CASE REPORT
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Isochromosome der(17)(q10)t(15;17) in acute promyelocytic leukemia resulting in an additional copy of the RARA-PML and loss of one p53 gene: report of two cases and literature review

Izohromozom der(17)(q10)t(15;17) u akutnoj promijelocitnoj leukemiji rezultira dodatnom kopijom RARA-PML i gubitkom p53 gena: prikaz dva slučaja i pregled literature

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Abstract

Introduction. The isochromosome of the long arm of derivative chromosome 17, that originates from the translocation t(15;17) [ider(17)(q10)t(15;17), or ider(17q)] in acute promyelocytic leukemia (APL), is a rare chromosome aberration associated with a poor prognosis. **Case report.** We report the clinical and laboratory data associated with ider(17q) for two APL patients. Cytogenetic analysis of bone marrow cells in both cases showed a mosaic karyotype with the ider(17q); reverse transcription polymerase chain reaction (RT-PCR) was positive for the long (L) isoform of the retionic acid receptor alpha (PML-RARA) fusion transcript in each patient. Fluorescence *in situ* hybridization (FISH) analysis with the DNA probes for the PML gene on 15q24.1, and the RARA gene on 17q21.2, confirmed the extra copy of the RARA-PML fusion gene or ider(17q). Additionally, the FISH analysis with a DNA probe for the p53 gene on 17p13.1 confirmed loss of one copy of the universal tumor suppressor p53 in both patients. **Conclusion.** Both reported APL patients with ider(17q) had predominance of the clone with ider(17q) compared to those with t(15;17) and/or the normal karyotype, indicating that duplication of der(17) may provide a growth advantage allowing the relevant clone to become dominant. Moreover, as an important oncogenic event and poor prognostic factor in leukemia, loss of one gene copy of the tumor suppressor p53, may also contribute to this growth advantage. Although the clinical and prognostic significance for the patients with an ider(17q) remains unclear, cytogenetic and molecular-genetic analysis should be combined to reveal more details about this complex and rare chromosomal abnormality.

Key words:
leukemia, myeloid; chromosome abberations; transcription factors; in situ hybridization, fluorescence; translocation, genetic; genes, p53; mortality; retinoic acid receptor alpha.

Apstrakt

Uvod. Izohromozom dugog kraka derivata hromozoma 17, koji potiče od translokacije t(15;17) [ider(17)(q10)t(15;17) ili ider(17q)] u akutnoj promijelocitnoj leukemiji (APL), je retka hromozomska aberacija, povezana sa lošom prognozom. **Prikaz bolesnika.** Prikazali smo dva bolesnika čiji su klinički i laboratorijski podaci ukazivali na dijagnozu APL. Citogenetička analiza ćelija kostne srži oba bolesnika, pokazala je mozaičan kariotip sa ider(17q); reverzna transkripcija lančane reakcije polimeraze (RT-PCR) bila je pozitivna za dugu (L) izoformu fuzionog PML-RARA (retinoinska kiselina receptor alfa) transkripta. Analiza, fluorescentna *in situ* hibridizacija (FISH) sa DNA probama za PML gen na 15q24.1 i RARA gen na 17q21.2, potvrdila je prisustvo dodatne kopije RARA-PML fuzionog gena ili ider(17q). Pored toga, FISH analiza sa DNA probom za p53 gen na 17p13.1 potvrdila je gubitak jedne kopije univerzalnog tumor supresor gena p53 kod oba bolesnika. **Zaključak.** Kod oba bolesnika registrovana je dominacija patološkog klona sa ider(17q) u odnosu na klon sa klasičnom translokacijom t(15;17) i/ili klon sa normalnim kariotipom, što ukazuje na mogućnost da duplicirani der(17q) obezbeđuje proliferativnu prednost patološkom ćelijskom klonu. Nastankom ove aberacije dolazi i do gubitaka jedne kopije univerzalnog tumor supresor gena p53. To je dodatni, onkogeni događaj u neoplastičnom pro-

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cesu i loš prognostički parameter za bolesnike sa APL, jer se time povećava efekat proliferativne prednosti leukemijskih ćelija. Iako klinički i prognostički značaj aberacije ider(17q) i dalje ostaje nejasan, kroz primer dva naša bolesnika možemo zaključiti da se isključivo kombinovanjem citogenetičkih i molekularno-genetičkih analiza mogu donekle obezbediti uslovi za razotkrivanje detalja o ovoj kompleksnoj i retkoj hromozomskoj abnormalnosti.

