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Case Report

Dicentric Chromosome (7;12)(p12.21;p12.10): A Rare Cytogenetic Aberration in Myelodysplastic Neoplasms Associated with High Likelihood of Leukemic Transformation

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ABSTRACT

Cytogenetic abnormalities are essential biomarkers in Myelodysplastic Neoplasms (MDS) to assess risk prognosis and guide therapeutic strategies. Most common chromosomal anomalies are represented into the current prognostic indexes, but these scores minimize the real impact of less frequent aberrations. Here, we present a 34-year-old with an intermediate-risk MDS, featuring a rare dicentric chromosome dic(7;12) into a complex karyotype setting and a *TP53* likely germinal variant, who rapidly progressed into leukemia. The dic(7;12) has been reported in acute leukemia's, but not previously seen in *de novo* MDS. This infrequent alteration might trigger an aggressive behavior and lead a leukemic transformation. Cytogenetic abnormalities are essential biomarkers in Myelodysplastic Neoplasms (MDS) to assess risk prognosis and guide therapeutic strategies. Current prognostic scores minimize the real impact of less frequent chromosomal aberrations. Dicentric chromosome dic(7;12), an infrequent alteration in *de novo* MDS, might trigger an aggressive behavior and lead a leukemic transformation.

Keywords: Dicentric chromosome; Myelodysplastic neoplasms; Li-Fraumeni; Prognostic factors

INTRODUCTION

Myelodysplastic Neoplasms (MDS) are a clinically and genetically heterogeneous group of Bone Marrow (BM) neoplasms characterized by ineffective hematopoiesis, uni-/multi-lineage dysplasia, clonal genetic markers and increased risk of evolution into Acute Myeloid Leukemia (AML). Several score systems had been developed for prognostication, such as the revised International Prognostic Scoring System (IPSS-R), the IPSS Molecular (IPSS-M), and the World Health Organization Score System (WPSS) [1-3]. Acquired cytogenetic alterations are main cornerstones diagnostic and prognostic factors, harbored in ~40%-60% of primary MDS patients at diagnosis, being the most frequent -5/del(5q), -7/del(7q), + 8, del(12p) and del(20q) [4-6]. Therefore, early and accurate detection of such abnormalities is important for appropriate disease management and precise risk stratification. Furthermore, variants in some genes essential in DNA-repair mechanisms or DNA-methylation could trigger chromosome instability undergoing rearrangements, losses, gains, and clonal evolution. Updated understanding of leukemogenesis has highlighted recurrent genomic mutations involving diverse molecular pathways, mainly concern components of the RNA-splicing machinery (SF3B1, SRSF2, U2AF1, ZRSR2), DNA-methylation (DNMT3A, TET2), histone-modification (ASXL1, EZH2, BCOR/BCORL1), DNA-transcription (RUNX1, *TP53*), signal transduction (KRAS, NRAS, PTPN11) and cohesion complex (SMC3, SMC1A, RAD21, STAG2) [7,5]. Finally, recent insights reflected more evidence of familiar MDS/AML in patients harboring germline mutations in several genes including *TP53* [3,8].

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CASE PRESENTATION

An asymptomatic 34-year-old man with an antecedent of oligophrenia, with hemoglobin level of 133 g/L, white blood cell count of 7.9 × 109/L, neutrophil count of 3.2 × 109/L, blasts 1%, platelet count of 111,4 × 109/L and absolute reticulocytes count of 25 × 109/L. Bone marrow aspirate revealed dyserythropoiesis in 12%, dysgranulopoiesis (62%) and hypolobated megakaryocytes (10%). The inmunophenotype showed a 0.4% of blasts CD13+ and CD11b+ [9].

Karyotype from conventional cytogenetic analysis at diagnosis displayed two different clones, one featuring 45,XY,del(5)(q13q33),t(7;12)(q12.21;p12.2),-12,add(19)(p13) and a normal diploid clone, 46,XY [5,10]. FISH studies confirmed the 5q deletion, and the presence of a Dicentric Chromosome (DC) containing both 7 and 12 centromeres in 73% of studied cells. Consequently, one *ETV6* gene copy (12p13) was lost. Furthermore, chromosome painting FISH revealed the involvement of chromosome 7 both in dic(7;12) and t(7;19). When complementary results were integrated the final karyotype designation was 45,XY,deI(5)(q13q33), dic(7,12) (p12.21;p12.2), t(7;19)(p15;p13)(18)/46,XY(5) (Figures 1A-1E) [10].Additionally, constitutional screening showed a normal karyotype upholding the hematological clonal origin detected aberrations and discarding their link to the patient's oligophrenia. Cytogenetic and FISH findings were further supported by SNP-array from diagnosis peripheral blood and no additional abnormalities were detected.

