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Acute Promyelocytic Leukemia with i(17)(q10).

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Case Report

Title:

A Case of Acute Promyelocytic Leukemia with i(17)(q10)

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Abstract

We herein report a rare chromosomal abnormality observed in an acute promyelocytic leukemia (APL) patient. She had several APL derivative clones including a clone with i(17)(q10) abnormality, which consists of two kinds of structural abnormalities, a cryptic translocation of t(15;17) and an isochromosome of 17q. Although an obvious microscopic t(15;17) change was not observed on either arms of the isochromosome, *PML/RARα* fusion signals were detected on an interphase fluorescence *in situ* hybridization analysis. By several cytogenetic analyses of her bone marrow cells, it was confirmed that the i(17)(q10) clone was derived from the classic t(15;17) clone via another intervening clone, cryptic t(15;17).

Key words: Acute Promyelocytic Leukemia, Cryptic Translocation, I(17)(q10)

Introduction

Acute promyelocytic leukemia (APL) is one of the most widely known hematological neoplasms and is associated with a typical chromosomal abnormality, the reciprocal translocation of t(15;17)(q22;q21). According to Cervera et al., additional chromosomal abnormalities are also seen in 28% of classic t(15;17)-positive APL patients (1). Although trisomy 8 or partial monosomy, i.e., 7q deletion, were representative in that study, an isochromosome change of 17q after the reciprocal translocation of t(15;17) was also occasionally observed, which was described as ider(17)(q10)t(15;17) (2). This chromosome does not have a short arm (17p), but rather has two of the same arms derived from long arms (17q after the reciprocal translocation) on both sides of the centromere.

In addition, APL cases without classic t(15;17) abnormalities have also been occasionally observed. According to Grimwade et al., the incidence of this finding in patients with APL is 9%, and the most common abnormality is cryptic t(15;17) (3). Because this abnormality involves the translocations of only submicroscopic fragments of chromosomes, the fusion gene *PML/RARα* exists on chromosome 15 or 17, without the detection of microscopic abnormalities on a routine chromosomal analysis.

On the other hand, there are only few case reports of APL with i(17)(q10) consisting of both the cryptic t(15;17) and isochromosome of 17q. This condition does not have evidence of microscopic t(15;17) changes, although it does involve *PML/RARα* fusion

genes (4-6).

We herein report a case of APL with i(17)(q10). Frequent cytogenetic analyses performed at the time of diagnosis and during treatment revealed that the patient had several APL clones, including the i(17)(q10) clone as well as the classic t(15;17) clone. These findings helped us to speculate the developmental mechanism of i(17)(q10) in APL patients.

Case Report

A 74-year-old woman was incidentally noted to have pancytopenia on a regular blood examination during a follow-up of reflux esophagitis and was introduced to our hospital. A blood examination showed pancytopenia and abnormalities in fibrinolysis: WBC 1,200/μL (neutrophils 64%, lymphocytes 29%, monocytes 5%, eosinophils 2%, no abnormal cells were detected), Hb 10.0 g/dL, Plt $67x10^3$/μL and fibrin degradation products (FDP) 25.6 μg/mL (reference value: 0.0-5.0 μg/mL). However, neither the prothrombin time nor activated partial thromboplastin time was prolonged. Bone marrow aspiration revealed hypocellular marrow (nuclear cell count: 5,000/μL), and 63.6% of the cells were abnormal cells with rich azurophilic granules or Auer bodies. The *PML/RARα* fusion gene was detected in the bone marrow cells on a reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, and she was diagnosed with APL.

