Families With Both Hodgkin Lymphoma and Multiple Myeloma in Their Pedigrees

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Abstract: Reports of familial clustering of hematologic malignancies have appeared for decades, but the cause of this uncommon observation is still unknown. Most modern investigations support a genetic rather than an environmental explanation. Clinically, most pedigrees of families with familial hematologic malignancies demonstrate age of onset anticipation (ie, diagnosis at an earlier age in successive generations). The cause of anticipation is clear in some familial neurologic disorders (eg, trinucleotide repeat expansion in Huntington disease) but unclear in familial hematologic malignancies. In preparation for molecular studies on familial clustering of hematologic malignancies, we collected pedigrees on 738 families. In these families, we observed anticipation in those with familial multiple myeloma, chronic lymphocytic leukemia, or non-Hodgkin lymphoma. Here we present preliminary data on 26 families with both multiple myeloma and Hodgkin lymphoma in their pedigrees, and demonstrate strong evidence for anticipation and predominantly male transmission of these neoplasms. We encourage all health care personnel to ask patients about their family’s medical history, to take careful family histories from individuals with uncommon illnesses, and to refer families with clustering of such illnesses for investigation.

Introduction and Methods

The study of familial hematologic malignancies is important because it may lead to the discovery of underlying genetic causes, or of genes that enhance susceptibility to an etiologic agent. To begin such studies, we collected pedigree information and medical records—including pathology reports and other material when possible—on 738 families with multiple hematologic malignancies. Many of the patients were referred to us by physicians and genetic counselors. Other patients were acquired through online support groups, patient chat rooms, and our own practices. Of note, we found that most of the family history data in the hospital charts of patients from other practices were partially or entirely inaccurate. Obtaining accurate data required questioning the propositus repeatedly, even
when the propositus was a physician. All members of each family studied gave written informed consent to participate, whether affected by a neoplasm or not.

## Results

This paper concerns 26 families that have both multiple myeloma (MM) and Hodgkin lymphoma (HL) with or without other hematologic malignancies in their pedigrees (Table 1). To our knowledge, such families have not been previously reported in detail.

In 14 of the 26 pedigrees, a parent and child were affected (11 father-child pairs; 3 mother-child pairs). These pairs included 9 father-son, 2 father-daughter, 2 mother-daughter, and 1 mother-son pairs. Eight of the 26 pedigrees had only 1 affected pair and 18 had multiple affected individuals. Male transmission was evident in 19 pedigrees, and female transmission was evident in 7 pedigrees. There were 5 sibling pairs in these families; four were sex concordant (2 MM-MM, 1 HL-HL, 1 MM-HL), and one was a brother-sister pair with MM and HL, respectively. HL and MM cases had at least 1 generation separating them in 7 pedigrees, occurred in sequential generations in 14 pedigrees, and occurred in the same generation in 5 pedigrees. In the youngest affected generation, MM was found in 8 pedigrees, HL in 13 pedigrees, and both in 5 pedigrees. The median age at diagnosis for HL was 30.8 years (range, 17-80 years), which is older than expected, and the median age at diagnosis for MM was 64.2 years (range, 31-81 years) as expected.

The presence or absence of anticipation could be assessed in 20 of the 26 pedigrees. Nineteen of those 20 pedigrees demonstrated evidence of age of onset anticipation (median difference in age at diagnosis, 26 years; range, 3-61 years). More advanced and aggressive disease, another feature of anticipation, was observed in 15 of 21 families. However, the presentation of disease and response to therapy in these families did not appear to be different from that of sporadic cases. Details of anticipation in parent-child pairs in these families are given in Table 2.

## Discussion

Anticipation has been previously documented in familial MM,\(^3\,\^4\) HL,\(^4\) chronic lymphocytic leukemia (CLL),\(^5\) and non-Hodgkin lymphoma.\(^6\) Anticipation typically is interpreted as evidence for a genetic cause of familial hematologic malignancy, although some studies suggest that environment together with genetic susceptibility may better explain these malignancies.\(^7\) Anticipation in many familial neurologic disorders results from expansion of unstable trinucleotide repeats through successive generations.\(^8\) However, trinucleotide repeat expansion is not the cause of anticipation in leukemias,\(^9\,\^11\) and the molecular basis for anticipation in leukemias and other hematologic malignancies remains unknown.