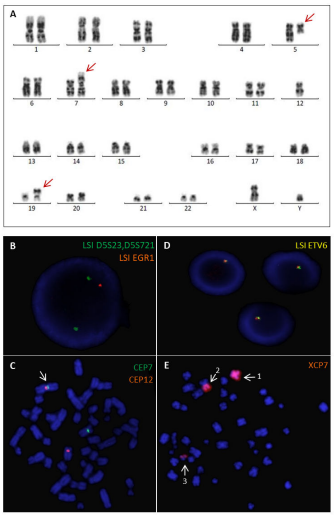

Figure 1: Conventional cytogenetic and FISH studies. (A) Bone marrow G-banded karyogram of the patient with 45,XY,del(5)(q13q33),dic(7;12)(p12.21;p12.2),t(7;19)(p15;p13). Abnormal chromosomes are indicated by arrows. Interphase FISH: (B) Two-color locus probes LSI EGR1 (5q31, orange)/ D5S23,D5S721 (5p15, green) revealed a deletion involving 5q31; (C) Dual color, break apart rearrangement LSI ETV6 (12q13) showed a single fusion signal. Metaphase FISH: (D) Simultaneous hybridization with CEP7 (green) and CEP12 (orange) probes confirmed the presence of chromosome 7 and 12 centromeres on dic(7;12) chromosome; (E) Whole chromosome painting of chromosome 7 (XCP7). Arrows indicate (1) normal chromosome 7, (2) dic(7;12) and (3) t(7;19).

BM morphology together with cytogenetic features led to an integrated diagnosis of MDS with Low Blasts (MDS-LB) according to current WHO criteria [9]. Prognostic scores indicated an intermediate risk by IPSS-R and a high risk by WPSS. The patient was rejected for allogeneic hematopoietic cells transplantation because his psychosocial situation.

Although the patient received seven cycles of 5-Azacitidine and showed a partial cytogenetic response, he evolved to MDS with Increased Blasts (MDS-IB1) (5% blasts in BM) only 12-months after diagnosis, which quickly transformation into an AML, myelodysplasia-related (46% blasts in BM) 3-months later. At leukemic stage, a clonal evolution was defined as the presence of a new clone with monosomy 7 and the acquisition of a chromosomal marker, 45,XY,deI(5)(q13q33),dic(7;12) (p12.21; p12.2), t(7;19) (p15;p13) (6)/45, idem, -7,+mar (11)/46,XY (3). At this time, additional genetic screening by NGS was performed using the Myeloid-Solution-Kit (SophiaGenetics®) and detected variants were categorized according to current international guidelines [11]. This analysis displayed CNVs in *NPM1*, *ETV6* and *KRAS* genes, located at chromosomes 5q and 12p, respectively, and supporting cytogenetic abnormalities described at the karyotype. Interestingly, a missense pathogenic variant in *TP53* (c.772G>A; p.Glu258Lys) was detected with a Variant Allele Frequency (VAF) of 76%, lacking concomitant del(17p) or uniparental disomy.

Finally, two consecutive different lines of treatment failed (cytarabine and idarubicin, 7+3 and FLAG-IDA regimens) and patient died 15-months after diagnosis as a result of septic shock.

RESULTS AND DISCUSSION

We present a particular case with intermediate-prognosis according to IPSS-R score who progressed quickly to AML. Different genetic adverse features as Complex Karyotype (CK), dic(7;12) and *TP53* mutation could contribute to this aggressive behavior.

