Myelodysplastic Syndrome with 6q Deletion as the Sole Chromosome Abnormality in an Iranian Patient: A Case Report with Review of Literature

Shirin FERDOWSI¹, Reza SHIRKOOGHI², *Gholamreza TOOGEH³

¹. Dept. of Hematology, Iranian Blood Transfusion Organization, Tehran, Iran
². Dept. of Molecular Genetics, Cancer Research Center, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
³. Dept. of Hematology-Oncology and BMT Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding Author: Email: h.hematology@yahoo.com

(Received 10 Jun 2013; accepted 11 Sep 2013)

Abstract

Background: The myelodysplastic syndrome (MDS) is a highly heterogenous disorder and karyotype analysis is helpful for diagnostic and prognostic estimation. Deletion in long arm chromosome 6 (6q del) as a sole abnormality is a rare event in MDS. This is the first case report of del (6q) as the only observed diagnostic change in Iran. We also reviewed the literature of this cytogenetic lesion.

Keywords: Myelodysplastic syndrome, Deletion 6q, Iran

Introduction

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell disorders characterized by cytopenia(s), dysplasia in one or more of the major myeloid cell lines, ineffective hematopoiesis, and increased risk for development of acute myeloid leukemia (AML) (1-3). Approximately 50% of patients have a detectable cytogenetic abnormality during routine G/TOG-banded karyotyping (4) and the most commonly involved chromosomal changes observed are monosomy 5 or del(5q), monosomy 7 or del(7q), trisomy 8, del (20q) and del(9q) (5-9). Several studies have established the prognostic value of cytogenetic analysis in MDS both for survival and progression to AML (10-12). For example, an isolated 5q deletion is characterized by longer survival and lower progression rates to AML (12). In MDS rare abnormalities can be observed frequently (7). To our knowledge, there has been no case report of del (6q) in MDS in Iran, and there are only four case reports worldwide (13-16).

Case Report

A 66-year-old woman was admitted at Imam Khomeini Hospital complexes affiliated to Tehran University of Medical Science, in August 2012 for further evaluation of moderate refractory anemia. The patient had received a treatment for iron, vitamins B12 and folic acid. This treatment had no influence on her hematologic condition. In addition, she had received supportive cure in the form of transfusions. At admission, the patient had ill appearance without fever and showed no
splenomegaly, lymphadenopathy, or organomegaly on physical examination. A complete blood evaluation revealed hematocrit of 24.7%, hemoglobin 7.7 g/dl, red cell count $2.26 \times 10^{6} / \mu l$, MCV 109 fl, reticulocytes 2.2% of red blood cells, leukocyte count $9.4 \times 10^{3} / \mu l$ (neutrophils 60%, lymphocytes 35%, monocytes 1%, eosinophils 1%) and platelet count $288 \times 10^{3} / \mu l$. Blood film demonstrated red cell anisocytosis, with macrocytosis and moderate numbers of target cells. Schistocytes were not observed. Most biochemical tests for liver and renal function tests were within the normal limits. Bone marrow examination was performed and presented erythroid hyperplasia with macroblastic reaction. Granulocytes showed shift to the left and dysplastic changes without ring sideroblasts and blasts comprised 1% of nucleated cells and +4 iron store. Megakaryocytes were adequate in number. The pathologic findings of aplastic anemia or BM failure diseases such as hypocellular or acellular marrow were not observed. Nutritional deficiencies and metabolic diseases were excluded based on medical history and physical examination. There was no medical history of carcinogen exposure. Diagnostic cytogenetic analysis performed on the diagnostic bone marrow sample revealed the karyotype as 46, XX, Del (6) (q13q16) in all 20 metaphase cells which analyzed (Fig. 1). The patient was diagnosed as having refractory cytopenia with unilineage dysplasia (RCUD) based on the 2008 WHO classification system.(17) She received only supportive treatment. After her general condition recovered, she was discharged and followed up with CBC and liver function tests.

