Haematologica 2002; 87:(05)ECR19

Secondary acute monocytic leukemia with a t(8;22)(p11;q13) translocation

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A 55-year-old man was admitted to our hospital because of worsening pancytopenia and increasing blast cells in peripheral blood. The patient had a fourteen-year history of IgM kappa primary macrogloblinemia which had been treated with melphalan, vincristine, cyclophosphamide, procarbazine, doxorubicin and ranimustine. Laboratory data on admission showed pancytopenia with immature myeloid series in peripheral blood, hypercellular bone marrow with increased monocytic blasts. Therefore, he was diagnosed as having acute monocytic leukemia, and combination chemotherapy was started. Chromosomal analysis revealed the development of 46 XY, t(8;22)(p11;q13) in all twenty cells analyzed. During the myelosuppression following intensive chemotherapy, he died with severe aspergillosis. The chromososmal translocation t(8;22)(p11;q13) has been reported relation to the chimeric MOZ-p300 gene which has been found in acute monocytic leukemia patients, but has rarely been reported in relation to therapy-related leukemia. Here we precisely report the case as secondary leukemia.

The MOZ gene, located on chromosome 8p11, was originally found in a distinct subset of acute monocytic leukemias carrying the t(8;16)(p11;p13) translocation, that results in the MOZ/CBP fusion protein.[1] The t(8;16)(p11;p13) translocation has been found in approximately 0.4% to 2% of cases of acute myelocytic leukemia (AML) showing FAB classification of M4 (myelomonocytic) or M5 (monocytic) phenotype.[2,3] The p300, an adenoviral E1A-associated protein, whose gene has been located on chromosome 22q13, has been reported to be fused with MLL or MOZ gene by chromosomal translocation, and those fusion products play a role in leukemogenesis.[1,4,5] The present case has been previouly reported as an acute monocytic leukemia caused by the fusion of MOZ and p300 genes,[5] but the details of the case have not been described. Here, we presented the detailed clinical features of the case and discuss then especially focusing on the possibility that histone acetyl transferase genes such as MOZ and p300 might be target genes of therapy-related leukemias.

Case report and Discussion. A 55-year-old man was admitted to our hospital in August 1998, due to worsening pancytopenia and increasing blast cells in peripheral blood. The patient had a fourteen-year history of IgM kappa primary macrogloblinemia, which had been treated with melphalan, vincristine, cyclophosphamide, procarbazine, doxorubicin and ranimustine; the total doses of each drug were 880 mg, 22 mg, 3600 mg, 8800 mg, 100 mg and 200 mg, respectively. Peripheral blood analysis showed anemia, decreased platelet count (5.1×10^4/mL) and leukocytopenia (2,200/μL) with increased blast cells (17%). A monoclonal increase of IgM (2400 mg/dL) with decreased IgG and IgA was observed. Bone marrow aspiration revealed hypercellular marrow with increased blast cells (58.5%). Erythrophagocytosis by the blast cells was occasionally found (Figure 1). The erythrophagocytosis by the leukemic cells has been reported a hallmark character of the cases with t(8;16), but never been stressed in those with t(8;22).[2,4,6] The blast cells were positive for peroxidase and a-naphthyl butyrate esterase stainings, but the latter was completely inhibited by treatment with sodium fluoride. Immunophenotypic analysis revealed that the blast cells were positive for CD4 (90.0%, positive for cells analyzed), CD11c (32.6%), CD33 (87.7%) antigens, but negative for CD2 (0.1%), CD5 (21.2%), CD7 (0.3%), CD13 (6.8%), CD14 (0.3%), CD 19 (1.9%), CD 20 (2.3%), CD34 (0.3%) and c-kit (0.4%). Chromosomal analysis showed 46, XY, t(8;22)(p11;q13) in all 20 cells analyzed. The t(8;22)(p11;q13) translocation in our case was, therefore, considered as therapy-

related. No other case has been reported of t(8;22) in relation to therapy-related leukemia.[4,6] The breakpoints of this translocation on chromosome 8 and 22 correspond to the MOZ and p300 loci, respectively. We previously reported the detailed structure of the fusion gene products of our case.[5] The features of t(8;22)(p11;q13) cases resemble those of a distinct subset of AML with t(8;16)(p11;p13), showing monocytic arrest and erythrophagocytosis. The t(8;16)(p11;p13) disrupts the MOZ gene and the CBP gene on 16p13, resulting in their fusion.[2,3] To date, more than 40 cases with t(8;16)(p11;p13) have been reported in the literature and ten of those cases are, at least, therapy-related.[7-14] Meanwhile, regarding the p300 gene, Ida *et al.* reported a case of AML with t(11;22)(q23;q13), by which the p300 gene was fused to the MLL gene on 11q23, and this case was also considered to be therapy-related.[15] Based on these observations, MOZ, p300 and CBP genes are considered to be a crucial target of therapy-related leukemias. Supporting this hypothesis, Rowley *et al.* reported that all cases with the t(11;16)(q23;p13.3), involving CBP gene, were therapy-related.[16] Therapy-related leukemia can be separated into two types.[17] The first type is associated with specific unbalanced cytogenetic aberrations mostly involving chromosome 5 or 7, and is related to a history of exposure to alkylating agents and/or radiation. The second type is found in patients who were mostly treated with topoisomerase II inhibitors, and associated with t(8;21), inv(16), t(15;17) or often with a balanced translocation between 11q23 and other chromosomes, primarily t(6;11), t(9;11) and t(11;19).[7] (Figure 2) In addition, as mentioned above, there might be a distinct subgroup in the second type which involes the MOZ, p300 and CBP genes. These genes encode proteins with histone acetyltransferase (HAT) activity or potential HAT activity. They interact with specific DNA-binding transcription activator and repressor proteins, suggesting that they modulate transcriptional activity of specific promotors by regulating local histone acetylation. Recently, Kitabayashi *et al.* reported that the fusion protein created by the t(8;16)(p11;p13) inhibited AML-1 mediated transcription and differentiation of M1 cells, suggesting that MOZ-CBP might induce leukemia by antagonizing the function of the AML-1 transcription factor complex.[18] The precise mechanisms of how chemotherapeutic agents such as topoisomerase II inhibitors make the chromosome translocations involving the genes encoding HAT activities and how leukmeias develop by these translocations needs to be elucidated.

