

T-Cell-Rich B-Cell Lymphoma

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We analyzed 23 cases of T-cell-rich B-cell lymphomas (BCL) to determine if the clinical features are characteristic of a discrete entity. Cases encoded as T-cell-rich BCL in the hematopathology archives of the University of Texas M.D. Anderson Cancer Center between 1988 and 1991 formed the basis of this study. At least 50% of the total population of cells were required to be of T-cell phenotype. Actually, all but one patient had more than 70% T cells in the total population. Sixty-five percent of all cases were referred with other diagnosis such as Hodgkin's mixed cellularity, peripheral T-cell lymphoma (PTCL), or diffuse mixed lymphoma, and had received therapy accordingly. With the exception of splenomegaly, which occurred in 35% of cases, the other clinical characteristics and the response to therapy did not indicate that this entity represents a distinct type of lymphoma. Ann Arbor stage

I-II presentations were seen in 10 of 23 (43%) T-cell-rich BCLs. Serum lactate dehydrogenase (LDH) was elevated in eight of 19 patients. Age, sex, and β_2 -microglobulin were not significantly different from classical B-cell large cell lymphoma. The clinical presentation and clinical outcome of T-cell-rich BCL did not differ from that of common B-cell large cell lymphoma, except for the higher proportion of splenomegaly seen in patients with T-cell-rich BCL. The presence of the T-cell-rich infiltrate varied: it frequently was not seen at relapse or at other sites of disease at presentation. It was thus considered an unstable parameter. The major importance of identifying this entity is to distinguish it pathologically from other disorders such as Hodgkin's disease and PTCL, which would be treated in a different manner.

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TCELL-RICH B-cell lymphoma (BCL) is a recently described histologic variant of BCL characterized by a minor population of clonal B cells distributed in a background of numerically preponderant polyclonal T lymphocytes.¹ While precise histologic criteria have not yet been defined, clonal B cells typically comprise 10% or less of the total cellular constituency. Controversy persists with regard to both the clinical relevance and the proper classification of this histologic variant. The latter is largely a semantic issue, provided these cases are distinguished from both peripheral T-cell lymphoma and Hodgkin's disease, with which they may be easily confused.² However, the issue of biologic behavior, and the related question of optimal therapeutic design, must be addressed. With this purpose, we report our experience with 23 patients with T-cell-rich BCL.

MATERIALS AND METHODS

The records of 23 patients diagnosed and encoded as having T-cell-rich BCL at the University of Texas M.D. Anderson Cancer Center between 1988 and 1991 were reviewed. Immunophenotyping was performed after review of the hematoxylin and eosin sections prompted the suspicion of T-cell-rich BCL. Three features suggested this diagnosis: (1) diffuse architecture, (2) minor population of atypical large cells, and (3) preponderance of cytologically mature small lymphocytes. In 15 patients, the disease was originally diagnosed, before referral, as diffuse mixed cell lymphoma not otherwise specified (four cases), peripheral T-cell lymphoma (two

cases), diffuse large-cell lymphoma (two cases), centrocytic lymphoma (one case), or Hodgkin's disease (six cases), and 12 had received therapy accordingly before transfer to our institution. Immunophenotypic studies were performed on frozen sections as previously described³ using antibodies to the following antigens: κ and λ light chains, Leu-1 (CD5), Leu-4 (CD3), and Leu-14 (CD22). Immunostaining of formalin-fixed, paraffin-embedded tissue sections by the avidin-biotin-peroxidase complex technique⁴ used the following antibodies: L-26 (CD20), UCHL-1 (CD 45RO), Leu-22 (CD43), Leu-M1 (CD15), and LCA (CD45). All histologic, immunophenotypic, and genotypic studies were reviewed by one of the investigators (W.C.P.) for diagnostic confirmation. Histologic evaluation was based on formalin-fixed tissue sections stained with hematoxylin and eosin. In all but one case, nonneoplastic T lymphocytes constituted 70% or more of cells; in the remaining case, T lymphocytes comprised slightly more than 50% of lymphoid cells. In all 23 cases, a histologic diagnosis of T-cell-rich BCL was substantiated by the demonstration of an L26⁺ UCHL-1⁻ phenotype in the atypical large cell population. Staining for Leu-M1 and LCA were negative and positive, respectively, in the seven cases in which they were examined. B-cell clonality was further confirmed whenever possible on fresh tissue by documentation of either light-chain restriction (two cases: one κ , 1 λ) or immunoglobulin gene rearrangement (six cases: IgH in six of six and Ig κ in two of two). In nine cases, histologic progression to B-cell large cell lymphoma of usual type was observed, either in subsequent biopsies or in biopsies from other sites. One patient had a history of follicular lymphoma. Southern blot analysis was performed as previously detailed³ using ³²P-labeled probes for the (1) Ig heavy-chain joining region gene (JH), (2) κ light-chain joining region gene (JK), and (3) β T-cell receptor constant region gene (CTB) (Oncor, Gaithersburg, MD). BamHI, EcoRI, and HindIII restriction digests were used for all analyses. Several variables known to have prognostic importance were analyzed, including age, sex, B symptoms, Ann Arbor stage, tumor burden as defined by Jagannath et al⁵ initial serum lactate dehydrogenase (LDH), and β_2 -microglobulin values, and number of involved extranodal sites. Staging and definition of extranodal sites were based on the Ann Arbor classification.⁶ The spleen was considered to be involved if it appeared enlarged on physical examination or by radiologic studies. First-line therapy included doxorubicin-containing regimens such as CHOP-Bleo (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine] [Eli Lilly Co, Indianapolis, IN], prednisone, bleomycin) (four regimens with additional local radiotherapy), Pro-MACE⁷ (methotrexate, Adriamycin [Adria, Dublin, OH], cyclophosphamide, etoposide), MACOP-B⁸ (methotrexate, Adriamycin, cyclophosphamide, Oncovin,

