Case Report
Concomitant isochromosome 17q and mutated SETBP1 in a myelodysplastic syndrome patient with a poor prognosis

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Abstract: We describe a novel case of simultaneous karyotypic abnormality of isochromosome 17q [(i(17)(q10)/i(17q)] and a molecular aberration of mutated SETBP1 in a myelodysplastic syndrome (MDS) patient with a poor prognosis. A 61-year-old Chinese man was admitted to the Hospital of Lanzhou University for evaluation of pancytopenia. Based on bone marrow studies, he was diagnosed with MDS-RCMD (2008 WHO classification)/MDS-MLD (2016 WHO classification). The karyotype abnormality was isochromosome 17q, and the molecular aberration was a SETBP1 mutation. Isochromosome 17q and mutation of SETBP1 have each been reported as rare; i(17)(q10), as a single anomaly, was included in the intermediate risk category, and the SETBP1 mutation is an independent poor prognostic factor. To our knowledge, this is a novel report of concurrent i(17)(q10) and mutated SETBP1 in an MDS patient with a poor prognosis. In this case, there are four other genes (EZH2, SF3B1, AXSL1, and RUNX1) that have different influences and may be new diagnostic markers or new therapy targets for MDS.

Keywords: Myelodysplastic syndrome, isochromosome 17q, SETBP1, prognostic, gene mutations

Introduction

The myelodysplastic syndromes (MDSs) are a heterogeneous group of diseases that are characterized by cytopenia in the peripheral blood and usually hyper-cellularity with dysplastic haematopoiesis in the bone marrow (BM) and a propensity for acute leukaemia transformation [1-3]. Current studies have found that the cytogenetic abnormality of MDS includes +8, followed by 1q+, 5q-, 20q-, 7/del (7q), -Y, complex 5q, complex trisomy 8, del 11q, inversion 9, trisomy 19, and i(17q), and the common abnormality found was trisomy 8 [4-6]. Genetic abnormalities [4, 7] include mutations that have been categorized into different subgroups depending on their prevalence, including RNA-splicing machinery (64%): SF3B1, SRSF2, ZRSR2, U2AF1, and U2AF2; DNA methylation (45%): TET2, DNMT3A, and IDH1/2; chromatin modification (27%): ASXL1, and EZH2; transcription factors (15%): TP53, RUNX1, ET1, and GATA2; Signal transduction/kinases (15%): FLT3, JAK2, MPL, GNAs, and KIT; The RAS pathway (12%): KRAS, NRAS, CBL, NF1, and PTPN11; the cohesin complex (13%): STAG2, CTCF, SMC1A, and RAD21; DNA repair (10%): ATM, BRCC3, DLR1C, and FANC1; And other mutations (10% SETBP1, mi-RNA, and ABCB7). Isochromosome 17q is a product of the breakage or inappropriate division of the pericentromeric region of chromosome 17 [8]. As an isolated cytogenetic abnormality, isochromosome 17q in myeloid malignancies is rare, with less than 150 reported cases [9]. Recent studies suggest that i(17q) has a low prevalence in MDS, and the incidence rate is less than 1% [10, 11]. Isolated i(17q) is of intermediate prognostic significance (Brunning et al, 2008 [12]; Greenberg et al, 2012 [13]; Schanz et al, 2012 [14]) [14-16]. SET binding protein 1 (SETBP1) is located at 18q21.1, and mutations of this gene are reported in several haematological malignancies but are rare in MDS. The SETBP1 mutation is associated with an adverse outcome in MDS [1, 17]. This mutation can be acquired during the clinical course, suggesting
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Therefore, the myelodysplastic syndromes with i(17q) and the SETBP1 mutation often indicate a poor prognosis, while at the same time may forebode high leukemic transformation.

