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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 prognosis[4]. 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/MPN[5] 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 x 10^9/L, MCV 83 fl, WBC 2.98 x 10^9/L and the absolute neutrophil count (ANC) 1.4 x 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 x 10^9/L and the WBC rose to 21.7 x 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) 100g/m^2/d iv d1-7 and idarubicin 12 mg/m^2/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 classification[8] most patients

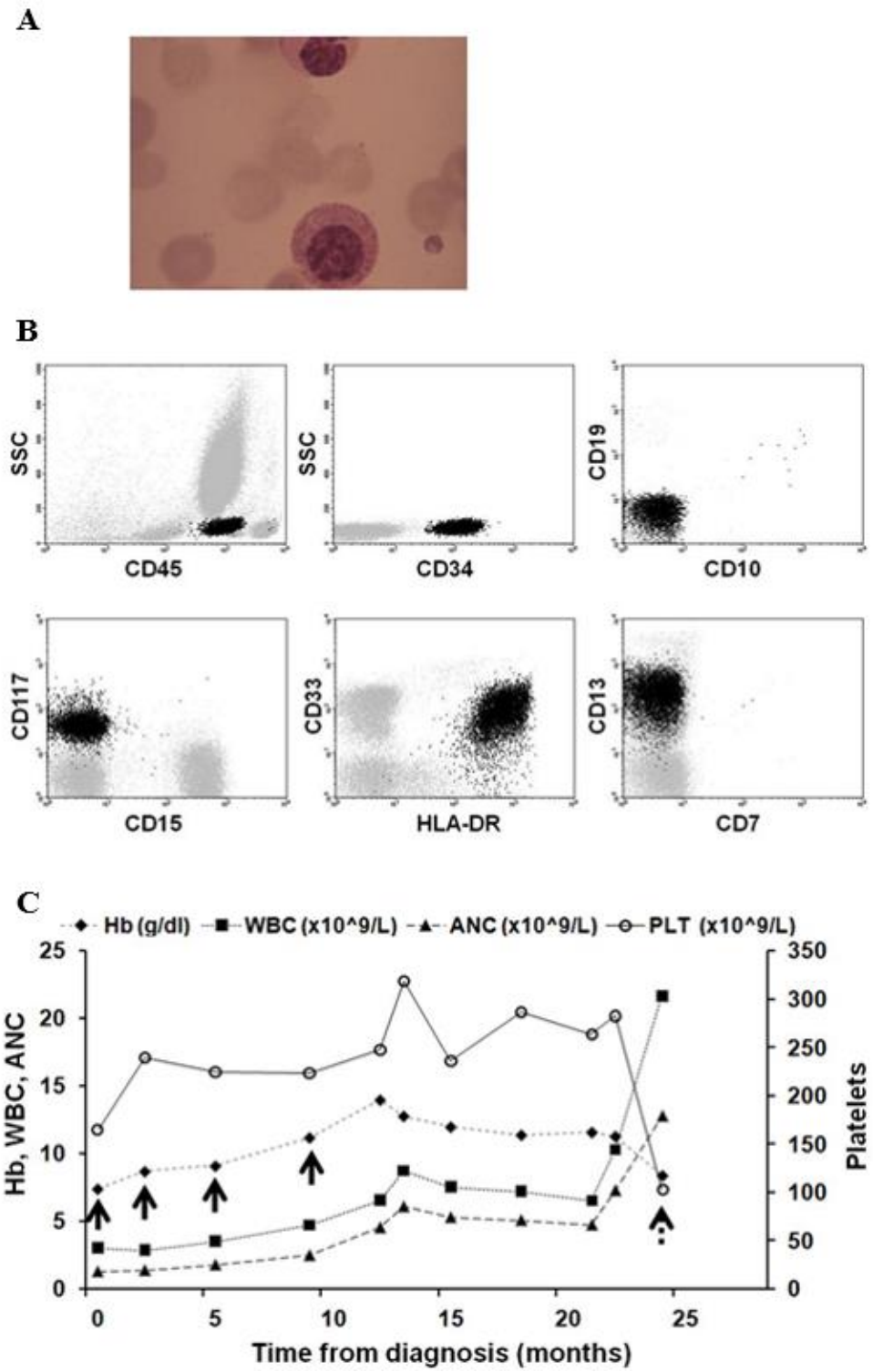


Figure 1. Morphological and immunophenotypic characteristics of i(17q).

