# Bone Marrow Involvement in T-Cell–Rich B-Cell Lymphoma

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**We describe the histologic and immunohistochemical findings in specimens from bone marrow (BM) biopsies performed for staging purposes in 13 patients with a previous tissue-based diagnosis of T-cell–rich B-cell lymphoma (TCRBCL). Bone marrow involvement was found in 8 (62%) of 13 cases and was often paratrabecular. The histologic appearance was not pathognomonic of TCRBCL, with the differential diagnosis including Hodgkin's disease and peripheral T-cell lymphoma. The infiltrates typically had a pale low-power appearance (due to histiocytic infiltration, relative hypocellularity, or both) that, in conjunction with the presence of a polymorphous infiltrate of scattered large atypical cells amid a mixed infiltrate of small lymphocytes and histiocytes, was suggestive of Hodgkin's disease. Immunohistochemistry revealed CD20 reactivity of the large atypical cells with the absence of CD15 and CD30 reactivity, supporting the diagnosis of TCRBCL. A prominent small T-cell infiltrate accompanying the large atypical cells was observed in all positive BM biopsy specimens. The increased incidence of BM involvement in TCRBCL is significantly higher than that found in de novo B-cell diffuse large cell lymphoma, suggesting a possible biologic difference between the two entities. Our cases share some similar clinicopathologic features with histiocyte-rich B-cell lymphoma and with diffuse lymphocyte-predominant Hodgkin's disease, paragranuloma type. We discuss the possible relationship to these two entities. (Key words: T-cell–rich B-cell lymphoma; Bone marrow lymphoma; Immunohistochemistry; Hodgkin's disease) Am J Clin Pathol 1997;108:570–578.**

T-cell–rich B-cell lymphoma (TCRBCL) is a large B-cell lymphoma morphologically characterized by an accompanying prominent reactive T-cell infiltrate that may obscure the scattered malignant cells. Morphologically, it may resemble Hodgkin's disease (HD) or peripheral T-cell lymphoma, a differential diagnosis that has important therapeutic and prognostic consequences. Proper diagnosis rests on the immunohistochemical identification of the scattered large malignant cells as B-cells amid a sea of small reactive T-lymphocytes.

Several questions about TCRBCL still remain. Currently, it is an ill-defined entity with no generally accepted diagnostic criteria, with the percentage of reactive T-cells necessary for the diagnosis ranging from more than 50%[1] to more than 90%.[2] Without specific histologic and immunophenotypic criteria, reported cases have encompassed a heterogeneous group of tumors, some arising from follicular lymphoma,[3,6] with others demonstrating a relationship to lymphocyte-predominant HD (LPHD).[3,4] Whether TCRBCL represents a distinct clinicopathologic entity or simply an unusual morphologic subtype of conventional large B-cell lymphoma remains uncertain.

In 1992, Delabie et al[5] described six cases of a large B-cell lymphoma characterized by a histiocyte-rich infiltrate admixed with small T-lymphocytes, which they called histiocyte-rich B-cell lymphoma (HRBCL). All six patients had advanced-stage disease, including bone marrow (BM) involvement, when they were examined initially. Delabie et al speculated about a relationship to diffuse LPHD based on similar clinical and morphologic features and suggested that the presence of small reactive T-cells may point to a relationship with TCRBCL.

Patients with TCRBCL often have advanced-stage disease when they are examined initially, and the incidence of extranodal localization is high. Reports of BM involvement at presentation range from 0%[6] to 67%[7]; BM involvement has not been fully described previously. The present study focuses on the histopathologic features of the BM in 13 cases of TCRBCL, with emphasis on the differentiation from morphologically similar entities and its possible relationship to diffuse LPHD and HRBCL.

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## MATERIALS AND METHODS

### *Patients*

Thirteen patients with a tissue-based diagnosis of TCRBCL were identified from the surgical pathology files of the British Columbia Cancer Agency (BCCA; Vancouver, BC) between 1988 and 1996. Fourteen BM biopsy specimens were available from 13 patients. Thirteen specimens were obtained at the time of diagnosis for staging purposes, and an additional biopsy specimen was obtained from one patient at relapse 11 months later. Clinical information was obtained from the BCCA patient registry.

From the BCCA files, patients with diffuse mixed, diffuse large, and immunoblastic lymphoma of B-cell immunophenotype diagnosed between 1988 and 1996 (n = 500) were selected to represent a comparison group of 40 patients with concordant large cell BM involvement treated with curative intent (40/500; 8%). Overall survival curves were determined using the Kaplan-Meier method. Comparison between curves was performed by log-rank analysis.

