Molecular Genetics of Gastrointestinal Non-Hodgkin's Lymphomas: Unusual Prevalence and Pattern of c-myc Rearrangements in Aggressive Lymphomas

By J.H.J.M. van Krieken, M. Raffeld, S. Raghoebier, E.S. Jaffe, G.J.B. van Ommen, and Ph.M. Kluin

Thirty-two extranodal lymphomas of the gastrointestinal (GI) tract underwent molecular genetic analysis by Southern blotting using probes for the immunoglobulin genes and the bcl-1, bcl-2, and c-myc loci, commonly involved in lymphomagenesis. No bcl-1 rearrangements were found. There was only one large-cell lymphoma with a bcl-2 rearrangement. A rearrangement of the c-myc gene was found in six of eight Burkittlike lymphomas of the intestine. In five of these six cases, a chromosomal translocation t(8;14) with an unusual breakpoint was demonstrated by comigration of the rearranged c-myc and a rearranged JH sequence. This pattern of rearrangement has not been previously associated with a specific group of non-Hodgkin's lymphomas. In contrast to all six low-grade lymphomas, c-myc rearrangements were found in 6 of 12 large-cell or high-grade mucosa-associated lymphomas of the stomach. No comigration of c-myc and immunoglobulin heavy-chain gene sequences were found. We conclude that primary GI lymphomas have different molecular genetic characteristics compared with node-based follicle center-cell lymphomas and as a group are not related to these lymphomas. In addition, the prevalence and patterns of c-myc rearrangements in the gastric large-cell lymphomas and ileocecal Burkittlike lymphomas are noteworthy and suggest a different and distinct pathogenesis for these tumors.

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contained enough tumor cells to evaluate for c-myc. Six of eight evaluable BL all diagnosed with a rearranged JH fragment, indicating that the sample contained enough tumor cells to be detected by Southern blotting (Table 2, Fig 1). We did not detect a bcl-1 rearrangement in any of our cases. There was no bcl-2 rearrangement found in any of the gastric or intestinal lymphomas, with one exception. This latter case was a large-cell lymphoma of the stomach; there was no comigrating JH fragment, and there was a c-myc rearrangement as well (Fig 1).

Rearrangement of the c-myc gene was detected in 12 cases of B-cell lymphoma of the stomach or intestine. One case of Burkitt-like and two cases of large-cell lymphoma were not evaluable for c-myc. Six of eight evaluable BL, all diagnosed in the intestine, had a c-myc rearrangement. In five of these there was comigration with a rearranged JH fragment. Five of ten large-cell lymphomas, all occurring in the stomach, also had a rearrangement of the c-myc gene. None of them showed comigration with a JH fragment. There were no c-myc rearrangements in the low-grade lymphomas, but this gene was rearranged in one of the two MAL with centroblastic progression. Also in this case there was no comigration with a rearranged JH fragment. The two T-cell lymphomas did not show c-myc rearrangement.

### RESULTS

All B-cell lymphomas and one T-cell lymphoma showed at least one rearranged JH fragment, indicating that the sample contained enough tumor cells to be detected by Southern blotting (Table 2, Fig 1). We did not detect a bcl-1 rearrangement in any of our cases. There was no bcl-2 rearrangement found in any of the gastric or intestinal lymphomas, with one exception. This latter case was a large-cell lymphoma of the stomach; there was no comigrating JH fragment, and there was a c-myc rearrangement as well (Fig 1).

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### DISCUSSION

Malignant lymphomas are traditionally classified using morphological and immunophenotypical criteria. This has led to the recognition of several distinct clinicopathologic entities, of which follicular lymphoma is one of the most common neoplasms. More than 90% of follicular lymphomas are characterized by a specific chromosomal translocation, t(14;18), which brings the bcl-2 gene, a putative oncogene, under the control of the regulatory genes of the immunoglobulin heavy-chain gene. Large-cell lymphomas form a heterogeneous group that consists partly of tumors that have progressed from low-grade lymphomas, such as follicular lymphoma, as demonstrated by the presence of t(14;18) in about 30% of these lesions.

Histologic classifications such as the Kiel-scheme and WF are based primarily on malignant lymphomas arising in lymph nodes. About 40% of the non-Hodgkin's lymphomas arise from extranodal sites, of which the GI tract is the commonest. Traditionally classification of extranodal lymphomas are traditionally classified using morphological and immunophenotypical criteria. This has led to the recognition of several distinct clinicopathologic entities, of which follicular lymphoma is one of the most common neoplasms. More than 90% of follicular lymphomas are characterized by a specific chromosomal translocation, t(14;18), which brings the bcl-2 gene, a putative oncogene, under the control of the regulatory genes of the immunoglobulin heavy-chain gene. Large-cell lymphomas form a heterogeneous group that consists partly of tumors that have progressed from low-grade lymphomas, such as follicular lymphoma, as demonstrated by the presence of t(14;18) in about 30% of these lesions.

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phomas has been based on the assumption that these lesions reflect their nodal counterparts. However, recent clinicopathologic studies have suggested that this assumption may not be correct. In molecular and cytogenetic studies published so far, no distinction between nodal and extranodal lymphomas has been made. Most recently Pan et al showed that t(14;18) is not present in low-grade mucosa-associated lymphoma, although a previously published case with a bcl-2 translocation was not included in the study. In the present study we found important differences between nodal and extranodal lymphomas: in contrast to nodal follicular lymphomas, no bcl-2 rearrangements were found in any of the eight mucosa-associated lymphomas (MAL). Also, in only one of 10 GI large-cell lymphomas was involvement of the bcl-2 gene found. Thus our results indicate that mucosa-associated lymphoma and probably also primary, gastric large-cell lymphoma are not related to follicular lymphoma of the lymph node.

The high frequency of c-myc rearrangements in primary, gastric large-cell lymphomas, which make up more than 50% of all gastric lymphomas, is not found in primary, nodal large-cell lymphoma. No comigration of c-myc with a JH gene was observed in the five gastric large-cell lymphomas. This pattern of c-myc rearrangement most closely resembles those described for sporadic Burkitt lymphomas in which c-myc has rearranged into the switch region of the Ig locus of the Ig locus deleting JH. Alternatively, the absence of JH comigration may indicate translocation into a different genetic region other than the Ig locus. Further study to elucidate the nature of these rearrangements is in progress. It might be speculated that in gastric large-cell lymphoma the rearrangement of c-myc is a secondary event related to tumor progression from low-grade MAL, as observed in one case of MAL-high.

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In summary, our studies of the molecular genetics of GI lymphomas support the growing clinicopathologic evidence that GILs are distinct from nodal lymphomas by showing that there are differences at the molecular level as well. In addition, we have identified what appear to be characteristic molecular associations in two subgroups of GILs: a group of ileocecal lymphomas that have c-myc rearrangements comigrating with JH and a group of gastric large-cell lymphomas that have noncomigration c-myc rearrangements.

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