Malignant Histiocytosis: A Specific t(2;5)(p23;q35) Translocation?
Review of the Literature

By Elisabeth Benz-Lemoine, André Brizard, Jean-Loup Huret, Philippe Babin, François Guilhot, Dominique Couet, and Joseph Tanzer

In this paper, the investigators report a well documented case of malignant histiocytosis (MH) with a t(2;5)(p23;q35) translocation. A breakpoint in 5q35 appears to be specific, either for the disease or for a subclass of the disease.

MALIGNANT HISTIOCYTOSIS (MH) is a neoplastic process characterized by fever, progressive wasting, lymphadenopathy, hepatosplenomegaly, and the proliferation of atypical histiocytes at all stages of maturation with frequent phagocytic activity. Diagnosis is often difficult and can be confused with malignant lymphoma or other histiocytic disorders. Cytogenetics would be useful for diagnostic ascertainment if a specific chromosomal anomaly could be identified. In this study, the investigators report a case of MH with a breakpoint in 5q35. On reviewing the literature, it appeared that 1) most cases were not well documented, which questions the accuracy of the diagnosis, and 2) a breakpoint in 5q35 could be specific for the disease (or a subclass of the disease), since it was found in ten of the 19 cases (including the investigators’ case) reported as MH.

Additional cases of MH with cytogenetics are needed. This will help to determine if one class of MH or several subclasses can be defined by cytogenetic anomaly(ies).

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history of pseudosepticemic fever, wasting, and enlarged lymph nodes. Radiobogic, ubtrasonographic, and abpha-l-antitrypsin. Immunologic and B). The neoplastic cells showed a positive reaction for lysozyme suggests that a breakpoint in 5q35 could be specific for the

gastrointestinal cells with frequent mitoses and erythrophagocytosis (Fig 1A and B). The neoplastic cells showed a positive reaction for lysozyme and alpha-1-antitrypsin. Immunologic studies were performed on freshly suspended cells by indirect immunofluorescence and on frozen sections by immunoperoxidase technique. Malignant cells represent a
totic vesicles (Fig 1A and B). The neoplastic cells showed a positive reaction for lysozyme and alpha-1-antitrypsin. Immunologic studies were performed on freshly suspended cells by indirect immunofluorescence and on frozen sections by immunoperoxidase technique. Malignant cells were positive for HLA-DR, but negative for CD 19, CD 1, CD 2, CD 4, CD 8, CD 13, and CD 33. Electron microscopy showed large cells with atypical nuclei, large nucleoli, and numerous erythrophagocytic vesicles (Fig 2). A karyotype from a lymph node (direct analysis, RHG banding, 15 mitoses analyzed) was 46, XX, t(2;5)(p23;q35) (Fig 3). Bone marrow was morphologically and karyotypically normal.

Complete remission was achieved after one course of vincristine, prednisone, doxorubicin, and cyclophosphamide, but a relapse occurred after the second course. The patient achieved a second remission with vinblastine, bleomycine, and carmustine treatment. In May 1987, an allogeneic bone marrow transplantation (BMT) was performed after conditioning with 5 mg/kg/d etoposide and 60 mg/kg/d cyclophosphamide, both for two days and total body irradiation 2 Gy twice a day for three consecutive days. In July 1988, the child was free of disease with complete hematologic reconstitution and no evidence of graft v host disease (GVHD).

### DISCUSSION

Data from the literature are often insufficient to ascertain the diagnosis of malignant histiocytosis, or point to other malignancies. However, of 19 cases reported as malignant histiocytosis where informative cytogenetic study was available (Tables 1 and 2), ten cases presented a breakpoint in 5q35,8,9,11,18,19 three a tetraploidy, and three a trisomy 8.11-19 This suggests that a breakpoint in 5q35 could be specific for the disease or a subclass of the disease and perhaps have prognostic significance.

Of ten cases with 5q35 involvement, a t(2;5)(p21 or p23;q35) was found in eight cases8,9,11 and in the investigators' case, a t(1;5) (p32;q35) was found in one case,10 and a t(5;6) (q35; p12) in one case (Table 1).10 These last two cases could represent a variant translocation of a t(2;5) analogous to Burkitt Leukemia in which a gene on chromosome 8 is constantly involved in translocations involving alternate genes on chromosomes 14, 2, or 22. Alternatively, there could be a submicroscopic translocation of a gene from 2p onto 5q35 in a complex translocation with a third chromosome as has been demonstrated in a case of chronic myelogenous leukemia with a complex t(6;22) translocation where 9q34

