DELETION OF CHROMOSOME 9p22 AS THE SOLE CYTOGENETIC ABNORMALITY IN A PATIENT WITH DE NOVO AML

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ABSTRACT

The diagnostic karyotype of acute leukemia can be used to identify biologically distinct subsets of this heterogeneous disease. Chromosome 9p rearrangement accounts for approximately 10% of adult acute lymphoblastic leukemia (ALL). However, to our knowledge, there has been no report of acute myeloid leukemia (AML) with deletion of 9p22 as the sole cytogenetic abnormality. We here describe a novel case of de novo AML with del(9p22). This report suggests that del(9p22) may not be exclusively associated with a poor prognosis. Further studies are required to investigate the presumed existence of a new tumor suppressor on chromosome 9p22.

Key Words: Deletion of Chromosome 9p22, Acute Myeloid Leukemia

INTRODUCTION

The diagnostic karyotype of acute leukemia can be used to identify biologically distinct subsets of this heterogeneous disease (James et al., 2009). Some of these chromosomal abnormalities are very rare and their clinical significance is not fully understood (David et al., 2010). Chromosome 9p rearrangement accounts for approximately 10% of adult acute lymphoblastic leukemia (ALL) (Heerema, 2013). However, to our knowledge, there has been no report of acute myeloid leukemia (AML) with deletion of 9p22 as the sole cytogenetic abnormality (James et al., 2009; David et al., 2010; Dessen and Huret, 2013). We here describe a novel case of de novo AML with del(9p22).

CASES

A 68-year-old man visited our clinic with abnormal findings upon a regular check-up in 2011. A peripheral blood smear and bone marrow biopsy revealed AML-M1 with del(9p22).

Cytogenetic Studies

Cytogenetic G-banding studies were performed using standard methods. Fluorescence in situ hybridization (FISH) studies for AML1/ETO (8q22: LSI ETO SpectrumOrange &21q22:AML1 SpectrumGreen, VYSIS, USA), CBF (16q22: centromeric side, SpectrumRed/telomeric side, SpectrumGreen) and MLL (11q23: centromeric side, SpectrumGreen/telomeric side, SpectrumOrange), using dual-color DNA probes, yielded negative results. Allele-specific reverse transcription PCR studies for AML1/ETO, CBF/MYH11, MLL rearrangement, FLT3/ITD, and FLT3/TKD D835Y also yielded negative results. We also assessed and confirmed the presence and integrity of CDKN2A (p16), which is known to be a tumor suppressor gene, using the Vysis LSI CDKN2A SpectrumOrange/CEP9 SpectrumGreen probes.

RESULTS

The patient was admitted with the following findings: WBC, 17,880/µL (83% blasts); Hgb, 12.4g/dL; and platelets, 17,000/µL; on May 30, 2011. Bone marrow biopsy revealed 80% cellular marrow with 65.1% myeloblasts, which were positive for CD34, CD117, CD13, CD33, and MPO. A diagnosis of AML-M1
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was made, and cytogenetic analysis revealed 46 chromosomes, including X and Y and del(9p22). GTL-bandling analysis showed a decrease in the length of the heterochromatin on the long arm of chromosome9, which was considered to be a normal variation (Figure 1). Hemavision results were all negative.

The patient underwent induction with cytarabine (100mg/m² for 7 days) and idarubicin (12mg/m² for 3 days) and showed complete remission. Follow-up bone marrow biopsy showed normal cytogenetic findings in the remission marrow.

He had required antibiotic therapy due to cellulitis and invasive aspergillosis after the first consolidation chemotherapy with cytarabine (2g/m² twice a day on days 1, 3, and 5). After second consolidation chemotherapy with cytarabine was performed, he developed *Klebsiella pneumoniae* sepsis. After recovering from sepsis and while we were planning the third consolidation chemotherapy, he suffered a relapse; this occurred a year after initial diagnosis. He underwent salvage chemotherapy with mitoxantrone (12mg/m² for 4 days), cytarabine (1.5g/m² for 4 days), and etoposide (100mg/m² on days 5–7). Prolonged neutropenia followed by sepsis developed and he died on June 15, 2012.

**DISCUSSION**

AML associated with del(9p22) is rare and the prognosis of this cytogenetic abnormality is unknown. Although there have been some reports of del(9p22) combined with other cytogenetic aberrations, the prognoses of such cases with complex cytogenetic abnormalities are poor. The case described here involved AML without maturation, i.e., M1.

Figure 1: The 46XY, del(9)(p22) karyotype. Arrow indicates deletion of the short arm of chromosome9
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A recent study showed that in the 2008 WHO classification scheme, the French-American-British(FAB) subclassification does not provide prognostic information for “AML, NOS” cases if data on NPM1 and CEBPA mutations are available (Roland et al., 2013). Given that the case we describe here is AML-NOS of WHO classification, the FAB classification, M1 cannot provide prognostic information. Although our patient had poor prognostic factors, viz, old age and multidrug-resistance gene (MDR-1) expression at the time of diagnosis, he survived 1 year. When compared with other identified disease entities, this may suggest that AML with del(9p22) has at least an intermediate prognosis (John et al., 2002). Chromosome 9p rearrangements are known usually to involve deletion of the genes p15 and/or p16on 9p21.3. These genes encode cyclin-dependent kinase inhibitor 2A and cyclin-dependent kinase inhibitor 2B, respectively, and are known to be tumor suppressor genes (Ayse et al., 1997). However, we examined FISH for p16 and confirmed the integrity of this gene. Allelic loss of 9p22–p24 has been detected in various human cancers, including bladder cancer, lung cancer, melanoma and breast cancer (Han-Xiang et al., 1999). In particular, the region between D9S285 and D9S162 distal to the CDKN2A locus has also been found to be lost in lung cancer (Kim et al., 1997; Neville et al., 1995) in melanoma (Puig et al., 1995) and in squamous cell carcinoma of the esophagus (Tarmin et al., 1994). These findings suggest that the alteration of genetic material at the subtelomeric region of 9p plays an important role in the pathogenesis of different human cancers. A previous study identified 12 SNPs at 9p22 that are associated with epithelial ovarian cancer risk (P<10^-8). All 12 SNPs were located in the same region on 9p22.2, with the nearest genes being BNC2 (encoding basonuclin 2), CNTLN (encoding centlein, a centrosomal protein), and hypothetical gene LOC648570. The authors concluded that there is little evidence of a role for BNC2 in cancer development and that further studies, including resequencing of the 9p22.2 region, are required to elucidate the correlation (Honglin et al., 2009). In conclusion, to our knowledge, this case is the first report of a de novo cases of AML with deletion of chromosome 9p22 as the sole cytogenetic abnormality. This report suggests that del(9p22) may not be exclusively associated with a poor prognosis. Further studies are required to investigate the presumed existence of a new tumor suppressor on chromosome 9p22.

REFERENCES


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