Previous studies have revealed a 2- to 4-fold increased risk of CLL in first-degree relatives of patients with MM\(^12\) or monoclonal gammopathy of unknown significance.\(^13\) Other observations support a link between MM and CLL as well\(^14\); for example, in both MM and CLL, healthy family members of patients may have subclinical evidence of the neoplasms (ie, paraproteinemia and a clonal population of B lymphocytes, respectively).\(^15\,\^16\)

The familial risk for HL in first-degree relatives of patients with HL is well recognized\(^17\) and, as stated above, the presence of anticipation in most families with multiple cases of HL supports a genetic basis for familial clustering. The genetic hypothesis is further strengthened by the observation that most sibling pairs with HL are of the same sex.\(^18\) This observation led to the postulate that a genetic locus in the pseudoautosomal region of the sex chromosomes might be at play in HL.\(^19\) That hypothesis was strengthened by the report of a family with Leri-Weill dyschondrosteosis (LWD) and HL.\(^20\) This family had a mother with LWD and her 2 daughters had LWD and HL. Because the LWD gene has been identified in the pseudoautosomal region of the X chromosome, an adjacent locus related to HL susceptibility seems possible. Interestingly, 4 of the 5 sibling pairs in our study were sex concordant.

There have also been studies on genetic susceptibility in HL. Salipante and colleagues\(^21\) discovered a gene located on 3p21.31 (KLHDC8B) and found a polymorphism in HL patients that decreases its translational expression. Decreased expression of the gene leads to the formation of binucleate cells (such as Reed-Sternberg cells) and twin births. Interestingly, HL is known to be more frequent in twins.\(^22\) More recently, Cozen and colleagues\(^23\) identified a novel locus at 19p13.3 located in intron 2 of the TCF3 gene (also known as E2A) that is associated with HL. The TCF3 gene is a regulator of B- and T-cell lineage commitment and is involved in the pathogenesis of HL.

Jain and colleagues\(^24\) reported on 8 families with familial MM and monoclonal gammopathy. In 2 families,

### Table 1. Cancer Research Foundation Registry of Families With Plasma Cell Myeloma and Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Malignancies in Family</th>
<th>No. of Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM + HL only</td>
<td>19</td>
</tr>
<tr>
<td>MM + HL + NHL</td>
<td>3</td>
</tr>
<tr>
<td>MM + HL + AML</td>
<td>2</td>
</tr>
<tr>
<td>MM + HL + ALL</td>
<td>1</td>
</tr>
<tr>
<td>MM + HL + PV</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PV, polycythemia vera.
there was a first-degree relative of the propositus with HL. Curiously, as in our study, the HL patients were older than the typical median age (34 and 37 years). Kulcsar and colleagues\textsuperscript{25} reported on an MM patient who developed HL after autologous stem cell transplantation, and Jønsson and colleagues\textsuperscript{26} reported on 1 family with HL and MM cases. These papers, taken together with our data, support the notion that there is a fundamental link between these 2 B-cell disorders that has not been previously recognized. However, not all studies have found an association between MM and HL.\textsuperscript{27,28}

Also in our database are 16 families with MM and non-Hodgkin lymphoma; 7 families with MM, non-Hodgkin lymphoma, and CLL; and 3 families with MM, non-Hodgkin lymphoma, and HL. None of these families have been included in the above analyses. Analysis is still ongoing for these families, but it is evident that anticipation is present in most of the pedigrees. Taken together with the MM-HL families, they suggest a common genetic basis for several familial B-cell disorders. This hypothesis is further strengthened by the 78 families in our database with only HL and non-Hodgkin lymphoma in their pedigrees. In the future, we also will study these families at a molecular level.

Although some have argued for an environmental cause of familial hematologic malignancies, this seems less likely than a genetic cause alone or a genetic and environmental interaction. None of the affected members of the MM-HL families had lived together in the same environment for years, usually for decades. Furthermore, an environmental cause alone would not likely explain the predominance of male transmission in most of the families or the predominance of sex concordance among most sibling pairs. Our working hypothesis is that there is a heritable genetic factor in these families that enhances susceptibility to an etiologic agent in the environment (eg, a virus), and that the agent can cause B-cell malignancies of various phenotypes. Consistent with this hypothesis is our observation that mouse mammary tumor virus may play a role in the etiology of both non-Hodgkin lymphoma and breast cancer in some patients with both neoplasms,\textsuperscript{29} and the fact that the SV40 virus can cause lymphoma, osteogenic sarcoma, and other tumors in hamsters.\textsuperscript{30}