- **a)** May-Grünwald-Giemsa stained peripheral blood smear at diagnosis revealed a hyposegmented neutrophils with ringed nuclei (×100).
- **b)** 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.
- **c)** 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 4.5[6] 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 30[7] and 26.5[11] 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)**
Epigenetic modifiers	***ASXL1***	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)
	EZH2	Visconte 2014[14]	0% (0/6)	0% (0/6)
		Kanagal-Shamanna 2016[3]	3.5% (1/29)	0% (0/3)
Spliceosome	***SRSF2***	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)
	SF3B1	Visconte 2014[14]	12.5% (1/8)	0% (0/6)
		Kanagal-Shamanna 2016[3]	0% (0/26)	0% (0/3)
	U2AF1	Visconte 2014[14]	0% (0/6)	0% (0/6)
		Kanagal-Shamanna 2016[3]	8% (2/26)	33% (1/3)
Cell signaling	***NRAS***	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)
	KRAS	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)
	***FLT3* ITD**	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)
	JAK2	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)
	CSF3R	Visconte 2014[14]	17% (1/6)	17% (1/6)
DNA methylation	***TET2***	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)
	DNMT3A	Visconte 2014[14]	0% (0/6)	0% (0/6)
		Kanagal-Shamanna 2016[3]	7% (2/29)	0% (0/3)
	IDH1/2	Visconte 2014[14]	0% (0/6)	0% (0/6)
		Kanagal-Shamanna 2016[3]	10% (3/29)	0% (0/3)
Others	***SETBP1***	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)
	TP53	Fioretos 1999[22]	0% (10/10)	
		Kanagal-Shamanna 2011[13]	0% (14/14) *	
		Meggendorfer 2013	17% (9/52) *	14% (1/7)

