Molecular Characterization of the t(2;5)(p23;q35) Translocation in Anaplastic Large Cell Lymphoma (Ki-1) and Hodgkin’s Disease

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The precise cellular origin and the pathogenetic mechanism(s) leading to the neoplastic transformation of anaplastic large cell lymphoma (ALCL) and the Reed-Sternberg cell of Hodgkin’s disease (HD) remains largely uncertain. Classical cytogenetic analysis has shown a unique translocation involving bands 2p23 and 5q35 bands in a variable number of ALCLs. It has been recently shown that the nucleophosmin/B23 (NPM) gene (5q35) and a novel anaplastic lymphoma kinase (ALK; 2p23) are the fused genes of t(2;5). To investigate the presence and the precise frequency of NPM-ALK gene products among ALCL and HD cases, a large and well-characterized panel of ALCL (n = 49) and HD (n = 72) cases was studied using multiple strategies including reverse transcriptase-polymerase chain reaction (RT-PCR), Southern blot analysis, and immunohistochemistry. Overall, 6 (3 T and 3 null) of 49 ALCL and 3 (2 nodular sclerosis and 1 mixed cellularity) of 72 HD showed the presence of NPM-ALK transcripts by RT-PCR. NPM-ALK gene rearrangements were detected in all RT-PCR, NPM-ALK-positive ALCL by Southern blot analysis. Furthermore, in all the available cases we were able to show the presence of ALK-related protein using a specific polyclonal antiserum recognizing the cytoplasmic domain of ALK by immunohistochemistry. Our data show that NPM-ALK gene transcripts are identified in a subpopulation of ALCL, almost exclusively in T or null cell origin, and in rare cases of HD. These findings show that some HD may be closely related to ALCL, giving us new insights on the pathogenesis and possibly biologic evolution of HD.

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MATERIALS AND METHODS

Pathologic samples. A panel of 49 and 72 well-characterized cases of ALCL (10 B-ALCL, 16 T-ALCL, 4 HD related-ALCL, and 19 null-ALCL) and HD (49 nodular sclerosis [NS], 10 mixed cellularity [MC], 6 lymphocytic predominance [LP], 1 lymphocytic depletion [LD], and 6 unclassified [U-HD]), respectively, were selected from among cases processed in the surgical pathology laboratories of the New York University Medical Center (New York, NY), University of Leuven (Leuven, Belgium), and University of Verona (Verona, Italy). The age of ALCL patients ranged from 15 to 65 years, with a mean of 45 years. Three CD30+ lymphoblastoid cell lines derived from CD30+ ALCLs (DHL, TS, and JB), K562, Daudi, JD38, BL60, ST486, KK125, B27, HUT102 cell lines, 10 normal tonsils (TS), 10 normal reactive lymph nodes (RLN), 5 spleen (SP), and 5 normal bone marrow aspirates (BM) were also included.

Alterations of proto-oncogene loci and disruption or loss of tumor-suppressor genes are consistently and specifically associated with several types of human neoplasms. Despite intense investigation, the molecular events leading to HD and ALCLs are only partially elucidated.4,5 In the early 1980s, we and others described a unique and apparently restricted translocation, t(2;5), in a subgroup of CD30+ ALCLs.7,8 However, only a limited number of cases have been studied, and the precise frequency and distribution among ALCLs and its distribution within other subgroups of NHLs and HD remain largely unknown. The discovery that the nucleophosmin/B23 (NPM) gene (5q35) and a novel anaplastic lymphoma kinase (ALK; 2p23) are the fused genes of t(2;5)1 allows us to characterize this unique chromosomal alteration among human lymphoproliferative disorders. Although the pathogenetic role of ALK is unknown, we may speculate that deregulated NPM-ALK products may have the capability to trigger a cascade of events, leading to cellular transformation similar to what has been observed with other tyrosine kinase receptors.12

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Supported by Grant No. CA64033 to G.I. and by Associazione per la Ricerca contro in Cancro.