Induction therapy with tretinoin was started. Bone marrow examinations were performed to assess the effect of tretinoin on days 14, 28 and 42, including a G-banding chromosomal analysis, interphase fluorescence *in situ* hybridization (FISH) analysis and quantitative RT-PCR analysis. Interphase FISH analyses were performed using *PML/RARα* dual-color dual-fusion probes. A yellow signal indicates a fusion signal of red and green signals, and a red or green signal indicates the *PML* or *RARα* gene, respectively. The results are shown in Table 1. At diagnosis, the chromosomal analysis

showed only one type of abnormality, 46,XX,i(17)(q10), in four of 10 analyzed cells (Fig.1). An interphase FISH analysis was not performed at that time. The quantitative RT-PCR analysis detected the *PML/RARα* fusion gene at $4.2x10^4$ copies/μg RNA. On day 14, the detected abnormal karyotype was 46,XX,t(15;17) in one of 20 analyzed cells, although the clone with 46,XX,i(17)(q10) was not detected according to the chromosomal analysis. According to the interphase FISH analysis, the rate of *PML/RARα* fusion-positive cells was 86%; two patterns were observed: yellow:red:green = 2:1:1 (67%) and 3:1:1 (19%). The amount of fusion gene decreased to $1.1x10^4$ copies/μg RNA according to a quantitative RT-PCR analysis. On day 28, the detected abnormal karyotype was 46,XX,t(15;17),add(17)(p13) in one of 20 analyzed cells on a chromosomal analysis. According to an interphase FISH analysis, the positive rate decreased to 47%; three patterns were observed: yellow:red:green = 2:1:1 (42%), 2:1:2 (4%), 3:1:1 (1%). The amount of fusion gene also decreased to $7.8x10^3$ copies/μg RNA using a quantitative RT-PCR analysis. On day 42, all of the abnormalities had disappeared on both the chromosomal and interphase FISH analyses, and the amount of fusion gene was decreased to $5.2x10^2$ copies/μg RNA using a quantitative RT-PCR analysis. Three courses of consolidation chemotherapy were performed after 63 days of tretinoin treatment. Complete molecular remission was achieved after the first course of consolidation therapy. After consolidation therapy, maintenance therapy using tretinoin was performed, and the patient has maintained in remission for 54 months.

Throughout the study period, the patient showed three types of abnormal karyotypes according to the chromosomal analyses, 46,XX,i(17)(q10), 46,XX,t(15;17) and 46,XX,t(15;17),add(17)(p13), and three types of *PML/RARα* fusion-positive signal patterns on the interphase FISH analyses, yellow:red:green = 2:1:1, 2:1:2 and 3:1:1. A clone with i(17)(q10) was also detected at diagnosis, although it disappeared, despite the appearance of the classic t(15;17) clone on day 14.

Discussion

It has been reported that acquired or constitutional isochromosomes originate from aberrant mitosis or meiosis (7,8). Not longitudinal, but rather the transverse, division of the chromosome can yield a symmetrical chromosome with two identical arms in a daughter cell, which is referred to as an isochromosome. It has also been shown that the isochromosome of 17q, also described as i(17)(q10), is occasionally observed as an additional abnormality among various neoplasias, including hematological malignancies and solid tumors (9). Additionally, in cases of APL, the isochromosome of 17q after the translocation t(15;17), described as ider(17)(q10)t(15;17), has been occasionally reported.

However, APLs associated with the i(17)(q10) clone with no evidence of microscopic t(15;17) are quite rare. As shown in Table 2, only six cases, including ours, have been described (4-6). The prognoses of these patients appear to be generally good. In case 2, the *PML/RARA* oncogene was detected using a PCR analysis; however, an interphase FISH analysis did not detect any fusion signals, although the precise reason was not described (5). In four of six patients, metaphase FISH analyses were performed, which can be used to directly clarify the location of the oncogene at discrete chromosomes. The oncogenes were located on chromosome 15 in one case (case 3) and on both arms of i(17)(q10) in three cases (cases 1, 4 and 5).

