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Jumping translocations in myelodysplastic syndromes

Cecilia C. S. Yeung [a,b,*], H. Joachim Deeg [a], Colin Pritchard [c], David Wu [c], Min Fang [a,b,c]

[a] *Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview ave N, Seattle, WA 98109, USA;* [b] *Department of Pathology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA;* [c] *Department of Laboratory Medicine, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA*

Jumping translocations (JT) have been identified in numerous malignancies, including leukemia, but infrequently in patients with myelodysplastic syndromes (MDS). The responsible genetic region has been mapped to the JTB gene at 1q21, but breakpoints involving other chromosomal loci, such as 3q and 11q, have been described as well. We have characterized the pathological and mutational landscape, and the clinical course of 6 new MDS patients with jumping mutations using chromosome genomic array testing (CGAT) and target gene panel next generation sequencing. In addition, we have performed a literature review for other MDS cases with JTs as defined by ISCN 2013. Results support the concept that MDS in patients with jumping translocations has a poor prognosis with a high risk of progression to leukemia, and suggest that these patients warrant aggressive therapy, including HCT, early in the disease course.

Keywords MDS, myelodysplasia, jumping translocation, CGAT, NGS

Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic diseases with ineffective hematopoiesis and variable prognoses. Patients with high risk MDS may show rapid progression to acute leukemia, often refractory to therapy. Major determinants of disease progression in patients with MDS are included in the revised International Prognostic Scoring System (IPSS-R) (1–4). Allogeneic hematopoietic cell transplantation (HCT) offers potentially curative therapy. However, post-HCT disease recurrence is common, and only partially explained by currently scored risk factors. Outcome in these patients is poor (5–8).

Jumping translocations (JT) in neoplastic diseases are very rare cytogenetic phenomena where a segment of a particular chromosome is duplicated and inserted into several other chromosomes, resulting in multiple gains of this chromosomal segment via multiple translocations and possible loss of segments of the recipient chromosomes (9,10). For the lay public, genetic counselors defined a jumping translocation ("Translocation Sauteuse") as describing a mitotic rearrangement whereby the same piece of one chromosome breaks off, on more than one occasion, and attaches to the tips of other chromosomes (11). Often, the site of breakage in the donor chromosome is characterized by the presence of an interstitial telomere, and this region offers the possibility of fusion with the recipient chromosomes. Although refined studies mapped the responsible locus to 1q11-21, and some reports specifically implicate the jumping translocation breakpoint (*JTB*) gene (12), JTs involving loci such as 3q, 11q, and other genomic loci have been described. However, the mutational landscape of these MDS cases with JT has not been defined previously. In the present study, we aimed at characterizing the mutational landscape by performing chromosomal genomic array testing (CGAT) and target gene panel next generation sequencing in MDS patients with JT seen at our center from 2000 to 2013. We posit that a JT represents a very high-risk cytogenetic abnormality, and propose that such patients should be considered for early aggressive therapy including HCT even if other disease parameters suggest low risk disease.

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* Corresponding author.
E-mail address: cyeung@FHCRC.org

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Material and methods

Study population

A retrospective review of the cytogenetic data of cases of MDS and MDS-based myeloid neoplasms observed over the past 10 years at the Seattle Cancer Care Alliance (SCCA) was conducted. Cases where conventional cytogenetic studies identified a JT during the disease course were selected for analysis.

All patients had been consented under standard SCCA patient consent for research studies. The studies were approved by the Fred Hutchinson Cancer Research Center institutional review board. Cytogenetics (including karyotype, fluorescence in situ hybridization (FISH), and CGAT), pathology and flow cytometry data were correlated with clinical course and outcomes.

DNA extraction

Sources of DNA for CGAT included fresh or frozen marrow and archived fixed cell pellets. DNA from fresh bone marrow and fresh frozen marrow aspirates was extracted using the Qiagen-PureGene method (Germantown, MD) according to the manufacturer's protocol. For DNA extraction from archived samples, cell pellets in methanol/acetic acid fixative were washed 3 times with cold phosphate-buffered saline (PBS), re-suspended in 100 µl of PBS, and loaded onto the Qiagen EZ1 Advanced XL according to the Qiagen EZ1 Virus Mini Kit v2.0. Elution volume was 60 µl. Extraction was performed per manufacturer guidelines. DNA was stored at 4 °C.

