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Chromosomal Abnormalities in Patients with Non-cutaneous T-cell Non-Hodgkin's Lymphoma

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In contrast to non-Hodgkin's lymphomas (NHL) with a B-cell phenotype, almost no data have been reported dealing with correlations between chromosomal abnormalities and characteristics of the disease in patients with T-cell NHL. In a retrospective analysis we studied all patients with a non-cutaneous T-cell NHL and chromosomal abnormalities that were evaluated at our institution; 20 patients could be identified. Numerical abnormalities involving chromosomes 3, 4, 5, 22 and X were observed most frequently. Structural abnormalities involved mainly the breakpoints 1q22–25, 6q23 and 11q13. There appeared to be an association between +7, breakpoints 2p23–24, 4p14–15, 8q21 and the presence of extranodal disease. All patients with +7 had a diffuse mixed histology. Patients with +2, +3, +11, +17, +18, +20 or breakpoint 1q22–25 had an immunoblastic lymphoma and patients with breakpoints 9q32–34 or 14q12 had a lymphoblastic lymphoma. No correlations were observed between chromosomal abnormalities and response to therapy, survival or phenotypic markers. Abnormalities involving the chromosomes containing the T-cell receptor genes and T-cell markers were infrequent. Several breakpoints were identified that correlate with already described oncogenes.
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INTRODUCTION

SEVERAL STUDIES describing chromosomal abnormalities in patients with non-Hodgkin's lymphoma (NHL) have been published. They not only suggest that some abnormalities occur frequently, but also that particular karyotypes are correlated with characteristics of the disease [1–11]. The overwhelming majority of patients studied have NHL with a B-cell phenotype. The number of patients with cytogenetically studied T-cell NHL is much smaller [6, 9, 12–16] and few correlations between chromosomal abnormalities and characteristics of the disease have been reported.

Therefore, in order to analyze the particular chromosomal abnormalities that are related with non-cutaneous T-cell NHL, we performed a retrospective analysis of all patients with non-cutaneous T-cell NHL who had an abnormal cytogenetic analysis and were treated by the Nebraska Lymphoma Study Group.

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MATERIALS AND METHODS

Patient characteristics

In a retrospective analysis of the records of the Nebraska Lymphoma Study Group, 20 patients could be identified with non-cutaneous T-cell NHL who had an abnormal cytogenetic analysis. All tissues examined were involved with lymphoma. A piece of the same tissue utilized for cytogenetic analysis was also studied histologically and, using an immunoperoxidase technique, was shown to be of T-cell origin. The working formulation classification was used [17].

The clinical staging consisted of a complete history and physical examination, chest radiograph, computed tomography scan of the abdomen and chest, and bone marrow biopsy. The patients were staged according to the Ann Arbor system [18].

In 14 patients (1–14), the tumor was studied at the time of primary diagnosis; in four patients (15–18) the tumor was studied at relapse. For three patients (6, 19, 20) no other information than the histological diagnosis, age and sex was available, because they were only referred for histological and cytogenetic analysis.

The clinical characteristics of the patients are listed in Table 1. The median age was 58 years (range 15–91). There was a preponderance of males (65%). No patients with cytogenetic abnormalities had NHL of low grade malignancy, seven patients had NHL of intermediate grade and 13 patients had high grade malignancy according to the working formulation [17]. Two patients had stage I disease, five stage II disease, one stage III disease and nine stage IV disease. 25% had B symptoms, 15% an elevated lactate dehydrogenase (LDH) (twice normal value), 35% bulky disease (diameter > 5 cm), 50% extranodal localizations of disease, 35% marrow infiltration and 15% skin involvement.

