



Case Report

Myeloid Neoplasms with Isolated Isochromosome 17q: a yet to be Defined Entity

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Abstract. Myeloid neoplasms with isolated isochromosome 17q [MN i(17q)] has been described as a distinct entity with poor prognosis. However, literature reports show a considerable clinical and molecular heterogeneity. We describe a 58-year-old male patient who was diagnosed as refractory anemia with multilineage dysplasia and ringed sideroblasts with isolated i(17q). Though he initially responded well to erythropoietin, he gradually progressed to an aggressive form of MDS/MPN refractory to azacytidine and died 29 months after the first diagnosis. Notably, in contrast to disease advancement, his karyotype reverted to normal, whereas his mutational profile remained unchanged. To our knowledge, this is the first report of karyotype normalization during disease progression in patients with MN i(17q). It suggests that the i(17q) anomaly is dispensable for the leukemic transformation and highlighting the underlying clinical and molecular complexity which both has to be resolved before the establishment of MN with isolated i(17q) as a distinct entity.

Keywords: Isochromosome, MDS, Spliceosome.

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Introduction. Isochromosome 17q is the most common isochromosome found in human cancer and frequently occurs in different hematopoietic and non-hematopoietic malignancies, including medulloblastoma, gastric and breast cancer, chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS) and non-Hodgkin lymphomas.¹ In most hematological malignancies i(17q) is associated with aggressive disease and a complex karyotype,² but the presence of i(17q) as a sole abnormality is mostly restricted to the blast phase of CML, AML and MDS.^{2,3} Early reports suggested that MN patients with isolated i(17q)

comprised a distinct group with mainly myelodysplastic/ myeloproliferative neoplasm (MDS/MPN) characteristics, resistant phenotype and dismal prognosis⁴. These findings were further confirmed by largest series,^{3,5,6} which concluded that isolated i(17q) usually arise during disease progression and reported a range of median overall survival (mOS) from 11 months in MDS/MPN⁵ to only 4,5 months in a mixed AML and MDS patient cohort.⁶ However, older series reported a considerably higher survival,⁷ while significant heterogeneity also appears to exist among the various reports concerning MDS subtype at presentation. Similarly, the mutational profile of

such patients is complex and heterogeneous encompassing mutations in various biologic functional categories.^{3,6}

In the present manuscript, we describe a 58-year old male patient with isolated i(17q) who initially presented at our department as refractory anemia with multilineage dysplasia with ringed sideroblasts (RCMD-RS). Two years later he progressed to a fibrotic MDS/MPN with excess blasts, while, at the same time, his karyotype converted to normal. Our case supports the existence of recurrent characteristic features in MDS with isolated i(17q) but argues on the effect on survival and the causality of isolated i(17q) anomaly in leukemic progression.

Case Report. A 58-year old male patient was referred to our department due to normocytic anemia and leucopenia in May 2008. His anamnesis included mild diabetes type II and solitary congenital kidney with normal renal function, and he was on no medication. A complete blood count performed a year ago was showing hemoglobin (Hb) 121 g/L and average leukocyte count (WBC) and platelet counts. The patient was in relatively good condition complaining only of mild fatigue, and the physical examination was unremarkable. Haemoglobin was 74 g/L, platelets $165 \times 10^9/L$, MCV 83 fl, WBC $2.98 \times 10^9/L$ and the absolute neutrophil count (ANC) $1.4 \times 10^9/L$, while biochemistry, including LDH, was normal. The rest laboratory workup revealed erythropoietin serum level of 19.6 IU/L (normal range 3.3-24.4 IU/L), ferritin levels 418 ng/dl and B12 levels 1166 pg/ml. The blood film showed dimorphic red cells, and hypogranular neutrophils with ringed nuclei (**Figure 1a**) and the bone marrow aspirate was consistent with refractory anaemia with multilineage dysplasia, and 40% ringed sideroblasts (RCMD-RS). Blast count was 1%. Bone marrow biopsy also revealed a hypercellular marrow with trilineage dysplasia and grade I reticulin fibrosis by Gomori's silver stain. Cytogenetic studies were performed in bone marrow by using conventional G-banding analysis and showed 12/20 metaphases carrying the 46, XY, i(17q)(q10) and 8/20 residual normal metaphases. By using PCR we found mutations in *SETBP1*, *U2AF1* and *KIT* genes, whereas no mutations were found in *SF3B1*, *JAK2*, *MPL*, *CALR*, *IDH1*, *IDH2*, *DNMT3A*, *SRSF2* and *ASXL1* and no chimeric transcripts of BCR/ABL were