### Table 1. Ten Cases Reported as Malignant Histiocytosis With a Breakpoint in 5q35

<table>
<thead>
<tr>
<th>Patients</th>
<th>5q35 Involvement</th>
<th>Other Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t(2;5)(p21;q35)</td>
<td>+i(1q), +17p+, +Mar</td>
</tr>
<tr>
<td>2</td>
<td>t(1;5)(p32;q35)</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>t(2;5)(p23;q35)</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>t(2;5)(p23;q35)</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>t(2;5)(p23;q35)</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>t(2;5)(23.1;q35.3)</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>t(2;5)(p23;q35)</td>
<td>22p+</td>
</tr>
<tr>
<td>8</td>
<td>t(2;5)(p23;q35)</td>
<td>t(X;22)(p22;q12)/Xp+</td>
</tr>
<tr>
<td>9</td>
<td>t(5;6)(q35;p12)</td>
<td>−13, +der(13)t(1;13)(q21 or 22;q34)</td>
</tr>
<tr>
<td>10</td>
<td>t(2;5)(p23;q35)</td>
<td>None</td>
</tr>
</tbody>
</table>

Superscript numbers are references.

### PATIENT AND METHODS

In January 1987, a 14-year-old girl presented with a 4 week history of pseudosepticemic fever, wasting, and enlarged lymph nodes. Radiologic, ultrasonographic, and tomodensitometric investigations showed enlarged mediastinal, mesenteric, and retroperitoneal lymph nodes, but no liver or spleen enlargement. Her hemoglobin was 9.7 g/dL; reticulocytes, 150 x 109/L; WBC 6.6 x 109/L with 69% neutrophils; 6% monocytes; 24% lymphocytes; and platelet count 458 x 109/L. Serum lactate dehydrogenase was 378 U/L (normal 100 to 190 U/L). Liver function tests were normal.

A lymph node biopsy showed a diffuse infiltrate of atypical pleomorphic naphthyl-ASD-acetate (NASDA) esterase positive histiocytic cells with frequent mitoses and erythrophagocytosis (Fig 1A and B). The neoplastic cells showed a positive reaction for lysozyme and alpha-1-antitrypsin. Immunologic studies were performed on freshly suspended cells by indirect immunofluorescence and on frozen sections by immunoperoxidase technique. Malignant cells were positive for HLA-DR, but negative for CD 19, CD 1, CD 2, CD 4, CD 8, CD 13, and CD 33. Electron microscopy showed large cells with atypical nuclei, large nucleoli, and numerous erythrophagocytic vesicles (Fig 2). A karyotype from a lymph node (direct analysis, RHG banding, 15 mitoses analyzed) was 46, XX, t(2;5)(p23;q35) (Fig 3). Bone marrow was morphologically and karyotypically normal.

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### Table 2. Nine Cases Reported as Malignant Histiocytosis Apparently Without the Involvement of 5q35

<table>
<thead>
<tr>
<th>Patients</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Diploidy/hyperploidy with +18 or del(22q) or DM and/or (?) derivative chromosomes, one of which being a der(5) (not fully described)</td>
</tr>
<tr>
<td>12</td>
<td>46,XX/47,XX, +8/48,XX, +8, +15</td>
</tr>
<tr>
<td>13</td>
<td>Diploidy/hyperploidy + markers (one of which (M3) being possibly a 5q+)</td>
</tr>
<tr>
<td>14</td>
<td>Diploidy/tetraploidy/hexaploidy/decaploidy (not fully described)</td>
</tr>
<tr>
<td>15</td>
<td>Near tetraploidy, + markers (karyotype not fully described)</td>
</tr>
<tr>
<td>16</td>
<td>45,X,del(18)(q11),Xp+,der(9)</td>
</tr>
<tr>
<td>17</td>
<td>48-49,XX, +p1+,del(2)(p14), +8, +11,17p+, +Mar</td>
</tr>
<tr>
<td>18</td>
<td>46,XX</td>
</tr>
<tr>
<td>19</td>
<td>46,XY/47,XY, +8/48,XY, +8, +7/tetraploidy</td>
</tr>
</tbody>
</table>

All superscript numbers are references.

Only cases with banded chromosomes have been taken into account. Case 2 in Kaneko et al18 was more likely to be a non-Hodgkin's lymphoma. Case 1 in Schouten et al19 is now recognized as a particular type of "monoblastic" leukemia with t(8;16).20 These two cases have not been taken into account.

The marker chromosome (M3) found in Schouten et al19 case 2 could be a 5q+: A breakpoint in 5q35 cannot be excluded.
involvement was hidden.\textsuperscript{21} The last possibility is that the breakpoint within 5q35 is the only crucial event. Located in the distal region of 5q are several genes which could play a role in the outcome of a malignant process involving mononuclear phagocytes. The CSF1 gene, located at 5q33,\textsuperscript{23,24} encodes a colony stimulating factor that promotes growth and differentiation of mononuclear phagocytes. The c-fms proto-oncogene, assigned to 5q33-34,\textsuperscript{23,24} encodes the receptor for CSF 1.\textsuperscript{25} Introduction of the v-FMS gene into CSF-1–dependent macrophage cells renders them independent of CSF-1 for growth, and tumorigenic in nude mice.\textsuperscript{26}

ACKNOWLEDGMENT

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