Cytogenetic methods

The methods of culturing and processing the lymph nodes are described elsewhere [20]. In short, after mechanically mincing the tissue in RPMI 1640 (Gibco, Grand Island, NY) including 20% fetal bovine serum and antibiotics the cell suspensions were incubated at 37.5°C and cultured for 24 and 48 h without the use of mitogens. After the exposure to Colcemid (0.05 μg/ml) (Gibco, Grand Island, NY), the preparations were resuspended in 0.074 mol/l KCl for 10 min and fixed with a 3:1 mixture of methanol and glacial acetic acid. After repeating the fixation process three times, the slide preparations were made, aged overnight at 60°C and G-banded with Wright's stain. All metaphase plates were microscopically analyzed, recorded, and photographed. An abnormal clone was defined as two or more cells with the same structural abnormality or the same extra chromosome, or the presence of three or more cells with the same missing chromosome. Normal cells were considered to be present if a single cytogenetically normal cell was seen. If these criteria were not fulfilled or less than five normal mitotic cells were present or the results were too poor to analyze, the test was classified as inconclusive and excluded from analysis. The karyotypes were designated according to the international system for human cytogenetic nomenclature (ISCN 1985) [21].

RESULTS

Twenty patients with a non-cutaneous T-cell NHL and an abnormal karyotype were identified. In 13 patients (1–9 and 16, 17, 19, 20) a mixture of normal and abnormal cells was found and seven patients (10–15 and 18) only displayed abnormal karyotypes. Patient 8 appeared to have two cytogenetically

Table 1. Clinical information about patients with non-cutaneous T-cell NHL and chromosomal abnormalities

Patient	Age/sex	Histology and stage*		Bulky disease†	Extranodal disease‡	Elevated LDH§	First therapy‖ and DFS	
1	56/M	IBL	IIIa	+	–	–	CAP-BOP,	
2	71/F	DM	IIa	+	–	–	CAP-BOP,	
3	86/F	IBL	Ia	–	–	–	RT,	
4	59/M	IBL	IIb	+	–	–	CAP-BOP,	
5	58/M	IBL	IVb	–	M	–	CAP-BOP,	
6	23/M	IBL	NA	NA	NA	NA	NA	
7	60/M	DM	IVb	–	L,G,H	–	CAP-BOP,	9
8	21/M	LB	IVa	–	M	–	CAP-BOP,	28
9	73/M	IBL	IVb	–	M	–	CAP-BOP,	12
10	77/F	DS	IVa	+	M,S	+	CAP-BOP,	60+
11	75/M	DL	IVa	–	M	–	CAP-BOP,	8
12	15/F	LB	IIa	+	–	+	CAP-BOP,	
13	22/M	LB	IVa	+	M	+	CAP-BOP,	0
14	37/M	DM	IVa	–	S	–	CAP-BOP,	23
15	22/M	LB	Ia	+	–	–	¶	2
16	74/F	DM	IIa	NA	S,N	NA	¶	0
17	64/F	IBL	IIa	–	–	–	¶	0
18	17/M	DM	IVb	–	M,H	–	¶	8
19	68/F	IBL	NA	NA	NA	NA	NA	12
20	91/M	IBL	NA	NA	NA	NA	NA	53+

*Histologic subtype [17]: DS: diffuse small cleaved NHL; DM: diffuse mixed NHL, DL: diffuse large cell NHL, IBL: immunoblastic lymphoma, LB: lymphoblastic lymphoma.

†Bulky disease: +: > 5 cm, –: < 5 cm, NA: no information available.

‡Extranodal disease: L: lung, G: gastrointestinal tract, S: skin, H: liver, M: marrow, N: nasopharynx, NA: no information available.

§+: elevated (twice normal), –: normal or elevated less twice normal, NA: no information available.

‖RT: involved field radiotherapy; CAP-BOP: cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, and prednisone [19].

¶: cytogenetic analysis at relapse.

DFS: disease-free survival.