Cytogenetic abnormalities are one of the hallmarks in MDS, being an important cause in the origin, progression, and relapse of the patients. Cytogenetic features are also age-related and reflect the heterogeneity of the disease, acting as a prognostic factor and used for risk-stratification and treatment definition [1-3]. A wide range of types of numerical and structural alterations have been described, some of them in a recurrent manner, with different impact on clinical management. Among them, DCs are detected in MDS with unsteady incidence and mainly found in more CKs. DCs undergo genomic instability triggering rearrangements of other chromosomes associated with monosomy of a participating chromosome, resulting in the clonal evolution of abnormal cells [12]. In MDS, CKs imply very poor prognoses with high-rates of transformation to AML [13]. Although DCs are relative common feature of MDS and AML, significantly more frequent in therapy-related than in *de novo* diseases, their real incidence could be underestimated [13-15]. During the diagnosis process of hematological neoplasms, DCs could be misread and often considered loss of chromosomes associated with unbalanced translocations. For

instance, in this case is necessary to verify the possible presence of hidden DCs by centromeric FISH probes [15].

In our patient, a DC involving short arms of chromosomes 7 and 12 was detected into a CK context and leads to the loss of the p-arms of both involved chromosomes causing haploid insufficiency of *ETV6* (*12p13*) and *HOXA* (*7p15*) genes. This abnormality has been reported in different hematological neoplasms of young patients but, to the best of our knowledge, not previously seen in de novo MDS. In particular, dic(7;12) is infrequent and has been previously reported only in 27 cases (Table 1), mainly affecting young males (median age: 15year) and associated with acute leukemia (19 patients with lymphoid malignancies, 6 with myeloid malignancies and 2 with mixed phenotype) [16]. Only one patient was diagnosed as secondary MDS with refractory anemia with excess of blasts but therapy-related, unlike our case. In most of these patients, karyotypes with dic(7;12) were complex leading a poor-prognosis, supporting the impact of DCs in the genome instability consistently associated with malignancy [12,13,15].

Case number	Age/Gender	Disease	Karyotype	Clinical Status	Reference
1.	2/M	Pre-B ALL	46,XY,+21,dic(7;12)(p11;p12),del(1)(q32)	CCR off therapy	S C Raimondi et al., 1991
2.	10/M	T-ALL	45,XY,dic(7;12)(p11;p12)/46,XY,+?18,dic(7;12)(p11;p12)/90,XXYY,2x(dic(7;12))	CCR off therapy	S C Raimondi et al., 1991
3.	8/F	Pre-B ALL	47,XX,+20,dic(7;12)(p11;p12),+dic(7;12),t(11;15)(q23;q15-q21)	CCR off therapy	S C Raimondi et al., 1991
4.	2/F	Pre-B ALL	45,XX,dic(7;12)(p11;p12),del(9)(p21)	CCR off therapy	S C Raimondi et al., 1991
5.	2/F	B-ALL	46,XX,dic(7;12)(p11;p11),+10,add(12)(p13), add(18)(p11)(7)	Second remission	United Kingdom Cancer Cytogenetics Group, 1992
6.	15/F	B-ALL, Down syndrome	46,XX,+21c,dic(7;12)(p11;p11), t(14;19)(q32;q 11)(10)/47,XX,+21c(11)	Event-free survival during more than 7 months	Pui et al., 1993
7.	76/M	AML-M4	44,XY,del(5)(q22q35),dic(7;12)(q11;p11), dic(11;16)(p11;q22),i(11)(q10),-13, -15,add(17)(p13)	N.A.	Misawa et al., 1998
8.	40/F	ALL	44,XX,del(10)(q22q26),dic(7;12)(p11.2;p12), t(12;?18)(p13;q21),−13(14)/46,XX(6)	N.A.	Snyder et al., 1999
9.	6/F	Pre-B ALL	45,XX,t(2;14)(p11;q32), -7,dic(7;12)(p11;p12),i(9)(q10)	N.A.	Silva et al., 2002
10.	2/M	B-ALL	45,XY,dic(7;12)(p11.2;p11.2),del(6)(q14q23)(2)/46,idem,+mar(3)/46,XY(2)	Died after 2.3 years of complete remission	S C Raimondi et al., 2003
11.	1/F	B-ALL	45,XX,del(1)(q32),dic(7;12)(p11.2;p11.2)(12)/46,XX(8)	10 years of remission	
12.	52/M	t-MDS RAEB	44,XY,ins(2;3)(p?16;q?21q2?5), der(5;17)(p10;q10),20(14)/44,XY, der(5;17)(p10;q10),dic(7;12)(p10;p13), del(14)(q11q14)(3)/46,XY(13)	6 months of survival	Stevens-Kroef et al., 2004