### *Criteria*

The cases were reviewed to confirm the histologic diagnosis based on the following criteria for TCRBCL: (1) diffuse growth pattern, (2) small T-cells making up more than 90% of the lymphoid population, (3) scattered large atypical cells with a B-cell phenotype ($CD20^+$) making up less than 10% of the lymphoid population, and (4) absent or very rare small reactive B-cells.

Criteria for BM involvement included the presence of masslike lesions with scattered large malignant lymphoid cells. Biopsy specimens were examined for the presence of lymphomatous infiltration, the degree of involvement (< 25%, 25%–75%, or > 75%), and the pattern of involvement (focal paratrabecular, focal random, interstitial, or diffuse).

### *Histology and Immunohistochemistry*

***Extramedullary sites***—Three-micron-thick tissue sections were cut from B5 and formalin-fixed material and stained with hematoxylin-eosin. Immunoperoxidase staining on sections was performed using the streptavidin-biotin complex method, with microwave antigen retrieval used as necessary. The chromogen used was diaminobenzidine. Each case was stained with B-lineage anti-CD20 (L26, DAKO, Carpinteria, Calif) and T-lineage anti-CD45RO (A6, Zymed, San Francisco, Calif; or UCHL1, DAKO) or T-lineage polyclonal anti-CD3 (DAKO). Additional stains were available in selected cases and included anti-CD15 (LeuM1, Becton Dickinson, San Jose, Calif) in 7 cases, anti-CD30 (BerH2, DAKO) in 6 cases, anti–epithelial membrane antigen (EMA; DAKO, clone E29) in 8 cases, and polyclonal anti-κ and anti-λ (DAKO) in one case.

***Bone marrow***—Unilateral BM trephine biopsies were performed on the posterior superior iliac spine with a Jamshidi needle, fixed in B5, and decalcified using 10% nitric acid for 1 to 2 hours. Bone marrow biopsy specimens were examined using hematoxylin-eosin–stained slides and immunohistochemical stains against CD20 and CD45RO. One case was also stained against CD79a (DAKO) and κ and λ light chains.

### *Molecular Studies*

DNA preparation, Southern blot (SB) analysis for IgH and Tβ-receptor gene rearrangements, and polymerase chain reaction (PCR) analysis of IgH-VJ and Tγ-receptor genes were performed as previously described.[8] The PCR analysis of the *bcl*-2 gene was performed as described by Horsman et al.[9]

The SB analysis for IgH gene rearrangements was performed on frozen tissue from extramedullary sites in five cases and on BM aspirates in two cases, and the SB analysis for Tβ-receptor gene rearrangement was performed on frozen tissue from extramedullary sites in three cases and on BM aspirate in one case. The PCR analysis of IgH-VJ receptor gene was performed on formalin-fixed paraffin-embedded tissue from extramedullary sites in seven cases and on BM aspirate in three cases; analysis of the Tγ-receptor gene was performed on formalin-fixed paraffin-embedded tissue from extramedullary sites in one case; and analysis of the *bcl*-2 gene was performed on formalin-fixed paraffin-embedded tissue from extramedullary sites in six cases.

## RESULTS

### *Clinical Information*

The clinical features are summarized in Table 1. The specimens were obtained from 10 men and three women. Mean age at diagnosis was 45 years (range, 24–72 years). The initial site of manifestation of the disease included lymph node (11 patients), liver (1 patient), and appendix vermiformis (1 patient). The BM was involved at the time of clinical staging in 8 patients.

**TABLE 1. CLINICAL FEATURES**

| *Case No.* | *Age (y)* | *Sex* | *Sites of Involvement* | *Bone Marrow Involvement* | *Clinical Stage* | *Treatment* | *Response* | *Outcome* |
|---|---|---|---|---|---|---|---|---|
| 1 | 37 | M | Lymph node | Yes | IVB | VACOP-B, BMT | Complete | NED at 28 mo |
| 2 | 69 | F | Lymph node | Yes | IVB | Treatment refused | — | AWD at 3 mo |
| 3 | 72 | F | Lymph node, liver | Yes | IVB | P/DOCE, with intrathecal treatment | Complete | Relapse at 9 mo; DOD at 14 mo |
| 4 | 32 | M | Lymph node, liver, prostate | Yes | IVB | VACOP-B with intensification* with intrathecal treatment | Complete | Relapse at 6 mo; DOD at 7 mo |
| 5 | 48 | M | Lymph node | Yes | IVB | VACOP-B with intensification* | Complete | Relapse at 11 mo; receiving treatment† |
| 6 | 49 | M | Lymph node | Yes | IVA | ACOP-12 | Complete | NED at 23 mo |
| 7 | 24 | M | Lymph node | Yes | IVB | VACOP-B with intensification* | — | Receiving treatment† |
| 8 | 28 | M | Lymph node, soft tissue | Yes | IIIBE | ACOP-12, BMT | — | Treatment-related death |
| 9 | 55 | M | Lymph node, bone, epidural space | No | IVA | ACOP-12, with intrathecal treatment | Complete | NED at 4 mo |
| 10 | 48 | F | Liver, pleura, soft tissue | No | IVB | VACOP-B | None | DOD at 4 mo |
| 11 | 48 | M | Intestine, liver | No | IVB | VACOP-B | — | DOD at 1 mo |
| 12 | 40 | M | Lymph node | No | IIIA | VACOP-B | Complete | Relapse at 27 mo followed by BMT; NED at 6 y |
| 13 | 36 | M | Lymph node, mediastinum | No | IIIBE | VACOP-B, radiation | Partial | DOD at 15 mo |