Table 2. Abnormal karyotypes of patients with T-cell NHL

Patient	Karyotype
1	46,XY/47,XY,+2,+3,−4,−13,+i(1q), t(1;7;11)(q22;q36;q13), t(4;14)(q26;?q32)
2	46,XX/45,XX,−6,del(6)(q23),t(10;?)(q25;?),dup(11)(q13q23)
3	46,XX/60,XX,+X,+1,−2,.+3,−4,+5,+6,+8,+9, +11,+12,+13,+17,+18,+20,+21,+22,+del(1)(q23)
4	46,XY/46,XY,−1,+t(1;1)(p32,q25),t(6;14)(q23;qter)
5	46,XY/47,XY,+22
6	46,XY/65,XY,+X,+1,+2,+3,+3,+5,+6,+12,+14, +15,+16,+17,+18,+20,+t(13;?)(p11;?). +t(19;?)(q13;?), +3mar
7	46,XY/47,XY,−1,−14,−15,+del(1)(p13), +del(1)(p13),t(6;8)(p24;q21), del(17)(q23), +2mar1
8	46,XY/46,XY,t(14;?)(q32;?)/46,XY,del(7)(p15), t(14;?)(q32;?)
9	46,XY52,XY,+2,+5,+11,+15,+19,+22, t(2;6)(q36;q23)
10	45,XX,−17,−17,t(2;8)(p24;q21), i(17q),+mar
11	50,XY,+X,+Y,−4,+5,+21, +der(4)t(4;11)(p14;q13)
12	47,XX,+5,t(9;14)(q32;q12)
13	46,XY,t(11;14)(p15;q12)
14	46,XY,t(9p;?)
15	54,XY,+X,+Y,+21,+22,t(2;3)(q37;q21), t(9;?)(q34;?), +4mar
16	46,XX/53,XX,+1,+6,+7,+8,+9,+12,+16
17	46,XX/47,XX,+11,i(15q)
18	47,XY,+7,del(2)(p23), del(4)(p15), del(18)(p11)
19	46,XX/47,XX,+3
20	46,XY/46,XY,t(1;?)(p36;?), t(5;?)(p15;?)/4n+/−

abnormal clones of malignant cells having a 14q rearrangement in common (see Table 2). All but three patients had numerical abnormalities. Most frequently, gains of chromosomes 3, 5, 22 and X were observed, but also gains of chromosomes 1, 2, 6, 11, 12 and 21 were found in three patients each (Fig. 1). In four patients marker chromosomes were present. Monosomies were also found and occurred more than once in chromosome 2 and 4. Combining these numerical abnormalities, chromosomes 1 and 5 were involved in five patients each, and chromosomes 2, 3, 22 and X in four patients each.

Structural abnormalities were found in 18 patients. The distribution of the abnormalities is shown in Fig. 2. Breakpoints 2q36–37, 2p23–24, 4p14–15, 8q21, 9q32–34, 14q12 and 14q32 were each involved in two patients and 1q22–25, 6q23 and 11q13 each in three patients. One patient (p13) had a t(11;14)(p15;q12).

All patients with +7 (n = 2), breakpoints 2p23–24 (n = 2), 4p14–15 (n = 2) or 8q21 (n = 2) had extranodal disease. All

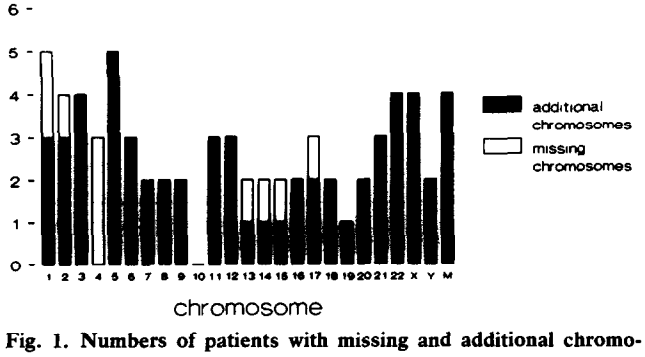

Fig. 1. Numbers of patients with missing and additional chromosomes.

