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

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

From the Departments of Hematology and Pathology Hôpital Jean Bernard, Poitiers, France.
Submitted November 9, 1987; accepted May 13, 1988.
Address reprint requests to Dr. Jean-Loup Huret, MD, Cytogénétique, Département d'Hématologie, CHU La Milétrie, F-86021 Poitiers, France.

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0006-4971/88/7203-0042$3.00/0
Patients 5q35 Involvement Other Anomalies

11 t(2;5)(p23;q35) +i(1q), +17p\(^+\), +Mar

25 t(11;5)(p32;q35) None

37 t(2;5)(p23;q35) None

49 t(2;5)(p23;q35) None

52 t(5;35) (23.1;q35.3) None

61 t(2;5)(p23;q35) 22p+

88 t(5;35) (23.1;q35.3) None

91 t(5;6)(q35;p12) -13, +der(13)t(1;13)(q21 or 22;34)

104 t(2;5)(p23;q35) None

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 10\(^9\)/L; WBC 6.6 x 10\(^9\)/L with 69% neutrophils; 8% monocytes; and 24% lymphocytes; and platelet count 458 x 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 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 represent a neoplastic vesicles (Fig 2).

To ascertain the diagnosis of malignant histiocytosis, or point to other malignancies. However, of 19 cases reported as malignant histiocytosis where informative cytogenetic analysis, RHG banding, 15 mitoses analyzed) was 46, XX, Burkitt Leukemia 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 reconstitution and no evidence of graft versus 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 5q35,10,14,15 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 cases4,8 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 6, 2, 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 reconstitution and no evidence of graft versus host disease (GVHD).

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involvement was hidden. 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 5q33.26 encodes a colony stimulating factor that promotes growth and differentiation of mononuclear phagocytes. The c-fms proto-oncogene, assigned to 5q33-3423.26 encodes the receptor for CSF 1. Introduction of the v-fms gene into CSF-1–dependent macrophage cells renders them independent of CSF1 for growth, and tumorigenic in nude mice.

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