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Short communication

Tetraploidy and 5q deletion in myelodysplastic syndrome: A case report

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Abstract Tetraploidy is a very rare cytogenetic abnormality in myelocytic malignancies, and its significance is unclear to date. We report here on a 68-year-old male diagnosed with myelodysplastic syndrome/refractory anemia with excess blasts (MDS/RAEB). Cytogenetic analysis of his bone marrow biopsy at initial clinical presentation and in subsequent studies revealed the presence of two abnormal clones, 92,XXYY and 92,XXYY,del(5)(q13q33). Interphase fluorescence in situ hybridization analysis of abnormal cells confirmed interstitial deletion in 5q, demonstrated predominance of the tetraploid clone and persistent presence of the tetraploid clone with 5q deletion. The patient was not responsive to Revlimid (lenalidomide) treatment, which is routinely used in patients with 5q− syndrome. However, a subsequent course of therapy with the methyl-transferase inhibitor decitabine resulted in clinical and cytogenetic remission. Our data suggest that the unique complex abnormality of tetraploidy and 5q deletion described here for the first time in MDS is characterized by distinct disease etiology, the mechanism of which could involve epigenetic inactivation of gene expression via methylation.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis and peripheral blood cytopenias [1]. They are categorized into high-risk (>10% marrow blasts) and low-risk (<10%) groups [1]. High-risk MDS bears considerable resemblance to acute myeloid leukemia (AML) and is more likely to evolve into AML [1]. Approximately 50–60% of patients with de novo MDS and more than 85% of individuals with secondary MDS (after cytotoxic therapy) show nonrandom chromosomal aberrations that may involve isolated or multiple abnormalities [2]. Therefore, analysis of recurrent cytogenetic abnormalities in MDS is widely used for diagnosis and for determining prognosis and management.

Deletion of the long arm of chromosome 5 [del(5q)] is the most common chromosomal abnormality in MDS, occurring at a frequency of 10–15% [3,4]. Del(5q) also occurs in AML [4] and several other cancers [5–7]. While the deleted region of chromosome 5 can vary greatly in size between individual patients, two regions have been identified that correspond to subtypes of MDS. A 4-megabase interval within 5q31 has been defined for patients with more aggressive MDS, including secondary MDS, while a more telomeric region is deleted in the patients with del(5q) syndrome[8]. The commonly deleted region (CDR) or critical region has been defined as 5q31~q33 [8,9] and contains multiple genes involved in cellular growth, hematopoiesis, cell cycle control, cell adhesion, and tumor suppression [2,10,11].

Massive hyperdiploidy (>50 chromosomes) and tetraploidy (4n) are rare cytogenetic abnormalities in myelocytic malignancies. A handful of MDS cases with massive hyperdiploidy have been published to date [12–18], whereas there is only one report, to the best of our knowledge, of two MDS patients with tetraploidy [15]. The combination of tetraploidy and del(5q) has not been reported previously in MDS. Hyperdiploidy has been associated with poor prognosis in MDS [12,14–16], but in light of the small numbers of reported cases, its significance is unclear.

In this report, we describe the clinical, cytogenetic, and molecular cytogenetic findings in a case of high-risk MDS with the unique finding of tetraploidy and 5q deletion.

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2. Materials and methods

2.1. Case report

The patient was a 68-year-old generally healthy man referred by his local primary care physician due to decreased hemoglobin and white cell count. Analysis of his blood and bone marrow aspirate demonstrated macrocytic anemia, severe neutropenia, megaloblastic changes in the red cell line, and occasional uninuclear morphology of megakaryocytes. Excess of blasts evaluated by differential cell count and flow cytometry with myeloid markers was 13 and 19%, respectively. Though the patient demonstrated clinical features of the 5q− syndrome (macrocytic anemia, normal to elevated platelet count, and neutropenia), he did not respond to treatment with Revlimid (lenalidomide), which was administered daily for 12 weeks. Moreover, during this period, his platelet count decreased from 350,000 to 118,000, and the patient developed AML, with a repeat bone marrow examination showing 35% myeloblasts marking for myelomonocytic lineage. However, subsequent treatment with two cycles of decitabine therapy resulted in marked improvement in the patient's condition, with resolution of severe neutropenia and decrease in blast count to 2 and 3% (estimated by differential cell count and flow cytometry, respectively). Finally, the patient achieved clinical and cytogenetic remission.