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0006-4971/96/8703-0118$3.00/0

Blood, Vol 87, No 3 (February 1), 1996; pp 1081-1088
Table 1. Frequency and Distribution of t(2;5) Translocation in ALCL and HD

<table>
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<th>Diagnosis No.</th>
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<th>B-ALCL</th>
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<th>Null-ALCL</th>
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<td>1/10</td>
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<td>0/6</td>
<td>3/32</td>
</tr>
</tbody>
</table>

* The three t(2;5) positive lymphoblastoid cell lines were not included in the total ALCL fresh cases.

in this study. Heparinized peripheral blood, bone marrow aspiration samples, and lymphoid biopsy specimens were collected as previously described. The diagnoses were obtained by three different pathologists (G.F., C.W., and F.M.) on hematoxylin and eosin-stained sections and supported by flow cytometric and immunohistochemical analyses.

Fig 1. Characterization of NPM-ALK and ALK gene transcripts in ALCL. cDNA obtained from 10 CD30+ ALCL and 1 ALCL cell line (DHL) were specifically amplified using oligonucleotides recognizing NPM (NPM-1, NPM-2) and ALK (ALK-2, ALK-3) by PCR. PCR-amplified fragments corresponding to NPM-ALK (NPM-1-ALKB; A), ALK-ALK (ALK-2-ALK3; B), and NPM-NPM (NPM-1-NPM-2; C) are shown after electrophoresis on a 2.5% agarose gel. PCR-amplified fragments corresponding to NPM-ALK after electrophoresis were denatured, transferred, and hybridized with P37 radiolabeled ALK-2 oligonucleotide probe (B). M indicates the DNA molecular marker and individual ALCL cases are shown (A2-A11; DHL, A1).

Fig 2. Sensitivity of RT-PCR for the detection of NPM-ALK fusion gene products. A total of 5 x 10^6 cells was used in each cell culture. cDNAs were transcribed using all the mRNA obtained in each cell mixture and a tenth (5 x 10^5) of it was amplified using specific primers. Values indicate the number of the DHL cells carrying t(2;5) translocation present in each individual mix culture. PCR-amplified fragments corresponding to NPM-ALK (A) and NPM-NPM (B) are shown after electrophoresis on a 2.5% agarose gel. The specificity of PCR products was confirmed using a P3' radiolabeled ALK oligonucleotide probe by Southern blot analysis (data not shown). M and W indicate the DNA molecular markers and negative (H2O) control, respectively.

DNA and RNA extractions. Genomic DNA and mRNA were obtained from cryopreserved mononuclear cell suspensions and tissue blocks using a salting-out procedure and a mini riboSep TM Ultra mRNA isolation kit (Becton Dickinson Labware, Bedford, MA) following the manufacturer’s instructions. cDNA preparation. cDNA was obtained from poly(A) mRNA (3 to 5 μg) after reverse transcription using gene specific oligonucleotide primers or a 14-18 poly(T) (dT-14-18) oligonucleotide (Pharmacia, Uppsala, Sweden) and Moloney murine leukemia virus reverse transcriptase. Briefly, contaminant genomic DNAs were first digested with DNases (Boehringer Mannheim, Indianapolis, IN) in the presence of MgCl₂ (1 mmol/L) for 10 minutes at room temperature. Poly(A) mRNA was first heated (70°C for 5 minutes) in the presence of oligoprimers (40 pmol/L for 10 minutes) and then quenched on ice (2 minutes). The volume of the RNA/primer mixture was then adjusted to 50 μL, giving the following final concentration: 10 mmol/L of dATP, dCTP, dGTP, and dTTP each; 10 mmol/L dithiothreitol; 50 mmol/LTris-HCL; 6 mmol/L MgCl₂; 40 mmol/L KCl; 20 U of RNAs: and 400 U of Moloney murine leukemia virus RNAse H-reverse transcriptase (BRL, Gaithersburg, MD). The reaction mixture was incubated at 37°C for 1 hour and then the reverse transcriptase was inactivated at 65°C for 10 minutes.