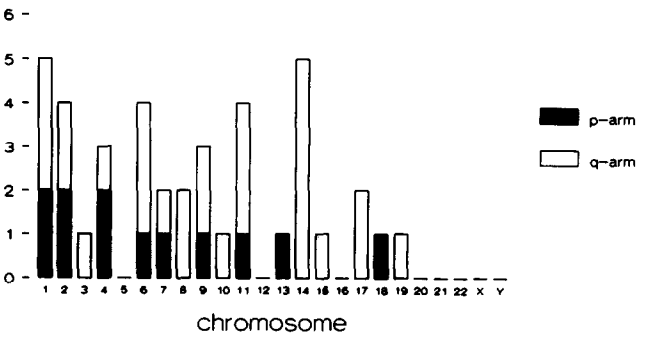

Fig. 2. Numbers of patients with structural abnormalities involving the short (p) and the long (q) arms.

patients with a breakpoint 8q21 (n = 2) or a +8 (n = 2), or a +11 (n = 3) or a breakpoint 6q23 (n = 3) had a higher age than the median of the entire group. The patients with +7 both had diffuse mixed lymphoma. All patients with +2 (n = 3), +3 (n = 4), +11 (n = 3), +17 (n = 2), +18 (n = 2), +20 (n = 2) or breakpoint 1q22–25 (n = 3) had an immunoblastic lymphoma. All the patients with breakpoint 9q32–34 (n = 2) or 14q12 (n = 2) had lymphoblastic lymphoma and were younger. The patients with 14q12 both had an elevated LDH. No correlations were found between a specific chromosomal abnormality and response to therapy or survival. We did not observe any relation between a particular chromosomal abnormality and the presence or absence of individual phenotypic markers (Table 3).

DISCUSSION

We have described the chromosomal abnormalities observed in 20 patients with a non-cutaneous T-cell NHL. A variety of abnormalities were found. These abnormalities could play a role in the development of the disease. This is most likely for the numerical abnormalities involving chromosomes 3, 4, 5, 22 and X (each in at least three patients) and the structural abnormalities occurring at the breakpoints 1q22–25, 6q23 and 11q13 (each in

Table 3. Immunologic phenotypes

	Phenotype					
Patient	CD2	CD3	CD4	CD5	CD7	CD8
1	+	+	+	+	ND	+
2	+	+	+	+	ND	−
3	+	+	+	+	ND	+
4	+	+	+	+	ND	+
5	+	+	+	+	−	−
6	+	+	−	+	ND	+
7	+	+	+	+	ND	−
8	+	+	−	+	ND	−
9	ND	+	+	+	+	−
10	ND	+	+	+	ND	−
11	+	+	+	+	+	−
12	+	+	+	+	+	+
13	ND	+	+	+	+	+
14	+	+	+	−	ND	−
15	−	+	−	+	+	−
16	+	+	+	+	ND	−
17	+	+	+	+	ND	+
18	ND	ND	ND	ND	ND	ND
19	+	+	−	+	ND	+
20	ND	+	+	−	−	−

three patients). Several other abnormalities were related with characteristics of disease.

Only one patient had a t(11;14), known to be associated with a T-cell phenotype [22–27]. All other previously described abnormalities such as t(8;14)(q124;q11), t(10;14)(q23;q11.2), inv(14)(q11;q32), t(14;14)(q11;q32), t(12;14)(q24;q11), t(7,9)(q34;q33) and t(1;14)(p32;q11) were not observed [28]. The T-cell receptor alpha and delta genes (TcRa and TcRd) are located on 14q11 [25,27] and an as yet unrecognized oncogene is possibly located at 11p13–15 [28]. In our study, two patients had a breakpoint at 14q12, in or close to this gene and only one patient had an abnormality involving 11p15.The other TcR genes are located at 7p15 (gamma) [29] and at 7q35 (beta) [30]. One patient had a breakpoint at 7p15 and another at 7q36 (close to TcR beta). Tcl–3 is located at 9q34 [31]. This area was abnormal in one patient; another had an abnormality involving 9q32. There is some evidence that breakpoint 17q23 might be of importance in T-cell neoplasms [32]; we had one patient with that breakpoint although not t(9;17) as was previously reported. So, in our study only a minority of patients had abnormalities of chromosomes involving the TcR genes as reported by others [12], and 14q32 was part of the abnormality in only two patients in contrast to others who reported a higher incidence [12]. The genes for CD2, CD7 and CD8 are located on chromosomes 4, 17 and 2, respectively [33–35]; no relation was found between these chromosomes and the presence or absence of these markers. Interestingly, the breakpoints occurring most frequently (1q22–25, 6q23 and 11q13) are known to be correlated with the oncogenes *ski*, *myb* and *bcl-1*/*int-2* [36].