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prednisone, bleomycin), CHOP-Bleo alternating with OPEN (Oncovin, prednisone, etoposide, Novantrone [mitoxantrone] [Lederle, Pearl River, NY]), and alternating triple therapy (ATT) with ASAP (Adriamycin, Solu-Medrol [methylprednisolone] [Upjohn, Kalamazoo, MI], ara-C [cytarabine], cisplatin), MBACOS (methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, Solu-Medrol), MINE (mesna, ifosfamide, Novantrone, etoposide). Initial therapy also included MOPP (mechlorethamine, Oncovin, procarbazine, prednisone), MOPP-ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine), or ABVD (two of which also included local radiotherapy) for patients with a referring diagnosis of Hodgkin's disease. One patient received cyclophosphamide-prednisone only. Complete remission (CR) was defined as the disappearance of all signs and symptoms of disease as determined by clinical, radiographic, and laboratory evaluations. Patients who responded to treatment and had minimal residual radiographic abnormalities that remained unchanged for more than 6 months after treatment were considered to be in CR. Partial remission (PR) was defined as a reduction of 50% or more in measurable disease for at least 1 month. Any other response, including mixed response, stable disease, progressive disease, early death, or death due to toxicity of therapy, was considered a failure. Time to treatment failure was measured from the date of initial treatment to clinical or radiographic evidence of progression.

RESULTS

Clinical features. Clinical features at presentation are detailed in Table 1. Twenty-three patients comprised 12 women and 11 men, ranging in age, from 21 to 82 years (median, 58). Eighteen patients presented with peripheral lymphadenopathy, four with mediastinal adenopathy, and one with no adenopathy. Eight patients had splenomegaly, which was characterized as massive in two. Sites of extranodal involvement included liver, lung, colon, base of tongue, central nervous system, and bone marrow. A primary vaginal tumor was observed in one case. One patient had Ann Arbor stage I disease, nine had stage II, five had stage III, and eight had stage IV. Only six patients presented with B symptoms. Tumor burden was assessed in accordance with previously published institutional criteria.⁵ Five patients were considered to have high tumor burden, eight intermediate, and 11 low. Using the same criteria,⁵ eight patients were classified as having bulky disease. LDH was high in eight of 19 patients in whom it was measured before therapy. Serum β_2 -microglobulin levels were ≥ 3 mg/dL in six of 10 patients (normal, ≤ 2.0 mg/dL).

Response to therapy. Response to therapy is detailed in Table 2. Of nine patients who were originally diagnosed with non-Hodgkin's lymphoma of various histologic types and who were treated at their referring institutions, eight received a doxorubicin-based regimen and one received surgery. Of the eight who received chemotherapy, four (50%) achieved a CR, two a PR, one a minor response, and one was refractory to treatment. Of the four patients who achieved a CR, two subsequently relapsed. Neither responded to second-line therapy, and both died of disease.