The process by which the APL clone with i(17)(q10) appears remains unknown

because of its extreme rarity. It might also be another reason that repetitive cytogenetic analyses were not performed, such that only limited information was available in past cases. In the present case, repetitive bone marrow tests revealed that the patient possessed several kinds of APL clones, including the clone with i(17)(q10) and the classic t(15;17) clone. The changes in the ratios of such different clones enabled us to speculate the mechanism of development of i(17)(q10) at the diagnosis of APL. In particular, we hypothesize the derivation process, as outlined in Fig. 2. First, a reciprocal translocation between chromosomes 15 and 17 occurs, and the classic APL clone with t(15;17) appears. This clone is indicated as “clone A.” The interphase FISH signal pattern of clone A is yellow:red:green = 2:1:1. Because the signals of *PML* and *RARα* are fused as one on chromosome 15 and one on chromosome 17, respectively, the results show two yellow signals. Thereafter, re-translocation between chromosomes 15 and 17 occurs on clone A, and “clone B” appears. Because the second breaking point is near to, but different from, the first breaking point, only minute chromosomal fragments are left on the respective chromosomes, although it again indicates a microscopically normal karyotype. We consider that the second breaking point is located on the same side of the respective t(15;17) juncture: either both proximal sides or both distal sides. As a result, on an interphase FISH analysis, the results continue to show two yellow signals, yellow:red:green = 2:1:1, which is the same signal pattern as that for clone A. Clone B is the so-called cryptic t(15;17) clone.

Finally, an isochromosome change of the long arm of chromosome 17 happens on clone B due to aberrant mitosis, and a new APL clone with isochromosome appears. This clone is “clone C,” which shows i(17)(q10) with no microscopic evidence of t(15;17) on a chromosomal analysis. However, this clone is positive for three fused signals according to an interphase FISH analysis; one of the three is from chromosome 15 and the other two are from the symmetric arms of i(17)(q10) (yellow:red:green = 3:1:1). This signal pattern was detected in our case on days 14 and 28 (Table 1). Kim et al., who reported three i(17)(q10) cases, also hypothesized that the i(17)(q10) clone is derived from the cryptic t(15;17) clone (6), although they did not have sufficient data to prove the existence of cryptic t(15;17). However, according to our data, it was presumed that the i(17)(q10) clone is derived from the classic t(15;17) clone via another intervening clone, the cryptic t(15;17) clone.

In the present case, the APL clone with cryptic t(15;17) was speculated to be derived from the classic t(15;17) clone. However, obtaining specific identification of the cryptic t(15;17) clone is impossible using a conventional cytogenetic analysis because it cannot be distinguished from normal cells based on a G-banding chromosome analysis or from classic t(15;17) cells based on an interphase FISH analysis. Therefore, there is a possibility that the existence of the cryptic t(15;17) clone is not recognized in many APL cases with both the classic t(15;17) clone and the cryptic t(15;17) clone. Even when classic APL is diagnosed, it is possible that the patient has both the classic and

cryptic t(15;17) clones, especially in cases involving major quantitative deviations between the chromosomal analysis and interphase FISH analysis.

Interestingly, although only the i(17)(q10) clone, not the classic t(15;17) clone, was detected at diagnosis in this case, the classic t(15;17) clone, not the i(17)(q10) clone, was conversely detected on day 14. We hypothesize that the patient's i(17)(q10) clone had a growth advantage and demonstrated hyperresponsiveness to tretinoin compared to the classic t(15;17) clone. If the second breaking point of both chromosomes 15 and 17 in the clone A is on the proximal side of the t(15;17) juncture, then the oncogene *PML/RARα* will move from chromosome 15 to 17. Hence, the two *PML/RARA* genes are on the i(17)(q10) chromosome. Due to the presence of dual oncogenes, the patient's i(17)(q10) clone might have been expanded mainly at diagnosis, whereas tretinoin possibly induced the i(17)(q10) clone to differentiate more rapidly than the t(15;17) clone.

The cytogenetic analyses showed other abnormalities (Table 1). The 46,XX,t(15;17),add(17)(p13) detected on day 28 is presumably another derivative of the APL clone. The FISH signal pattern of yellow:red:green = 2:1:2 noted on day 28 might also indicate the existence of another distinct APL clone, while no explicable karyotypes were detected in our analyses. The clinical course of our case appeared to be favorable, as in past reports of APLs with i(17)(q10), although the patient has such various APL clones. Therefore, the i(17)(q10) chromosome in cases of APL does not appear to be a

poor prognostic factor, although a further accumulation of cases is necessary.