Polymerase chain reaction (PCR) analysis. The efficiency and quality of each individual cDNA preparation was tested by PCR amplification using specific oligonucleotides recognizing the human microglobulin and/or NPM genes. Only the samples resulting in good amplification control products were further evaluated. The presence of chimeric NPM-ALK gene products was investigated using...
multiple combinations of specific oligonucleotides recognizing NPM (NPM-1: 5'-TGAGCCCTGAGCCCAGTA, bp 26-46; U04946; bp 116-136: M26697; NPM-2: 5'-TCTTGGGCTTTGAAT- AAACCC, bp 262-287; U04946; bp 351-376: M26697; NPM-3: 5'-GCTACCTACCTCGGGCCAG, bp 536-516; M26697) and ALK (ALK-1: 5'-CGAGTTGGGAGGTATGCAG, bp 438-417; ALK- 2: 5'-CCGGTGGGTGTTGTTAG, bp 557-576; ALK-3: 5'- TTGTTGGGGATCTGATGG, bp 1184-1165; U04946) genes, respectively. A touchdown PCR was used to amplify both NPM and NPM-ALK gene products. Briefly, 2 to 4 μL of cDNA was amplified under appropriate conditions (10 pmol/L of each primer, 250 pmol/L dNTPs, 10 mmol/L Tris [pH 8.8], 50 mmol/L KCl, 1.5 mmol/L MgCl₂, 0.01% gelatin, and 0.5 U Taq polymerase, in a final volume of 10 μL) for 5 cycles (annealing at 68°C), followed by another 5 cycles (annealing at 66°C) and 25 cycles (annealing at 64°C) using a Cetus Perkin-Elmer (Norwalk, CT) thermocycler apparatus.

Southern blot hybridization analysis. Five-microgram to 10-μg aliquots of genomic DNA were digested, electrophoresed, denatured, and transferred to nitrocellulose filters according to Southern.6 The NPM and ALK loci were evaluated on BamHI- and HindIII-digested DNAs using the 16.3 FI probe obtained after Bgl II and Sac I digestion of the 16-3/1.25 probe11 and PCR-derived ALK-specific probe (557-1184 bp: U04946), respectively. Appropriately treated PCR products (10 μL) were hybridized with radiolabeled oligonucleotide (1 pmol/L, 2 × 10⁶ cpm/mL).15

Cloning and sequencing of PCR products. PCR products were cloned in the pCRll TM vector using the TA cloning system (In- vitrogen Corp, San Diego, CA), following the manufacturer’s instructions. DNA sequencing was performed as previously described.6 Immunohistochemical staining. The immunophenotype of the ALCLs was determined at the time of diagnosis using a large panel of antigens and MoAbs by immunohistochemical staining of frozen or paraffin tissue sections and/or by immunofluorescent flow cytometry. ALK gene products (p80) were detected using a specific polyclonal rabbit antisera16 using a modified ABC technique and Ventana ES instrument.

