%)	40
Presence of evident infiltrative edges	5	3	>3 (100%)	2	>2 (100%)	37 (93%)
Paratrabecular location	9	3	>1 (33%)	6	>3 (50%)	20 (50%)
Presence of evident cell atypia	1	1	>1 (100%)	0	>0 (0%)	22 (55%)
Size of aggregates: small to medium	100	85	>3 (4%)	15	>1 (7%)	10 (25%)
Size of aggregates: large	37	17	>0 (0%)	20	>4 (20%)	30 (75%)

[a] Including cases with germinal center formation.
[b] All cases were diagnosed as malignant within 1 year of initial bone marrow biopsy, and subsequent follow-up period ranged between 2 and 4 years.
[c] Including cases with a diagnosis of MCL, CLL, FL, DLBCL, LPL, MZL, and PTCL with nodular marrow involvement.

reaction (PCR) detection of B-cell clonality was restricted to the use of V_H FRII and FRIII forward primers and a J_H consensus reverse primer to amplify across the highly variable CDRII and CDRIII regions. PCR products from FRII-J_H and FRIII-J_H combinations were analyzed on polyacrylamide gel electrophoresis gels to detect monoclonal bands in the rages of 240 to 280 and 70 to 130 base pairs, respectively. IFNαR2 primers amplifying a 420-base-pair product were used as an internal control.

3. Results

3.1. Clinical features

Table 1 presents the clinical features of the patients and immunostaining patterns of the lymphoid aggregates seen in these cases. The age of the patients ranged from 12 to 99 years, with a mean age of 57 years. The incidence of BLA increased with advancing age. Many of the cases were associated with infectious disorders including HIV (8 cases), hepatitis B or C (12 cases), mycobacteriosis (2 cases) or miscellaneous fungal or bacterial infections (9 cases). Twenty-four patients with BLA had a proven diagnosis of an associated immune-mediated disorder or an inflammatory condition. A diagnosis of primary immune thrombocytopenia, made in 6 patients, was the most common.

3.2. Morphologic features

The lymphoid aggregates were categorized based on their size, location in the marrow space (paratrabecular or random distribution), and distribution of lymphocyte populations within the aggregates (Table 2). To classify the B- and T-cell distribution in the lymphoid aggregates, we defined 5 patterns using CD3 and CD20 immunostains. Pattern 1 consisted of lymphoid aggregates predominantly made up of T cells. In pattern 2, the lymphoid aggregates were composed of a mixture of B and T cells, haphazardly arranged. Pattern 3 demonstrated a core of T cells, surrounded by B cells. In pattern 4, a core of B cells was surrounded by T cells. Pattern 5 was predominantly composed of B cells (Table 1 and Fig.).

The BLAs in all age groups showed a predominance of T cells or a mixed haphazard pattern (patterns 1-3), with a minority of cases showing a B-cell pattern (patterns 4 and 5). In the age group less than 25 years, 2 of 3 cases contained aggregates with a T-cell pattern (patterns 1-3). In the 25- to 44-year age group, 82% (27/33) of the cases exhibited a T-cell pattern. In the 45- to 64-year age group, 76% (37/49) of the cases showed a T-cell pattern. In the age group of 65 years and above, 67% (35/52) of the cases had a predominant T-cell pattern. Overall, of the 137 cases studied, 102 cases (74%) had a T-cell–dominant pattern, and 35 (26%) had a B-cell–dominant pattern. Fourteen of these 137 cases contained more than 1 aggregate displaying a mixture of different patterns. Nine of the 14 cases displayed discrepant patterns, and in such situations, the case was labeled based on the dominant overall pattern. For statistical purposes, the proportions of T-cell patterns were evaluated in both the reactive and the malignant groups. Reactive cases found to be malignant upon follow-up were considered in the malignant group for analysis purposes. There were 129 remaining reactive cases, 99

