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). © 1988 by Grune & Stratton, Inc.

Fig 1. (A) Lymph node print (magnification × 750). Poorly differentiated histiocytes with erythrophagocytosis. (B) Semi-thin section of lymph node (magnification × 710). Malignant histiocytes. Arrow: erythrophagocytosis; arrowhead: phagocytosis of a nucleated cell.

Fig 2. Electron microscopy (TEM) (magnification × 5000). Erythrophagocytosis.

Fig 3. Partial karyotype showing a t(2;5)(p23;q35) (lymph node sample, direct analysis, RHG banding).

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cytotoxic vesicles (Fig 2). A karyotype from a lymph node (direct
frozen sections
representation of this document as if you were reading it naturally.

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 investi-
gations showed enlarged mediastinal, mesenteric, and retroperito-
eal lymph nodes, but no liver or spleen enlargement. Her hemoglo-
bin was 9.7 g/dL; reticulocytes, 150 × 10^9/L; WBC 6.6 × 10^9/L
with 69% neutrophils; 6% monocytes; 1% eosinophils; 24% lympho-
cytes; and platelet count 458 × 10^9/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 his-
tiocytic 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

by immunoperoxidase technique. Malignant cells
represent a

in which a gene on chromosome 8 is
involvement of 5q35
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 reconstruc-
tion and no evidence of graft vs 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 avail-
able (Tables 1 and 2), ten cases presented a breakpoint in
5q35,\(^{6,10}\) 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 cases\(^6,9\) and in the investigators'
case, a t(1;5) (p32;q35) was found in one case,\(^7\) 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

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 reconstruc-
tion and no evidence of graft vs host disease (GVHD).


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(^6)</td>
<td>t(2;5)(p2:1;q35)</td>
<td>+i(1q), +17p(^+), +Mar</td>
</tr>
<tr>
<td>2(^7)</td>
<td>t(1;5)(p32;q35)</td>
<td>None?</td>
</tr>
<tr>
<td>3(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>None?</td>
</tr>
<tr>
<td>4(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>None?</td>
</tr>
<tr>
<td>5(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>None?</td>
</tr>
<tr>
<td>6(^8)</td>
<td>t(2;5)(23.1;q35.3)</td>
<td>None?</td>
</tr>
<tr>
<td>7(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>22p+</td>
</tr>
<tr>
<td>8(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>t(X;22)(p22;q12)/Xp+</td>
</tr>
<tr>
<td>9(^7)</td>
<td>t(5;6)(q35;p12)</td>
<td>−13, +der(13)t(1;13)(q21 or 22; q34)</td>
</tr>
<tr>
<td>10(^7)</td>
<td>t(2;5)(p23;q35)</td>
<td>None</td>
</tr>
</tbody>
</table>

Superscript numbers are references.

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(^11)</td>
<td>Diploid/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(^12)</td>
<td>46,XX/47,XX, +8/48,XX, +8, +15</td>
</tr>
<tr>
<td>13(^13)</td>
<td>Diploid/hyperploidy + markers (one of which (M3) being possibly a 5q+)</td>
</tr>
<tr>
<td>14(^14)</td>
<td>Diploid/tetraploid/hexaploid/hexamaploid (not fully described)</td>
</tr>
<tr>
<td>15(^16)</td>
<td>Near tetraploidy, + markers (karyotype not fully described)</td>
</tr>
<tr>
<td>16(^16)</td>
<td>45,X,del(18)(q21),Xp(^+), der(9)</td>
</tr>
<tr>
<td>17(^17)</td>
<td>48-49,XX,1p(^+), del(2)(p14), +8, +11, 17p(^+), +Mar</td>
</tr>
<tr>
<td>18(^18)</td>
<td>46,XX</td>
</tr>
<tr>
<td>19(^18)</td>
<td>46,XY/47,XY, +8/48,XY, +8, +7/near tetraploid</td>
</tr>
</tbody>
</table>

All superscript numbers are references.

Only cases with banded chromosomes have been taken into account. Case 2 in Kaneko et al\(^18\) was more likely to be a non-Hodgkin’s lymphoma. Case 1 in Schouten et al\(^13\) 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 al\(^13\) 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{22} encodes a colony stimulating factor that promotes growth and differentiation of mononuclear phagocytes. The c-fms proto-oncogene, assigned to 5q33-q34,\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}

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**REFERENCES**

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