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

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

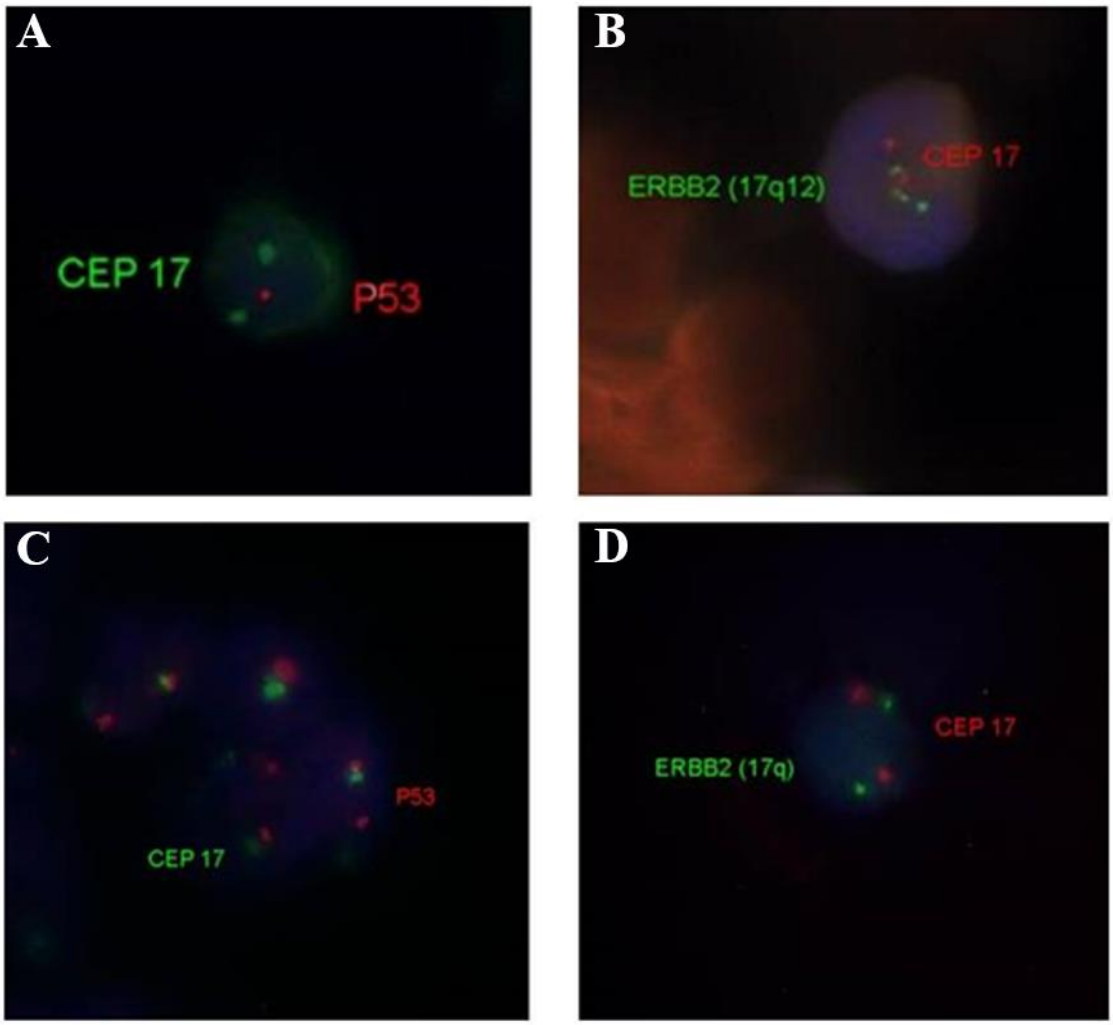
detected the *KIT* (p.D816V) mutation, which is observed in over 90% of systemic mastocytosis cases and at lower frequencies in patients with core binding factor AML conferring a poor prognosis.[18] Activating mutations of *KIT* in AML are considered as a class I aberrations which provide a proliferative 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(17)q formation. Nevertheless, the similarity in the clinical presentation of cases with isolated i(17)q 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 literature[9] 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.

References:

1. Mertens F, Johansson B, Mitelman F. Isochromosomes in neoplasia. Genes Chromosomes Cancer. 1994;10(4):221-30. https://doi.org/10.1002/gcc.2870100402 PMid:7522535
2. Fioretos T, Strombeck B, Sandberg T, Johansson B, Billstrom R, Borg A, et al. Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. Blood. 1999;94(1):225-32. PMid:10381517
3. Kanagal-Shamanna R, Luthra R, Yin CC, Patel KP, Takahashi K, Lu X, et al. Myeloid neoplasms with isolated isochromosome 17q demonstrate a high frequency of mutations in SETBP1, SRSF2, ASXL1 and NRAS. Oncotarget. 2016;7(12):14251-8. https://doi.org/10.18632/oncotarget.7350 PMid:26883102 PMCid:PMC4924712
4. Mitelman F, Brandt L, Nilsson PG. Relation among occupational exposure to potential mutagenic/carcinogenic agents, clinical findings, and bone marrow chromosomes in acute nonlymphocytic leukemia. Blood. 1978;52(6):1229-37. PMid:719175
5. Kanagal-Shamanna R, Bueso-Ramos CE, Barkoh B, Lu G, Wang S, Garcia-Manero G, et al. Myeloid neoplasms with isolated