Fig.   The composite picture shows the distribution patterns of CD3-positive T cells and CD20-positive B cells in bone marrow lymphoid aggregates. Pattern 1, predominantly T cells; pattern 2, mixed B and T cells, haphazardly arranged; pattern 3, mixed with a core of T cells; pattern 4, mixed with a core of B cells; and pattern 5, predominantly B cells.
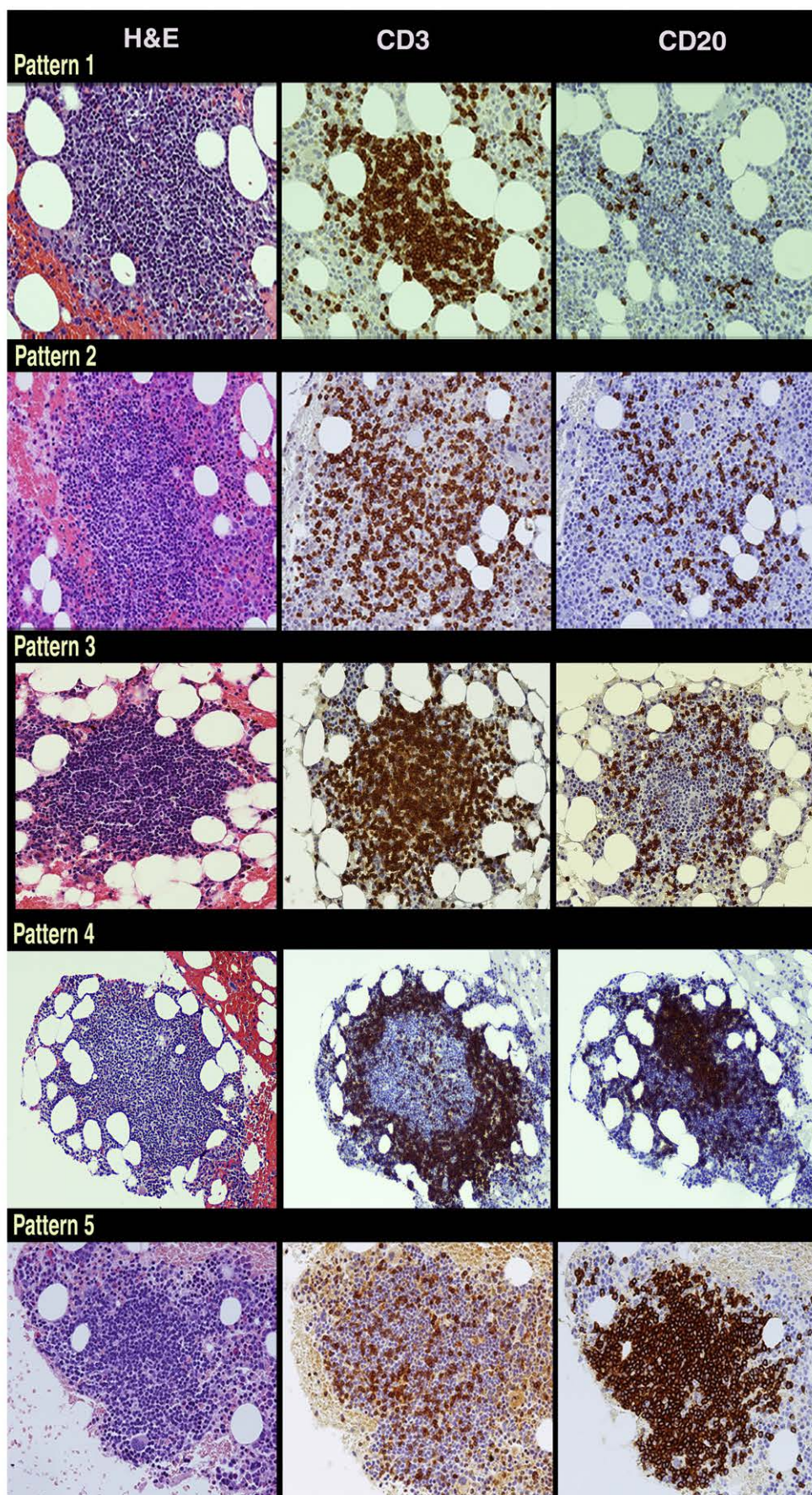
Table 3 Features of cases with B-cell gene rearrangement studies by PCR