The management of 5 of these 9 patients merits further comment. One patient, diagnosed before referral as having centrocytic lymphoma, was treated initially with cyclophosphamide, prednisone, and interferon, and sustained only a minimal response. On transfer to our institution, the diag-

Table 1. Clinical Features

Age, years (median)	21-82 (58)
Sex, (%)	
Male	11 (48)
Female	12 (52)
Constitutional symptoms, no. (%)	6 (26)
Ann Arbor stage, no. (%)	
I	1 (4)
II	9 (39)
III	5 (22)
IV	8 (35)
Total	23 (100)
Tumor burden, no. (%)	
High	5 (22)
Intermediate	7 (30)
Low	11 (48)
LDH, no. (%)	
Normal	11 (48)
High	8 (35)
Not Available	4 (17)
β_2 -microglobulin, no. (%)	
<3.0	4 (17)
≥ 3.0	6 (26)
Not available	13 (57)
Bulky mass(es), no. (%)	
1	4 (17)
>1	3 (13)
0	16 (70)
Organ involvement at presentation, no.	
Any lymph node	22
Peripheral lymph node	18
Mediastinal mass	4
Spleen	8
Liver	1
Lung	2
Bone marrow	3
Tongue	1
Vaginal	1
Epidural mass	1
Colon	1
Central nervous system	1

nosis was revised to T-cell-rich BCL. The patient was begun on our standard alternating triple therapy (ATT) regimen. She achieved a CR and was free of disease at 12 months of follow-up. A second patient received only a single course of Pro-MACE from an anticipated Pro-MACE-CytaBOM (cytarabine, bleomycin, Oncovin, methotrexate) regimen⁹ because of a severe allergic reaction. The treatment was changed to CHOP after referral to M.D. Anderson. The patient achieved a CR, but subsequently relapsed and refused further chemotherapy. Two patients diagnosed with large-cell lymphoma received MACOP-B. One patient did not respond to this therapy, whereas the second achieved a PR. Both patients' disease failed to respond to salvage treatment at our institution. Finally, the ninth patient was still in CR 8 months after a right hemicolectomy and partial ileectomy for intestinal lymphoma that involved regional lymph nodes. No adjuvant therapy was administered.

Six patients were diagnosed with Hodgkin's disease at

Table 2. Response to Therapy

Patient No.	Treatment	Response			Status	Follow-up (mo)
		1st Line	2nd Line	Relapse		
1	CYT/PRED, IFN, ATT	MR	CR	Y	A, NED	32+
2	MOPP-Bleo/XRT; MOPP-ABV/XRT	PR	PR	Y	DD	11
3	DNAP/CHOD	CR		N	A, NED	36+
4	CHOP-Bleo/OPEN	CR		N	A, NED	13+
5	CHOP/XRT	PR	NR	Y	AWD	18+
6	Surgery	CR		N	A, NED	8+
7	MACOP-B/MINE/ESHAP	CR	NR	Y	DD	9
8	Pro-MACE/CHOP	NR*	CR	Y	AWD	23+
9	ATT	CR		N	A, NED	8+
10	ATT	CR		Y	A	
11	ATT	U		U	A, U	4+
12	MOPP/XRT; ASHAP, ABMT	CR	PR	Y	DD	16
13	XRT/CHOP; MINE/HAPES	CR	PR	Y	DD	15
14	MACOP-B; MINE/ESHAP/XRT	PR	PR	Y	AWD	17+
15	CHOP-Bleo/XRT; MINE/ESHAP	CR	CR	Y	A, NED	140+
16	Pro-MACE-MOPP	CR		N	A, NED	5+
17	CHOP/XRT; COP; MINE/ESHAP	PR	PR	Y	AWD	30+
18	MOPP-ABVD; ABMT	CR		Y	DD	24
19	ATT	CR		N	A, NED	7+
20	ATT	U		U	A	2+
21	ABVD; MINE/ESHAP	CR	U	Y	A	8+
22	CHOP/OPEN/XRT	U		U	A	1+
23	CHOP/OPEN	U		U	A	1+

Abbreviations: A, alive; ATT, alternating triple therapy; AWD, alive with disease; CR, complete response; CYT, cytarabine; DD, dead of disease; IFN, interferon; NED, no evidence of disease; N, no; NR, no response; PR, partial response; PRED, prednisone; U, unassessable (currently receiving treatment); XRT, radiotherapy; Y, yes.

their referring hospitals. Of these, four patients were treated with MOPP, MOPP-ABVD, or ABVD before coming to our institution. Three of these four patients died of disease. Two initially attained a CR, but relapsed within 12 months of starting treatment.