Conflicts of interest

The authors declare that they have no conflicts of interest (COI).

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Figure Legends

Fig.1 A G-banding chromosomal analysis at the diagnosis. An isochromosome of 17q was detected, although there was no evidence of microscopic t(15;17) changes on either chromosome 15 or the isochromosome. The karyotype was described as 46,XX,i(17)(q10).

Fig.2 Hypothesis of the i(17)(q10) clone derivation process. “Clone A” is the classic APL clone with t(15;17). “Clone B” is the so-called cryptic t(15;17) clone, which is derived from Clone A via re-translocation, and minute fragments are left on both chromosomes 15 and 17 reciprocally. “Clone C” is derived from Clone B via an isochromosome change on 17q. Both the normal clone and Clone B show a normal karyotype on chromosomal analyses. Both Clone A and Clone B show the same signal pattern, yellow:red:green = 2:1:1, on interphase FISH analyses. Clone C shows i(17)(q10) with no evidence of translocation on a chromosomal analysis and shows yellow:red:green = 3:1:1 signals on an interphase FISH analysis.

Table 1. Results of the bone marrow analysis.

	Chromosomal analysis	Interphase FISH analysis		Quantitative RT-PCR analysis (copies/μgRNA)
		Fused signal	Signal pattern Yellow:Red:Green	
At diagnosis	46,XX,i(17)(q10) [4] 46,XX [6]	(Not performed)		$4.2x10^4$
Tretinoin day 14	46,XX,t(15;17) [1] 46,XX [19]	86%	2:1:1 (67%) 3:1:1 (19%) 0:2:2 (14%)	$1.1x10^4$
Tretinoin day 28	46,XX,t(15;17), add(17)(p13) [1] 46,XX [19]	47%	2:1:1 (42%) 2:1:2 (4%) 3:1:1 (1%) 0:2:2 (53%)	$7.8x10^3$
Tretinoin day 42	46,XX [20]	0%	0:2:2 (100%)	$5.2x10^2$
After 1st consolidation	(Not performed)	0%	0:2:2 (100%)	Not detected