No.	Age (y)	Sex	Pattern	PCR results	Flow cytometry results	Clinical history	Diagnosis	Comments
1	27	F	1	Inconclusive	No evidence of a monoclonal B-cell population	Diabetes	Normocellular marrow	No follow-up evidence of lymphoma
2	30	F	2	Inconclusive	No evidence of a monoclonal B-cell population	DLBCL	Normocellular marrow negative for lymphoma	No follow-up available
3	64	F	2	Inconclusive	No evidence of a monoclonal B-cell population	Classical Hodgkin lymphoma	Normocellular marrow negative for lymphoma	No follow-up available
4	73	M	2	Positive	A small lambda-restricted B-cell population is identified (3%).	Unremarkable	Acute promyelocytic leukemia	Significant involvement by leukemic cells in addition to identifying 2 small lymphoid aggregates. A subsequent bone marrow biopsy showed the same results.
5	62	F	2	Negative	No evidence of a monoclonal B-cell population	CNS DLBCL	Normocellular marrow negative for lymphoma	No follow-up evidence of lymphoma
6	39	F	2	Inconclusive	No evidence of a monoclonal B-cell population	Leukocytosis	Normocellular marrow	Follow-up shows an infectious process
7	71	M	2	Inconclusive	No evidence of a monoclonal B-cell population	Hyper IgE syndrome	Normocellular marrow with mild eosinophilia	No follow-up available
8	63	F	2	Negative	No evidence of a monoclonal B-cell population	Diabetes mellitus	Hypocellular marrow with trilineage hematopoiesis	No follow-up evidence of lymphoma
9	61	M	3	Negative	No evidence of a monoclonal B-cell or plasma cell population	LPL	Minimal involvement by lymphoma (1%)	Flow cytometry findings were negative but kappa and lambda immunostains showed minimal rimming of the aggregates by lambda-restricted B cells that express PAX-5. Plasma cells were polyclonal.
10	81	M	3	Positive	No evidence of a monoclonal B-cell or plasma cell population	Multiple myeloma and hypertension	Plasma cell dyscrasia involving 5% of the marrow	Results from cytogenetics studies were negative. Reviewing the subsequent clinical notes (36 mo) showed persistent plasma cell dyscrasia but no evidence of lymphoma.
11	78	M	3	Positive	No evidence of a monoclonal B-cell population	Sepsis and pneumonia	Normocellular marrow	Reviewing the patient's clinical notes for the subsequent 24 mo shows no evidence of malignancy.
12	85	M	3	Negative	No evidence of a monoclonal B-cell population	Coronary artery disease, diabetes, and prolonged anemia	Hypercellular marrow with features of MDS	Cytogenetics consistent with MDS, no follow-up evidence of lymphoma
13	31	F	4	Negative	No evidence of a monoclonal B-cell population	Pancytopenia	Normocellular marrow	No follow-up evidence of lymphoma

Table 3 (*continued*)

No.	Age (y)	Sex	Pattern	PCR results	Flow cytometry results	Clinical history	Diagnosis	Comments
14	87	M	4	Positive	No evidence of a monoclonal B-cell population	Acute myeloid leukemia	Acute myeloid leukemia arising from MDS	No follow-up available
15	77	F	4	Inconclusive	No evidence of a monoclonal B-cell population	ITP, hepatitis B, and diabetes	Normocellular marrow	No follow-up evidence of lymphoma
16	99	M	4	Positive	No evidence of a monoclonal B-cell population	Hypertension and anemia	Hypercellular marrow with features of MDS	No follow-up evidence of lymphoma
17	52	M	4	Negative	No evidence of a monoclonal B-cell population	Chronic myelogenous leukemia	Normocellular marrow with no evidence of active disease	No follow-up evidence of lymphoma
18	42	F	4	Negative	Flow cytometry not performed	Felty syndrome	Normocellular marrow	No follow-up available
19	57	F	5	Inconclusive	No evidence of a monoclonal B-cell population	Breast carcinoma and AML	Residual AML (10%)	No follow-up evidence of lymphoma
20	48	M	5	Inconclusive	Flow cytometry not performed	Lytic lesions on the spine rule out multiple myeloma	Normocellular marrow with no evidence of myeloma	Immunostains show no evidence of clonal plasma cells. No follow-up available

Abbreviations: M, male; F, female; IgE, immunoglobulin E; LPL, lymphoplasmacytic lymphoma; ITP, idiopathic thrombocytopenic purpura; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

(76.7%) of which had a T-cell pattern. There were 48 malignant cases in total, of which 7 (14.6%) had a T-cell pattern. A 2-tailed z test comparing the reactive and malignant groups demonstrated significant difference ($z = 7.504$, $P < .001$).

Staining for PD-1 was negative in all cases on which it was performed, whereas rare positivity was noted for CD23 and bcl-6 in a minority of the cases. The occasional positive bcl-6 cells may suggest the presence of residual germinal center cells, although the corresponding hematoxylin and eosin morphology only rarely showed germinal center formation. The few cases with germinal center formation contained less than expected bcl-6–positive cells, but this may reflect the decrease in size and the disappearance of the germinal centers in deeper sections. The rare CD23-positive cells probably represent the presence of activated lymphocytes because the staining pattern did not show the characteristic dendritic processes usually seen within follicular dendritic networks.