Ključne reči:
leukemija, mijelocitna, akutna; hromosomi, aberacije; faktori transkripcije; hibridizacija in situ, fluorescentna; translokacija (genetika); geni p53; mortalitet; retinoična kiselina, receptor alfa.

Introduction

Acute promyelocytic leukemia (APL) is a well-defined clinical and biological entity in acute myeloid leukemias, characterized by unique morphology of leukemic cells and specific t(15;17), present in approximately 80% of APL cases [1, 2]. The t(15;17)(q22;q21) fuses the PML (promyelocytic leukemia) gene on chromosome 15 encoding a transcription factor with the RARA (retinoic acid receptor alpha) gene located on chromosome 17, a member of a steroid hormone nuclear receptor family that is important for regulation of both normal and malignant cellular differentiation and proliferation [3]. The ider(17)(q10)t(15;17)(q22;q21) is an infrequent variant of cytogenetic abnormality among the APL patients, which has been rarely reported. It is considered that ider(17q) is an additional chromosome aberration to t(15;17) and the second step in leukemogenesis in APL. Additional chromosome aberrations to t(15;17) have been observed in 23%–43% of APL cases, but their prognostic significance is still controversial [4–9]. The majority of evidence supports the concept that the patients with additional chromosome abnormalities have the same favorable prognosis as the patients with t(15;17) alone [5, 8]. However, some reports described a worse outcome both in newly diagnosed and relapsed patients [6, 7]. The most frequent secondary aberration to t(15;17) is trisomy 8 (+8). Other additional chromosome changes include del(9q), del(7q), abnormalities of chromosome 1, 3 and 6, trisomy 21, as well as an isochromosome of the long arm of the derivative chromosome 17 originating from the translocation t(15;17) [ider(17)(q10)t(15;17) or ider(17q)] [9]. However, the clinical significance of ider(17q) has not been elucidated yet. The clinical features and prognosis of patients with this chromosomal abnormality are currently unclear [4, 10]. To our knowledge, 74 APL cases associated with ider(17q) have been described to date [2–5, 10–22].

Here, we describe two cases of adult APL with ider(17)(q10), identified by conventional cytogenetics, fluorescence *in situ* hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR). We discuss the clinical course and follow-up data of these patients. Also, we present a combination of cytogenetic and molecular-genetic analyses which indicate that ider(17q) may be critical in providing a proliferative advantage and driving clonal evolution to overt hematologic neoplasia.

Case report

Cytogenetic analysis and fluorescence in situ hybridization

The bone marrow cells were subjected to a cytogenetic analysis by a direct preparation after 24 hours culture (RPMI 1640 medium supplemented with 25% fetal calf serum, at 37ºC). Chromosomes were stained by the modified Giemsa HG-banding technique, as previously described [23]. The karyotypes were reported in accordance with the Guidelines of the International System for Human Cytogenetic Nomenclature (ISCN) [24].

Interphase and metaphase fluorescence *in situ* hybridization (FISH) studies were performed on the bone marrow cytogenetic specimens previously used for the karyotype analysis. The PML-RARA and RARA-PML fusion genes were detected using the DF SureFISH® 15q24.1 probe to label PML together with the DF SureFISH® 17q21.2 probe to label RARA (Agilent Technologies®, Cedar Creek, TX, USA). The p53 gene was detected using the LSI TP53® (17p13.1) probe (Vysis®, Downers Grove, Ill., USA). The DNA probes were applied according to standard procedures recommended by the manufacturer. The slides were examined on an Olympus® BX51 fluorescence microscope. The Dual-color FISH images were digitally generated using the CytoVision® 4.02 imaging software (Leica Biosystems®).