VACOP-B = etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone; BMT = bone marrow transplantation; NED = no evidence of disease; AWD = alive with disease; P/DOCE = doxorubicin, vincristine, cyclophosphamide, etoposide, prednisone; DOD = died of disease; ACOP-12 = doxorubicin, cyclophosphamide, vincristine, prednisone.
*Intensification treatment consisted of high-dose etoposide and cyclophosphamide replacing the week-9 treatment.
†At the time the article was written.

Initial therapy included multiagent chemotherapy (see Table 1) in 12 patients, combined with allogeneic BM transplantation (BMT) in 2 patients. One patient refused treatment and was alive with disease 3 months after the initial examination. Complete remission was achieved in 7 patients, 4 of whom experienced a relapse at 6 months, 9 months, 11 months, and 27 months. In 1 patient, a partial remission was achieved, and in another, no remission was achieved. Two patients are currently receiving treatment, 1 for initial disease and 1 for relapse. Four patients are alive with no evidence of disease, 5 died of disease progression, and 1 died of a treatment-related cause.

### *Primary Site*

All cases fulfilled the diagnostic criteria for TCR-BCL listed in the "Materials and Methods" section. Table 2 summarizes the histologic and immunohistochemical features. In addition to the infiltrate of small lymphocytes, all cases contained a variable number of reactive histiocytes. Nonepithelioid and epithelioid histiocytes were observed in every case, in varying proportions. Three cases (cases 7, 9, and 12) contained histiocyte-poor infiltrates, with occasional histiocytes showing nonepithelioid and epithelioid features. The remaining cases contained histiocyte-rich infiltrates:

**TABLE 2. MORPHOLOGIC AND IMMUNOHISTOCHEMICAL RESULTS IN TCRBCL**

| *Case No.* | *Predominant Morphologic Features* | *CD20** | *CD15** | *CD30** | *EMA* | *Histiocyte Infiltrate* |
|---|---|---|---|---|---|---|
| 1 | Immunoblastic; occasional L&H | + | – | – | ND | HR, NE |
| 2 | Immunoblastic | + | – | – | ND | HR, E |
| 3 | Immunoblastic | + | ND | ND | ND | HR, E |
| 4 | Immunoblastic | + | ND | ND | ND | HR, NE |
| 5 | Occasional L&H | + | – | – | – | HR, NE, and E |
| 6 | L&H | + | ND | ND | ND | HR, E |
| 7 | L&H | + | – | – | + | HP, E |
| 8 | Immunoblastic | + | – | – | – | HR, NE, and E |
| 9 | Occasional L&H | + | – | – | – | HP, NE |
| 10 | Immunoblastic | + | – | ND | – | HR, NE |
| 11 | Large noncleaved | + | ND | ND | – | HR, NE, and E |
| 12 | L&H | + | ND | ND | + | HP, NE |
| 13 | L&H | + | ND | ND | + | HR, NE, and E |

TCRBCL = T-cell–rich B-cell lymphoma; + = positive; – = negative; EMA = epithelial membrane antigen; L&H = lymphocytic and histiocytic; ND = not done; HR = histiocyte rich; NE = nonepithelioid; E = epithelioid; HP = histiocyte poor.

*B-lineage anti-CD20 (L26, DAKO, Carpinteria, Calif); anti-CD15 (LeuM1, Becton Dickinson, San Jose, Calif); anti-CD30 (BerH2, DAKO).