detected. The patient was transfused and started on recombinant erythropoietin (EPO) at 40.000 IU/week. Two months after, Hb was 87 g/L, and we doubled the EPO dose at 80.000IU/week. He remained untransfused for 7 months when his Hb rose at 112 g/L, and although EPO was reduced to 40.000 IU/week, after 3 months the Hb levels reached 140 g/L, and EPO was discontinued. He did not receive further EPO for 12 months, being asymptomatic with normal Hb levels, whereas due to a synchronous rise in WBC and platelet counts we performed JAK2V617F mutation analysis with negative results. However, 24 months after diagnosis the patient developed splenomegaly 5cm below left costal margin and low-grade fever peaking in the afternoon. His Hb dropped at 84 g/L, his platelet count at $103 \times 10^9/L$ and the WBC rose to $21.7 \times 10^9/L$. Peripheral blood smear showed 9% blasts, and immunophenotypic analysis by 4-color flow cytometry demonstrated a CD45^{low} population with typical myeloblast phenotype, positive for CD34, CD117, CD33, HLA-DR and CD13, and negative for CD15, CD19, CD10, CD56, CD7 and CD61 (**Figure 1b**). The aspirate was unsuccessful (dry tap) and the bone marrow biopsy showed a hypercellular marrow with myeloid and megakaryocytic hyperplasia, decreased erythropoiesis, 9% blasts, and reticulin fibrosis grade 2-3, whereas low-grade collagen fibrosis was also present. A new cytogenetic study was pursued and, unexpectedly, revealed a regular 46, XY[30] karyotype and normal FISH findings (**Supplemental Figure S1**), whereas his mutational profile remained unchanged. The patient received 5 courses of subcutaneous azacytidine at 75 mg/m^2 for seven days on 28-day cycles, but his splenomegaly progressed, and along with the ongoing fever he developed night sweats and weight loss. We administered induction chemotherapy with cytarabine (Ara-C) $100\text{g/m}^2/\text{d}$ iv d1-7 and idarubicin $12 \text{ mg/m}^2/\text{d}$ iv d1-3, but the patient succumbed to sepsis after 23 days. The course of the patient's CBC is shown in **Figure 1c**.

Discussion. Patients with myeloid neoplasms with isolated i(17q) share several common characteristics regarding morphology, disease type, course, and prognosis. However, there is still significant heterogeneity in all of the above features among the reported patients (**Table 1**). By using 2008 WHO classification⁸ most patients