Molecular genetics

The RT-PCR assay was employed to detect the PML-RARA fusion gene. Total RNA was extracted from the bone marrow cells and then reverse transcribed to cDNA with oligo(dT) primers. For determination of the PML/RAR-α transcript we applied a standardized RT-PCR method [25]. This enabled us to detect the most common PML/RAR-α transcripts due to the right combination of primers (Table 1), both in the first and second (nested) PCR cycles. The PCR products were separated by electrophoresis on 2% agarose gel and visualized with ethidium bromide.

Case 1

A 64-year-old female patient was referred with bleeding gums and bruises on her lower extremities. The hematological work-up revealed anemia (hemoglobin 85 g/L), a very low platelet count (10×10^9/L) and leucopenia (2.2×10^9/L), with 10% blasts and 36% promyelocytes. The coagulation tests showed: normal fibrinogen level (3.2 g/L), decreased prothrombin time (PT 58%), normal activated partial thromboplastin time (PTT 26 s) and elevated D-dimer (31 mg/L). The calculated International Society of Thrombosis and Hemostasis disseminated intravscular coagulopathy (ISTH DIC) score was 6. A bone marrow biopsy revealed a hypercellular marrow with abundant promyelocytes (80%).

Table 1

Primers for RT-PCR analysis of the PML-RARA fusion gene

RT-PCR	Primer code	Sequence (5'-3')
First round of PCR	PML-A1 (forward)	CAGTGTACGCCTTCTCCATCA
	PML-A2 (forward)	CTGCTGGAGGCTGTGGAC
	RARA-B (reverse)	GCTTGTAGATGCGGGGTAGA
Second round of PCR	PML-C1 (forward)	TCAAGATGGAGTCTGAGGAGG
	PML-C2 (forward)	AGCGCGACTACGAGGAGAT
	RARA-D (reverse)	CTGCTGCTCTGGGTCTCAAT

RT-PCR – reverse transcription-polymerase chain reaction; PML – promyelocytic leukemia; RARA – retinoid acid receptor alpha.

Immunophenotyping of leukemia cells from the bone marrow also confirmed predomination of promyelocytes with a typical immunophenotype: CD117^{+low} CD13$^{+hetero}$ CD33^{+high} cMPO^{+high} CD15$^{+hetero}$ CD34^{neg} HLA-DR^{neg} CD11a^{neg} CD11b^{neg} CD56^{neg} CD2^{neg}. The patient was treated according to the PETHEMA 2005 regimen (all-trans retinoic acid – ATRA and idarubicine). During the induction therapy, she experienced forehead necrosis in a previous hematoma. After necrectomy with reconstruction, the patient successfully completed the induction and with intensified treatment according to the same PETHEMA protocol achieved complete remission. She also completed the maintenance schedule and is still in complete remission with a good health status.

Case 2

A 58-year-old man was admitted to the Clinic of Hematology, Clinical Centre of Serbia, Belgrade, with breathlessness, weight loss, night sweats and fever. Physical findings revealed numerous bruises and hematuria. His blood counts revealed severe pancytopenia with hemoglobin at 106 g/L, a white blood cell count of 1.7 × 10^9/L, with 24% undifferentiated blasts and a low platelet count of 17 × 10^9/L. The hemostasis testing also showed prolonged PT (61%), but normal PTT. D-dimer was highly elevated, but a fibrinogen concentration was preserved (6.9 g/L). The ISTH DIC score was also elevated to > 6. The bone marrow examination revealed 84% of blasts with bilobar nuclei and multiple Auer rods ("faggots"). Immunophenotyping confirmed the presence of a pathological population of promyelocytes with a typical immunophenotype: CD117^{+low} CD13^{+low} CD33^{+low} cMPO^{+high} CD15^{neg} CD34^{neg} HLA-DR^{neg} CD11a^{neg} CD11b^{neg} CD56^{neg} CD2^{neg}, corresponding to APL. The patient was also treated according to the PETHEMA 2005 regimen, but unfortunately a lethal outcome occurred within several days due to the acute respiratory distress syndrome together with a deterioration of DIC and bleeding in spite of supportive measures.

Cytogenetics

Cytogenetic analysis in both patients revealed the chromosome 17 aberration, ider(17)(q10). The translocation t(15;17), as the primary aberration, was detected in one case. The cytogenetic results are presented in Table 2 and the karyotypes of the cell clones with ider(17q) are shown in Figures 1 and 2.