RESULTS

Classical cytogenetic analysis has shown a unique translocation involving bands 2p23 and 5q35 in a variable number of ALCLs (30% to 100%)2,7-10,17 and in rare CD30⁺ NHLs.18,19 Because only a small number of ALCLs have been cytogenetically studied, the exact incidence of t(2;5) and its presence among B, T, and null ALCLs is largely undetermined. Because of the paucity of RS cells in HD, their low mitotic index, poor-quality banding pattern, and the presence of a considerable number of normal activated host lymphoid cells, the karyotypic status of the RS cells remains unclear.20,21 Therefore, the occurrence of t(2;5) in HD may have been largely underestimated. We decided to use a multiple approach strategy to study t(2;5) occurrence among a large and well-characterized panel of ALCL and HD cases obtained from North American and European Western countries. We investigated, by RT-PCR, the presence of NPM-ALK gene fusion products in 49 ALCLs, including T, B, null, and HD-related cases and three CD30⁺, t(2;5)-positive lymphoblastoid cell lines (DHL, TS, and JB; Table 1). Using this approach, specific NPM-ALK chimeric products were obtained in the three (2;5)-positive lymphoblastoid cell lines and in 6 of 49 ALCLs (Fig 1A). Notably, all NPM-ALK-positive cases belong to T-ALCLs and no fusion products were observed when normal TS, RLN, SP, BM, and other cell lines were studied (Table 1). The specificity of these products was further shown by a specific P3²⁺ labeled ALK oligonucleotide (ALK-2) and Southern blot analysis (Fig 1A) and by DNA sequencing. All NPM-ALK PCR fragments were cloned, and at least two different clones, derived from each individual patient, containing the appropriate PCR fragments were sequenced. In all the cases, we confirmed the presence of NPM-ALK gene sequences and showed that the breakpoint occurred at the same NPM-ALK mRNA level, as previously described.11 Although considerable progress has been made on the morphologic and molecular characterization of ALCL, its relationship with other hematologic neoplasms, particularly with HD, remains controversial. To investigate a possible molecular relationship between these two entities a total of 72 well-characterized HD cases, including LP, NS, MC, and LD samples, were selected. Because RS cells represent a minute subpopulation, we first studied the sensitivity of our NPM-ALK RT-PCR. Positive t(2;5) DHL lymphoblastoid cells were appropriately mixed with normal peripheral blood lymphocytes and mRNA was extracted from each individual culture. The corresponding cDNA was obtained and amplified using oligonucleotides specifically recognizing NPM-NPM and NPM-ALK sequences. Positive NPM-NPM amplifications were obtained in each case (Fig 2B) and NPM-ALK fusion products could be successfully amplified when at least 1 t(2;5)-positive neoplastic cell was present among 104 normal lymphocytes (Fig 2A). Because RS cells represent at least 0.1% of the total tissue cells, RS cells carrying and transcribing NPM-ALK fusion gene products should be successfully identified by this approach. When we tested our selected 72 HD cases, 3 HD samples showed
NPM-ALK PCR products (Fig 3A). To confirm this finding, multiple mRNA extractions were performed in all positive NPM-ALK HD cases. Several negative HD samples were also included in each series of experiments to exclude the possibility of undesired PCR contamination. Furthermore, each cDNA preparation was first amplified with a set of oligonucleotides corresponding to inner NPM (NPM-2) and ALK (ALK-2) sequences and then a new PCR was performed using a pair of oligonucleotides recognizing outer NPM (5'-NPM-I) and ALK (3'-ALK-3) gene sequences. In all the experiments, we were able to successfully amplify NPM-ALK chimeric products from these three HD cases and no positive PCR products were identified in the appropriate negative controls.

Translocations involving 5q35 are primarily seen in association with the 2p23 region and, only in rare cases, an alternative chromosomal alteration can be identified. This finding indicates that a putative gene (NPM) located in 5q35 is generally juxtaposed to a common partner and less frequently to other heterologous gene(s). Southern blot analysis was performed to study the relative frequency of NPM and/or ALK gene rearrangements among our ALCLs (n = 25) and HD (n = 31) cases using two specific probes recognizing a DNA genomic region immediately located at 5' of the coding region of NPM gene and a cDNA region of ALK genes (ALK2-ALK3, 627 bp). Gene rearrangement analysis confirmed the presence of NPM-ALK gene rearrangements in all tested ALCL cases expressing NPM-ALK transcripts (Fig 4). One ALCL case showed the presence of only ALK gene rearrangement (Fig 4B, lane 9) and no detectable NPM-ALK fusion gene mRNA products could be documented using RT-PCR. On the other hand, no detectable NPM and/or ALK rearrangement gene products could be identified in all HD, which included 2 of 3 HD cases with positive NPM-ALK transcripts. These negative results are most likely due to the fact that RS cells of classical HD represent only a minority (>3%) of the total cells within the HD lesions. On the other hand, the number of neoplastic cells in ALCL is generally greater than 5%, which is above the sensitivity of detection of Southern blot analysis.

Based on the fact that ALK gene products are usually not expressed in normal lymphoid tissues, we decided to investigate the presence of ALK transcripts and their related protein using RT-PCR and immunohistochemistry techniques. When specific ALK oligonucleotides recognizing ALK transcripts located 3' of the putative breakpoint site were used (ALK-2 and ALK-3), positive PCR amplification was detected in all ALCLs and HD cases carrying NPM-ALK fusion (Fig 1B). This finding indicates that ALK gene sequences are constitutively transcribed in those cases carrying NPM-ALK gene fusion products.

