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Case Report

Acute promyelocytic leukemia with cryptic t(15;17) on isochromosome 17: a case report and review of literature

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Abstract: Acute Promyelocytic Leukemia (APL) is one of the most curable leukemia which shows great sensitivity to all-trans retinoic acid (ATRA) although a small number of the patients present poor prognosis and short survival. Isochromosome 17 in APL which usually bears an additional copy of RARA/PML fusion gene is considered to be a negative factor on its prognosis. Cryptic t(15;17) on i(17q) leads to an extra copy of PML/RARA rather than RARA/PML which may confer a worse prognosis. We describe here a rare APL case with complex chromosomal abnormality including isochromosome 17 bearing cryptic t(15;17) showing poor outcome. The patient lacks a classic t(15;17) and fluorescence in situ hybridization (FISH) presents 2 PML/RARA fusion signals on both long arms of the isochromosome. The patient also acquired a secondary mutation at relapse when the initial karyotype was already a complex karyotype involving chromosome 13, 17 and 22 at the same time. The poor response of this patient to traditional chemotherapy like ATRA and novel therapy like arsenic trioxide (ATO) suggests that early auto-hematological stem cell transplantation may be the choice of APL with isochromosome 17 especially with cryptic t(15;17) on i(17q). We are the first to show a clear history and evidence of FISH of these kind of cases. A small summary of cases with cryptic t(15;17) on isochromosome 17 is also made.

Keywords: Acute promyelocytic leukemia, cryptic insertion, complex karyotype, isochromosome 17

Introduction

Acute promyelocytic leukemia (APL) is featured with cytogenetic abnormality t(15;17), which can be seen in 86%-90% of all APL cases [1, 2]. Isochromosome 17 is frequently involved with t(15;17) in APL which is identified as ider(17)(q10)t(15;17) carrying two RARA/PML fusion genes on both long arms of isochromosome 17. Although it tends to give rise to unfavorable prognosis, specific prognostic significance of isochromosome 17 is still unclear due to the low incidence and incomplete follow-up information for those cases [3-6]. APL lacking classic t(15;17) is either in cases associated with complex chromosomal translocations involving both 15, 17 and other ones, or in cases with cryptic t(15;17) created by insertion events which usually occurs on chromosome 15 [7, 8]. In this report, we describe a case of APL with cryptic PML/RARA rearrangement on both long arms of isochromosome 17 confirmed by fluorescence in situ hybridization (FISH) and real-time polymerase chain reaction (RT-PCR). The patient went into hematological complete remission (HCR) with all-trans retinoic acid (ATRA) and chemotherapy but relapsed twice later and finally died of sepsis. To our knowledge, there have been 3 patients with APL with cryptic PML/RARA on i(17q) who were reported before. A small summary on similar cases is also made to help us have a more profound understanding of the specific type of APL.

Case report

In January 2008, a 21-year-old man was admitted to Tongji Hospital because of melena and

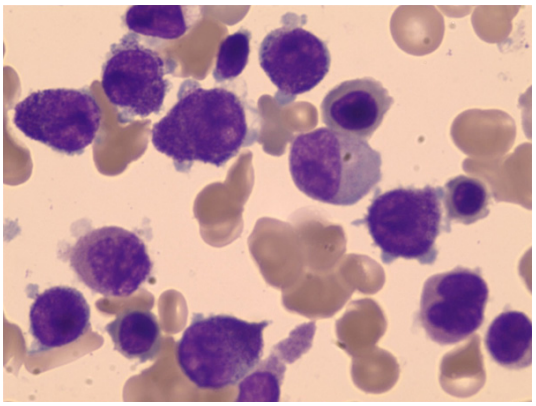

Figure 1. Bone marrow aspirate smear at diagnosis. Hypergranular promyelocytes accounted for 77.6% of nucleated cell (Wright-Giemsa stain, original magnification 1000×).

bleeding tendency for 4 days. The bone marrow aspirate was hypercellular with 77.6% promyelocytes of nucleated cells (**Figure 1**). RT-PCR of bone marrow revealed a positive PML/RARA fusion gene transcript. Diagnosis of APL was made according to the French-American-British (FAB) criteria. Conventional cytogenetic analysis of bone marrow cells obtained before initial chemotherapy showed a karyotype 46,XY,del(13)(q31),i(17)(q10),add(22)(q13) [20] (**Figure 2**). The patient then received ATRA (20 mg/m^2/d) and chemotherapy including daunorubicin (50 mg/m^2/d) and cytarabine (200 mg/m^2/d). HCR1 was obtained after initial induction therapy, which was followed by 3 courses of consolidation with ATRA and chemotherapy.