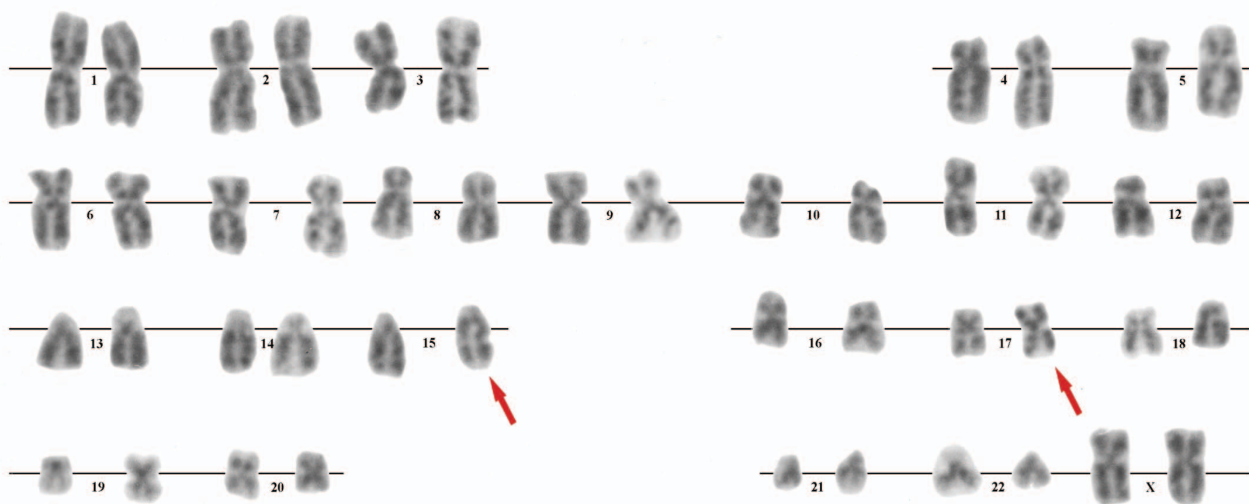

Fig. 1 – Giemsa HG–banded bone marrow karyotype of the Case 1 showing 46,XX,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)(q22;q21). The arrows indicate abnormal chromosomes.

Table 2

Results of cytogenetic, FISH and RT-PCR analyses of bone marrow cells of the patients with ider(17q)

Case No.	Sex/ age	Karyotype	FISH*				RT-PCR
			Probes	Clone (%)	Probe	Clone (%)	PML-RARA
	F/M		DF SureFISH 17q21.2 and 15q24.1		LSI TP53 17p13.1		isoforms (S, V, L)[†]
1	F/64	46,XX,der(15)t(15;17)(q22;q21), ider(17)(q10)t(15;17)(q22;q21)[5]/ 46,XX[15]	nucish(PML,RARA)x4 (RARAconPMLx3)[86/200], (PML,RARA)x3 (RARAconPMLx2)[64/200], (PML,RARA)x2[20/200]	43/32/25	nucish(p53x1)[81/200], (p53x2)[119/200]	41/59	L
2	M/58	46,XY,der(15)t(15;17)(q22;q21), ider(17)(q10)t(15;17)(q22;q21)[10]/ 46,XY,t(15;17)(q22;21)[8]/46,XY[2]	nucish(PML,RARA)x4 (RARAconPMLx3)[69/200] (PML,RARA)x3 RARAconPMLx2)[101/200], (PML,RARA)x2[33/200]	35/51/17	nucish(p53x1)[81/200], (p53x2)[119/200]	38/62	L

***FISH signals counting of 200 interphase nuclei. The cut-off value for positivity was the presence of more than 10% of nuclei for fusion signals of PML-RARA and for *p53* monosomy.**
[†]S, V, L -short, variant, long isoforms of *PML-RARA*
FISH – Fluorescence *in situ* hybridization; PML-RARA – promyelocytic leukemia-retinoic acid receptor alpha.

