

Surface Marker Identification of Small Cleaved Follicular Center Cell Lymphomas with a Highly Favorable Prognosis¹

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ABSTRACT

Between 1976 and 1980, 143 cases of non-Hodgkin's lymphoma have been prospectively analyzed for correlations between surface marker phenotype, histomorphology, and prognosis. This study analyzed 44 adults with tumors classified by Lukes-Collins criteria as small cleaved follicular center cell lymphomas. Two surface marker phenotypic subsets were studied based on the expression of either the second surface membrane immunoglobulin, immunoglobulin D (IgD), or a receptor for the third component of the complement system (C₃) (Group I = IgD⁺ and/or C₃⁺, group II = IgD⁻C₃⁻). Eleven of the 44 patients have died with a projected median survival of 58 months. Four patients in Group I have died with a median survival of 58 months while seven patients in Group II have died with a median survival of 30 months. The difference in the survival curves for the two subgroups is statistically significant ($p = 0.01$). An analysis of variables such as stage, age, sex, and sites of involvement revealed no differences between the two groups. When classified histologically, the two groups were morphologically indistinguishable and had similar distributions of nodular (follicular) and diffuse variants. Of interest, five patients in Group I were judged to require no initial therapy whereas none in Group II remained untreated initially. The expression of the second heavy chain δ and/or a receptor for C₃ appears to define a subgroup of small cleaved follicular center cell lymphomas with an indolent course and an excellent prognosis.

INTRODUCTION

Characterization of the surface marker phenotype of human lymphoid neoplasms has provided unique insights into human immunobiology. The clinical application of such studies has likewise added greatly to the ability to predict the biological behavior and response to treatment of this diverse group of neoplasms (1, 4, 8, 14, 20). Two indolent lymphoid tumors with a diffuse histological pattern, WDLL³ and CLL, with few exceptions, express a surface marker phenotype characterized by the second immunoglobulin IgD associated with IgM and a receptor for C₃ (1, 13). The purpose of this study was to examine whether this phenotype, if expressed by neoplastic

SCFCCs, a morphologically less well-differentiated malignant lymphoid neoplasm, was associated with a similar indolent behavior. SCFCC tumors which expressed a C₃ receptor and/or surface IgD in association with surface IgM were compared to cases in which these markers were absent.

Our results suggest that surface marker criteria can identify a subset of patients with SCFCC tumors with a highly favorable prognosis.

MATERIALS AND METHODS

Patient Selection

This investigation is a prospective study of surface marker phenotype in non-Hodgkin's lymphoma ongoing at Tufts-New England Medical Center and its associated institutions since 1976. All cases of non-Hodgkin's lymphoma seen by the Tufts-Lymphoma Group have been entered in this study, and as of December 1980, 143 adults over 15 years of age have been analyzed prospectively. Fresh tissue biopsies were simultaneously processed for routine pathological examination and surface marker phenotype determinations. Biopsies were classified without knowledge of the marker results according to both Rappaport (9) and Lukes-Collins (7) histopathological schemes. According to these criteria as generally applied, the Rappaport category poorly differentiated lymphocytic lymphoma allows up to approximately 30% large cells admixed with a predominant small-cell population. The category mixed lymphohistiocytic lymphoma contains approximately 30 to 50% large cells. Tumors with more than 50% of large cells would fall into the category "histiocytic" and would be classified by the Lukes-Collins scheme into a variety of large-cell categories. Surface marker phenotype determinations were made without knowledge of the histopathological diagnoses.

Within this group, a subset of 44 cases classified as SCFCC tumors by Lukes-Collins criteria were identified and form the basis of this report. Patients with CLL and its variants and those with WDLL were not included in the SCFCC tumor group. In addition, patients with concurrent second cancers, those who had been treated at the time of biopsy, or patients whose marker phenotype was based on blood or bone marrow analysis alone were excluded as well. Phenotype and histological analyses were done on initial diagnostic biopsies in 38 patients. Six patients included in the analysis presented in relapse several years after initial diagnosis. Two of them had previously received local radiotherapy or single-agent chemotherapy, but none were being treated at the time of rebiopsy. In each of these cases, the repeat histological category corresponded to the initial interpretation.