Case report

A 61-year-old male presented with intermittent skin purpura with fatigue for one year and aggravating accompanying dizziness and tinnitus half of month. The blood cell count at initial diagnosis showed mild leukopenia and anaemia: the white blood cell count was 0.88×10^9/l with normal differentiation, the haemoglobin was 4.3 g/dl, and the platelet count was lower (4×10^9/l). The primary diagnosis was pancytopenia. The pancytopenia diagnosis compelled us to perform a bone marrow examination. His bone marrow aspiration showed that bone marrow was actively proliferating, and the marrow had dysplasia such as dysgranulopoiesis (unhealthy granulocyte lobulation, karyopyknosis, unbalanced caryoplasm development and a myeloblast cell count of 2%), and significant erythroid hyperplasia (easily seen original and early erythroblastic and megaloblastic cells, Figure 1A; some dual-core karyopyknosis, Figure 1B; and tri-core). The presence of ringed-sideroblasts or fibrosis was not detected. Bone marrow biopsy showed active bone marrow hyperplasia and dysgranulopoiesis (immature progenitor cells and ALIP), dyserythropoiesis, and scarce megakaryocytes Figure 2. The presence of ringed-sideroblasts or fibrosis was also not detected. Cytogenetic analysis showed the presence of an abnormal clone in 14 out of 20 metaphases analysed by G-banding: 46, XY i(17)(q10) [14] Figure 3A. i(17q) was also demonstrated by fluorescence in situ hybridization (FISH) analysis, which found an absence of TP53; Figure 3B. Next-generation sequencing showed that the 14 MDS-related genes (NRAS, CBL, JAK2, TP53, RUNX1, ETV6, DNMT3A, TET2, IDH1, IDH2, EZH2, ASXL1, SRSF2, SF3B1, EZH2, SF3B1, ASXL1, and RUNX1 had mutated; Table 1. According to the PCR results, we found SETBP1 specifically was mutated; Figure 3C. The patient was diagnosed as high-risk MDS-MLD (IPSS R-IPSS or WPSS). Due to familial economic conditions, the patient rejected use of hypomethylating agents (Decitabine) and requested expectant treatment. We treated the patient with cyclosporine A and provided support such as TPO, RBC transfusion and PLT. During treatment, the pancytopenia was still present, the white blood cell count was 0.45-4.25×10^9/l, the haemoglobin was 4.3-6.9 g/dl, and the platelet count was 3-24×10^9/l. The patient was deceased after a month due to cerebral haemorrhage.

Discussion

Isochromosome 17 (i(i7)(q10)) is a rare cytogenetic abnormality resulting in the loss of the short arm and duplication of the long arm of chromosome 17 [8, 18]. It is a relatively common karyotypic abnormality in medulloblastoma and gastric, bladder, and breast cancers. In myeloid disorders, it is observed during disease progression and in the evolution to acute myeloid leukaemia (AML) in Philadelphia-positive chronic myeloid leukaemia. It has been
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reported in rare cases of myelodysplastic syndrome (MDS), with an incidence of 0.4-1.57% [10]. Isochromosome 17q can occur as either a primary or secondary cytogenetic abnormality and is usually a part of a complex karyotype with another karyotype abnormality but scarcely as an isolate [11]. In the present study, i(17q) was detected in 0.4%-0.8% of defined MDS patients. Reports concerning an SETBP1 mutation in MDS are scarce, as the frequency of MDS is approximately 2-5% [1, 4, 7, 19], although a study reported that patients with isochromosome 17q present with a high incidence of SETBP1 mutations [15]. Thus we can

Figure 3. A. Giemsa-banding karyotype analysis revealed 46, XY, i(17)(q10) in 14 out of 20 metaphases examined. B. The signal loss of the p53 site. PS: The FISH probe to p53/CEP17; the test site is 17p13.1/17p11.1-q11.1; and the loss rate is 55%. C. Mutations in the SETBP1 gene at exon 4 were analysed by polymerase chain reaction (PCR).