Two years later in January 2010, the patient was readmitted to our hospital with a hypercellular bone marrow showing 91% promyelocytes of nucleated cells by cytomorphology analysis. The diagnosis of first relapse of APL was made. The same induction regimens combined with arsenic trioxide (ATO, 0.16 mg/kg/d) was immediately applied. HCR2 was soon obtained within a month. A total of 7 courses of consolidation including daunorubicin, cytarabine and ATO were subsequently given during the next year. Intrathecal administration of methotrexate (10 mg), cytarabine (50 mg) and dexamethasone (5 mg) were also done to prevent central nervous system relapse. No PML/RARA transcript was detected in May 2010, and a second cytogenetic analysis of bone marrow performed in May 2011 showed a normal karyotype of 46, XY [20], suggesting a molecular CR and cytogenetic CR.

However, in October 2011, quantitation of PML/RARA in bone marrow became positive with a very low rate around 0.05%. Meanwhile, APL blasts were detectable in his cerebrospinal fluids. Accordingly, second relapse of APL in both bone marrow and central nervous system was made. The patient received one course of ATO treatment and intrathecal administration (as stated before) every month until November 2012. At that time, he developed hematological relapse (**Figure 3**). with flow cytometric analysis of bone marrow revealing 22.4% of myeloblasts expressing CD13, CD9, CD33, CD117 and negative for CD34, HLA-DR, CD7 and CD19 (**Figure 4**). RT-PCR of PML/RARA in bone marrow showed a rate of 121.85%. Consequently, a third conventional cytogenetic analysis was performed in which 20 well-spread metaphases were analyzed and karyotyping indicated 47,add(X)(p22)Y,del(13)(q31),i(17)(q10),add(22)(q13)*2,+22[18]/46,X (**Figure 5**). FISH revealed 2 red/green fusion signals on both long arms of isochromosome 17 suggesting 2 PML/RARA transcripts on isochromosome 17 (**Figure 6**). The patient then received two courses of systemic chemotherapy containing Pirarubicin, ATRA and ATO during which he suffered from severe fungal infection of oral mucosa. HCR3 was achieved in February 2013 while PML/RARA transcript was still positive. The patient finally died of sepsis in October 2013 out of hospital. Written informed consent was obtained according to the Declaration of Helsinki, and the studies were approved by the institutional review board of Tongji hospital.

Discussion

In this report, we describe an APL case characterized by a complex karyotype including isochromosome 17 with cryptic t(15;17) translocation. Although HCR1 was soon gained by ATRA and chemotherapy, he relapsed twice later with the longest CR duration less than 2 years and finally died of sepsis. The poor clinical outcome may be due to multiple factors.

Isochromosome 17 is the most frequent isochromosome seen in neoplasm although its incidence in various hematological malignances is only 1.4%-2.4% [9]. As reported, 20% of chronic myeloid leukemia patients in blast crisis carry this abnormality, suggesting the anomaly may be associated with disease progression [10]. In APL, its incidence rate is 0.6%-4.9% [1, 2, 11-14]. Whether it is a negative