Fig. 1: Bone marrow karyotype of patient. 46, XX, Del (6) (q13q16)
Discussion

In our patient, a diagnosis of RCUD was made on the basis of peripheral blood and bone marrow findings. RCUD including 10%–20% of the cases of MDS (18) and deletion of the long arm of chromosome 6 as the only diagnostic finding is rare in MDS based on other studies (13-16). Cytogenetic abnormalities associated with RA include del (20q), +8 and abnormalities of chromosome 5 and/or chromosome 7 (11). Specific chromosomal abnormalities, such as -5/5q- and -7/7q-, play an important role in the development of new therapeutic options and clinical management of MDS. However, due to cytogenetic heterogeneity, the additive prognostic impact of distinct single additional abnormalities remains obscure as yet. To our knowledge there are only four case reports worldwide about del (6q) in MDS (13-16). In 2000, Fernandez et al. (13) described the chromosomal abnormality 46,XX,del (6)(q21) in a 18-year-old woman with RA and a 42-year-old man with "refractory anemia with excess blasts in transformation" (RAEB-T) that last one gradually progressed to AML. It should be noted that the category of RAEB-t has been abandoned in the new WHO classification of MDS. The majority of patients which previously belonged to this group are now including in AML classification (19). Therefore this chromosomal abnormality cannot attribute to AML progression. In 2006, Cen et al. (15) reported one case with 6q- in cytogenetic analysis of bone marrow cells of the 50 MDS patients. In 2009, Gozzetti et al. (14) reported 46,XX,del(6)(q15q27) in a 72-year-old woman with refractory anemia (MDS-RA). The patient did not demonstrate of progression after 10 months of follow up. In 2011, Chaubey et al. (16) described two rare chromosomal abnormalities (6q-, 3q-) with unknown prognostic significance. Approximately 90%–95% of patients with refractory anemia have low or intermediate International Prognostic Scoring System (IPSS) (11). In addition, when adjustments were made for age, patients with MDS and Transfusion dependency (TD) had more than a two-fold higher risk for mortality and six-fold higher risk of leukemic transformation compared with patients without TD during the initial three years after diagnosis (20). On the other hand, Mecucci et al. (21) recognized a significant correlation between myelodysplasia and previous exposure to toxic products such as alkylating agents. Our patient was not exposed to toxic products and she had Eastern Cooperative Oncology Group (ECOG) performance status of 1 (22) with no evidence of progression after 12 months of follow-up. The genetic changes in the malignant cells of MDS result mainly in the loss of genetic material, including probable tumor suppressor genes. It is noteworthy that deletions of the long arm of chromosome 6 and gain of chromosome 6 have already been described as poor prognosis in MDS and AML (23, 24). The finding indicates that 6q- deletions are accompanied by structural and functional alterations of the c-myb locus which may be involved in the pathogenesis of leukemias and lymphomas (25). Due to the profound cytogenetic heterogeneity, the impact of many rare abnormalities such as del (6q) in patients with MDS is still unknown and further such cases are needed to find the impact of this abnormality on progress and prognosis.

Conclusion

Identification of all possible rearrangements is valuable for obtaining a better understanding of the leukemogenic process and for determining genetic pathways. These may also play an important role in the development of new therapeutic options in MDS.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.
Acknowledgment

We would like to thank Hematology-Oncology and BMT Research Center, Imam Khomeini Hospital for assistance in providing sample and patient information. The authors declare that there is no conflict of interest.