Table 1. The five genes mutations in myelodysplastic syndrome with prognostic and treatment implications (4, 7)

<table>
<thead>
<tr>
<th>Mutated Genes</th>
<th>Mutation Location</th>
<th>Frequency</th>
<th>Function</th>
<th>Prognostic Impact</th>
<th>Potential Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SETBP1</td>
<td>c.2608G&gt;A; p.G870S</td>
<td>2-5%</td>
<td>Typical Cell proliferation</td>
<td>Unfavorable</td>
<td>None</td>
</tr>
<tr>
<td>AXSL1</td>
<td>c.2444T&gt;C; p.Leu815Pro</td>
<td>15-20%</td>
<td>Histone modification H3 methylation</td>
<td>Unfavorable</td>
<td>HDAC inhibitor</td>
</tr>
<tr>
<td>EZH2</td>
<td>c.2196-61_2196-57dupAAGTC</td>
<td>0.7%</td>
<td>Histone modification Histone methyltransferase, gene repression</td>
<td>Unfavorable</td>
<td>HDAC inhibitors, EZH2 inhibitors</td>
</tr>
<tr>
<td>RUNX1</td>
<td>c.500G&gt;A; p.Ser167Asn c.614-34C&gt;T</td>
<td>0-15%</td>
<td>Transcription factors Regulates myeloid Differentiation</td>
<td>Unfavorable</td>
<td>None</td>
</tr>
<tr>
<td>SF3B1</td>
<td>c.1720-13_1720-12dupTT</td>
<td>15-30%</td>
<td>RNA splicing Pre-mRNA splicing</td>
<td>Favorable</td>
<td>None</td>
</tr>
</tbody>
</table>
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infer the MDS patients with i(17q) and SETBP1 mutations are rare, with an incidence of less than 1%.

To the best of our knowledge, i(17q) and SETBP1 mutations not only indicate poor prognosis, but other researchers have also reported high leukemic transformation. i(17q) is classified as an “intermediate” cytogenetic prognostic subgroup per the revised International Prognostic Scoring System (IPSS) for MDS [9, 15] and as an “adverse” cytogenetic prognostic subgroup per the revised Medical Research Council classification for AML [9]. Furthermore, SETBP1 mutation is an independent poor prognostic factor for OS irrespective of age, sex, and the International Prognostic Scoring System [1]. SETBP1 mutation is associated with an adverse outcome [20]. Therefore, we can infer that patients with i(17q) and SETBP1 mutations have poor prognoses. A report concluded that myeloid neoplasms with isolated isochromosome 17q represented high-risk of leukemic transformation [9, 11]. At the same time, some studies have also reported that the presence of SETBP1 mutations predicted not only shorter survival but higher probability of AML transformation [17, 21, 22]. As a result, we imply myelodysplastic syndrome with i(17q) and SETBP1 has a poor prognosis and undergoes rapid progression to AML.

Through the literature, several studies showed that some alterations of the chr17 are associated with the presence of hypercellularity, pseudo-Pelger-Hu, cells containing small vacuoles, prominent basophilia and eosinophilia, and marked increase of micromegakaryocytes [16]. However, our bone marrow smear and biopsy demonstrated significant erythroid hyperplasia, but we did not observe typical micromegakaryocytes (Figures 1 and 2). Some results provide insights into the molecular consequences of i(17q), which leads to the obligatory loss of a single TP53 allele located at 17p13.1 [9]. Isochromosome 17q is a non-random cytogenetic abnormality that involves deletion of the short “p” arm and duplication of the long “q” arm of chromosome 17 [11, 18]. According to some studies, it has also been postulated that i(17q) may be associated with TP53 mutations, despite a recent study that found no association [15]. Our FISH analysis result suggests that i(17) (q10) was easy to obtain in the absence of TP53 mutations and possibly typical, but more studies are needed to clarify this. However, it has been reported that SETBP1 never mutated solely. SETBP1 mutation is associated with i(17q), and some studies have reported indications of acquisition of SETBP1 mutations during the disease course in patients with i(17) (q10), [18] and some have reported that SETBP1 mutations often accompany other mutated genes.