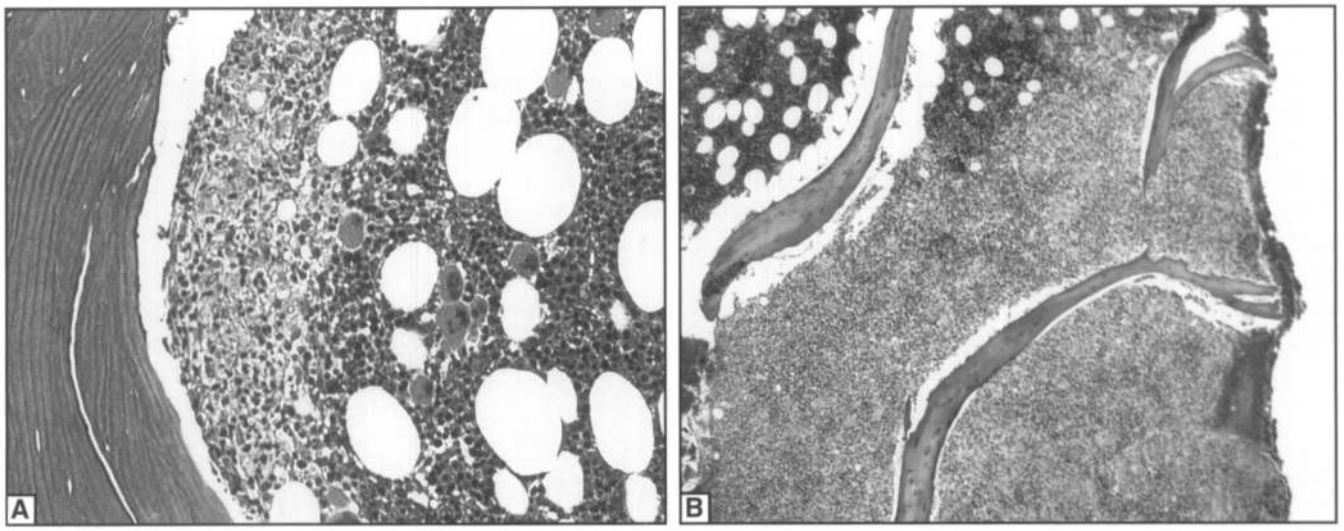


FIG 1. Bone marrow trephine biopsy specimens. A, Case 3, tumor infiltrates occur most commonly as paratrabecular lesions (hematoxylin-eosin, ×180). B, Case 6, tumor infiltrates also occur as large deposits occupying the intertrabecular spaces, a pattern that resembles bone marrow involvement with Hodgkin's disease on low power (hematoxylin-eosin, ×45).

three were predominantly nonepithelioid, three were predominantly epithelioid, and four were mixed.

The neoplastic cells were highlighted by the CD20 stain and showed variable morphology. Four cases (cases 6, 7, 12, and 13) had morphologic features similar to lymphocytic and histiocytic (L&H) cells of LPHD. These nuclei were multilobated with a vesicular appearance and one or more inconspicuous nucleoli. Three cases (cases 1, 5, and 9) contained occasional neoplastic cells with L&H morphologic features, with the majority of neoplastic cells showing immunoblastic morphology. The remaining cases contained neoplastic cells with immunoblastic or large noncleaved morphologic features, with no L&H cells identified. Three of eight cases had EMA staining of the large cells. CD15 and CD30 were negative in six of six cases.

### *Bone Marrow Findings*

Specimens obtained by BM trephine biopsies performed for staging purposes at time of diagnosis were involved by lymphoma in 8 (62%) of 13 cases. This contrasts with the 40 (8%) of 500 in the comparison group of conventional B-cell diffuse large cell lymphoma (DLCL) with concordant large cell BM involvement. Six of 8 cases contained paratrabecular deposits (Fig 1, A). Four cases contained diffuse lymphomatous

infiltrates occupying entire areas between bone trabeculae (Fig 1, B). In addition to the paratrabecular deposits, lymphomatous infiltrates were seen focally in an interstitial pattern in two cases. Four biopsy specimens showed more than 25% replacement; four cases showed between 25% and 75% replacement.

The cellular composition of the BM deposits was similar to that found in the primary diagnostic biopsy specimens. All BM specimens showed a prominent infiltrate of small lymphocytes, with scattered large atypical cells (Fig 2, A). The morphologic features of the atypical cells correlated with those found in the diagnostic tissue biopsy specimen. Two cases (cases 6 and 7) showed predominantly L&H morphologic features. No diagnostic Reed-Sternberg cells were identified. In all but one trephine biopsy specimen, the tumor deposits had a pale eosinophilic appearance on low power because of the presence of infiltrates rich in histiocytes, the relative hypocellularity compared with the surrounding marrow, or both. A histiocyte-rich infiltrate was present in six cases, with histiocytes showing epithelioid and nonepithelioid features.