Staging and Treatment

During this period, patients were staged according to the Ann Arbor staging system (5). Staging studies in each case included a bone marrow biopsy and either a lymphangiogram or a total body computer tomography scan. Staging laparotomy was performed in selected cases.

The general policy during this period was to treat Stage I and II patients with curative radiotherapy. Stage III and IV patients were treated according to histological criteria. Patients with nodular (follicular)

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³ The abbreviations used are: WDLL, well-differentiated lymphocytic lymphoma; CLL chronic lymphocytic leukemia; C₃, third component of the complement system; SCFCC, small cleaved follicular center cell; Smlg, surface membrane immunoglobulin.

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ular) tumors had either no initial therapy or treatment with a single alkylating agent. If significant risk factors were present then multiagent chemotherapy with Cytoxan-vincristine-prednisone (11) was used. Diffuse tumors were treated with the Adriamycin-containing multiagent regimen bleomycin Adriamycin-Cytoxan-Oncovin-prednisone (19), Cytoxan-Adriamycin-Oncovin-prednisone (6), or Cytoxan-Oncovin-prednisone-procarbazine (18) if there was a contraindication to the use of both Adriamycin and bleomycin.

Histopathological Studies

The fresh biopsy material was divided into 2 portions. One portion was processed for routine pathology, including Wright-Giemsa-stained touch preparation, hematoxylin and eosin staining of formalin- and B-5-fixed material, and a battery of special histochemical stains such as periodic acid-Schiff, methyl green pyronin, and reticulin. Nonspecific esterase and acid phosphatase stains were used in certain cases.

Surface Marker Studies

The second portion of the biopsy material was submitted for surface marker analysis. Single-cell suspensions were prepared by mincing of tissue in Hanks' balanced salt solution under sterile conditions with subsequent passage through hypodermic needles of decreasing bore. The cells were then layered on a Ficoll-Isopaque density gradient and centrifuged at 1500 x g for 0.5 h. Mononuclear cells at the interface were washed in Hanks' balanced salt solution, and the monocyte content was assessed by *in vivo* and Wright-stained morphology, glass adherence, neutral red dye staining, and latex particle ingestion. Cells were rid of cytophilic antibody by incubation of the cell suspension at 37° for 0.5 h followed by centrifugation and resuspension in fresh medium. Cell populations were divided into aliquots and examined for the following surface receptors.

Erythrocyte Rosettes. Erythrocyte rosette-forming cells were detected utilizing untreated and neuraminidase-treated sheep RBC by standard methods (2).

Surface Membrane Immunoglobulin. Cells were incubated with fluorescent conjugated antiimmunoglobulin reagents rendered monospecific for individual heavy and light chains as described previously (16, 17). If results were inconclusive in terms of distinguishing immunoglobulin monoclonality, additional assays were performed with fluorescent labeled F(ab')₂ fractions of antiimmunoglobulin reagents. Cells were also treated with trypsin, and then Smlg was reassessed after reexpression in tissue culture.

Complement Receptor. The C₃ receptor was determined according to the method of Bianco (3) using fresh mouse serum as a source of complement.

Definitions. Cell populations were defined as B-derived (Smlg⁺) when more than 40% of the tumor cell population expressed Smlg which was restricted to either κ or λ chain expression. In this series, 3 cases failed to express conventional markers and 2 of these were termed nonexpressive (null). The third was composed exclusively of erythrocyte rosette-positive cells and was defined as T derived.

Tumor populations were considered to be C₃⁺ when at least 15% of cells expressed this marker. In the vast majority of cases, >30% of the cells were positive; however, in 3 cases, 15 to 30% of cells expressed the marker and were considered to be C₃ positive.

Two subsets of SCFCC tumors were defined based on the expression of the second Smlg heavy chain IgD and a receptor for C₃. Group I consisted of cases which were Smlg⁺ (usually IgM) and IgD⁺ and/or C₃⁺. Group II was defined as all cases which failed to express IgD and C₃ receptors.

Statistical Analysis

The survival experience of subsets of patients was analyzed using life table methods and is expressed as total survival (10). Comparisons

of survival curves for significance were made using the log rank test (10).

RESULTS

Clinicopathological Characteristics of SCFCC Tumors. The clinicopathological characteristics of the entire group of 44 patients are summarized in Table 1.

