Case Research

Recurrent isochromosome 21 and multiple abnormalities in a patient suspected of having acute myeloid leukemia with eosinophilic differentiation—a rare case from South India

Sangeetha Vijay¹, Santhi Sarojam¹, Sureshkumar Raveendran¹, Vani Syamala¹, Sreeja Leelakumari¹, Geetha Narayanan², Sreedharan Hariharan¹

Abstract

Acute myeloid leukemia (AML) is a phenotypically heterogeneous disorder. The M4 subtype of AML is frequently associated with the cytogenetic marker inversion 16 and/or the presence of eosinophilia. Blast crisis is the aggressive phase of the triphasic chronic myeloid leukemia (CML), which is a disease with Philadelphia (Ph) chromosome as the major abnormality. In the present study, we report a 76-year-old patient suspected of having AML with eosinophilic differentiation (AML-M4), which in clinical tests resembles CML blast crisis with multiple chromosomal abnormalities. Isochromosome 21 [i(21)(q10)] was the most recurrent feature noted in metaphases with 46 chromosomes. Ring chromosome, tetraploid endoreduplication, recurrent aneuploid clones with loss of X chromosome, monosomy 17, monosomy 7, and structural variation translocation (9;14) were also observed in this patient. Fluorescent in situ hybridization (FISH) confirmed the absence of Ph chromosome. This report shows how cytogenetic analyses revealed atypical structural aberrations in the M4 subtype of AML.

Key words: i(21)(q10), AML-M4 [E0], atypical cytogenetic abnormalities, tetraploid endoreduplication, ring chromosome

Acute myelogenous leukemia (AML) is a hematopoietic malignancy, with the accumulation of immature cells in the marrow, peripheral blood, and eventually other tissues. Primary chromosomal abnormalities in AML are highly specific and considered to be associated with leukemic transformation, whereas secondary changes are less specific and probably contribute to disease progression. The common chromosomal abnormalities in the French-American-British Cooperative Group (FAB) subtype M4, or acute myelomonocytic leukemia, include monosomy 5 or deletion of 5q [del(5q)], monosomy 7 or del (7q), trisomy 8, t (6;9)(p23;q34), and others. Karyotype is generally an important prognostic factor in AML, with prognosis being associated with even minor karyotypic changes. In this report, we describe an adult male patient diagnosed with hematological and clinical characteristics of AML-M4 with eosinophilic differentiation (AML-M4 [E0]) showing atypical cytogenetic features.

Case Presentation

A 76-year-old man of Indian origin, with history of ischemic heart disease, was presented to the Outpatient Clinic of Medical Oncology, Regional Cancer Centre due to marked variation in blood count, in addition to anemia, thrombocytopenia, mild splenomegaly, and leukocytosis. Initial complete blood count displayed 4.8 g/dL of hemoglobin, leukocyte count of 50 500 cells/mm³ undiluted blood, and thrombocyte count of 65 000 cells/mm³ undiluted blood. Blood picture showed predominant neutrophils, marked shift to the left with atypical monocytes, 12% blasts, and 6% basophils. Initial bone marrow study revealed hypercellular marrow with 35% blasts and mild
Discussion

Isochromosome forms when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of only two short arms or two long arms. Isochromosomes have rarely been reported as acquired aberrations in hematological malignancies, except in some survey data that shows the presence of isochromosome 21 [i(21)(q10)] in hematological malignancies and 10% of all neoplasms with cytogenetic aberrations[1]. Worth et al.[2] has reported a transient leukemic condition in a phenotypically normal newborn bearing i(21)(q10) clones, suggesting that the q arm of chromosome 21 contains sufficient genetic information for the development of transient leukemia. Among the common types of isochromosomes observed in AML, i(11q), i(17q), and i(21q) are the most prominent[3]. In our study, i(21)(q10) was the single recurrent abnormality observed in 84% (42/50) of the spreads (Figure 1A). It was either the sole abnormality (19/50 spreads) or present in conjunction with other