All tumor deposits contained a prominent infiltrate of small lymphocytes that were most easily appreciated in the CD45RO-stained sections because of the presence of large numbers of reactive T cells. Using sections stained for CD20, the scattered large atypical cells were more easily visualized in seven of the nine cases, showing uniform membranous staining in all the large cells (Fig 2, B). Two cases (cases 4 and 7) contained large neoplastic cells that failed to stain for CD20. The large cells in case 4 were also negative with CD79a (another B-lineage marker), but they showed positive cytoplasmic staining for κ light chain with absence of λ staining. The lymph node biopsy specimens from both of these cases contained large neoplastic cells showing reactivity against CD20, confirming the diagnosis of TCRBCL.

One patient (case 5) who experienced relapse of disease at 11 months, underwent a second BM biopsy; examination of the specimen revealed a histologic and immunohistochemical staining pattern similar to the initial staging BM examination. No reduction in the number of small reactive T cells was appreciated.

### *Genotypic Analysis*

Molecular genetic studies were available for nine cases. Evidence of B-cell monoclonality was determined by immunoglobulin (Ig) gene rearrangement using SB analysis in five cases and by Ig heavy chain PCR (VJ-PCR) in seven cases. Three cases showed evidence of a clonal B-cell population: case 7 by the SB technique on BM and extramedullary tissue and cases 3 and 5 by VJ-PCR on extramedullary tissue. Six cases showed no evidence of B-cell clonality. No evidence of *bcl*-2 rearrangement was detected in any of the six cases tested, and no evidence of T-cell receptor gene rearrangement was evident in four cases tested.

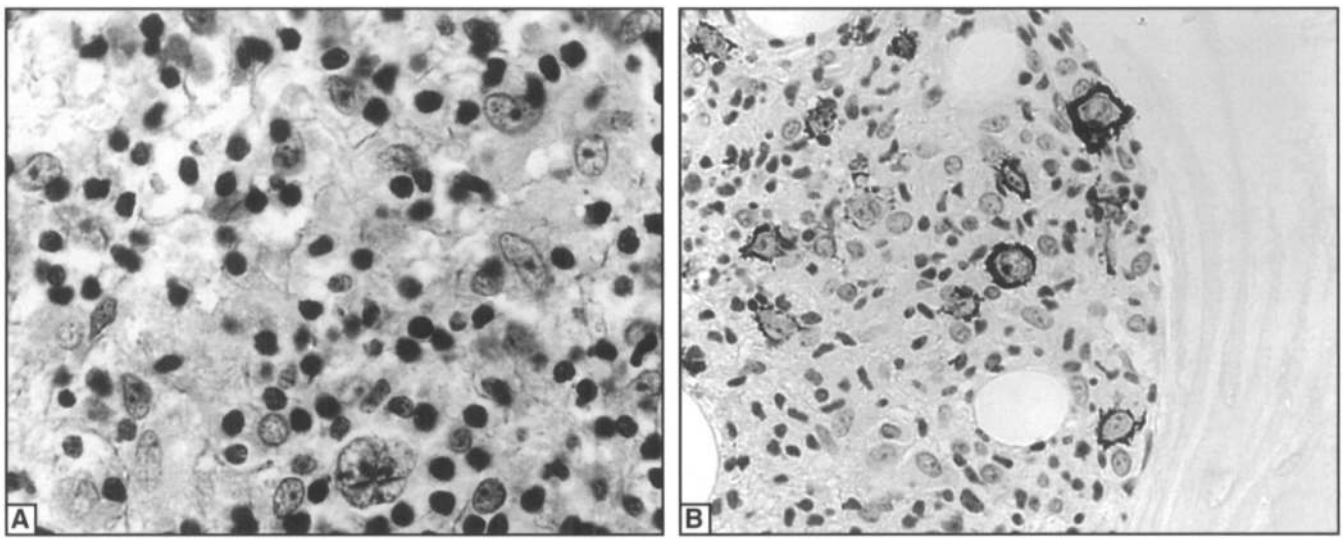


FIG 2. Detail of neoplastic infiltrate. A, Case 6, scattered large malignant cells are accompanied by an infiltrate of small lymphocytes and histiocytes. The malignant cells include cells resembling lymphocytic and histiocytic (L&H) cells (hematoxylin-eosin, ×720). B, Case 3, the malignant cells are accentuated by L26 staining (immunoperoxidase, hematoxylin counterstain, ×450).