In a recent study, Berger *et al.* [12] published their results for 17 patients and gave an overview of the literature. They observed that chromosomes 1 and 6q and breakpoints 2p11–14, 2p23–35, 17cen, 9p21–23 and 10p13–15 are of importance. In addition to Berger *et al.*'s observation we provided evidence for the importance of chromosomes 3, 4, 5, 22 and X. Levine *et al.* [5] also observed a high frequency of breaks at 1q21, 2q21, 3q27, 4q21 and 17q21 and also +19 in relation to T-cell lymphoma. Two of their patients with a +7 had a diffuse mixed histology as in our patients. However, Levine *et al.*'s patients with a large cell or lymphoblastic NHL did not have the chromosomal abnormalities we observed. The importance of chromosome 3 has already been discussed [37]. In our study +3 was related with an immunoblastic lymphoma. Fujita *et al.* [38] observed this abnormality in a patient with a large cell lymphoma but also in a patient with a diffuse mixed NHL. The Fifth International Workshop [9] observed that +3 was always associated with a diffuse mixed type or adult T-cell leukemia/lymphoma. We did not observe abnormalities of 14p and 19p, as described by Fujita *et al.* [38]. In our study, +12 was always accompanied by other cytogenetic abnormalities and never with small lymphocytic histology as reported elsewhere [9]. In our study, only one patient had a 6p24 breakpoint close to 6p23 shown to be correlated with a T-cell phenotype by others [6, 9]. We could not confirm the significant correlation between 1p and T-cell NHL [9]; only two patients had an abnormal 1p, with different breakpoints. We are not aware of reports suggesting correlations between a particular chromosomal abnormality and age or presence of extranodal disease.

Chromosomal studies in malignant lymphoma are very promising in unravelling correlations between cytogenetic abnormalities and characteristics of disease. Future studies involving more patients and also including oncogene analysis are necessary to enhance our knowledge.

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Thymidine Labelling Index as Prognostic Factor in Resected Non-Small Cell Lung Cancer

Angela Alama, Massimo Costantini, Lazzaro Repetto, P.F. Conte, Jacopo Serrano, Angelo Nicolin, Federica Barbieri, Andrea Ardizzoni and Paolo Bruzzi

To assess the prognostic value of tumor proliferative activity, 89 patients with operable non-small cell lung cancer were studied. Tumor samples were obtained during surgery and cell kinetics were analyzed by the *in vitro* thymidine labelling index (TLI). The overall median TLI (2.9) was used to identify two subsets of patients with high and low proliferating tumors. In univariate analysis survival was significantly longer in patients with lower TLI ($P = 0.047$) and with stage I–II ($P = 0.003$) and T1–T2 tumors ($P = 0.043$). In multivariate analysis, stage was the most important prognostic parameter ($P = 0.004$). The risk of death for patients with TLI higher than 2.9 was increased (hazard ratio = 2.01, CI = 0.96–4.27).
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INTRODUCTION

PROGNOSIS in patients with non-small cell lung cancer (NSCLC) is generally poor, even when the disease is resectable at diagnosis. Among operated patients, 5 year survival ranges from 27% to 37% and no factor, except stage, has been consistently shown to influence survival [1, 2]. The thymidine labelling index (TLI) is the percentage of cells in DNA synthesis in a tumor population, which reflects proliferative activity [3, 4]. Tumor proliferative activity correlates with clinical factors, including receptor status, grading, histology, tumor size, and with prognosis in tumors such as breast cancer, non-Hodgkin's lymphoma, myeloma and leukemia [5–9]. In contrast, little is known about NSCLC growth rate and its importance in prognosis [10, 11]. We have investigated the relation between clinical and kinetic indices and have assessed the prognostic importance of TLI in patients operated on for NSCLC.

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