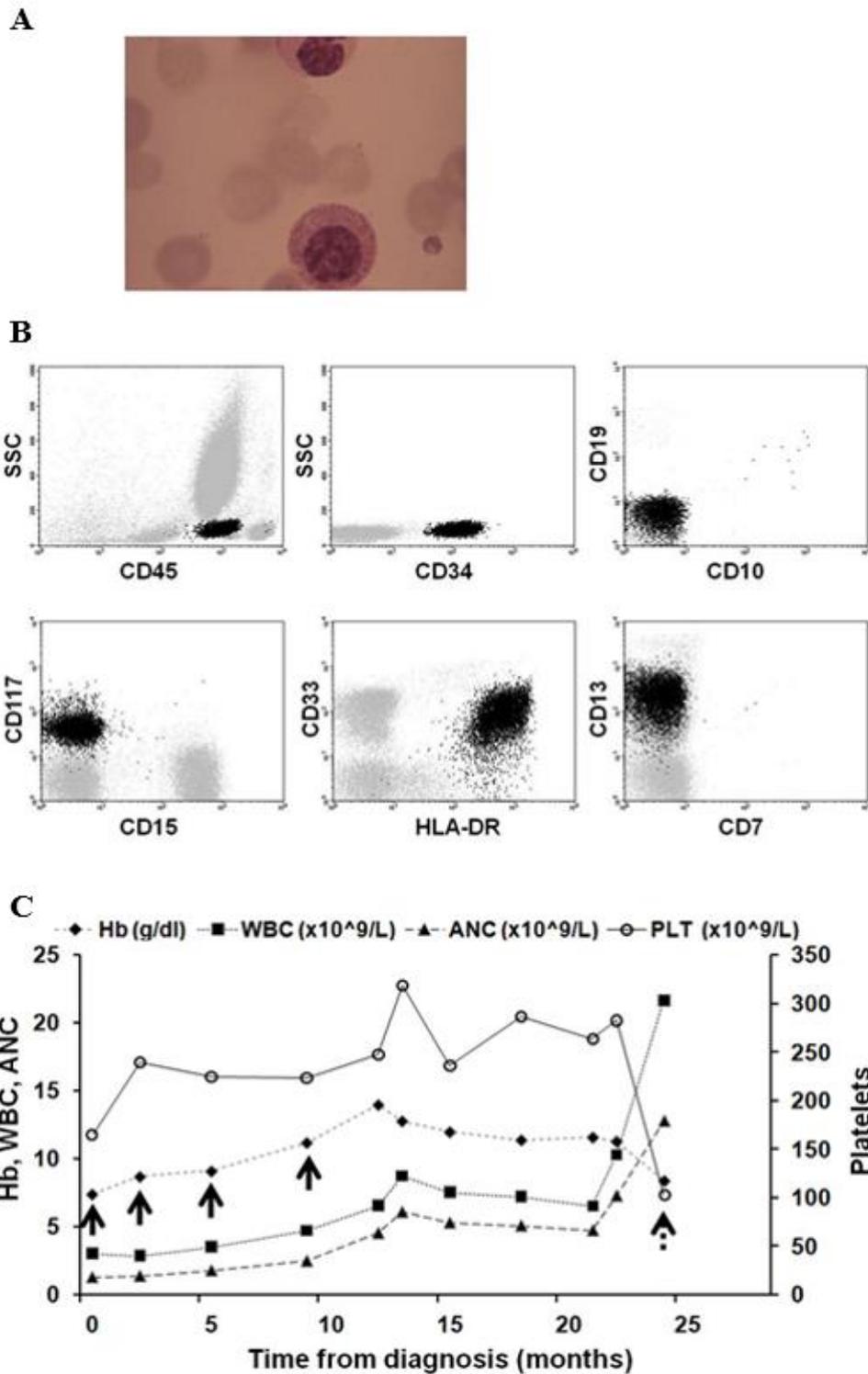


Figure 1. Morphological and immunophenotypic characteristics of *i(17q)*.

- May-Grünwald-Giemsa stained peripheral blood smear at diagnosis revealed a hyposegmented neutrophils with ringed nuclei ($\times 100$).
- Representative flow cytometry plots showing blast positivity (black color) for CD34, CD117, HLA-DR, CD33 and CD13 and negativity for CD19, CD10, CD15 and CD7.
- Course of Hemoglobin, white blood cells (WBC), absolute neutrophils counts (ANC) and platelets during patient follow up. Recombinant erythropoietin was administered at the times indicated by solid arrows. Dashed arrow shows initiation of 5-azacytidine.

Table 1. Clinical and biological characteristics of MDS patients with i(17q) in studies including ≥ 10 patients.