### *Survival Data*

Clinical response and survival data were available for all 13 patients with TCRBCL. The 4-year overall survival for these patients was 38%; the 4-year overall survival for the patients with BM involvement was 45% (Fig 3). There was no statistically significant difference between the 4-year overall survival in patients with TCRBCL with BM involvement compared with a control group of patients with B-cell DLCL with concordant large cell BM involvement treated with curative intent (overall survival, 45% *vs* 51%, $P$ = not significant).

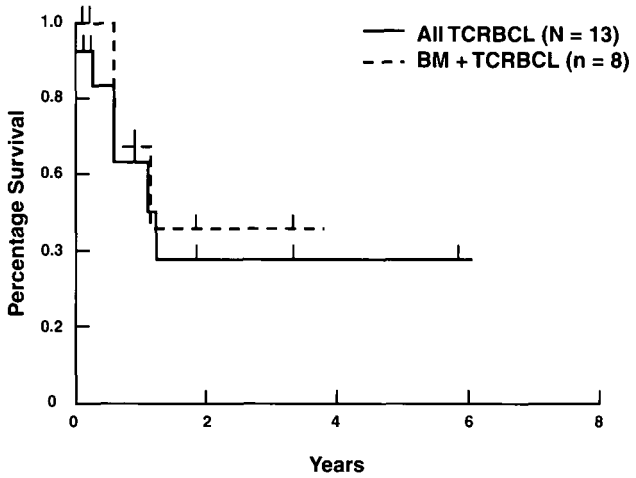


FIG 3. Overall survival curves of patients with T-cell–rich B-cell lymphoma (TCRBCL) based on bone marrow involvement (BM+).

## DISCUSSION

Bone marrow involvement at manifestation of disease was seen in 8 (62%) of 13 patients with TCRBCL, which contrasts with conventional B-cell DLCL at our center demonstrating 8% BM positivity. The positive BM trephine biopsy specimens were generally involved by discrete masses of lymphomatous infiltrates that most commonly had a paratrabecular location. Half of the cases with positive BM showed diffuse involvement with tumor occupying entire areas between bone trabeculae. Under low power, the appearance of the deposits was that of pale masses that were well demarcated from the surrounding marrow, an appearance suggestive of HD involving the marrow. This pale appearance was due to histiocyte-rich infiltrates, relative hypocellularity compared with the surrounding marrow, or both. Under high power, the appearance of scattered large atypical cells amid a mixed infiltrate of small lymphocytes and histiocytes was also suggestive of HD. The differential diagnosis of nodal TCRBCL from classic HD has been addressed in previous reports,[10] and the approach in the BM is similar. The proper diagnosis depends on correlating the pathologic findings of the BM with those of the nodal disease in which the large atypical cells express CD20 with absent CD15 and CD30 expression. Making the initial diagnosis of TCRBCL from the BM biopsy specimen alone may be difficult. We encountered two cases in which the large atypical cells in the BM biopsy specimens failed to stain for CD20. In both cases, the diagnosis of TCRBCL had been made initially by the examination of lymph node biopsy specimens. If the initial biopsy specimen for a patient is from the BM, the finding of scattered large atypical cells lacking CD20 reactivity amid a polymorphous infiltrate of small lymphocytes and benign histiocytes could be easily mistaken for HD. The diagnosis of TCRBCL should be considered if the clinical picture is that of a non-Hodgkin's lymphoma, the neoplastic cells stain strongly for CD20 but fail to express CD15 and CD30, and clonality can be demonstrated by light-chain restriction in paraffin sections or by molecular genetic methods. In one of our cases that failed to stain with CD20 (case 8), the large cells showed κ light-chain restriction, and rearrangement of the Ig heavy chain was demonstrated by SB analysis.

The differentiation of TCRBCL from HD has therapeutic and prognostic importance. Two series of patients with TCRBCL[10,11] that included patients initially misdiagnosed as having HD have been published. These patients initially had been treated with chemotherapy regimens for HD, resulting in a partial response with early relapse. Although these findings are limited to only a few cases, they stress the importance of an accurate diagnosis of TCRBCL. The patients in our series were initially diagnosed as having TCRBCL and treated accordingly, with a complete response achieved in seven patients.

The infiltrate of small reactive T cells that defines the entity in lymph nodes was also present in all BM biopsy specimens from our patients. Several series on TCRBCL report the histologic progression of TCRBCL into conventional DLCL, characterized by the loss of reactive T cells and more frequent large neoplastic B cells. This has been described most commonly at the time of disease relapse (in BM[12] and extramedullary sites[13–15]), but also has been found as a synchronous finding in BM biopsy specimens at clinical manifestation of the disease.[3] There are also reports of DLCL recurring as TCRBCL.[13] This association was not

observed in our patients; however, all but one of the BM biopsies were performed at the time of disease manifestation, with only one additional biopsy performed in one case at relapse, 11 months after disease manifestation. This second biopsy specimen retained the prominent small T-cell infiltrate.