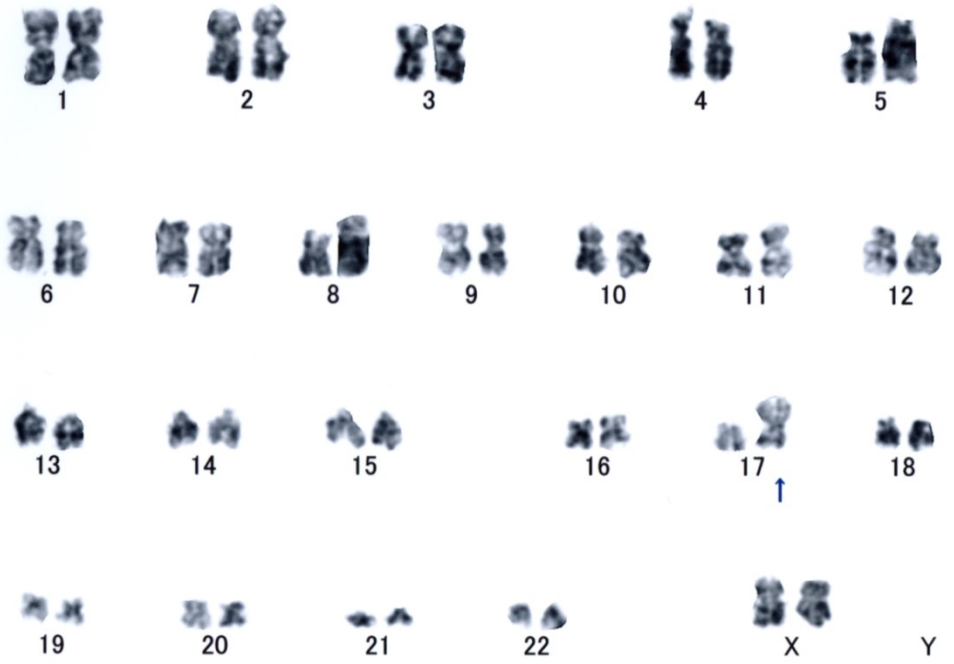
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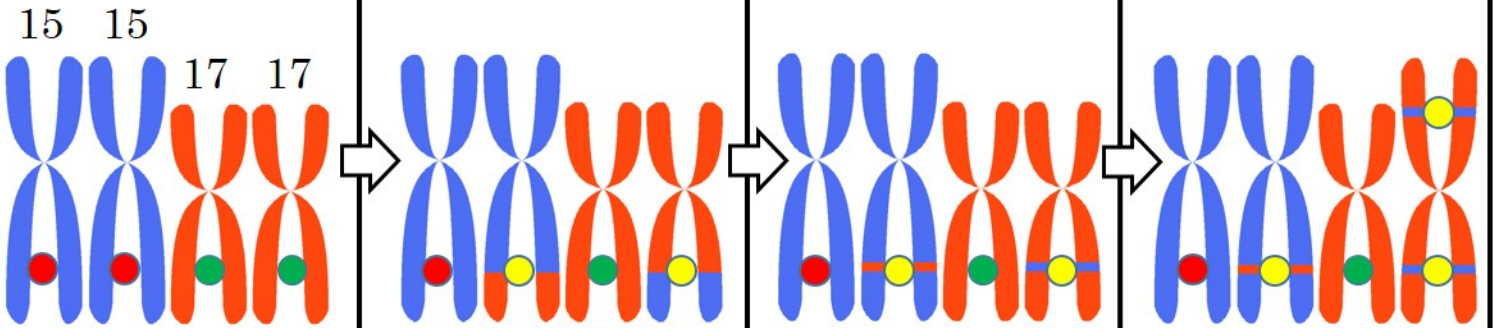
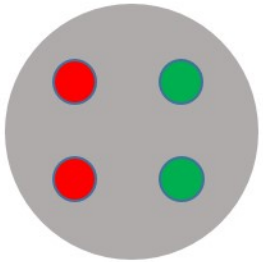
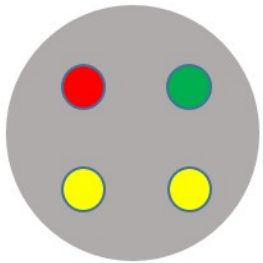
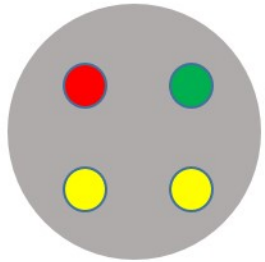
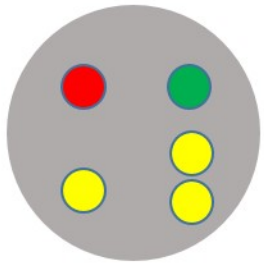
Table 2. Reported Cases of APL with i(17)(q10).

	References	Age Sex	*PML-RARA* fused gene detection	Complete remission	Relapse	Detection of classic t(15;17) clone
1	4	51F	Interphase FISH Metaphase FISH RT-PCR	Yes[a]	No	No
2	5	44F	RT-PCR	Yes	Not described	No
3	6	10F	Metaphase FISH RT-PCR	Yes	No	No
4	6	13F	Metaphase FISH RT-PCR	Yes	Yes	No
5	6	42F[b]	Metaphase FISH RT-PCR	Yes	No	No
6	Our case	74F	Interphase FISH RT-PCR	Yes	No	Yes

[a] The patient developed an acute monoblastic leukemia 10 months later with no evidence of relapse of APL.

[b] The karyotype is 46,XX,del(7)(q31q33),i(17)(q10)

	Normal Clone	"Clone A"	"Clone B"	"Clone C"
Scheme of Chromosomes				
Chromosomal Analysis	Normal Karyotype	t(15;17)	Normal Karyotype	i(17)(q10)
Interphase FISH Analysis	 Yellow:0 Red:2 Green:2	 Yellow:2 Red:1 Green:1	 Yellow:2 Red:1 Green:1	 Yellow:3 Red:1 Green:1