Table 2. Anticipation in Parent-Child Pairs in Pedigrees With Hodgkin Lymphoma and Multiple Myeloma

<table>
<thead>
<tr>
<th>Family</th>
<th>Parent</th>
<th>Diagnosis</th>
<th>Age, y\textsuperscript{a}</th>
<th>Child</th>
<th>Diagnosis</th>
<th>Age, y\textsuperscript{a}</th>
<th>Anticipation\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Father</td>
<td>MM</td>
<td>61</td>
<td>Son</td>
<td>MM</td>
<td>42</td>
<td>-19</td>
</tr>
<tr>
<td>2.</td>
<td>Father</td>
<td>MM</td>
<td>59</td>
<td>Son</td>
<td>MM</td>
<td>40</td>
<td>-29</td>
</tr>
<tr>
<td>3.</td>
<td>Father</td>
<td>HL</td>
<td>64</td>
<td>Son</td>
<td>MM</td>
<td>43</td>
<td>-21</td>
</tr>
<tr>
<td>4.</td>
<td>Father</td>
<td>HL</td>
<td>59</td>
<td>Son</td>
<td>MM</td>
<td>44</td>
<td>-15</td>
</tr>
<tr>
<td>5.</td>
<td>Father</td>
<td>HL</td>
<td>40</td>
<td>Son</td>
<td>MM</td>
<td>36</td>
<td>-4</td>
</tr>
<tr>
<td>6.</td>
<td>Father</td>
<td>HL</td>
<td>52</td>
<td>Son</td>
<td>HL</td>
<td>33</td>
<td>-19</td>
</tr>
<tr>
<td>7.</td>
<td>Father</td>
<td>HL</td>
<td>19</td>
<td>Son</td>
<td>HL</td>
<td>12</td>
<td>-7</td>
</tr>
<tr>
<td>8.</td>
<td>Father</td>
<td>HL</td>
<td>27</td>
<td>Son</td>
<td>HL</td>
<td>18</td>
<td>-9</td>
</tr>
<tr>
<td>9.</td>
<td>Father</td>
<td>HL</td>
<td>19</td>
<td>Son</td>
<td>HL</td>
<td>21</td>
<td>+2</td>
</tr>
<tr>
<td>10.</td>
<td>Father</td>
<td>HL</td>
<td>24</td>
<td>Daughter</td>
<td>MM</td>
<td>40</td>
<td>+16</td>
</tr>
<tr>
<td>11.</td>
<td>Father</td>
<td>MM</td>
<td>64</td>
<td>Daughter</td>
<td>HL</td>
<td>29</td>
<td>-35</td>
</tr>
<tr>
<td>12.</td>
<td>Mother</td>
<td>HL</td>
<td>60</td>
<td>Daughter</td>
<td>MM</td>
<td>49</td>
<td>-11</td>
</tr>
<tr>
<td>13.</td>
<td>Mother</td>
<td>MM</td>
<td>49</td>
<td>Daughter</td>
<td>HL</td>
<td>14</td>
<td>-35</td>
</tr>
<tr>
<td>14.</td>
<td>Mother</td>
<td>MM</td>
<td>66</td>
<td>Son</td>
<td>MM</td>
<td>58</td>
<td>-8</td>
</tr>
</tbody>
</table>

Median 55.3 38.6 -19

\textsuperscript{a}Age at diagnosis.

\textsuperscript{b}Difference in years between ages of parent and child at diagnosis.

HL, Hodgkin lymphoma; MM, multiple myeloma; y, years.

**Conclusion**

We have begun molecular studies on our HL-MM families and will present our results as they are obtained. We encourage others to investigate a possible relationship between HL and MM, and to report on patients with familial hematologic malignancies. It also may be important to investigate other diseases that appear to segregate with hematological malignancies more commonly than expected, such as multiple sclerosis\textsuperscript{31,32} and systemic lupus erythematosus.\textsuperscript{33-35} We expect that modern molecular
techniques for examining the genome will yield important information on the genetic bases for hematologic malignancies in the near future.

Acknowledgements
Presented in part at the American Federation for Medical Research Eastern Regional Meeting, April 9, 2014, in Washington, DC. Supported in part by the Cancer Research Foundation of New York.

Disclosures
The authors have declared no financial conflicts of interest.

References