| Composite karyotypes observed | No. of metaphases (n = 50) | Other abnormalities |
|-------------------------------|-----------------------------|---------------------|
| 46, XY                        | 4                           |                     |
| 46, XY, i(21)(q10)            | 19                          |                     |
| 46, XY, −17, i(21)(q10)       | 2                           |                     |
| 46, XY, −17, i(21)(q10)[cp6]  | 6                           |                     |
| 46, XY, −7, i(21)(q10)[cp4]   | 4                           |                     |
| 46, Y, −X, +14, −18, i(21)(q10)[cp3] | 3 |                     |
| 46, XY, i(21)(q10) [cp5]      | 5                           |                     |
| 47, XY, +14[cp5]              | 5                           |                     |
| 48, XY, i(21)(q10)[cp2]       | 2                           |                     |
AML-M4 suspect with atypical cytogenetic abnormalities

Several cytogenetic abnormalities have been reported in chronic eosinophilic leukemia, but there is no unique clonal cytogenetic abnormality associated with chronic eosinophilic leukemia. Del(16q22) was reported in only one chronic eosinophilic leukemia case and was associated with other chromosomal abnormalities, including trisomy 8, trisomy 19, and addition of 2q12. Notably, the patient subsequently developed AML. In our study, inv(16) and 1(16;16) were not observed among the analyzed metaphases. However, the status of del(16q22) remains to be determined. Additional recurrent chromosomal abnormalities observed in the clones with i(21)(q10) included monosomy 17, monosomy 7, loss of X chromosomes, and others.

The second most common aneuploidy observed in our subject, occurring in an average of 16% of clones, was loss of a copy of chromosome 17. p53 mutations were found more frequently in patients with monosomy 17p. In addition, 17p anaply-like monosomy 17/17p has been observed in myelodysplastic syndrome and AML patients with poor prognosis and been found to occur as adjunct to secondary MDS/AML after chemotherapy and/or radiotherapy, usually in association with other complex chromosomal anomalies.

Monosomy 7 was also observed in several clones analyzed. An association between the complete or partial loss of chromosome 7 and preleukemic myelodysplasia or AML has been recognized from the early days of tumor cytogenetic analysis. Detection of such abnormalities usually heralds a poor prognosis. Amare et al. reported monosomy of chromosomes 7 and 17 as secondary chromosomal abnormalities that occur when disease progresses from CML to a more aggressive blast phase or transforms into lymphoid leukemia-like acute myeloid, lymphoid leukemia, or lymphoid blast crisis of CML. Sabine et al. have shown that monosomy 7/del(7q) causes loss of miR-29a, an important tumor suppressor, and up-regulation of Ski oncogene in AML. Zhang et al. showed that benzene significantly induced monosomies of a specific set of chromosomes including chromosome 7 in a dose-dependent manner. Monosomy 7 as observed in our study has also been linked to loss of the chromosome 7 gene KCNH2 [potassium voltage-gated channel, subfamily H (Eag-related), member 2], which was found to play a role in causing cardiac arrest death. We hypothesize that some patients may show genomic imbalances and changes in the gene copy number that lead to genetic instability.

Bakshi et al. reported the loss of sex chromosomes in AML and Philadelphia chromosome (Ph)–negative CML cases. Loss of X chromosome is purportedly due to evolution of malignant clones, but the influence of this loss on the process of evolution is not known. The loss of sex chromosomes has been shown to be clearly related to increasing age. In our case, we also
observed X chromosome loss in several metaphases (6%).