SCFCC tumors have a modest predominance (male/female = 1.4) and occur in an older age group. Although 2 younger patients (<40 years) were seen, the majority were elderly (median, 62 years) with 13 patients over 70 years of age. The majority of patients had advanced disease (Stages III and IV). Only 5 patients (11%) were in Stages I and II. Extranodal sites of involvement in Stage IV patients were consistent. Most patients had involvement of reticuloendothelial organs such as marrow, liver, spleen, and blood. A second large category of involvement was the gastrointestinal tract.

Clinicopathological and Immunological Phenotype Characteristics of the IgD⁺ and/or C₃⁺ (Group I) and IgD⁻C₃⁻ (Group II) Subsets. The group of 44 patients was divided into 2 groups based on the expression of a C₃ receptor and/or IgD. In the positive group, the percentage of cells in each population expressing a C₃ receptor ranged from 18 to 86% with a mean of 43%. The percentage of cells expressing IgD in each population was similar ranging from 15 to 90% with a mean of 45%.

The detailed clinicopathological characteristics of each group are listed in Table 2. The 2 groups were compared for various parameters to determine whether significant differences existed. The median age was similar for the 2 groups, 61 years (range, 40 to 85) for Group I and 59 years (range, 24 to 81) for Group II, and the number of elderly patients (>70 years) was equal (n = 6) in both groups. Group I, however, contained 12 females and 10 males as compared to the increased number of males in Group II (15 males and 7 females).

The distribution of stages and extranodal sites of involvement were also similar for the 2 groups. The majority of cases were Stages III and IV, with a similar incidence of bone marrow, liver, spleen, and gastrointestinal tract involvement. Group I con-

Table 1
Clinicopathological characteristics of 44 SCFCC tumors

Characteristic	No.	%
Sex		
Male	26	59
Female	18	41
Age		
Median (yr)	62	
Range (yr)	24-85	
>70 yr	13	
Stage		
I	2	5
II	3	7
III	8	18
IV	31	70
Extranodal sites of involvement		
Marrow	15	
Liver	9	
Spleen	5	
Gastrointestinal tract	8	
Blood	2	
Gonad	2	

tained 16 cases with Stage IV and 4 cases with Stage III disease as compared to Group II which contained 15 cases with Stage IV and 4 cases with Stage III disease.

It is important to note that the distribution of nodular (follicular) and diffuse variants was virtually identical in the 2 phenotypic groups. In Group I, there were 12 nodular tumors as compared to 13 in Group II. There were 7 patients in Group I with mixed nodular and diffuse tumors compared to 10 patients in Group II. Exclusively diffuse tumors were found in 10 patients

in Group I and 9 patients in Group II.

Patients were treated according to the schema outlined previously. A comparison of treatment revealed that the number of patients in each group receiving radiation therapy and single-agent chemotherapy was identical (4 and 2 in each group, respectively). The number receiving multiagent chemotherapy was also similar; 6 in Group I (versus 9 in Group II) received Cytoxan-vincristine-prednisone and 5 in Group I (versus 7 in Group II) received ≥ 3 drug combination chemotherapy. Group

Table 2
Clinicopathological and immunological phenotypic characteristics of Group I and Group II patients with SCFCC lymphomas