DNA quality was assessed by NanoDrop 2000 Spectrophotometer (Thermo Scientific, Waltham, MA), which measures DNA concentration and purity by 260/280 nm readings. The DNA was also visualized on a 1% agarose gel with ethidium bromide to detect/exclude degradation. The criteria for acceptable DNA quality included visible bands by 1% agarose gel and spectrophotometer reading by A260nm/A280nm ratio of 1.4–2.

Chromosomal genomic array testing (CGAT)

CGAT for the detection of DNA copy number aberration (CNA) or copy-neutral loss of heterozygosity (cnLOH) by single nucleotide polymorphism (SNP) genotyping was performed with CytoScan HD (Affymetrix, Santa Clara, CA) according to the manufacturer's protocol. The size filter for an abnormal call was 100 kb (and 25 probes) for CNA and 10 Mb for cnLOH.

Targeted gene panel next generation sequencing

We preformed targeted sequencing of 194 cancer-related genes (Oncoplex, University of Washington, Seattle, WA) with 2 101-bp, paired-end reads and on a HiSeq2000 sequencing system or a MiSeq (Illumina, San Diego, CA). An average of >850,000 base pairs of DNA were sequenced at a depth of >500× coverage, as described in detail before (13).

Literature review

In addition, a literature review was conducted in PubMed and Web of Science using the following terms:

((“Myelodysplastic Syndromes”[Mesh] AND Case Reports[ptyp])) AND “Jumping Translocations”

(“Myelodysplastic Syndromes”[Mesh]) AND jumping translocations

“Myelodysplastic Syndromes”[Mesh] AND “Jumping Translocations”

“Jumping Translocations” AND (Case Reports[ptyp])

Papers were reviewed and cases that did not comply with the ISCN (2013) definition of JT were excluded.

Results

We identified six JT-MDS cases. Four patients were male and 2 female, 53–76 years of age. Two patients presented with refractory anemia with excess blasts-2 (RAEB-2), one with RAEB-1, one with therapy-related MDS, one with unclassifiable MDS/MPN, and one with refractory cytopenia with unilineage dysplasia (RCUD) (14). One patient had both initial diagnostic and post-transplant relapse samples available for comparison. The mean time to JT identification from initial MDS diagnosis or, in transplanted patients, from the time of HCT, was 22 months. In 5 of the 6 cases, JT involved chromosome 1q, and in one case chromosome 3q.

Five of the 6 patients received HCT (one patient was transplanted twice), and one patient died following MDS transformation to AML without being transplanted. At the time of HCT, MDS had progressed to AML in 4 of 5 patients. With 1–2 years of follow up, 3 [2 after HCT and one from progressive disease without transplantation] of 6 patients have died from relapsed disease. Three patients are surviving, one of these in relapse.

The index case of this series (patient 1) was a 66-year-old male who initially presented with refractory anemia with excess blasts (5%) with normal karyotype in 2011 (Figure 1). The blast count declined in response to Vidaza but in the fall of 2012, the blast count had increased again and cytogenetics showed t(X;12) and multiple JTs involving chromosome 1q. CGAT showed multiple 1q gains, cnLOH of 4q, and deletion of 18q. The region of 4q cnLOH involved *TET2*—tet methylcytosine dioxygenase 2.

Targeted sequencing showed a novel single base pair mutation in *TET2* (c.3594 + 5G>A) at cDNA position 3594 resulting in a splice site mutation, confirmed by two separate informatics programs (SIFT and fruitfly.org). In addition, there was a missense mutation in *SF3B1* at codon 625 (c.1873C>T:p.R625C) (15,16), and a *CBL* single base pair mutation (c.1477C>T:p.L493F) leading to an amino acid change. This mutation, not previously described in MDS, was confirmed by informatics prediction scores (pheophen, SIFT, Mutation Taster, and Gerp), implying a detrimental effect. Further, a single base pair mutation was present in SRSF2 (c.284C>A:p.P95H). This mutation, which leads to an amino acid change has been described in other MDS cases before (15,17–19).