Involvement of the NUP98 Gene in a Chromosomal Translocation t(11;20)(p15;q11.2) in a Patient With Acute Monocytic Leukemia (FAB-M5b)

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Abstract

We report here a case of acute monocytic leukemia (M5b subtype according to the French-American-British [FAB] classification) with chromosomal translocation t(11;20)(p15;q11.2). Fluorescence in situ hybridization analysis with a probe for the NUP98 gene, which is located at chromosome band 11p15, showed that the probe hybridized to both derivative chromosomes 11 and 20 as well as to the remaining normal chromosome 11, indicating that the NUP98 gene was split and involved in this translocation. This is the first report of t(11;20)(p15;q11.2) involving the NUP98 gene in overt leukemia. Int J Hematol. 2001;74:53-57.

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Key words: t(11;20)(p15;q11.2); NUP98; Fluorescence in situ hybridization

1. Introduction

Cytogenetic abnormality involving 11p15 is occasionally seen in de novo acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndromes (MDS), as well as in therapy-related AML and MDS (t-AML/MDS). Of the chromosomal translocations involving 11p15, t(11;20)(p15;q11.2) has been reported in a small number of patients, and the NUP98 gene, located in 11p15 [1,2], has been one of the candidate genes involved in this translocation. In this report, we describe a patient with acute monocytic leukemia (M5b subtype according to the French-American-British [FAB] classification) accompanied by t(11;20)(p15;q11.2). Fluorescence in situ hybridization (FISH) analysis with a specific probe for NUP98 showed that NUP98 is involved in this translocation.

2. Case Report

A 47-year-old woman was admitted to Ohtsu Red Cross Hospital in January 1996 because of severe anemia. She had not been exposed to any cytotoxic agents or drugs. Physical examination results were nonspecific except for anemic palpebral conjunctiva. Hematologic examination indicated a white blood cell count of 2.5 × 10⁸/L with 2% blasts, hemoglobin concentration of 4.8 g/dL, and platelet count of 208 × 10⁹/L. The results of serum biochemical and serological tests including serum lactate dehydrogenase and C-reactive protein were all within normal limits. Bone marrow aspirate
showed normocellular marrow with 45.6% immature and 20.0% mature monocytes (Figure 1). These monocytes were positive for α-naphthyl butyrate esterase but negative for peroxidase staining. Dysplastic features such as scant granules and Pelger-Huët–like nuclei of neutrophils were seen (Figure 2). Cytogenetic analysis of bone marrow cells showed an abnormal karyotype of 46, XX, t(11;20) (p15;q11.2), del(8)(q23) in 19 of the 20 cells analyzed. The remaining cell had a normal female karyotype of 46, XX. The patient's disease was diagnosed as AML-M5b based on the FAB classification. The patient's condition could have arisen from MDS. Complete remission was obtained and the abnormal karyotype disappeared after 3 courses of induction therapy; 2 cycles of chemotherapy consisting of enocitabine, daunorubicin, 6-mercaptopurine, and prednisolone; and 1 course in which daunorubicin was replaced with aclarubicin (BHAC-AMP). In February 1997, the leukemia recurred and BHAC-AMP chemotherapy resulted in a stable dysplastic hematopoiesis corresponding to MDS–refractory anemia (MDS-RA) with persistent t(11;20)(p15;q11.2). In August 1997, the patient was admitted to Kobe City General Hospital to receive bone marrow transplantation (BMT). Blood examination showed pancytopenia with 3% blasts. The bone marrow aspirate showed normocellular marrow with 10% blasts, 2% monocytes, and a number of dysplastic hematopoietic cells, indicating that the patient's disease was RA with an excess of blasts (MDS-RAEB). Persistence of t(11;20) (p15;q11.2) was also observed. Allogeneic BMT was performed in September 1997, using marrow cells from an HLA-matched sibling. The conditioning regimen consisted of cyclophosphamide (120 mg/kg for 2 consecutive days) followed by total body irradiation of 12 Gy. On day 6 after BMT, the patient developed septicemia with bacillus, which was complicated with rhabdomyolysis. She died of intracranial hemorrhage on day 12 after BMT. The autopsy demonstrated systemic rhabdomyolysis, focal necrosis in the centrilobular zones of the liver associated with bacterial embolism of the central vein, and massive necrosis or infarction of the lung.

3. Material and Methods

3.1. Cytogenetic Analysis

Cytogenetic analysis of bone marrow cells was performed at the time of diagnosis and relapse. Briefly, bone marrow cells were cultured for 24 hours at 37°C in 5% CO₂ in RPMI 1640 medium supplemented with 15% (vol/vol) fetal bovine serum without any mitogen. Colcemid was added to the culture medium for 15 to 30 minutes before cell harvesting. The harvested cells were then treated with hypotonic potassium chloride and fixed with methanol/acetic acid (3:1). Chromosomes were stained using the conventional trypsin-Giemsa method. Karyotypes were determined according to the recommendations of the International System for Human Cytogenetic Nomenclature (ISCN 1995).

3.2. DNA Probes and FISH Analysis

A P1 clone, P505, was isolated by polymerase chain reaction (PCR) screening using the primers NF20 (5′-CCGTGATACCGAAGTTGAAAG-3′) and NR23 (5′-CATGGAGGTAAGAAAAGT-3′) corresponding to the 3′ non-coding exon of the NUP98 gene from the total human P1 genomic library. PCR amplification was performed for 35 cycles (denaturation at 94°C for 20 seconds, annealing at 58°C for 40 seconds, and extension at 72°C for 60 seconds). The P505 clone was labeled with biotin-16-dUTP (Boehringer Mannheim Biochemica, Mannheim, Germany) by nick translation. To confirm the identification of chromo-