The ALCL cells carrying t(2;5) translocation are the most likely source of NPM-ALK fusion gene products; however, the precise origin of NPM-ALK mRNA in the HD case is more speculative. Thus, we investigated whether only ALCL and RS cells display ALK-related proteins and studied their subcellular localization. We previously showed that ALK molecules can be successfully identified by immunohisto-
chemistry using a specific polyclonal antiserum against ALK protein (P80). Positive, predominantly cytoplasmic staining was only identified in the neoplastic ALCL and RS cells of those ALCL and HD cases from which we had successfully amplified NPM-ALK products (Fig 5B and F). Notably, the only case displaying ALK gene rearrangement with no NPM-ALK transcripts showed a weak cytoplasmic positivity in the neoplastic cells. The remaining ALCL and HD cases did not show any positivity under these experimental conditions (Fig 5 and Table 1). In occasional cases we noted weak, granular cytoplasmic staining in some fibroblasts and monocytes as previously described.

**DISCUSSION**

In the present study, we investigated the presence of t(2;5) translocation gene products in a large and well-characterized panel of ALCL and HD using a multiapproach strategy. Our findings show that a discrete subpopulation of T and null ALCL carry the t(2;5) translocation and their corresponding transcripts. In contrast, only a very small minority of the HD (approximately 5%) undergo NPM-ALK gene fusion. The presence of detectable ALK-related proteins in only those ALCL and HD carrying ALK translocation show that ALK gene rearrangements may have an important tumorigenic role.

The molecular characterization of chromosomal aberrations, consistently and specifically associated with several types of human neoplasms, has allowed the identification of a series of genes, mainly proto-oncogene and tumor-suppressor genes, that are strongly implicated in tumorigenesis. Since 1967, when Seif and Spriggs provided the first evidence that a clonal aneuploid cell population exists within HD, numerous cytogenetic studies of HD have been performed. Nonetheless, the chromosomal content of RS cells remains unclear and no pathogenetic chromosomal aberration(s) have been found. This is primarily due to the nature of HD that limits cytogenetic analysis. Foremost is the paucity of neoplastic cells relative to benign cells in HD lesions and the fact that the RS cells have a low mitotic index and poor-quality banding pattern combined with a complex karyotype.

In contrast, ALCLs have been more extensively karyotyped and the t(2;5)(p23;q35) translocation is the most common chromosomal abnormality found in this group of lymphomas. Using classic cytogenetics, the overall incidence of the t(2;5) translocation among ALCL ranges from 30% to 100%.

In addition to the t(2;5) translocation, a series of translocations involving either chromosome 2 or chromosome 5 have been described in ALCL. In the case of chromosome 5, all these translocations appear to involve the bands q34-35. No molecular genetic analysis was performed to identify whether the NPM gene is rearranged in these cases. However, Yoneda et al have recently shown that, in the t(3;5)(q24;q34) seen in myelodysplastic and acute myelogenous leukemias, the NPM gene is fused with a new gene called myelodysplasia/myeloid leukemia factor. In our study, 1 case showed ALK but not NPM gene rearrangement products by Southern blot analysis. This finding suggests the possibility that, in this case, the ALK gene locus underwent gene rearrangement with a so-far unknown gene partner. Based on the fact that ALK gene products were detected in the neoplastic cells using immunohistochemistry, it is also conceivable to speculate that this rearrangement results in the productive expression of a new ALK chimeric protein. Additional studies to identify this new putative gene are in progress.

Very little is known regarding the pathogenetic mechanisms leading to the transformation of ALCL cells and RS tumorigenesis. We have previously shown that the c-myc proto-oncogene is activated in a subgroup of B-ALCLs and postulated that c-myc proto-oncogene activation may represent a second hit, analogous to Burkitt's lymphomas, or, alternatively, as an additional step occurring in already transformed cells, mimicking the tumor progression pathway of some low-grade lymphoproliferative disorders. Interestingly, rare alterations of c-myc proto-oncogene were found in T-ALCL, suggesting that different molecular pathogenetic mechanisms may be preferentially involved in the transformation of B- and T-cell–restricted cells. Notably, t(2;5) translocation has been primarily identified in T-cell and less frequently in null and B-cell ALCLs.

