

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*, *ETV1*, and *GATA2*; Signal transduction/kinases (15%): *FLT3*, *JAK2*, *MPL*, *GNAS*, and *KIT*; The RAS pa-

thway (12%): *KRAS*, *NRAS*, *CBL*, *NF1*, and *PTPN11*; the cohesin complex (13%): *STAG2*, *CTCF*, *SMC1A*, and *RAD21*; DNA repair (10%): *ATM*, *BRCC3*, *DLRE1C*, and *FANCL*; And other mutations (10% *SETBP1*, *mi-RNA*, and *ABC7*). Isochromosome 17q is a product of the breakage or inappropriate division of the pericentromere, leading to duplication of the long arms and loss of the short arm 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 occurrence in MDS, and the incidence rate is less than 1% [10, 11]. Isolated i(17q) is of intermediate prognostic significance (Brunner 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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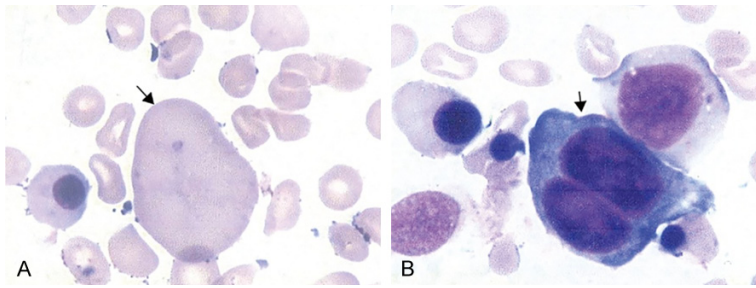


Figure 1. A. Giant red cell in the bone marrow. B. Dual-core red blood cells in the bone marrow are a morphologic characteristic of the patient.

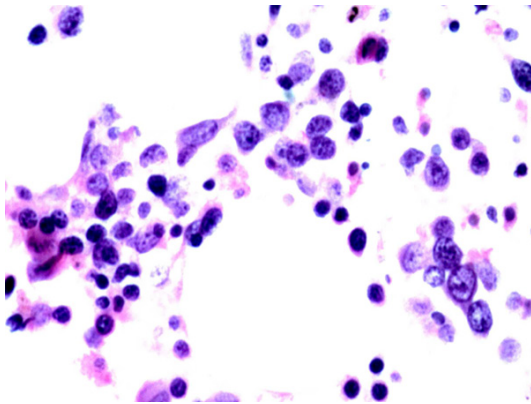


Figure 2. The bone marrow biopsy shows active bone marrow hyperplasia and dysgranulopoiesis (immature progenitor cells and ALIP).

that it may play a role in disease progression [1]. 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 $0.88 \times 10^9/l$ with normal differentiation, the haemoglobin was 4.3 g/dl, and the platelet count was lower ($4 \times 10^9/l$). 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 cytoplasm 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. Cyto-genetic 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*, *EVT6*, *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 $0.45-4.25 \times 10^9/l$, the haemoglobin was 4.3-6.9 g/dl, and the platelet count was $3-24 \times 10^9/l$. The patient was deceased after a month due to cerebral haemorrhage.