Polyploidy and endoreduplication (P&E) were also observed in our study (Figure 1B). P&E of chromosomes occur more often in patients with disseminated cancer and vary with the extent of disease. Our data is substantiated by a prior report by Bottura et al. that depicts the link between polyploidization in leukemia cells, specifically in AML. In our case, we observed ring chromosomes in 2 metaphases with 47 chromosomes (Figure 1C). It is probably not only the ring structure or the neoplastic nature of the host cell that determines ring instability, but also the function of the genes carried in the ring. Structural variation t(9;14) in one of the metaphases (Figure 1D) was also a notable anomaly in our case. This type of translocation, t(9;14), has been detected in 50% of lymphocytoid lymphoma, a subtype of B-cell non-Hodgkin’s lymphoma. A similar case of t (9;14) among a complex karyotype has been reported in a patient with AML-M7. Compared to other hematological malignancies, AML is frequently reported to have ring chromosomes. Although certain clinical and

Figure 1. Genotyping for a 76-year-old man with suspected AML-M4. A, G-banded metaphase and karyotype shows 46,XY,i(21)(q10). B, a metaphase shows tetraploid endoreduplication. C, a metaphase with 47 chromosomes shows two ring chromosomes. D, a partial karyotype of t(9;14).
hematological parameters of our case showed a slight inclination towards CML blast crisis, Ph chromosome was not observed by GTG-banding in any of the observed metaphases. To rule out the presence of any cryptic bcr-abl fusion gene, we performed FISH analysis (Figure 2), which confirmed the diagnosis of AML-M4 [E6].

Cyrogenetic abnormalities play an important role in diagnosing hematological malignant diseases and are important independent predictors of disease progression and survival. Although karyotype is an important prognostic factor in AML, the prognostic significance of additional cytogenetic abnormalities like isochromosome 21 in acute leukemia remains to be elucidated. Atypical cytogenetic findings have been sporadically reported in AML-M4, but the scarcity of these abnormalities poses a challenge to using such changes as prognostic factors, reinforcing the need for the collection of clinical data on rare events. To the best of our knowledge, this is the first case report involving a spectrum of abnormalities associated with poor prognosis in AML-M4 [E6]. The atypical findings suggest a cumulative poor prognosis, and further follow-up of this patient is needed to justify this derivation.

Acknowledgment

This work was supported by a grant from Kerala State Council for Science, Technology and Environment (KSCSTE), Govt. of Kerala, India.

References

[1] Welbom J. Acquired Robertsonian translocations are not rare events in acute leukemia and lymphoma. Cancer Genet Cytogenet, 2004;151(1):14–35.
[2] Worth LL, Zipursky A, Christensen H, et al. Transient leukemia with extreme basophilia in a phenotypically normal infant with blast cells containing a pseudodiploid clone, 46,XY,i(21)(q10). J Pediatr Hematol Oncol, 1999;21(1):63–66.
[3] Mertens F, Johansson B, Meidman F. Isochromosomes in neoplasia. Genes Chromosomes Cancer, 1994;10(4):221–230.
[4] Wu DM, Jiang M, Zhang M, et al. KCNE2 is colocalized with KCNQ1 and KCN1 in cardiac myocytes and may function as a negative modulator of IKs current amplitude in the heart. Heart Rhythm, 2006;3(12):1490–1496.
[5] Toyoda F, Ueyama H, Ding WG, et al. Modulation of functional properties of KCNQ1 channel by association of KCNE1 and KCNE2. Biochem Biophys Res Commun, 2006;344(3):814 – 820.
[6] Neben K, Tews B, Wrobel G, et al. Gene expression patterns in acute myeloid leukemia correlate with centrosome aberrations and numerical chromosome changes. Oncogene, 2004;23(13):2379–2384. (doi:10.1038/sj.onc.12074017)
[7] Krämer A, Neben K, Ho AD. Centrosome aberrations in hematological malignancies. Cell Biol Int, 2005;29(5):375–383. (doi:10.1016/j.cellbi.2005.03.004)
[8] Neben, K. Ott G, Schweizer S, et al. Expression of centrosome-associated gene products is linked to tetraploidization in mantle cell lymphoma. Int J Cancer, 2007, 120(8):1669–1677. (doi:10.1002/ijc.22404)
[9] Ye X, Niu Y, Fang ZY. Correlation of centrosome abnormality and aneuploid instability to tumor. Chin J Cancer, 2005,24(10):1290–1292. [in Chinese]
[10] Mysauchi J, Ito Y, Tsukamoto K, et al. Blasts in transient leukemia in neonates with Down syndrome differentiate into basophil/mast-cell and megakaryocyte lineages in vitro in association with down-regulation of truncated form of GATA1. Br J Haematol, 2010, 148(6):898–909.
[11] Adriaenssen HJ, te Boekhorst PA, Hagemeijer AM, et al. Acute myeloid leukemia M4 with bone marrow eosinophilia (M4EO) and inv (16)(p13q22) exhibits a specific immunophenotype with CD2 expression. Blood, 1993,81(11):3043–3051.
[12] Goltib J, Cools J, James M, et al. The FIP1L1-PDGFR fusion tyrosine kinase in hyper eosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood, 2004,103(8):2879–2891.
[13] Fenaux P, Joveaux P, Quigand L, et al. P53 gene mutations in acute myeloid leukemia with 17p monosomy. Blood, 1991,78(7):1652–1657.
[14] Pedersen Bjergaard J, Philip P, Olsen Larsen S, et al.
Chromosomal aberrations and prognostic factors in myelodysplasia and nonlymphocytic leukemia. Blood, 1980, 76 (6): 1083–1091.