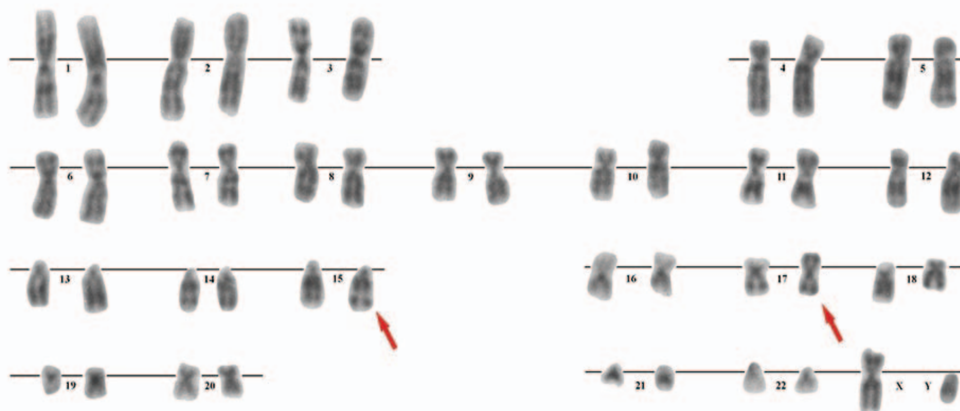

Fig. 2 – Giemsa HG–banded bone marrow karyotype of the Case 2 showing 46,XX,der(15)t(15;17)(q22;q21),ider(17)(q10)t(15;17)(q22;q21). The arrows indicate abnormal chromosomes.

The banding studies suggested that the aberrant chromosome resulted from duplication of the long arm of chromosome 17 or duplication of der(17)(10)t(15;17). The newly created chromosome looked like a classical i(17)(q10). Therefore, it was necessary to apply the metaphase and interphase FISH and RT-PCR analysis to determine whether the *PML-RARA* gene fusion is present on the i(17q).

Fluorescence in situ hybridization

Using the DNA probes for the PML and RARA genes, we detected the typical fusion pattern as well as the variant fusion pattern in the metaphase and interphase cells. The variant fusion pattern with one fusion gene for PML-RARA and two for RARA-PML corresponded to the clone with ider(17q), while the typical fusion pattern with one fusion for PML-RARA and one fusion for RARA-PML corresponded to the clone with t(15;17). Using a DNA probe for the p53 gene on 17p13.1 we registered loss of one copy of this normal tumor suppressor in both patients. Furthermore, in metaphases with ider(17q), the p53 probe showed a single signal derived from the normal chromosome 17, confirming a loss of the short arm of chromosome 17 as a consequence of duplication of der(17q). The FISH results for both patients are presented in Table 2 and Figures 3 and 4.

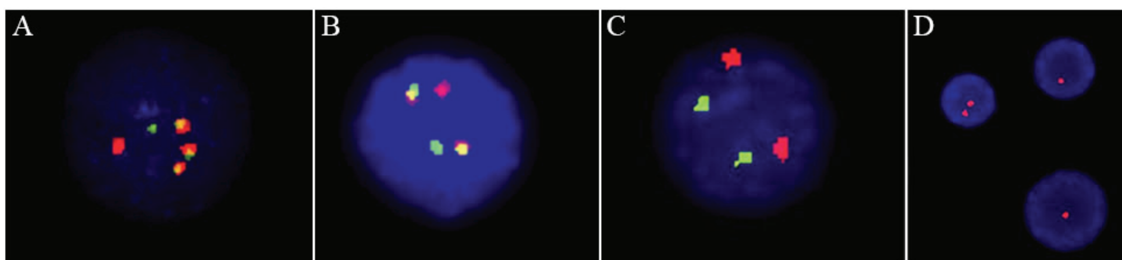

Fig. 3 – Fluorescence *in situ* hybridization (FISH) analysis at initial diagnosis of the Case 1.