The high content of reactive T cells within the BM deposits also may suggest the diagnosis of peripheral T-cell lymphoma, a disease with a high incidence of BM involvement.[16] This problem may be compounded by the lack of CD20 staining of the neoplastic cells in the BM biopsy specimens in some cases. As in the distinction from HD, the pathologic findings in the marrow must be correlated with the pathology of the primary biopsy site, in which immunohistochemistry performed on paraffin-embedded tissue demonstrates that the large malignant cells express CD20. If performed, molecular genetic studies to search for evidence of T-cell receptor rearrangement are expected to be negative, as was observed in four of our cases.

In our experience, molecular genetic techniques for the detection of B-cell monoclonality had low sensitivity. The low sensitivity of the SB technique (monoclonality demonstrated in one of four cases) is easily explained by the small numbers (<10%) of malignant cells in the specimens. Sensitivity of VJ-PCR in previous reports of TCRBCL ranges from 64%[6] to 100%.[7] In our experience, however, we were able to detect a B-cell clone by this technique in 2 (29%) of 7 cases. This low sensitivity may be because of the infrequent malignant cells in the biopsy specimen or, alternatively, failed amplification. This consensus PCR strategy for IgH chain gene rearrangements does not detect all cases with a clonal IgH SB analysis.[17]

By using strict diagnostic criteria for nodal TCRBCL, we found BM involvement at manifestation (62%) to be significantly higher than the average incidence of BM involvement (23%) reported in the literature (Table 3).[1–4,6,7,10–15,18–26] The wide variability of reported BM involvement (from 0% to 67%) in series varying in size from 5 to 44 cases (excluding case reports) may reflect the lack of well-defined diagnostic criteria for nodal TCRBCL used in these studies. Whereas criteria for the percentage of T cells vary from greater than 50%[1] to more than 90%[2] in previous studies, we only diagnosed cases as TCRBCL from lymph node biopsy specimens if the small T cells constituted more than 90% of the lymphoid population. In addition, as part of the definition of T-cell–rich, the reactive lymphoid population must be purely T cell,

**TABLE 3. BONE MARROW STATUS AS REPORTED IN THE TCRBCL LITERATURE**

| *Author* | *No. of Cases* | *No. of Cases With Information on BM Status* | *No. (%) of BM Positive at Presentation** |
|---|---|---|---|
| Ramsay et al[2] | 5 | 5 | 2 (40) |
| Scarpa et al[12] | 1 | 1 | 0 (-) |
| Ng et al[1] | 21 | 20 | 2 (10) |
| Osborne et al[14] | 7 | 7 | 3 (43) |
| Chittal et al[11] | 9 | 9 | 3 (33) |
| Macon et al[13] | 19 | 15 | 3 (20) |
| Khan et al[18] | 8 | 7 | 1 (14) |
| Arai et al[19] | 1 | 1 | 0 (-) |
| Rodriguez et al[15] | 23 | 23 | 3 (13) |
| Brouland et al[20] | 1 | 1 | 0 (0) |
| Ohshima et al[7] | 6 | 6 | 4 (67) |
| Betman et al[21] | 1 | 1 | 0 (-) |
| Krishnan et al[6] | 30 | 30 | 0 (-) |
| Navarro et al[22] | 1 | 1 | 0 (-) |
| Baddoura et al[23] | 8 | 8 | 2 (25) |
| Brousset et al[24] | 1 | 1 | 1 (-) |
| Schmidt et al[4] | 7 | 6 | 2 (33) |
| Greer et al[25] | 44 | 38 | 12 (32) |
| De Jong et al[3] | 12 | 8 | 4 (50) |
| McBride et al[10] | 9 | 9 | 3 (33) |
| La Starza et al[26] | 1 | 1 | 1 (-) |
| **Total** | **215** | **198** | **46 (23)†** |

TCRBCL = T-cell–rich B-cell lymphoma; BM = bone marrow.
*% of BM-positive cases, excluding case reports.
†Includes case reports.

with absent or rare small reactive B cells, a criterion that has never been used in the existing literature.