The SETBP1 mutation is clustered in the SKI homologous region of SETBP1 within a stretch of 16 aa (aa 858 to 874). The most prevalent mutation was p.Asp868Asn, followed by p.Gly870Ser, p.Ileu871Thr and p.Gly870Asp [17, 19]. Our detection of SETBP1 by PCR agrees with this description. The SETBP1 mutation rarely occurs alone. Through the review of the literature, SETBP1 often co-exists with ASXL1. The ASXL1 protein, its gene mapping to chromosome 20q11 [19], regulates histone modification by interacting with the PRC2. PRC2 methylates H3K27 and is a key regulator of haematopoiesis. ASXL1 loss is associated with haematopoietic transformation and increased self-renewal. ASXL1 mutations are found in 11% of patients with MDS, portending an inferior OS, and are associated with a higher risk of secondary AML [7, 23]. Interestingly, mutations of ASXL1 and SETBP1 not only co-occurred significantly more often than by chance but also resulted in shorter overall survival and a higher incidence of leukemic transformation, indicating that combined mutation of these genes provides a selective advantage and that an additional SETBP1 mutation plays a pivotal role in disease progression [21]. Sequential analyses showed all SETBP1-mutations occurred during disease progression and frequently acquired other novel genetic alterations, except ASXL1, at the same time.

According to gene testing, we found four other mutated genes. In addition to ASXL1, other mutated genes are EZH2, SF3B1, and RUNX1. In MDS, EZH2 mutations are seen in 6-12% of patients. EZH2, a histone-lysine N-methyltransferase enzyme, catalyses the addition of methyl groups to histone H3 at lysine 27 (H3K27). It is a key component of polycomb repressive complexes (PRCs), participating in transcription repression. EZH2 mutations are associated with disease transformation. Consequently, EZH2 mutations are observed in high-grade MDS and are associated with a
higher risk of secondary AML and worse OS [7].
*RUNX1* is a key regulator of myeloid differentiation. *RUNX1* mutations are found in 0-15% of patients, often high-risk MDS, and independently confer an inferior prognosis and increased risk of AML [4, 7, 17, 21]. Papaemmanuil et al [24] and Yoshida et al [25] have demonstrated *SF3B1* mutation in low-risk RARS-MDS, and mutations in *SF3B1* appeared to be markedly high in RARS-MDS, with an incidence of 60%-80% of these patients and of 10-20% in those with unselected MDS, which opposite of the other genes.

Regarding the four genes-mutation, the first three have been reported in a recent report. The *RUNX1* gene has not been mentioned in context of MDS diagnosis and therapy. The influence of *RUNX1* and its role on diagnosis and therapy have never been found. It may be the new diagnostic marker and the new therapy target. At the same time, The identification of mutations in *SETBP1* recently presented a molecular marker in atypical chronic myeloid leukaemia (aCML), although the function of the *SETBP1* protein is not fully understood [18]. Hence, *SETBP1* may be a novel molecular marker in MDS. Recent studies suggest *EZH2* may serve as a potential drug target [4]. Taken together, no matter what application scoring system is used (IPSS, R-IPSS or WPSS), the patient was high risk, his prognosis was poor with high leukemic transformation. Thus, his OS was short. This molecular aberration will be a novel tool for MDS diagnosis and therapy. Therefore, more studies are needed to clarify the functions and influences of the genes in MDS.

In conclusion, to the best of our knowledge, the case of concurrent i(17)(q10) and *SETBP1* in a patient with MDS with poor prognosis is rarely reported. The myelodysplastic syndromes with i(17)q and *SETBP1* mutations often indicate poor prognosis and high leukemic transformation. Although the clinical significance of additional gene mutations in patients with i(17)q is unclear, we consider the presence of gene mutations together with i(17)(q10) to be a poor prognostic factor with high leukemic transformation. In addition, such gene mutations may be new diagnostic markers and therapy targets, but further reports are necessary to verify this.

Disclosure of conflict of interest

None.

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