13.	75/F	t-AML-M2	41,XX,-4,-5,dic(6;18)(q11;p11), dic(7;12)(q11;p11),der(11)(q10q14q22q25),-16,der(21)t(16;21)(p11;p11)	N.A.	Andersen et al., 2005
14.	39/F	AML-M1	45,XX,t(4;12)(q12;p13),dic(7;12)(q11;p13)	Morphologic and cytogenetic remission	Kuchenbauer et al., 2005
15.	34/F	B-ALL	46,XX,-X,inv(1)(p1?q4?),add(4)(p?),+5,+del(5)(q2?),t(6;14)(p22;q32), dic(7;12)(p1?;p1?),add(8)(p?),der(9)t(X;9)(q1?3;p1?3),-13,+mar(cp6)	N.A.	Russell et al., 2008
16.	53/M	AML-M1	45,XY,dic(7;12)(p12.21;p12.2)(30)/46,XY,del(7)(p11),del(12)(p11)(5)	Died in a month because of a heart failure	Tapinassi et al., 2008
17.	50/M	AMLL	45,XY,dic(7;12)(p11;p11)(2)/46,XY(18) (bone marrow) 45,XY,dic(7;12)(p11;p11)(4)/45,idem,+mar1,+mar2(5)/46,XY(11) (lymph node)	No recurrence after 43 months post-BMT	Matsumoto et al., 2009
18.	27/M	CML in blast crisis	46,XY,dic(7;12)(p12.21;p12.2),t(9;22)(q34;q11.2),i(12)(q10)(14)/46,XY(6)(cp14)	CHR 4 weeks after start of therapy.	De Oliveira et al., 2012
19.	N.A./M	B-ALL	45,XY,dic(7;12)(p11.2;p11.2)(7)/46,XY(13)	N.A.	Holmfeldt et al., 2013
20.	1/F	B-ALL	45,XX,dic(7;12)(q11.2;p11.2),add(19)(p13.3)(cp2)/46,XX(44)	N.A.	Holmfeldt et al., 2013
21.	7/M	T-ALL	45,XYY?c,dic(7;12)(p11.2;p11.2),del(9)(p13p24), t(10;11)(p12;q14),-21(3)/47,XYY?c(17)	N.A.	Matlawska-Wasowska et al., 2016
22.	16/F	B-ALL	45,XY,dic(7;12)(p11;p11)	Complete remission	Marincevic-Zuniga et al., 2016
23.	2/F	B-ALL	45,XX,del(1)(q42.2),dic(7;12)(p12.1;p11.21), del(9)(p13.2p13.2)	N.A.	Olsson et al., 2018
24.	3/M	B-ALL	45,XY,der(1)t(1;12)(q42.3;p13.2),dic(7;12)(p11.2;p11.22),del(14)(q32.2),del(16)(q12.1q22.1)	N.A.	

25.	1/M	B-ALL	46,XY,dic(7;12)(p11;p11),del(9)(p11),+mar/46,idem,+12,-mar	N.A.	Gupta et al., 2019
26.	51/M	T/myeloid MPAL	45,XY, dic(7;12)(p11;p11)	Complete morphological remission	Gajendra ET AL., 2021
27.	24/M	B-ALL	45,XY,dic(7;12)(p11;p11)	N.A.	Siegele et al., 2022
28.	34/M	MDS-LB	45,XY,del(5)(q13q33),dic(7,12)(p12.21;p12.2),t(7;19)(p15;p13)(18)/46,XY(5)	Progression to AML and died	Present case

Abbreviations: M: Male; F: Female; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; t-AML-Therapy-related AML; AMLL: Acute Mixed Lineage Leukemia; MPAL: Mixed Phenotype Acute Leukemia; CML: Chronic Myeloid Leukemia; MDS: Myelodysplastic Neoplasms; MDS: LB: MDS with Low Blast; RAEB: Refractory Anemia with Excess of Blasts; t-MDS: Therapy-related MDS; BMT: Bone Marrow Transplantation; CHR: Complete Hematologic Remission; CCR: Complete Clinical Response; BM: Bone Marrow; CNS:Central Nervous System; N.A: Not Available.