| Reference | No of pts ^a | Gender M/F | Age (median-range) | Disease subtype | Splenomegaly | Treatment | BM fibrosis | Progression to AML | Median OS (months) |
|--------------------------------------|------------------------|------------|--------------------|--|------------------------|--------------------------------|-----------------------------|-------------------------|--|
| Fioretos 1999 ² | 10/7 | 8/2 | 73.5 (53-82) | MDS (6) AML(1) | N/A | N/A | N/A | N/A | N/A |
| McClure 1999 ¹⁵ | 15/11 | 10/5 | 62 (37-83) | MDS/MPN | N/A | N/A | 2/15 | 64% (7/11) | 30 ^b |
| Kanagal-Shamanna, 2011 ¹³ | 22/18 | 12/10 | 65 (23-90) | MDS/MPN (14) AML (8) | MDS/MPN (6) AML (3) | CTX:9 HMAs:8 | MDS/MPN (9/14) AML (2/8) | 4/10 ^c | MDS/MPN (11) AML (14.5) |
| Visconte 2014 ¹⁴ | 21/12 | 11/10 | 70,5 | MDS/MPN (11) AML (10) | 42% | HI-CTX:4 LI- CTX:5 SCT:3 | 43% | N/A | Isolated:4.5 Non-isolated:4 |
| Adema 2015 ²¹ | 27/14 | 17/10 | 76 (24-91) | MDS (22) CMML-1 (4) | N/A | N/A | N/A | N/A | Isolated:26.5 +1 abn:21.3 CK:3.8 |
| Kanagal-Shamanna, 2016 ³ | 32/29 | 17/15 | 66 (24-83) | MDS/MPN (13) AML (17) MDS(1) MPN(1) | N/A | N/A | N/A | 27% ^d (4/15) | 9.4 |

^a: All patients/isolated i(17q); ^b: Available data on 11/15 pts ; ^c: 4/14 MDS/MPN pts presented initially as secondary AML; ^d: cytogenetic evolution; M: male; F: female; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; MDS/MPN: myelodysplastic syndrome/ myeloproliferative neoplasm; CMML: chronic myelomonocytic leukemia; HMAs: Hypomethylating

with isolated i(17q) fall into the MDS/MPN category. However, there are cases classified as various MDS, MPN and AML subtypes including acute promyelocytic leukemia and even hypereosinophilic syndrome.^{2,3,5,6,9-11} Another controversial issue is prognosis. Isolated i(17q) has repeatedly been reported to confer a dismal outcome ranging from an mOS of 4.5⁶ to up to 14.5 months^{3,5} in 3 large series.

By contrast, in line with the 29-month survival of our patient, two other large series recorded an mOS of 30⁷ and 26.5¹¹ months. The exclusion of AML patients from the latter studies may account for the discrepant findings; indeed, MDS patients with isolated i(17q) are assigned to the intermediate-risk category by the revised international prognostic scoring system (IPSS-R) and have a predicted mOS of 32 months.¹² Of note, MDS/MPN patients fared worse than the AML ones in one study, but 4 out of 14 MDS/MPN cases were actually secondary AML.⁵

As concerns treatment, myeloid neoplasms with isolated i(17q) are apparently resistant to standard regimens, and such patients are candidates for allogeneic transplantation early in the course of the disease.^{5,10} Data regarding the efficacy of hypomethylating agents in these patients are very limited; Kanagal-Shamanna et al. reported on 5 patients, three in azacytidine and two in decitabine, all of which failed to respond, similarly to our patient.⁵

The more obvious consequence of the formation of isochromosome 17q is the deletion of one allele of TP53 gene located at 17p13. Loss of 17p might be responsible for the Pelger-Huët dysgranulopoiesis,¹³ but coding mutations in the remaining allele are rare and usually accompanied by additional cytogenetic abnormalities, rendering TP53 an improbable player in the pathobiology of the syndrome.^{2,3}

ASXL1, *SRSF2*, *RAS*, and *SETBP1* are the most frequently mutated genes in isolated i(17q) (**Table 2**). The former three mutations may antedate the formation of i(17q), whereas *SETBP1* mutations are associated with i(17q).³ Our patient had mutations in *SETBP1*, *U2AF1*, and *c-KIT*, whereas *ASXL1* was unmutated and no mutation analysis was performed in *SRSF2* and *RAS*. Mutations in *SETBP1*, mainly gain of function, are often observed in CMML, secondary AML and atypical CML, while they are rare in childhood, de novo and therapy-related AML.^{14,15} Though linked with characteristics of poor prognosis, reports on the effect of *SETBP1* mutations on survival are conflicting.^{14,15} Our patient also had the *U2AF1* (p.Q157P) mutation, rarely reported in MDS with isolated i(17q),³ while it is more common in poor prognosis, advanced myelomonocytic leukemias.¹⁶ *U2AF1* mutations appear to lead to pathological splicing of several genes involved in leukemogenesis and are strongly associated with leukemic evolution and dismal outcome.¹⁷ We also

