Microsatellite Instability Is Rare in B-Cell Non-Hodgkin’s Lymphomas


Microsatellite instability (MSI), a symptom of defect in DNA mismatch repair function, represents a type of genomic instability frequently detected in many types of cancers. However, the involvement of MSI in non-Hodgkin’s lymphomas (NHL) has not been conclusively investigated. In this study, we have tested the presence of MSI in 69 cases of B-cell NHL (B-NHL) representative of the various histologic categories of the disease and including 17 cases of acquired immunodeficiency syndrome (AIDS)-related B-NHL (AIDS-NHL). In addition, for selected B-NHL cases, consecutive samples obtained before and after clinical progression (with and without concomitant histologic transformation) were also investigated. Five distinct microsatellite repeat sequences (2 dinucleotide, 2 trinucleotide, and 1 tetranucleotide repeats) were analyzed by polymerase chain reaction in all cases. MSI, defined by the presence of microsatellite alterations in two or more of the five microsatellite loci tested, was not found in NHL. In contrast to a previous study reporting the frequent association between MSI and AIDS-NHL, we found this abnormality in only 1 of 17 cases of AIDS-NHL representative of the major subtypes. Overall, these data indicate that defects in DNA mismatch repair do not contribute significantly to the molecular pathogenesis of B-NHL.

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From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, NY; Department of Medical Sciences, University of Torino, Novara, Italy; Cell Biology and Genetics Program and the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY; Division of Pathology, I.N.R.C.C.S.-C.R.O., Aviano, Italy; Laboratory of Clinical Immunology, Genova, Italy; Department of Pathology, New York Hospital—Cornell Medical Center, New York, NY; and the Department of Pathology, University of Southern California School of Medicine, Los Angeles, CA.

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Address reprint requests to Riccardo Dalla-Favera, MD, Division of Oncology, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, NY 10032.

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975
A total of 69 B-NHL cases was investigated for the presence of MSI. The panel was representative of B-NHL of the immunocompetent host at diagnosis and after clinical progression (11 cases) as well as of AIDS-NHL (17 cases). All samples were tested at five microsatellite loci, including 2 dinucleotide repeats, 2 trinucleotide repeats, and 1 tetranucleotide repeat. Alterations in the size of microsatellites in the tumor sample were revealed as differences in the electrophoretic migration of the tumor DNA as compared with control DNA from autologous tissues. Only tumors showing alterations at ≥2 microsatellite loci were scored positive for MSI. Since single-locus changes in microsatellites are detectable at low frequency (1 to 4 × 10^{-3} per cell generation) in nontumor DNA in the absence of detectable defects in DNA mismatch repair, this threshold would significantly lower the probability of detecting background mutations.

**RESULTS**

A total of 69 B-NHL cases was investigated for the presence of MSI. The panel was representative of B-NHL of the immunocompetent host at diagnosis and after clinical progression (11 cases) as well as of AIDS-NHL (17 cases). All samples were tested at five microsatellite loci, including 2 dinucleotide repeats, 2 trinucleotide repeats, and 1 tetranucleotide repeat. Alterations in the size of microsatellites in the tumor sample were revealed as differences in the electrophoretic migration of the tumor DNA as compared with control DNA from autologous tissues. Only tumors showing alterations at ≥2 microsatellite loci were scored positive for MSI. Since single-locus changes in microsatellites are detectable at low frequency (1 to 4 × 10^{-3} per cell generation) in nontumor DNA in the absence of detectable defects in DNA mismatch repair, this threshold would significantly lower the probability of detecting background mutations.

**DISCUSSION**

This study demonstrates that the molecular pathogenesis of B-NHL does not involve MSI. The absence of MSI in B-NHL is independent of the host’s immune function, since both B-NHL of the immunocompetent host and AIDS-related B-NHL are devoid of MSI in virtually all cases. In addition, when considering the marked degree of heterogeneity of B-NHL, it is notable that lack of MSI involvement is a consistent feature throughout the entire B-NHL clinicopathologic spectrum, which includes indolent lymphomas characterized by a low proliferative index and a slow clinical course, such as small lymphocytic lymphoma and follicular lymphoma, as well as high-grade lymphomas characterized by a high proliferative index and an aggressive clinical course, such as diffuse large cell lymphoma and Burkitt’s lymphoma. Interestingly, it has been recently reported that

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**Table 1. Microsatellite Markers Used for MSI Analysis of B-NHL**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Repeat Unit</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS404</td>
<td>Dinucleotide</td>
<td>5</td>
</tr>
<tr>
<td>DSS255</td>
<td>Dinucleotide</td>
<td>8</td>
</tr>
<tr>
<td>D14S50</td>
<td>Trinucleotide</td>
<td>14</td>
</tr>
<tr>
<td>FGA</td>
<td>Trinucleotide</td>
<td>4</td>
</tr>
<tr>
<td>AR</td>
<td>Tetranucleotide</td>
<td>X</td>
</tr>
</tbody>
</table>

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**Table 2. Frequency of Microsatellite Alterations in B-NHL at Diagnosis**

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Cases Tested</th>
<th>Cases showing Microsatellite Alterations at 1 Locus</th>
<th>Cases showing Microsatellite Alterations at ≥2 Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse large cell lymphoma</td>
<td>12</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Five microsatellite loci were tested in each case.
MALT lymphoma (not included in this study) display MSI at high frequency using criteria for defining MSI analogous to this study, suggesting that these tumors may be associated with distinct pathogenetic mechanisms. Finally, our data show that not only MSI is not involved in B-NHL at diagnosis, but it is also not responsible for the clinical progression and histologic transformation that may occur in the late phases of the natural history of these tumors.

The lack of association between MSI and B-NHL development, as indicated by our survey, is consistent with other findings obtained in experimental mice and in related lymphoid malignancies. Mice carrying homozygous deletions of the \textit{MSH2} gene, whose wild-type protein product protects the cellular genome from the occurrence of DNA replication errors including microsatellite alterations, do not develop B lymphomas, but rather T-cell lymphomas characterized by MSI. The observation that the \textit{MSH2} \textsuperscript{−/+} genotype does not lead to B-NHL development confirms the notion that these lymphoid malignancies are not associated

**Table 3. Frequency of Microsatellite Alterations in B-NHL of the Immunocompetent Host After Clinical Progression**

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>No. of Cases Tested</th>
<th>Cases Showing Microsatellite Alterations*</th>
<th>At 1 Locus</th>
<th>At ≥2 Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>With histologic transformation†</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Without histologic transformation</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Clinical progression was defined by enlargement of adenopathy, involvement of new sites or stage progression (Lo Coco et al, 1993).26
* Five microsatellite loci were tested in each case.
† Histologic transformation was defined as B-NHL evolution from follicular to diffuse large cell architecture.

**Table 4. Frequency of Microsatellite Alterations in AIDS-Related B-NHL**

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Cases Tested</th>
<th>Cases Showing Microsatellite Alterations*</th>
<th>At 1 Locus</th>
<th>At ≥2 Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large noncleaved cell lymphoma</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Large cell immunoblastic-plasmacytoid lymphoma</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Five microsatellite loci were tested in each case.
The molecular mechanism underlying these lesions remains unknown.

REFERENCES

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