References

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton D, Gralnick H, Sultan C (1982). Proposals for the classification of the myelodysplastic syndromes. Br J Haematol, 51:189-199
2. Cazzola M, Malcovati L (2005). Myelodysplastic syndromes--coping with ineffective hematopoiesis. N Engl J Med, 352:536-538.
3. Vardiman JW, Harris NL, Brunning RD (2002). The World Health Organization (WHO) classification of the myeloid neoplasms. Blood, 100:2292-2302.
4. Kawankar N, Rao Vundinti B (2011). Cytogenetic abnormalities in myelodysplastic syndrome: an overview. Hematology, 16:131-138.
5. Haase D, Steidl C, Schanz J, Schabla R, Pfeilstöcker M, Nösslinger T, Hildebrandt B, Kuendgen A, Lübbert M, Kunzmann B (2005). Correlation of Cytogenetic Findings with Morphology, Clinical Course and Prognosis in 2124 Patients with MDS. Blood, 106:787-787.
6. Vundinti BR, Kerketta I, Jijina F, Ghosh K (2009). Cytogenetic study of myelodysplastic syndrome from India. Indian J Med Res, 130:153.
7. Haase D, Germing U, Schanz J, Pfeilstöcker M, Nösslinger T, Hildebrandt B, Kuendgen A, Lübbert M, Kunzmann R, Giagounidis AA (2007). New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood, 110:4385-4395.
8. Bernasconi P, Klersy C, Boni M, Cavigliano PM, Calatrone S, Giardini I, Rocca B, Zappatore R, Caresana M, Dambruoso I (2007). World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with de novo primary myelodysplastic syndromes. Br J Haematol, 137:193-205.
9. Sole F, Luno E, Sanzo C, Espinet B, Sanz GF, Cervera J, Calasanz MJ, Cagadosa JC, Milla F, Ribera JM (2005). Identification of novel cytogenetic markers with prognostic significance in a series of 968 patients with primary myelodysplastic syndromes. Haematologica, 90:1168-1178.
10. Morel P, Hebbar M, Lai J, Duhamel A, Preudhomme C, Wattel E, Bauters F, Fenaux P (1993). Cytogenetic analysis has strong independent prognostic value in de novo myelodysplastic syndromes and can be incorporated in a new scoring system: a report on 408 cases. Leukemia, 7:1315-23.
11. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D (1997). International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood, 89:2079-2088.
12. González Manso AI, García Marcilla A, Barreiro E, Gilsanz F (1992). Cytohematologic and cyto-genetic prognostic factors at diagnosis and in the evolution in 46 primary myelodysplastic syndromes. Cancer Genet Cytogenet, 61:174-182.
13. de Souza Fernandez T, Ornellas MH, Otero de Carvalho L, Tabak D, Abdelhay E (2000). Chromosomal alterations associated with evolution from myelodysplastic syndrome to acute myeloid leukemia. Leuk Res, 24:839-848.
14. Gozzetti A, Crupi R, Defina M, Bocchia M, Raspadori D, Lauria F (2009). Isolated deletion of 6q in a patient with myelodysplastic syndrome. Cancer Genet Cytogenet, 192:51.
15. Cen L, Zhou M, Zhao Y (2006). [Analysis of the clinic and cytogenetics of myelodysplastic syndrome]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi, 23:668-9.
16. Chauhey R, Sazawal S, Dada R, Mahapatra M, Saxena R (2011). Cytogenetic profile of Indian patients with de novo myelodysplastic syndromes. Indian J Med Res, 134:452-457.
17. Gupta G, Singh R, Kotasthane DS, Kotasthane VD (2010). Myelodysplastic syndromes/neoplasms: recent classification system based on World Health Organization Classification of Tumors--international Agency for Research on Cancer for Hematopoietic and Lymphoid Tissues. J Blood Med, 1:171-82.
18. Germing U, Strupp C, Kuendgen A, Isa S, Knipp S, Hildebrandt B, Giagounidis A, Aul C, Gattermann N, Haas R (2006). Prospective validation of the WHO proposals for the classification of myelodysplastic syndromes. 
Haematologica, 91:1596-1604.

19. Ohyashiki K, Nishimaki J, Shoji N, Miyazawa K, Kimura Y, Ohyashiki JH (2001). Re-evaluation of refractory anemia with excess blasts in transformation. Leuk Res, 25:933-939.

20. Goldberg SL, Chen E, Corral M, Guo A, Mody-Patel N, Pecora AL, Laouri M (2010). Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. J Clin Oncol, 28:2847-2852.

21. Mecucci C, Michaux J-L, Louwagie A, Boogaerts M, Van Den Berghe H (1988). The short arm of chromosome 6 is nonrandomly rearranged in secondary myelodysplastic syndromes. Cancer Genet Cytogenet, 31:147-155.

22. Blagden S, Charman S, Sharples I, Magee L, Gilligan D (2003). Performance status score: do patients and their oncologists agree? Br J Cancer, 89:1022-1027.

23. Hirata J, Abe Y, Taguchi F, Takatsuki H, Nishimura J, Nawata H (1992). Deletion of chromosome 6q in two cases of acute myeloblastic leukemia and a review of the literature. Cancer Genet Cytogenet, 58:181-185.

24. Mohamed AN, Varterasian ML, Dobin SM, McConnell TS, Wolman SR, Rankin C, Willman CL, Head DR, Slovak ML (1998). Trisomy 6 as a primary karyotypic aberration in hematologic disorders. Cancer Genet Cytogenet, 106:152-155.

25. Barletta C, Pelicci P-G, Kenyon LC, Smith SD, Dalla-Favera R (1987). Relationship between the c-myb locus and the 6q-chromosomal aberration in leukemias and lymphomas. Science, 235:1064-1067.