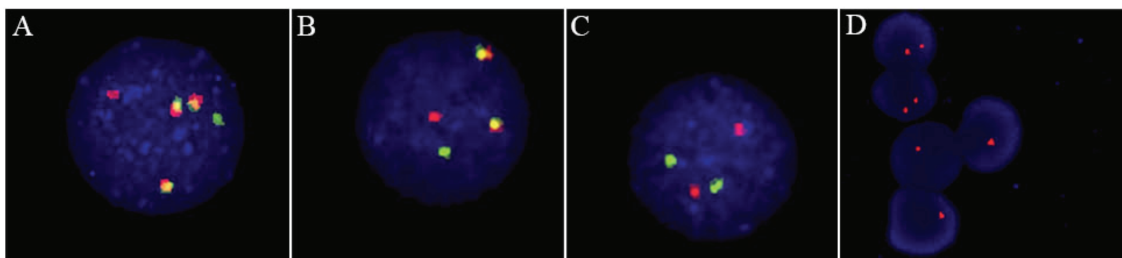

Fig. 4 – Fluorescence *in situ* hybridization (FISH) analysis at initial diagnosis of the Case 2.

Fig. 3 and Fig. 4 – FISH study using a Promyelocytic leukemia–retinoic acid receptor alpha (PML-RARA) DF SureFISH probes (Agilent Technologies, Ceder Creek, TX, USA) and a p53 LSI TP53 probe (Vysis, Downers Grove, Ill., USA) at the initial diagnosis of both cases. (A) The interphase cell showing one PML-RARA and two RARA-PML fusion signals, one orange (PML) signal, and one green (RARA), consistent with the karyotype of ider(17q). (B) The interphase cell showing one PML-RARA, and one RARA-PML fusion signal, one orange (PML) signal, and one green (RARA) signal, consistent with the karyotype of the t(15;17). (C) The interphase cell sowing two orange (PML), and two green (RARA) signals, consistent with the normal karyotype. (D) The interphase cells showing one orange p53 signal, consistent with the karyotype of ider(17q), and two orange p53 signales, consistent with the t(15;17) or the normal karyotype.

The FISH signals from the PML and RARA probes in case 1 indicated that 43% of the cells had the ider(17q), 32% of them were with the t(15;17), and 25% of the examined cells were normal for *PML* and *RARA* (Figure 3 A, B, C).

The FISH signals from the p53 gene indicated that 41% of the cells had lost one gene copy of p53, while 59% of them were normal (Figure 3D).

The FISH signals from the PML and RARA probes in case 2 indicated that 35% of the cells were with the ider(17q), 51% of them had the t(15;17), while 17% of them were normal for PML and RARA (Figure 4 A, B, C).

The FISH signals from the p53 gene indicated that 38% of the cells showed a loss of one gene copy of p53, while 62% were normal (Figure 4D).

Molecular genetics

The reverse transcription polymerase chain reaction analysis for the *PML-RARA* rearrangement in both patients gave positive results for bcr-1 (long-L isoform) (Table 2) and the diagnosis of APL was confirmed.

Discussion

An isochromosome of the long arm of the derivative chromosome 17 is rarely observed in the APL patients [2–5, 10–22]. Thus, ider(17q) is almost always detected in an evolutionarily more advanced cell clone, as an additional chromosomal aberration [4]. Both of our cases had the typical features of APL at a diagnosis. Molecular cytogenetic analysis demonstrated an extra copy of RARA-PML as a consquence of der(17)(q10)t(15;17), indicating that two events had occurred involving the same chromosomes (15 and 17). The first results in the typical t(15;17)(q22;q21) structure with one PML signal on the normal chromosome 15, one RARA signal on the normal chromosome 17 and two fusion signals [one for PML-RARA on der(15) and one for RARA-PML on der(17)]. The second event, considered as karyotype evolution, involves duplication of the long arm of the der(17), with consequent formation of ider(17q) involving an additional copy of RARA-PML and loss of the whole short (p) arm of chromosome 17.

In one of our cases, a clone with ider(17q), but without t(15;17) was detected by the conventional cytogenetic analysis. However, the FISH analysis on interphase nuclei revealed the presence of both clones. The other patient exhibited coexistence of two pathologic clones, which were confirmed by both of cytogenetic and FISH analyses. We noticed that the clone with t(15;17) was predominant in interphase cells, while the other one with ider(17q) was more frequent in metaphases, indicating higher proliferative capacity.