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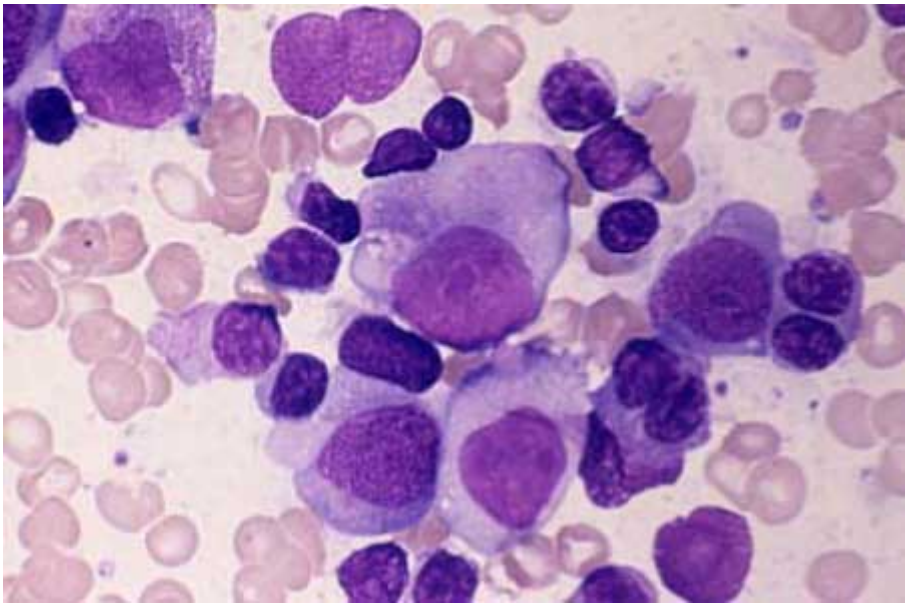

Figure 1. Hemophagocytosis of red blood cells by the monocytoid blast cells were observed at diagnosis. (May-Gimsa staining, original magnification x 400).

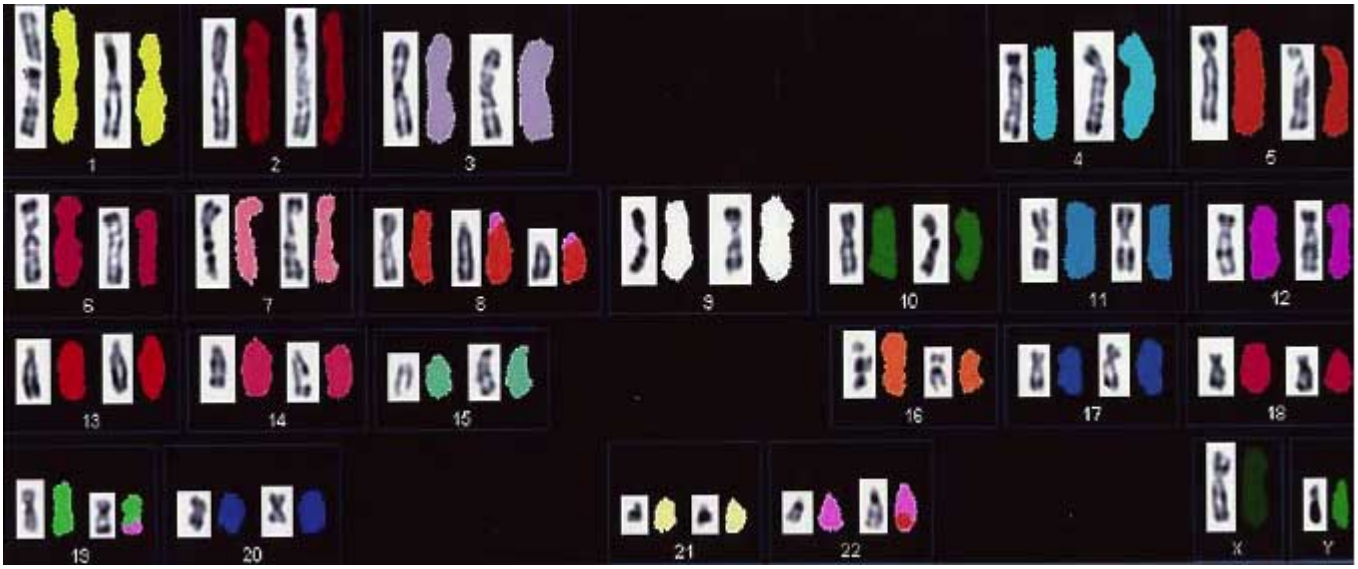

Figure 2. Karyotype showing the 46, XY, t(8;22)(p11;p13). Karyotype table produced by combining spectral karyotyping (SKY) and G-band-like images. For each chromosome, G-band-like images are shown on the left side and classified color images on the right.