Attempts to perform B-cell gene rearrangement studies by PCR on the clot biopsy sections of 20 cases with different lymphocytic distribution patterns (patterns 1-5) were successful in only 12 cases because of the lack of sufficient DNA in 8 cases (Table 3). Of the 12 cases, 7 cases had a T-cell–predominant pattern, whereas 5 cases had a B-cell–predominant pattern. A total of 5 cases showed positive results, 3 cases with a T-cell–predominant pattern (patterns 2 and 3) and 2 cases with a B-cell–predominant pattern (pattern 4). Of the 3 positive cases with a T-cell–predominant pattern, the first case showed significant involvement by acute promyelocytic leukemia with 2 small lymphoid aggregates and positive flow cytometry results for a small clonal B-cell population (2%) and was interpreted as suspicious of minimal involvement by a low-grade B-cell lymphoproliferative disorder in addition to the acute leukemia. The second case showed involvement by plasma cell myeloma, one small lymphoid aggregate, and negative flow cytometry results for a light chain–restricted B-cell population. The third case showed a normocellular marrow with left-shifted myeloid maturation in a patient with sepsis. Flow cytometry result was negative for a light chain–restricted B-cell population, and positive PCR results were obtained despite the patient's negative history and negative follow-up for lymphoma at approximately 24 months. Of the 2 positive cases with B-cell–predominant patterns, the first case was diagnosed as acute myeloid leukemia with flow cytometry negative for a light chain–restricted B-cell population. The second case showed a slightly hypercellular marrow with features suggestive of myelodysplastic syndrome. Results from cytogenetic studies were negative, and flow cytometry finding was negative for a light chain–restricted B-cell population. Unfortunately, no follow-up was available for these 2 cases. We were unable to perform molecular studies on additional cases with a B-cell–predominant pattern, exhibited suspicious features, and had clinical follow-up because the aggregates were limited to trephine biopsy sections, where decalcification hindered the extraction of

high-quality DNA. An attempt to perform PCR on one such case was unsuccessful.

4. Discussion

The identification of lymphoid aggregates in the bone marrow is relatively uncommon (1%-2%), although it has been reported by some to be detected in up to 13% in older individuals [9,14]. Distinguishing between benign and malignant lymphoid aggregates in the bone marrow can be problematic in many cases, and a variety of criteria have been reported to aid in that distinction [2,9,11]. BLAs are typically small (<600 μm), are relatively uniform in size, have a distinct border, and have a nonparatrabecular location [1,2,9]. Although exact measurements of lymphoid aggregates are typically not conducted, BLAs are more likely to be lost in deeper sections, as seen in 14 of our cases, or become smaller as seen in many of our cases, whereas larger lymphomatous aggregates are more likely to remain in deeper sections [15,16]. Among our 40 lymphoma cases used for comparison purposes and in cases that contained aggregates suspicious for lymphoma, the aggregates not only persisted, but in some cases, their paratrabecular location became more evident.

Few immunohistochemical markers have been reported in the study of BLAs. Bcl-2 was among the first to be evaluated, and although originally reported to be specific or indicative of lymphomatous involvement [17,18], results have been challenged [19]. In our experience, most benign aggregates, whether composed of small T cells or non–germinal center B cells, show expression of bcl-2, and the only indication of a lymphoproliferative disease occurs when an aggregate containing an apparent germinal center clearly expresses bcl-2. Another antiapoptotic protein, survivin was investigated as a potential marker to identify malignant lymphoid infiltrates, but without success [18]. Overexpression of CD23 has also been studied as a potential marker of malignant aggregates [8]. Others have noted that in normal bone marrow, immunohistochemical stains against low-affinity nerve growth factor receptor highlight a fine network of adventitial reticular cells, whereas the nodular aggregates of various lymphomas are characterized by the distortion of the adventitial reticular cell network and a change in the expression of low-affinity nerve growth factor receptor [20].

Molecular tests have also been used to define the clonal nature of lymphoid aggregates. PCR for immunoglobulin heavy-chain gene rearrangement may help distinguish benign from malignant bone marrow lymphoid aggregates by demonstrating clonality [21,22], although false-negative results have been encountered in some of these studies [22,23]. Others have advised caution in the use of PCR and DNA sequence analysis because they may have a high false-positive rate in benign aggregates, particularly in patients with associated immune-mediated disorders [24]. In our study, we performed B-cell gene rearrangement studies on a subset of the cases, to assess the molecular clonality of the lymphoid aggregates. The results of the gene rearrangement study were concordant with the morphologic and immuno-histochemical findings in some cases but showed possible false-positive and false-negative results in other cases, warranting careful correlation with defined morphologic and immunophenotypic criteria and not relying on molecular genetic results alone.