The FISH analysis in both patients revealed a loss of one gene copy of the universal tumor suppressor, p53, which certainly could not be detected by the classical cytogenetic analysis. The FISH results for RARA-PML [ider(17q)] directly confirmed that ider(17q) is fully responsible for the loss of this tumor suppressor.

Our findings indicate that ider(17)(q10) might provide a proliferative and growth advantage for the leukemic clone to become dominant during the disease progression, which is in accordance with the previously published cases [2–4, 10, 11]. Unfortunately, due to the limited number of patients with ider(17q) studied by the FISH analysis, the prognostic significance of the clone size (described as the relative number of cells with ider(17)(q10)) in APL is still unclear.

The chromosomal breakpoints regions were variously mapped to regions 15q22-24 and 17q11-21 in classical translocation t(15;17) [25]. Three PML-RARA isoforms known as L-, V- and S-type transcripts are generated by breakpoints located within the bcr-1, bcr-2 and bcr-3 regions respectively, pointing to the variability in the chromosome 15 breakpoints. The most frequent isoforms are L and S (55% and 40%), while the V isoform is rare in APL (5%) [25]. Thus, ider(17)(q10) is observed in all subtypes of the PML-RARA fusion gene, but with an increased frequency of the L isoform [4]. At diagnosis, no correlations were found with respect to sex, platelet count, presence of coagulopathy or retinoic syndrome, when comparing patients with L and S-isoform PML-RARA transcripts [25].

However, Manola et al. [4] reported four adult APL cases with ider(17)(q10) and gave an extensive review of 49 previously reported APL cases with this unique chromosomal abnormality. They concluded that ider(17)(q10) was more frequent in the male than in female patients (2.12:1) with predominance of the L isoform PML-RARA fusion transcript, as well as a low initial white blood cell count. They also reported that the most frequent accompanying secondary chromosomal abnormality is trisomy 8.

Among our patients with APL, this rare finding has been seen in only two cases during the last 20 years, so we cannot speculate further about its frequency and distribution among the sexes. Leukopenia was evident in each case. Moreover, both patients had the L-isoform of the PML-RARA gene rearrangement, without additional aberrations.

In the neoplastic process generating APL, the ider(17q) bearing RARA-PML fusion represents a unique rearrangement that is a specific molecular marker for this entity.

The newest fusion RARA partner is the STAT5b gene, identified initially in a patient carrying the AML-M1 FAB entity, with a proportion of blasts exhibiting microgranular APL morphology [26]. Like the RARA gene, the STAT5b gene is localized on chromosome 17q21.1-21.2 and the two genes are estimated to be about 3Mb apart [27].

In the APL patients, the prognostic significance of ider(17q) and two copies of RARA-PML as a consequence is currently unknown. This is mainly due to the low incidence of ider(17q), as well as the sporadic limited data regarding the clinical course and outcome for the previously reported patients with ider(17q) [2–5, 10–22].

It has been known, up to now, that the PML-RARA gene, expressed in 97%-100% of all APL cases with t(15;17) at diagnosis, is involved in primary APL pathogenesis and confers sensitivity to ATRA [4, 28, 29]. However, the knowledge about the role of RARA-PML in the pathogenesis of APL is very obscure [30]. This fusion gene is expressed in 70%-80% of t(15;17) positive APL cases [4]. Expression of RARA-PML alone is sufficient for the cytological APL phenotype, but

does not confer sensitivity to ATRA [29, 30]. Furthermore, some experimental findings suggested that RARA-PML may potentiate the leukemogenesis of PML-RARA via mechanisms that are not yet understood, and therefore the exact role of RARA-PML has not been elucidated yet.

Conclusion

In this report two patients with APL with the chromosomal abnormality ider(17)(q10) and spliced long-type PML-RARA fusion isoforms were described. The cytogenetic and FISH analysis identified karyotypes with this rare chromosomal abnormality, while RT-PCR provided additional important information about the alteration in the PML-RARA fusion gene. Prospective studies combined with cytogenetic and molecular-genetic techniques in the patients with an ider(17)(q10) may enable better understanding of the clinical, cytogenetic and molecular features, as well as the prognostic significance of APL with this chromosomal abnormality.

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