Recently Morris et al have characterized the t(2;5) translocation and identified the involved genes, NPM and ALK. ALK is a member of the tyrosine kinase receptors (RTK). The RTKs are physiologically activated after dimerization and phosphorylation by specific ligand-mediated interactions. Various hypotheses have been proposed regarding the oncogenic role of RTK chimeric gene products. Constitutively, phosphorylation status of the RTK chimeric proteins and/or an abnormal subcellular localization(s) appear to play a crucial role. In the case of NPM-ALK gene fusion protein, both hypotheses may be possible. In fact, p80 is constitutively phosphorylated and primarily localized in the cytoplasm and/or nucleus as shown by our immunohistochemical findings.

In the last few years it has become increasingly evident that ALCL and some subtypes of HD (NS and LD) share considerable histopathologic and immunophenotypic similarities. Furthermore, a continuous spectrum of lesions as well as the evolution of HD into ALCL have been also described. Despite the fact that pathogenetic mechanisms leading to the cellular transformation of RS and ALCL are still largely unknown, both lesions share common immunogenotypic features, lack Ig and TCR, express a variety of lymphokines, and contain EBV genome products. The cyto-
genetic analysis of these lesions is particularly confusing. No common cytogenetic abnormalities have been identified in HD. In contrast, ALCL, particularly those of T-cell origin, appear to present with chromosomal aberrations involving 5q35. The present study was performed not only to study the relative frequency of the t(2;5) translocation in ALCL and HD, but also to identify whether these two diseases share common molecular abnormalities which may lead to a better understanding of their relationship. Using multiple approaches, we have confirmed that a subpopulation of ALCL (~20%) and a very small minority of HD (<5%) cases undergo NPM-ALK gene fusion. Recently, other investigators have used similar approaches to study the presence of the t(2;5) translocation in ALCL and HD. In the case of ALCL, the frequencies range from 16% to approximately 50%.[5,16,19,26-28,35] The precise reasons between these differences are unclear; however, higher frequencies have been observed among younger patients with ALCL. On the other hand, very contradictory findings have been reported on the frequency of (t;5) in HD. [19,26,36-39] Several studies have recently shown the absence of NPM-ALK fusion in HD. [20,37,39] In contrast, three other investigations have shown the t(2;5) translocation in HD (21% to 85% of the cases using Southern blot or RT-PCR analyses). [28,38,39] These conflicting findings may be due to sample selection, diagnostic criteria, geographic distribution, and possibly technical reasons. Based on these findings, no definitive conclusion can be drawn and additional studies are necessary. Thus, the precise relationship between ALCL and HD still remains unclear. However, the identification of a few HD cases carrying t(2;5) may suggest that at least a small subset of HD are more closely related to ALCL. Because we do not know whether t(2;5) represents an early or a late pathogenetic event, we can only speculate that a minority of HD, and perhaps only those derived from T-RS, are related to ALCL, but, if t(2;5) represents a late event, HD and ALCL may possibly represent two different stages of the same disease. Furthermore, because the t(2;5) translocation can be found in NHL without anaplastic morphology and in CD30+ tumors,[18,19] the presence of NPM-ALK products in some ALCL and HD may be coincidental. Certainly the remarkable morphologic and immunophenotypic similarities shared by these two entities suggest that these neoplasms may share a common and so far unknown aberration(s).

Despite the considerable progress in the understanding of HD and ALCL and their possible relationship, a large number of pieces of this remarkable puzzle remain unknown. The evaluation of HD and ALCL genetic aberrations using new technology such as comparative genomic hybridization and representation difference analysis should permit us to further understand these fascinating and still mysterious diseases.

ACKNOWLEDGMENT

We sincerely thank Bang Ying Zhu, Luis Chiriboga, and Joseph Rocco for their excellent technical assistance.

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