Discussion

Isochromosome 17 (i(17)(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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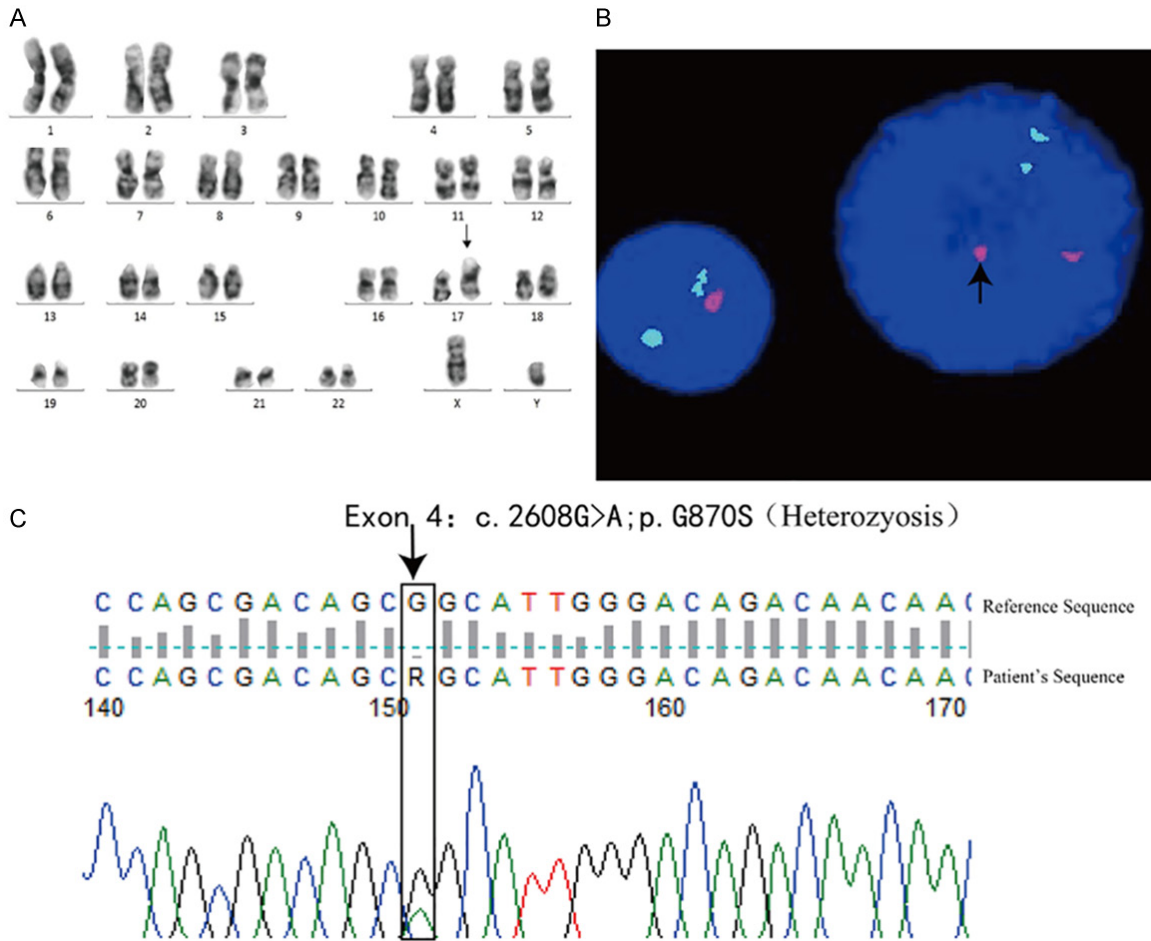


Figure 3. A. Giemsa-banding karyotype analysis revealed 46, XY, i(17)(q10) in 14 out of 20 metaphases examined. B. The signal loss of the p53 site. PS: The FISH probe to p53/CEP17; the test site is 17p13.1/17p11.1-q11.1; and the loss rate is 55%. C. Mutations in the SETBP1 gene at exon 4 were analysed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

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

Mutated Genes	Mutation Location	Frequency	Function	Prognostic Impact	Potential Targeted therapy
SETBP1	c.2608G>A; p.G870S	2-5%	Typical Cell proliferation	Unfavorable	None
AXSL1	c.2444T>C; p.Leu815Pro	15-20%	Histone modification H3 methylation	Unfavorable	HDAC inhibitor
EZH2	c.2196-61_2196-57dupAAGTC	0-7%	Histone modification Histone methyltransferase, gene repression	Unfavorable	HDAC inhibitors, EZH2 inhibitors
RUNX1	c.500G>A; p.Ser167Asn c.614-34C>T	0-15%	Transcription factors Regulates myeloid Differentiation	Unfavorable	None
SF3B1	c.1720-13_1720-12dupTT	15-30%	RNA splicing Pre-mRNA splicing	Favorable	None

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

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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(17q)* and *SETBP1* mutations often indicate poor prognosis and high leukemic transformation. Although the clinical significance of additional gene mutations in patients with *i(17q)* 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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