Eight patients had been initially evaluated and treated at M.D. Anderson. Three are currently receiving therapy and are not assessable for response. All five remaining patients achieved a CR; however, one patient relapsed 3 months after termination of therapy. Interestingly, this patient presented with pulmonary and mediastinal disease 30 years after having received radiotherapy for breast carcinoma. At this writing, the other four patients had CRs ranging from 5 to 36 months in duration.

In summary, of the 13 patients treated with regimens considered standard for intermediate grade lymphomas, nine (70%) attained a CR. At the time of this report, eight of these (89%) were alive with no evidence of disease (median follow-up, 8 months).

DISCUSSION

The occurrence of clonal B-cell neoplasms with a preponderant infiltrate of presumably reactive T lymphocytes was first recognized by Jaffe et al¹⁰ in a report of "pseudo-peripheral T-cell lymphoma." Mirchandani et al¹¹ later reported a series of similar cases. The term T-cell-rich BCL was coined by Ramsay et al, who described five B-cell lymphomas in which clonal B cells were estimated to comprise less than 10% of lymphoid cells.¹

A relatively large series of T-cell-rich BCL composed of 19 cases was recently published by Macon et al.¹² These findings are parallel to ours in regard to the confusion with other histologic types and the favorable response to therapy when treated appropriately. Because of the paucity of neoplastic cells, histologic examination and evaluation of light-chain restriction may be insufficient to establish a diagnosis of T-cell-rich BCL. Osborne et al³ found Southern blotting to be a consistently reliable and definitive method of distinguishing such cases from peripheral T-cell lymphoma. However, clonal proliferations accounting for less than 5% of a cell population may be difficult to detect by conventional Southern blot analysis. Special modifications of the polymerase chain reaction using primers for complementary determining regions and consensus JH and variable region sequences have proven useful in our hands in documenting the presence of B-cell clones that elude detection by Southern blotting (unpublished observations, February 1992).

The patient population reported herein exhibited clinical features and responses to doxorubicin-based regimens that were comparable to those of B-cell large cell lymphoma of usual type. The 35% incidence of splenomegaly was higher than expected and is perhaps a characteristic clinical sign. However, the number of patients was small, and the potential clinical importance of splenomegaly will require examination in larger patient cohorts. A long history of localized peripheral adenopathies, as noted by Cooper et al,¹³ was not seen in our series. Conclusions about therapeutic response are limited by the number of patients and the short follow-

up interval. Of 13 patients treated with standard regimens for intermediate-grade lymphomas, 9 (70%) achieved a CR, a result consistent with the norm. The clinical significance of the preponderant T-cell response that characterizes these lymphomas is uncertain. Various investigators² have postulated a host-immune response to the neoplastic clone, analogous to that seen in Hodgkin's disease. In keeping with this hypothesis is the observation by some¹⁴ that the T-cell reaction tends to diminish as the disease progresses and escapes immune surveillance. Alternatively, it could represent a response of the reactive T cells to some cytokine secreted by the tumor cells. In our study, histologic progression to large cell lymphoma of usual type was noted in 9 of 11 cases in which multiple biopsies, either from different sites or from different times, were studied. In four instances, this was observed in concurrent biopsies from different anatomic sites, and in five patients progression was observed over periods ranging from a few weeks to 10 months. Thus, T-cell-rich histology apparently is a highly unstable parameter of this disease. If this is true, it is not surprising that T-cell-rich BCL exhibits a clinical behavior that closely parallels that of B-cell large cell lymphoma of usual type.

Based on the foregoing and the accumulated experience to date, it would seem that the critical issue in T-cell-rich BCL is the need to distinguish it pathologically from Hodgkin's disease and other non-Hodgkin's lymphomas, principally peripheral T-cell lymphomas, with which it may be easily confused. Underscoring this imperative is the fact that six of our cases were referred with diagnosis of Hodgkin's disease. Of the four patients who received treatment based on this diagnosis, three have died of disease. Thus, the administration of inadequate initial therapy may compromise the potential for salvage and long-term survival. In summary, many aspects of T-cell-rich BCL remain unsolved. Among these are the precise immunophenotype and modulatory role of the infiltrating T cells and the question of whether, with longer follow-up, the response to therapy (including time to treatment failure and overall survival) will differ significantly from that obtained in patients with diffuse large-cell lymphomas of usual type. Prospective studies with more patients and sufficient follow-up periods will be required to answer these queries; however, the prelimi-

nary data presented herein do not support the contention that the T-cell-rich infiltrate exerts a significant clinical impact on the behavior of large cell lymphomas of B lineage.

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