Many investigators consider TCRBCL an unusual morphologic subtype of diffuse large B-cell lymphoma based on the frequent histologic progression to conventional DLCL shown on subsequent biopsy specimens and a similar response to DLCL treatment regimens. They reason that because the T-cell–rich infiltrate, the defining feature of this entity, is an inconsistent feature, the diagnosis should be B-cell DLCL based on the constant feature of the disease, namely, the large neoplastic B cells. Our finding of 62% BM involvement in TCRBCL is significantly higher than the 8% to 9% of de novo B-cell DLCL manifesting with concordant large cell BM involvement that has been observed at our institution and at other institutions.[27] This finding suggests that TCRBCL may be a biologically different disease, characterized by a high incidence of BM involvement. However, when such cases are compared with cases of patients with DLCL and concordant BM involvement, there is no statistically significant difference in outcome, suggesting that coexistent BM involvement is the important factor dictating outcome.

The finding of frequent BM involvement at manifestation, along with other clinicopathologic features, resembles that of HRBCL. This entity was first described in 1992 in a series of 6 patients by Delabie et al.[5] All 6 patients with HRBCL were men, with an average age of 41 years, with advanced-stage disease, including BM involvement, when they were first examined. The tumors were histologically characterized by diffuse nodal effacement by a prominent reactive nonepithelioid histiocyte infiltrate that obscured the scattered malignant B cells. The malignant cells resembled the L&H cells of LPHD, paragranuloma type, and stained with EMA in 2 of 6 cases. The reactive infiltrate also contained small reactive T cells with no reactive B cells. In the description of HRBCL, the authors stressed that the diagnostic feature was the evidence of nonepithelioid features in the histiocytes. Histiocyte-rich infiltrates have been described in several reports of TCRBCL, but they were described as epithelioid[1,2,13,23] or they were not qualified.[4] Ten of our 13 cases of nodal TCRBCL contained histiocyte-rich infiltrates, but only 4 were predominantly nonepithelioid. Those with an epithelioid histiocyte infiltrate did not seem to behave differently.

Based on our criteria, a tumor may be T-cell rich (> 90% of lymphoid population) and histiocyte rich. Both of these "infiltrate-rich" large B-cell lymphomas typically occur in men in their 30s and 40s; the disease is advanced at manifestation, and the BM is involved. The existence of TCRBCL as a distinct entity is further confounded by the fact that many lymphomas may contain a T-cell–rich infiltrate. By adopting the criteria including a diffuse growth pattern containing more than 90% T cells with absent or rare small B cells, we may be defining a distinct entity, in contrast to the studies that include a wide spectrum of lymphoproliferative disorders containing large numbers of reactive T cells.[1,2,6,13]

Delabie et al[5] postulated a possible relationship between HRBCL and LPHD based on similar clinicopathologic features, such as male preponderance, age distribution, L&H morphologic features of the neoplastic cells, and EMA staining. Two forms of LPHD, nodular and diffuse, have been described. The nodular form is considered a distinct clinicopathologic entity characterized by effacement of nodal architecture by a macronodular infiltrate containing scattered L&H cells surrounded by an infiltrate of predominantly small B lymphocytes.[28] The diffuse form of LPHD, however, has not been clearly defined, and its existence has been recently questioned.[29] Because the architecture of LPHD may change from nodular to diffuse, the number of reactive B cells can decrease with a concomitant increase of the number of small T cells.[30] As has been described, TCRBCL and diffuse LPHD share several common features, including diffuse growth pattern with scattered atypical cells and an admixed reactive T-cell infiltrate. Criteria for differentiating these two entities have not been well established. Schmidt et al[4] state that TCRBCL can be distinguished from diffuse LPHD based on the following: (1) presence of centroblastlike and immunoblastlike cells mixed with the L&H cells, (2) negative EMA reactivity, and (3) a reactive T-cell infiltrate without reactive B cells. Recently, the same authors also suggested that these two entities could be distinguished from one another by the quantity of MB1-positive and 4KB5-positive small reactive lymphocytes in the background, which are scanty in TCRBCL and more numerous in LPHD.[31]

The question of EMA positivity in TCRBCL remains a contentious issue, with widely differing results in studies. In various series, the EMA reactivity ranges from 14% to 100%.[3,4,11] In our experience in which microwave antigen retrieval was not used, EMA was seen in three of eight cases. Our experience, however, suggests that EMA reactivity may be seen in more cases if antigen retrieval is performed (R.D.G., unpublished observations, 1997).

In conclusion, we found a high incidence of BM involvement in TCRBCL, which is significantly different

from conventional B-cell DLCL and HD. The appearance of the BM may mimic that in HD, but it is easily distinguished in most cases using routine immunohistochemistry. The similar clinicopathologic features that our cases of TCRBCL share with HRBCL suggest that both morphologic entities may be part of a single distinct clinicopathologic entity, but the relationship to diffuse LPHD remains unanswered. Further study of a large number of cases previously defined as diffuse LPHD may provide insights into the relationship between this entity and cases classified as TCRBCL and HRBCL.

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