[15] Johnson E, Cotter FE. Monosomy 7 and 7q—associated with myeloid malignancy. Blood, 1997;11(1):46–55.

[16] Amare PS. Chronic myeloid leukemia: cytogenetics and molecular genetics. Indian J Hum Genet, 2002;8:111–116.

[17] Sabine T, Thomas I, Josephine R, et al. MicroRNA29a regulates the expression of the nuclear oncogene Ski. Blood, 2011. Prepublished online (doi: 10.1182/blood-2010-09-306258).

[18] Zhang L, Lan Q, Guo W, et al. Chromosome-wide aneuploidy study (CWAS) in workers exposed to an established leukemogen, benzene. Carcinogenesis, 2011,32(4):605–612.

[19] Banerjee B, Peiris DN, Koo SH, et al. Genomic imbalances in key ion channel genes and telomere shortening in sudden cardiac death victims. Cytogeten Genome Res, 2008,122(3–4):350–355.

[20] Bakshi SR, Kakadia P, Brambhat M, et al. Loss of sex chromosome in acute myeloid leukemia. Indian J Hum Genet, 2004,10(1):22–25.

[21] Guttmanb M, Koschorz B, Bernthaler U, et al. Sex chromosome loss and aging: in situ hybridization studies on human interphase nuclei. Am J Hum Genet, 1995,57 (5):1143–1150.

[22] Bottura C, Ferrari I. Endoreduplication in acute leukemia. Blood, 1983.21(2):207–212.

[23] Gisselsson M, Hoglund F, Mertens B, et al. The structure and dynamics of ring chromosomes in human neoplastic and non-neoplastic cells. Hum Genet, 1999,104(4):315–325.

[24] Lida S, Rao PH, Nallasivam P, et al. The t(9;14)(p13;q32) chromosomal translocation associated with lymphoplasmacytoid lymphoma involves the PAX-5 gene. Blood, 1996,88(11):4110–4117.

[25] Toretsky JA, Enever EM, Padilla-Nash HM, et al. Novel translocation in acute megakaryoblastic leukemia (AML-M7). J Pediatr Hematol Oncol, 2003,25(5):396–402.

[26] Birbas K, Nandhini B, Nevathi R. Ring chromosome 8 and trisomy 8 in a patient with acute myeloid leukemia. Indian J Hematol Blood Transfus, 2008,25(1):30–32.