isochromosome 17q represent a clinicopathologic entity associated with myelodysplastic/myeloproliferative features, a high risk of leukemic transformation, and wild-type TP53. Cancer. 2012;118(11):2879-88. https://doi.org/10.1002/cncr.26537 PMid:22038701
6. Visconte V, Tabarroki A, Zhang L, Hasrouni E, Gerace C, Frum R, et al. Clinicopathologic and molecular characterization of myeloid neoplasms harboring isochromosome 17(q10). American journal of hematology. 2014;89(8):862. https://doi.org/10.1002/ajh.23755 PMid:24796269
7. McClure RF, Dewald GW, Hoyer JD, Hanson CA. Isolated isochromosome 17q: a distinct type of mixed myeloproliferative disorder/myelodysplastic syndrome with an aggressive clinical course. British journal of haematology. 1999;106(2):445-54. https://doi.org/10.1046/j.1365-2141.1999.01537.x PMid:10460605
8. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-51. https://doi.org/10.1182/blood-2009-03-209262 PMid:19357394
9. Lazarevic V, Djordjevic V, Magic Z, Marisavljevic D, Colovic M. Refractory anemia with ring sideroblasts associated with i(17q) and mutation of the TP53 gene. Cancer Genet Cytogenet. 2002;136(1):86-9. https://doi.org/10.1016/S0165-4608(02)00510-1
10. Becher R, Carbonell F, Bartram CR. Isochromosome 17q in Ph1-negative leukemia: a clinical, cytogenetic, and molecular study. Blood. 1990;75(8):1679-83. PMid:2328318
11. Adema V, Larrayoz MJ, Calasanz MJ, Palomo L, Patino-Garcia A, Agirre X, et al. Correlation of myelodysplastic syndromes with i(17)(q10) and TP53 and SETBP1 mutations. British journal of haematology. 2015;171(1):137-41. https://doi.org/10.1111/bjh.13355 PMid:25716545
12. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65. https://doi.org/10.1182/blood-2012-03-420489 PMid:22740453 PMCid:PMC4425443
13. Lai JL, Preudhomme C, Zandecki M, Flactif M, Vanrumbeke M, Lepelley P, et al. Myelodysplastic syndromes and acute myeloid leukemia with 17p deletion. An entity characterized by specific dysgranulopoiesis and a high incidence of P53 mutations. Leukemia. 1995;9(3):370-81. PMid:7885035
14. Damm F, Itzykson R, Kosmider O, Droin N, Renneville A, Chesnais V, et al. SETBP1 mutations in 658 patients with myelodysplastic syndromes, chronic myelomonocytic leukemia and secondary acute myeloid leukemias. Leukemia. 2013;27(6):1401-3. https://doi.org/10.1038/leu.2013.35 PMid:23443343
15. Meggendorfer M, Haferlach C, Zenger M, Macijewski K, Kern W, Haferlach T. The landscape of myeloid neoplasms with isochromosome 17q discloses a specific mutation profile and is characterized by an accumulation of prognostically adverse molecular markers. Leukemia. 2016;30(7):1624-7. https://doi.org/10.1038/leu.2016.21 PMid:26859077
16. Makishima H, Visconte V, Sakaguchi H, Jankowska AM, Abu Kar S, Jerez A, et al. Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. Blood. 2012;119(14):3203-10. https://doi.org/10.1182/blood-2011-12-399774 PMid:22323480 PMCid:PMC3321850
17. Przychodzen B, Jerez A, Guinta K, Sekeres MA, Padgett R, Maciejewski JP, et al. Patterns of missplicing due to somatic U2AF1 mutations in myeloid neoplasms. Blood. 2013;122(6):999-1006. https://doi.org/10.1182/blood-2013-01-480970 PMid:23775717 PMCid:PMC3739042
18. Schnittger S, Kohl TM, Haferlach T, Kern W, Hiddemann W, Spiekermann K, et al. KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. Blood. 2006;107(5):1791-9. https://doi.org/10.1182/blood-2005-04-1466 PMid:16254134
19. Schlenk RF, Dohner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. The New England journal of medicine. 2008;358(18):1909-18. https://doi.org/10.1056/NEJMoa074306 PMid:18450602
20. Bacher U, Haferlach T, Kern W, Haferlach C, Schnittger S. A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia. Haematologica. 2007;92(6):744-52. https://doi.org/10.3324/haematol.10869 PMid:17550846



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 intrephase 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.