Table 2. Most frequently mutated genes in isolated i(17q).

| Pathway | Mutated genes | Frequency (% of patients) in selected studies | | |
|-------------------------------------|-------------------------------------|---|-----------------|---------------------|
| | | Reference | Isolated i(17q) | Non-isolated i(17q) |
| <i>Epigenetic modifiers</i> | <i>ASXL1</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) |
| | | Meggendorfer 2016 ³⁰ | 81% (22/27) | 19/35 |
| Kanagal-Shamanna 2016 ³ | | 50% (14/28) | 100% (3/3) | |
| | <i>EZH2</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) |
| | | Kanagal-Shamanna 2016 ³ | 3.5% (1/29) | 0% (0/3) |
| <i>Spliceosome</i> | <i>SRSF2</i> | Visconte 2014 ¹⁴ | 66.6% (4/6) | 17% (1/6) |
| | | Meggendorfer 2016 ³⁰ | 65% (40/62)* | |
| | | Kanagal-Shamanna 2016 ³ | 54% (14/26) | 67% (2/3) |
| | <i>SF3B1</i> | Visconte 2014 ¹⁴ | 12.5% (1/8) | 0% (0/6) |
| | | Kanagal-Shamanna 2016 ³ | 0% (0/26) | 0% (0/3) |
| | <i>U2AF1</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) |
| | | Kanagal-Shamanna 2016 ³ | 8% (2/26) | 33% (1/3) |
| <i>Cell signaling</i> | <i>NRAS</i> | Kanagal-Shamanna 2011 ¹³ | 30% (3/10) * | |
| | | Visconte 2014 ¹⁴ | 0% (0/8) | 17% (1/6) |
| | | Meggendorfer 2016 ³⁰ | 10% (6/62) * | |
| | | Kanagal-Shamanna 2016 ³ | 34% (10/29) | 0% (0/3) |
| | <i>KRAS</i> | Kanagal-Shamanna 2011 ¹³ | 0% (0/10) * | |
| | | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) |
| | Kanagal-Shamanna 2016 ³ | 7% (2/29) | 33% (1/3) | |
| <i>FLT3 ITD</i> | Kanagal-Shamanna 2011 ¹³ | 12.5% (2/16) * | | |
| | Visconte 2014 ¹⁴ | 17% (1/6) | 0% (0/6) | |
| | Kanagal-Shamanna 2016 ³ | 10% (3/29) | 0% (0/3) | |
| <i>JAK2</i> | Kanagal-Shamanna 2011 ¹³ | 6% (1/18) * | | |
| | Visconte 2014 ¹⁴ | 0% (0/8) | 17% (1/6) | |
| | Kanagal-Shamanna 2016 ³ | 7% (2/29) | 0% (0/3) | |
| <i>CSF3R</i> | Visconte 2014 ¹⁴ | 17% (1/6) | 17% (1/6) | |
| <i>DNA methylation</i> | <i>TET2</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 17% (1/6) |
| | | Meggendorfer 2016 ³⁰ | 24% (15/62) * | |
| | | Kanagal-Shamanna 2016 ³ | 8% (2/28) | 0% (0/3) |
| <i>DNMT3A</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) | |
| | Kanagal-Shamanna 2016 ³ | 7% (2/29) | 0% (0/3) | |
| <i>IDH1/2</i> | Visconte 2014 ¹⁴ | 0% (0/6) | 0% (0/6) | |
| | Kanagal-Shamanna 2016 ³ | 10% (3/29) | 0% (0/3) | |
| <i>Others</i> | <i>SETBP1</i> | Meggendorfer 2013 ³² | 54.3 (19/35) | 21.5% (18/84) |
| | | Visconte 2014 ¹⁴ | 62.5% (5/8) | 28.5 (2/7) |
| | | Adema 2015 ²¹ | 64% (9/14): | 15% (2/13) |
| | | Meggendorfer 2016 ³⁰ | 48% (30/62) | 27/62 |
| | | Kanagal-Shamanna 2016 ³ | 58% (15/26) | 67% (2/3) |
| | <i>TP53</i> | Fioretos 1999 ²² | 0% (10/10) | |
| Kanagal-Shamanna 2011 ¹³ | | 0% (14/14) * | | |
| Meggendorfer 2013 | | 17% (9/52) * | 14% (1/7) | |