The distribution of B and T lymphocytes within aggregates has not been well described in previous studies, or only limited to descriptions of relative numbers of these 2 cell types. Generally, the predominance of small T lymphocytes within the aggregates is believed by many to be an indicator of the benign nature of the aggregate [9,25,26]. The presence of germinal centers within the aggregates usually indicates a reactive process, although it can be seen in certain lymphomas, particularly MCL and splenic MZL, where reactive germinal centers can be seen in association with the lymphomatous infiltrate [27]. In our study, distinct distribution patterns for B and T cells were observed (Table 1 and Fig.). Overall, predominance of T cells was found in most cases, and patterns 1, 2, and 3 (predominantly T cells, haphazard mixture of T and B cells, and centrally located T cells) were most common. Aggregates with these 3 patterns when correlated with the patient's clinical features, diagnosis, and follow-up specimens (when available) were predictive of a benign process. In contrast, the predominance of B cells or the presence of a central core of B cells surrounded by T cells (excluding the presence of a reactive germinal center) was worrisome for, but not indicative of, lymphomatous involvement.

Of the 137 total cases examined in our study, follow-up (either by reviewing clinical data and pathology reports or by reviewing subsequent bone marrow biopsy specimens) was available in 61 (45%) cases. Eight of these 61 cases showed malignant lymphoid aggregates and evidence of lymphoma on follow-up, and most of these cases were originally reported as atypical or suspicious with a comment recommending clinical follow-up. These cases were described as atypical in the pathology reports owing to the presence of 1 or more of the following: infiltrative edges, paratrabecular location, or the predominance of B cells. The follow-up specimens exhibited features similar to those seen in the original bone marrow specimens. All 8 cases were diagnosed as malignant within 1 year of the initial diagnosis, and subsequent follow-up of these cases ranged from nearly 2 to 4 years. Five of the 8 cases had a predominant B-cell pattern in the original specimen and were subsequently diagnosed as FL, MCL, and CLL. Two of the 3 cases with a T-cell pattern were diagnosed on follow-up bone marrow specimens as angioimmunoblastic T-cell lymphoma. Both cases contained multiple relatively small aggregates with ill-defined margins and an increased number of interstitial T cells. One of these 2 cases had a paratrabecular location on the original specimen. The third case was diagnosed as acute promyelocytic leukemia with flow cytometry positive for a small light

chain–restricted B-cell population (2%). The aggregates were small and showed pattern 3 (central core of T cells), but exhibited evident infiltrative edges. Results from B-cell gene rearrangement studies by PCR performed subsequently were positive. Follow-up bone marrow biopsies showed a slightly increased number of aggregates with positive flow cytometry results and were diagnosed as minimal involvement by CLL, although the patient has not been treated and remains under close follow-up. Aside from these 8 cases, follow-up of the other cases was unremarkable, and any evidence of malignancy diagnosed subsequently was unrelated to the lymphoid aggregates identified in the original specimens. The 40 cases with known malignant aggregates that were selected as a control group exhibited a B-cell–predominant pattern in 36 (90%) of the 40 cases. Thirty-nine of these cases had a diagnosis of a B-cell lymphoma (CLL, MCL, FL, DLBCL, MZL, and LPL). The remaining case had a diagnosis of PTCL with nodular involvement and showed a T-cell–predominant pattern; however, the aggregates exhibited infiltrative margins and contained cytologically atypical T cells.

The predominance of T cells or the presence of a central core of T cells was also noted in patients after chemotherapy (including rituximab) and in patients with immune-related disorders. It has previously been recognized that rituximab-associated BLAs are composed entirely of T cells and that this is a useful feature to distinguish them from residual B-cell lymphoma [6,7]. We observed similar features in all of our rituximab-associated cases (mostly T cells or a central core of T cells). In HIV-positive patients, we noted many previously described features including increased size, poorly circumscribed margins, and a lymphohistiocytic pattern with no distinct granuloma formation [9,28-30]. Moreover, the loss of benign aggregates in deeper sections, an observation made by Salisbury et al [15,16], was also a prominent feature in our study.

In conclusion, benign aggregates often consist predominantly of normal-appearing T cells, contain a central core of T cells surrounded by B cells, or have a mixed haphazard distribution of B and T cells. The predominance of B cells within the aggregates, the presence of a core of B cells surrounded by T cells (except in germinal center formation), cytologic atypia, paratrabecular location, infiltrative edges, and large lymphoid aggregates that increase in size in deeper sections are all features that should raise suspicion of bone marrow involvement by a lymphoproliferative disease. Data analysis from our study revealed a statistically significant difference in the proportion of T-cell patterns in the reactive and malignant groups, where T-cell patterns were significantly associated with a reactive process.

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