Case no.	Age (yr)	Sex	C ₃	IgD	Stage	Rappaport category	Extranodal sites	Treatment	Survival (mos.)
IgD⁺ and/or C₃⁺ (Group I)									
1	40	F	+	-	IV	DPDLL ^a	Ovary	C-MOPP	58
2	59	M	+	-	III	DPDLL	Marrow	BACOP	56+
3	63	M	+	-	IV	DPDLL	Marrow, liver	BACOP	48
4	47	M	+	-	IV	NPDLL	Marrow	CVP	46+
5	69	M	-	+	I	NPDLL		Radiotherapy	42+
6	65	M	-	+	IV	NPDLL		None	39
7	79	F	-	+	IV	DPDLL	Marrow	CP	31+
8	83	F	+	-	III	DPDLL		CVP	22+
9	55	M	-	+	II	NPDLL		None	30+
10	76	M	-	+	IV	NDMLH ^b	Marrow, blood, liver	None	29+
11	61	F	-	+	III	DPDLL		None	29+
12	73	F	+	+	IV	DPDLL	Marrow, liver	CHOP	23+
13	72	F	-	+	IV	DMLH ^b	Marrow, liver, spleen		39+
14	60	F	-	+	IV	DPDLL	Marrow, spleen, kidney, lung	None	48+
15	67	M	+	-	II	NPDLL		Radiotherapy	24+
16	61	F	-	+	IV	NPDLL	Spleen, blood	Radiotherapy	135+
17	45	F	-	+	IV	NPDLL	Marrow, liver, spleen	C	156+
18	50	M	-	+	III	NPDLL		CVP	6+
19	60	F	+	-	IV	DPDLL	Lung	CHOP	11+
20	85	M	+	+	IV	NPDLL	Marrow, liver, G.I.	CVP	4+
21	45	F	+	-	IE	DPDLL	G.I.	Radiotherapy, surgery	87+
22	55	F	+	-	II-IV	NPDLL	G.I.	CVP	4+
IgD⁻ C₃⁻ (Group II)									
23	24	M	-	-	IV	NPDLL	Marrow, liver	BACOP	8
24	57	F	-	-	II	NPDLL		Radiotherapy, CVP	21+
25	74	M	-	-	IV	NPDLL	Liver, G.I.	CVP	15+
26	49	M	-	-	III	NPDLL		CVP	15+
27	76	M	-	-	IV	DPDLL	Marrow	BACOP	12+
28	41	F	-	-	IV	NPDLL		CVP	7+
29	51	M	-	-	IV	NPDLL	G.I.	CVP	2+
30	45	F	-	-	IV	DPDLL	Cheek, eye	CHOP	10+
31	55	M	-	-	IE	DPDLL	Waldeyer's ring	Radiotherapy	13
32	78	M	-	-	IV	DPDLL	Marrow, blood, spleen	CHOP	30
33	81	M	-	-	IV	DPDLL	Peritoneum, G.I.	CVP	2
34	36	M	-	-	IV	NPDLL	Marrow, G.I.	BACOP	43+
35	77	F	-	-	IE	DPDLL	Parotid	Radiotherapy	31+
36	41	F	-	-	IV	NPDLL	Ovary, G.I.—mesentery	CVP	27+
37	47	M	-	-	III	NPDLL		Chlor, CVP	24
38	62	F	-	-	IV	NPDLL	Spleen, liver	CVP	36+
39	67	M	-	-	III	DPDLL		CVP	24+
40	60	M	-	-	IV	DPDLL	Central nervous system	BACOP	5
41	70	M	-	-	I	NPDLL		Radiotherapy	9+
42	65	M	-	-	III	DPDLL		C-MOPP	21+
43	80	F	-	-	IV	DMLH ^b	Marrow	CVP	9
44	35	M	-	-	IV	NPDLL	Marrow	C	24+

^a DPDLL, diffuse poorly differentiated lymphocytic lymphoma; NPDLL, nodular poorly differentiated lymphocytic lymphoma; NDPDLL, nodular diffuse poorly differentiated lymphocytic lymphoma; NDMLH, nodular diffuse mixed lymphohistiocytic lymphoma; DMLH, diffuse mixed lymphohistiocytic lymphoma; G.I., gastrointestinal tract; C-MOPP, Cytoxan-Oncovin-prednisone-procarbazine; BACOP, bleomycin-Adriamycin-Cytoxan-Oncovin-prednisone; CVP, Cytoxan-vincristine-prednisone; CP, Cytoxan-prednisone; CHOP, Cytoxan-Adriamycin-Oncovin-prednisone; C, Cytoxan; Chlor, chlorambucil.

^b These tumors were composed of a mixed cell population containing approximately 30% large lymphoid cells and were classified as SCFCC by the Lukes-Collins system.

II therefore was a somewhat more aggressively treated group. The major difference was, however, that 5 patients in Group I received no initial therapy as compared to none in Group II. The decision to withhold treatment was based on the clinical assessment by the physician that the biological behavior of the tumor was indolent.