Table 1: Summary of previously reported cases harbouring dicentric chromosome dic(7;12).

In MDS, cytogenetic abnormalities are mandatory to establish risk prognosis and AML transformation through well-known IPSS-R and WPSS prognostic scores [1-3]. Our patient was stratified as intermediate-risk by IPSS-R and a high-risk through WPSS due to the CK. However, non-recurrent chromosomal aberrations may misclassify as lower-risk patients by IPSS-R [2]. These genetic alterations may alter risk stratification in a subset of patients with low and intermediate-risk with a high-risk behavior [17]. Recently, the IPSS-M has been developed to improve previous scoring system suitable for daily clinical practice, considering gene mutations but still excluding infrequent cytogenetic abnormalities [3]. Nevertheless, for our patient, the presence of *TP53* point mutation did not modify risk-classification being grouped into intermediate-risk category. This peculiar case might suggest that the dic(7;12) could be an announcement of a disease progression to AML, and thus, an interesting alteration to be further studied as a possible poor prognosis marker in MDS.

On the other hand, MDS cases in young adults are frequently associated with germline genetic predisposition and represents 4%-15% of MDS patients [8,18]. Our case harbored a missense pathogenic variant in *TP53* in 76% of the studied cells with an unaffected *TP53* allele retained, suggesting a possible germline etiology. Although several efforts to study more relatives in order to confirm this fact, it could not be conducted due to their geographical relocation. However, this variant has been previously reported as germline linked to brain tumours, supporting an inherit predisposition etiology. The elevated VAF of *TP53* variant, together with the slight mental delay, young age and a familiar history of three siblings with mental disorders, one of them with a high-grade glioma at the age of 41year, made us suspect about a Li-Fraumeni Syndrome (LFS) [19-21]. According to current published algorithms, this patient achieves the classical LFS criteria and the Chompret criteria, first-degree relative with any cancer before age 45year (his brother) and proband with LFS tumors (leukemia) before age 46year, respectively [22,23]. LFS increases risk of myeloid malignancies at young age, such as MDS and AML, displaying outcomes extremely poor [19,20]. Although in LFS patients MDS tends to be secondary to previous treatment, *de novo* MDS is also reported [20]. Germline *TP53* variants are also frequent in LFS and in MDS patients are widely associated with a higher genomic complexity, and confer poor prognosis and treatment resistance, supporting the severe clinical evolution of our patient.

Finally, highlight the ineffectiveness of azacitidine in preventing or delaying the transformation to AML in our patient. Drugs that inhibit DNA methylation function optimally in cases with *TP53* mutation [24]. However, hypomethylating agents are not curative despite initial responses due to selection of resistant sub clones and the incomplete clearance of leukemia-specific mutations [25,26].

CONCLUSION

In conclusion, MDS outcome is variable, and genetic factors contribute to their pathophysiology. This patient displays a combination of genetic features with an individual poor prognosis. The concomitance of *TP53* mutation together with the presence of a DC could lead to an extremely genomic instability that triggers a rapid clonal evolution with fatal clinical course. Unfortunately, specific mechanisms of disease transformation are still unclear and are currently under study.

AUTHOR CONTRIBUTIONS

Conceptualization RC; methodology MU, RG-S, IL, ME, RR-L; formal analysis IL, MTO, ML; data curation DI, CV, MTO, BA, OM, CJ; writing-original draft preparation MU and RG-S; supervision ML, MI and RC. All authors have read and agreed to publish this version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was performed in line with the principles of the Declaration of Helsinki and adhered to Good Clinical Practice. However Ethical review and approval were waived for this study due to the study reports data obtained during the standard procedures for diagnostic laboratory and for which the approval of the ethics committee is not required.

INFORMED CONSENT STATEMENT

Samples were obtained with written informed consent in accordance with the Declaration of Helsinki.

CONFLICT OF INTEREST

The medical writer for this manuscript was supported by AbbVie with no input into the preparation, review, approval and writing of the manuscript. The authors maintained complete control over the manuscript content, and it reflects their opinions.

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