| | | | | |
|--------------|------------------------------------|-------------------------------------|-----------------|-----------|
| | <i>TP53</i> | Visconte 2014 ¹⁴ | 12.5% (1/8) | 57% (4/7) |
| | | Adema 2015 ²¹ | 7% (1/14) | |
| | | Meggendorfer 2016 ³⁰ | 15% (9/62)* | 33% (1/3) |
| | | Kanagal-Shamanna 2016 ³ | 7% (2/29) cases | |
| | <i>NPM1</i> | Kanagal-Shamanna 2011 ¹³ | 0% (0/15) * | |
| | | Kanagal-Shamanna 2016 ³ | 3.5% (1/29) | 0% (0/3) |
| <i>RUNX1</i> | Meggendorfer 2016 ³⁰ | 11% (7/62) * | | |
| | Kanagal-Shamanna 2016 ³ | 7% (2/28) | 0% (0/3) | |

*Percentages refer to patients with both isolated and non-isolated i(17q)

detected the *KIT* (p.D816V) mutation, which is observed in over 90% of systemic mastocytosis cases and at lower frequencies in patients with core binding factor AML conferring a poor prognosis.¹⁸ Activating mutations of *KIT* in AML are considered as a class I aberrations which provide a proliferative and survival advantage to the leukemic cells.¹⁹ In MDS the above mutation is rarely found and is restricted to advanced stages,²⁰ whereas only one case of a different *KIT* mutation has been reported so far as a sole molecular aberration in a patient with AML with myelodysplasia-related changes and isolated i(17q).³ Interestingly, both *U2AF1* and *KIT* mutations antedated leukemic progression by two years in our patient, emphasizing the often existing discordance between mutational profiles and clinical course and the need for caution in the clinical translation of molecular findings. In addition, the intriguing conversion of our patient's karyotype to normal during disease progression suggests that genetic pathways unrelated to chromosome 17 are potentially involved in the multifactorial pathobiology of this MDS entity. A hint of the dispensability of i(17q) for the leukemic progression has been previously reported in one patient with primary myelofibrosis who developed a transient and progressively shrinking i(17q) clone without changing his mutational profile. Another indication that the development of i(17q) anomaly may represent an epiphenomenon and not the initial oncogenic event is the fact that