A summary of immunological phenotype expressed by the 2 groups is seen in Table 3. The predominant immunoglobulin expressed on the cell surface was IgM, but several IgG-bearing clones were seen in Group II. There was a predominance of λ -bearing clones in Group II causing a reversal of the usual κ/λ ratio that was seen in Group I.

Survival According to Surface Marker Characteristics. The actuarial survival experience of the entire group of patients with SCFCC tumors was analyzed and is seen in Chart 1. To date, 11 of 44 patients have died with a projected median survival of 58 months. Chart 2 illustrates the actuarial survival of the 2 phenotypic subgroups. Four patients in Group I have died as compared to 7 in Group II. The median survival for Group I is 58 months as compared to 30 months for Group II. The difference between these curves is highly statistically significant ($p = 0.01$). It should be noted that 2 patients in the

Table 3
Immunological characteristics of patients with SCFCC lymphomas

Smlg	Group I	Group II
Immunoglobulin isotype		
M κ	11	6
M λ	8	8
G κ	2	0
G λ	1	5
Total κ	13	6
Total λ	9	13

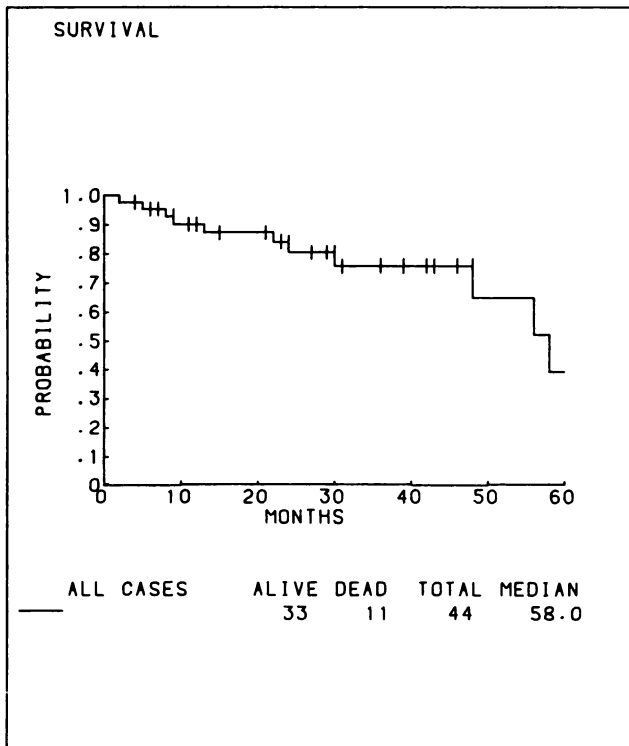


Chart 1. Actuarial survival for all SCFCC lymphomas.

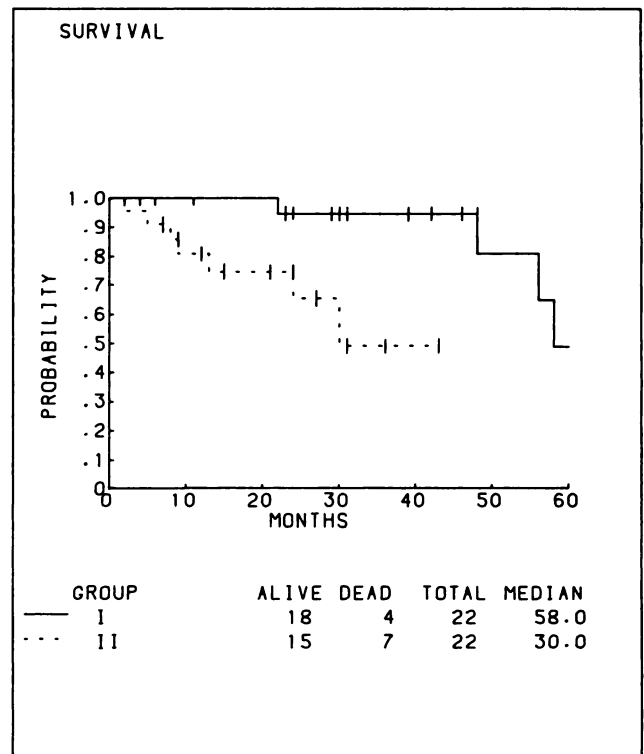


Chart 2. Actuarial survival for SCFCC lymphomas according to the membrane marker phenotypes Smlg⁺C₃⁺ and/or IgD⁺ (Group I) and Smlg⁺C₃⁻IgD⁻ (Group II).

positive group died at 56 and 22 months of causes unrelated to their lymphoma. For the purpose of this analysis, they were considered as censored data. They are responsible for a large portion of the dip in the Group I survival curve. Had they been included as noncensored data in the calculation, the difference in the curves would have been even more significant.