2.2. Cytogenetics and fluorescence in situ hybridization (FISH) analysis

Bone marrow was cultured in RPMI 1640 media (Invitrogen, Carlsbad, CA) and Chang BMC media (Irvine Scientific, Santa Ana, CA), harvested, and slides were prepared according to standard laboratory methods. Metaphase cells were imaged and karyotypes were generated using the Cytovision System version 3.6 (Applied Imaging, Santa Clara, CA). Cytogenetic abnormalities were described according to the International System of Human Cytogenetic Nomenclature (ISCN) 2005 [19].

FISH analysis for del(5q) was performed using probes EGR1 (5q31), CSF1R (5q33~q34), and control probes D5S23 and D5S721 (5p15.2) on slides prepared from fixed cell pellets according to the manufacturer's recommended procedure (Abbott Molecular/Vysis, Des Plains, IL).

3. Results

Cytogenetic analysis of the bone marrow aspirate revealed the presence of cells with normal karyotypes as well as two abnormal cell lines: a tetraploid clone and a clone with tetraploidy and del(5q) (Fig. 1; Table 1). It is noteworthy that the abnormal mitotic cell population at presentation and subsequent cytogenetic tests at 1 and 3 months were dominated by the tetraploid cell line with 5q deletion. However, at the 5-month follow-up (when AML was diagnosed), while the tetraploid/del (5q) clone was persistent, the majority of abnormal dividing cells were represented by the tetraploid clone without 5q deletion (Table 1). Later, the patient was started on decitabine therapy, and by the next cytogenetic evaluation at 10 months, no abnormal cells were observed by routine cytogenetic analysis; the patient had reached cytogenetic remission (Table 1).

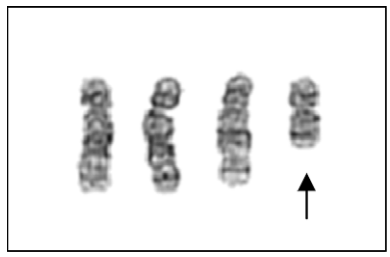

Figure 1. Representative chromosomes 5 showing tetraploidy and deletion of one 5q (arrow).

To detect the presence of residual disease, we performed interphase FISH. We used two probes specific for the 5q CDR, namely CSF1R and EGR1 (see Materials and methods). Both probes have shown similar results (data not shown) and proved to be equally suitable for the identification of the 5q deletion in our case. According to the FISH results, tumor burden at 1 month was 12.4%, and it increased twofold by the fifth month (Table 2), when the patient evolved to AML (see Materials and methods). However, after decitabine treatment, at the 10-month follow-up, the number of abnormal cells had fallen to 3.5%. This value correlates well with the number of blasts measured by differential cell count and flow cytometry (2 and 3%, respectively, see Materials and methods). Interestingly, during the whole observation period, despite of the overall number of abnormal cells, the ratio between the two clones (tetraploid and tetraploid with 5q deletion) remained the same, 2:1 (Table 2).

4. Discussion

Chromosomal abnormalities in neoplastic marrow cells often correlate closely with specific clinical and biologic characteristics of the disease and serve as a tool to predict the clinical outcome and develop effective therapeutic approaches. In this paper, we describe the successful treatment of a myelodysplastic syndrome-refractory anemia with excess blasts patient with the unique finding of tetraploidy and 5q deletion.

Tetraploidy is a very rare abnormality in hematologic malignancies, especially in MDS. In fact, we are aware

Table 1
Results of routine cytogenetic studies

Date	46,XY	92,XXYY	92,XXYY,del(5)(q13q33)
At presentation	18	–	2
1 month	5	–	2
3 months	17	–	3
5 months	15	4	1
10 months	20	–	–