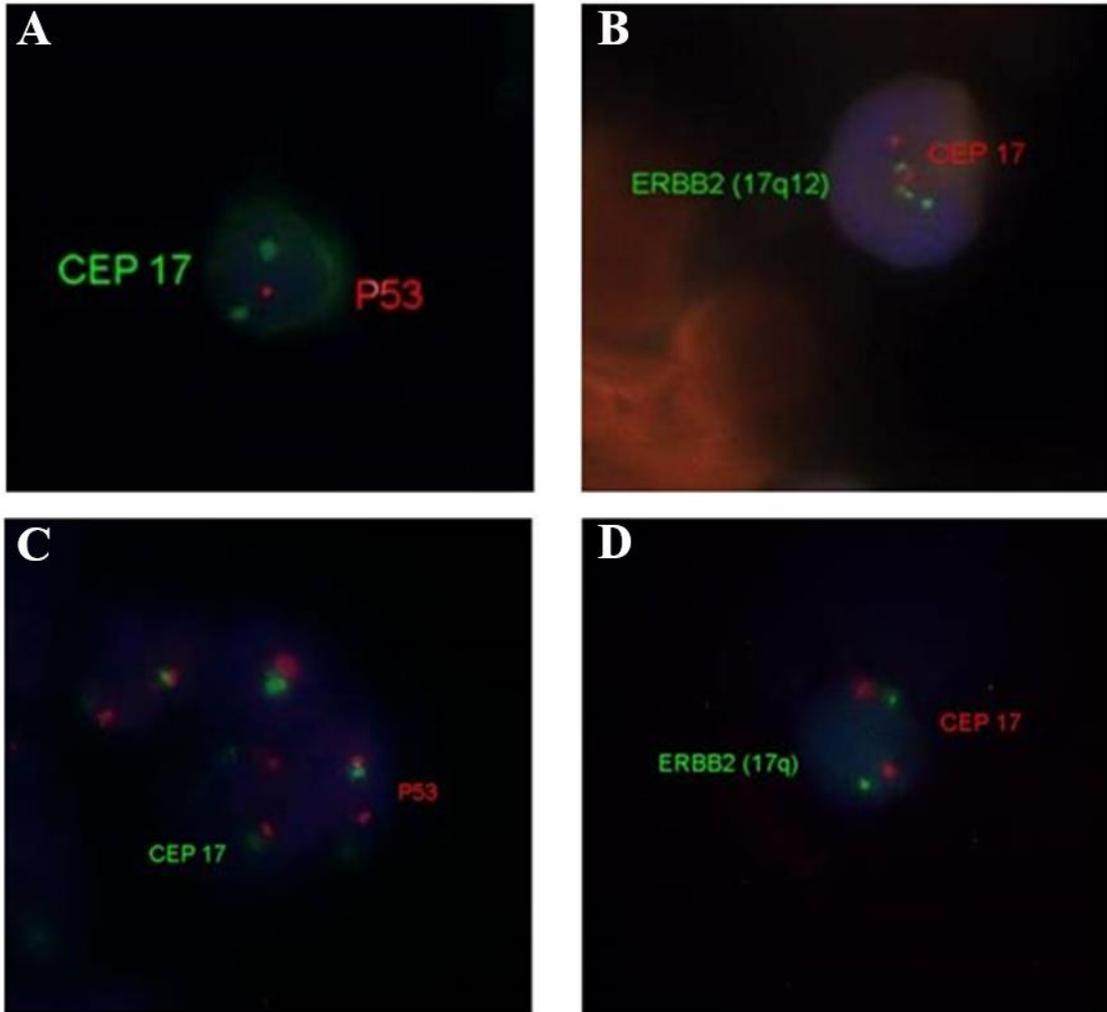
though the mutational profile of our patient remained unchanged, the mutational load of each mutated gene increased significantly during disease progression (data not shown). Thus, the leukemogenic effect of one or more of *SETBP1*, *U2AF1* and *KIT* mutants appears to be independent of the i(17q) formation. Nevertheless, the similarity in the clinical presentation of cases with isolated i(17q) still suggests a role of this abnormality in the characteristic features shared by these patients.

Conclusions. We describe a patient with RCMD-RS who displayed most of the typical characteristics of MDS/MPN with isolated i(17q) during his disease course. Our patient is the second one with a diagnosis of acquired idiopathic sideroblastic anemia with isolated i(17q) reported in the literature⁹ and his 29-month survival stresses the fact that the prognosis of myeloid tumors with isolated i(17q) potentially depends mainly on the MDS subtype at initial presentation. More important, we report for the first time the paradoxical disappearance of the i(17q) and karyotype normalization during disease progression, a phenomenon that challenges the requirement and the contribution of the i(17q) anomaly in the leukemogenic process. Our case stresses the importance of the collection of an adequate amount of clinical data and elucidation of the molecular basis of MDS to accurately define and classify a new entity.

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Supplementary Figure S1. Interphase FISH from peripheral blood at diagnosis and at disease progression. FISH analysis was performed with probes for *TP53* and *ERBB2* gene. In isochromosome 17q formation the first gene is deleted and the second triplicated. At first diagnosis uniallelic *TP53* expression (A) and triplication of *ERBB2* (B) gene was found in 51% of interphase cells confirming the presence of i(17)q anomaly. By contrast, at leukemic progression *TP53* deletion was not observed (C) and *ERBB2* (D) gene was normally expressed.