In spite of the more favorable survival experience of Group I patients, durable complete remissions to treatment were not often observed. All patients in Group I who were treated and achieved remission status have since relapsed at a time distant to induction. Relapse, however, was not generally associated with subsequent death since most patients could be managed successfully with alternate treatment. Furthermore, patients who only achieved partial remission status did not succumb rapidly to their disease. They survived in partial remission for long periods of time requiring periodic therapy. Finally, with regard to the 5 patients in this group who initially were given no treatment, 4 of the 5 remain alive and still require no treatment from 29 to 48 months since initial diagnosis. The fifth patient died at 39 months.

DISCUSSION

This study examined patients with neoplasms of SCFCCs in order to distinguish whether there are distinct surface marker phenotypic subgroups with differing prognoses within this histomorphological variant. We chose to analyze 2 groups based on the expression of the second amplifier immunoglobulin, IgD, and a receptor for C₃ since these markers are expressed on the bulk of normal peripheral B-lymphocytes and this marker phenotype is commonly expressed by the 2 indolent (well-

differentiated) lymphoid neoplasms, CLL and WDLL. It was our intent to establish the existence of this marker phenotypic subset within the morphologically less well-differentiated lymphoma of SCFCC and compare clinical, histopathological, immunological, and survival characteristics of the 2 phenotypic variants.

Our data is consistent with the concept that SCFCC tumors as defined by the Lukes-Collins classification are derived from the B-cell subset. With 3 exceptions, these tumors express monoclonal Smlg. In this series, one-half of the tumors expressed the phenotype Smlg⁺ (IgD⁺ and/or C'3⁺). The remainder expressed only Smlg (IgM or IgG), or uncommonly, no conventional markers were expressed (null). By applying either of the commonly used histopathological schemes, one could not distinguish these 2 marker phenotypic subsets. Group I and Group II had similar distributions of nodular (follicular) and diffuse histological patterns and did not differ significantly in cellular morphological characteristics. Survival for the group of 44 SCFCC tumors as a whole was favorable (median, 58 months). However, 11 of 44 patients died during the study period. Our data suggests that immunological phenotype analysis may be useful in distinguishing a highly favorable subset of these tumors. The analysis of survival between Group I and II patients revealed a significant survival advantage for the IgD⁺ and/or C'3⁺ patients. The less aggressive biological behavior of the Group I tumors parallels the behavior CLL and WDLL in spite of the difference in morphological appearance. It would appear that this phenotype confers a favorable prognosis in spite of the overlap in morphological categories.

Portlock and Rosenberg (12) have recently described a subset of patients with several histological types of non-Hodgkin's lymphoma with an extremely indolent course and a highly favorable prognosis. Many of these patients received no initial or subsequent treatment and survived for many years in apparent symbiosis with their disease. In this series, we report 5 patients in Group I who received no initial therapy since their tumor was judged to be not biologically aggressive. We would suggest that certain of these patients as defined by surface marker criteria may be equivalent to the patients identified by Portlock and Rosenberg (12) on the basis of a retrospective clinical analysis. If confirmed, surface marker criteria may be useful in prospectively identifying relatively asymptomatic patients in whom initial treatment may be withheld.

Finally, the results of treatment in this group of SCFCC tumors should also be commented upon. Group I contained no patients followed for 3 years or more who have not relapsed following primary therapy or who are currently free of disease. Patients in this group have tended to have nonaggressive disease which is widespread and difficult to eradicate completely even with intensive chemotherapy. Furthermore, in those patients who do achieve complete remission status, late relapse was often the rule. It would appear that, although certain SCFCC tumors have an excellent prognosis, the ability to produce durable complete remissions may be limited. The

question of potential chemotherapy curability of SCFCC tumors must await longer follow up of this group of patients.

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