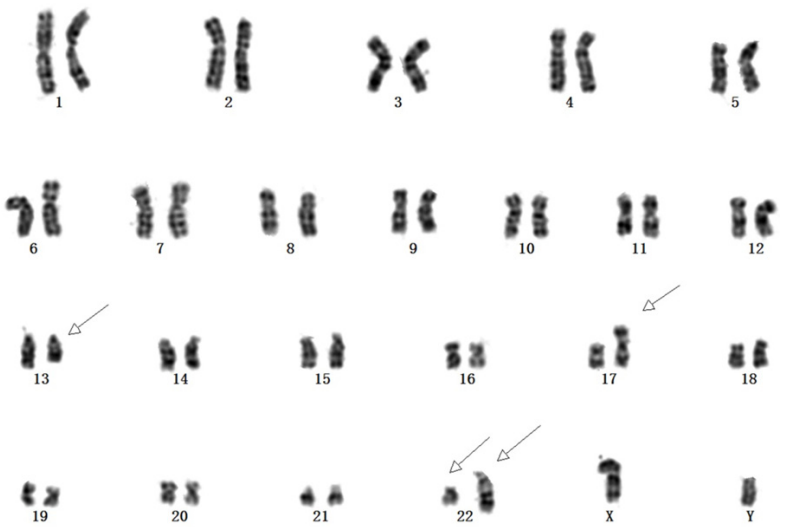

Figure 2. Partial karyograms of the patient at diagnosis. Karyotype of G banding showing 46,XY,del(13)(q31),i(17)(q10),add(22)(q13). Arrows indicate structurally abnormal chromosomes.

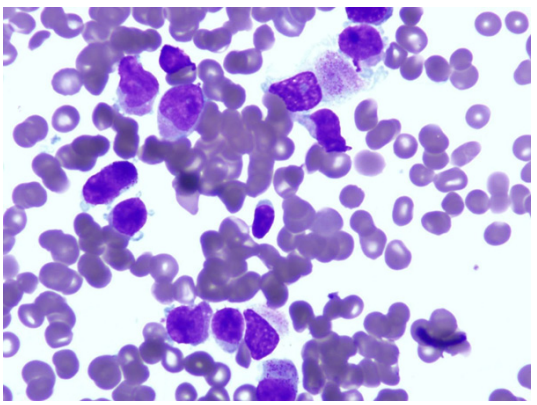

Figure 3. Bone marrow aspirate smear at second relapse. There was abnormal promyelocytes with numerous granules and Auer rods (Wright-Giemsa stain, original magnification 1000×).

prognostic factor in APL is still controversial. Manola et al reviewed 53 cases of APL with ider(17)(q10)t(15;17) concluding that the aberration did not confer an adverse prognosis in APL patients treated with ATRA and chemotherapy [5]. In contrast, Kim et al established a positive relationship between ider(17)(q10) t(15;17) and poor prognosis by reviewing 4 childhood APL cases. As a result, large scale prospective or retrospective clinical trial is needed to uncover the relationship between the isochromosome and prognosis.

Conventional t(15;17) can be detected in 86%-90% of all cases in APL cases [1, 2]. Those with rearrangements involving neither a chromosome 15, nor a chromosome 17 apparently at cytogenetic level are described as cryptic translocations [15]. Rearrangement on chromosomes other than 15q or 17q was quite rare [7, 8]. To our knowledge, there have been only three APL cases having i(17q) with cryptic PML/RARA rearrangement detected on both long arms of involved isochromosome 17 described before [2, 16]. One relapsed in a totally different karyotype with AML-M5 15 months after CR1, another died of sepsis in CR2 after autologous hematopoietic stem cell transplantation (auto-HSCT), the third remained in CR1 with duration more than 23 months (**Table 1**). Together with our case, these patients showed good response to treatments and good chances to achieve CR. However, short CR duration and high incidence of relapse rate strongly suggest that i(17q) with cryptic t(15;17) may confer a worse impact on APL cases. Different from the double RARA/PML copy in traditional ider(17)(q10)t(15;17), i(17q) with cryptic translocation has an extra copy of PML/RARA rather than RARA/PML. As a result, its impact on prognosis should be investigated separately. However, due to very few cases reported, specific prognostic significance of an extra copy of PML/RARA is still unclear.

Hematological malignances are usually clonal diseases that originate from one single cell with mutations. Here, we conjecture that the cryptic rearrangement was followed by the formation of isochromsome 17 since both long arms of the isochromosome present PML/RARA rearrangement. It is possible that rearrangement on 17q increases the instability of the chromosome and thus contributes to the formation of isochromosome. Interestingly, Kimet al found that the incidence rate of isochromosome 17 in cryptic t(15;17) cases is much higher than that in classic t(15;17) cases (25% vs. 4.9%) [2]. Similar result was reported by Cervera showing the ratio as 1.4% vs. 0.7% [1]. Probably, cryptic insertion to 17q, compared with classic t(15;17), has a greater impact on the mitosis of chromosome 17 and increase the incidence of transverse misdivision of the affected chromosome

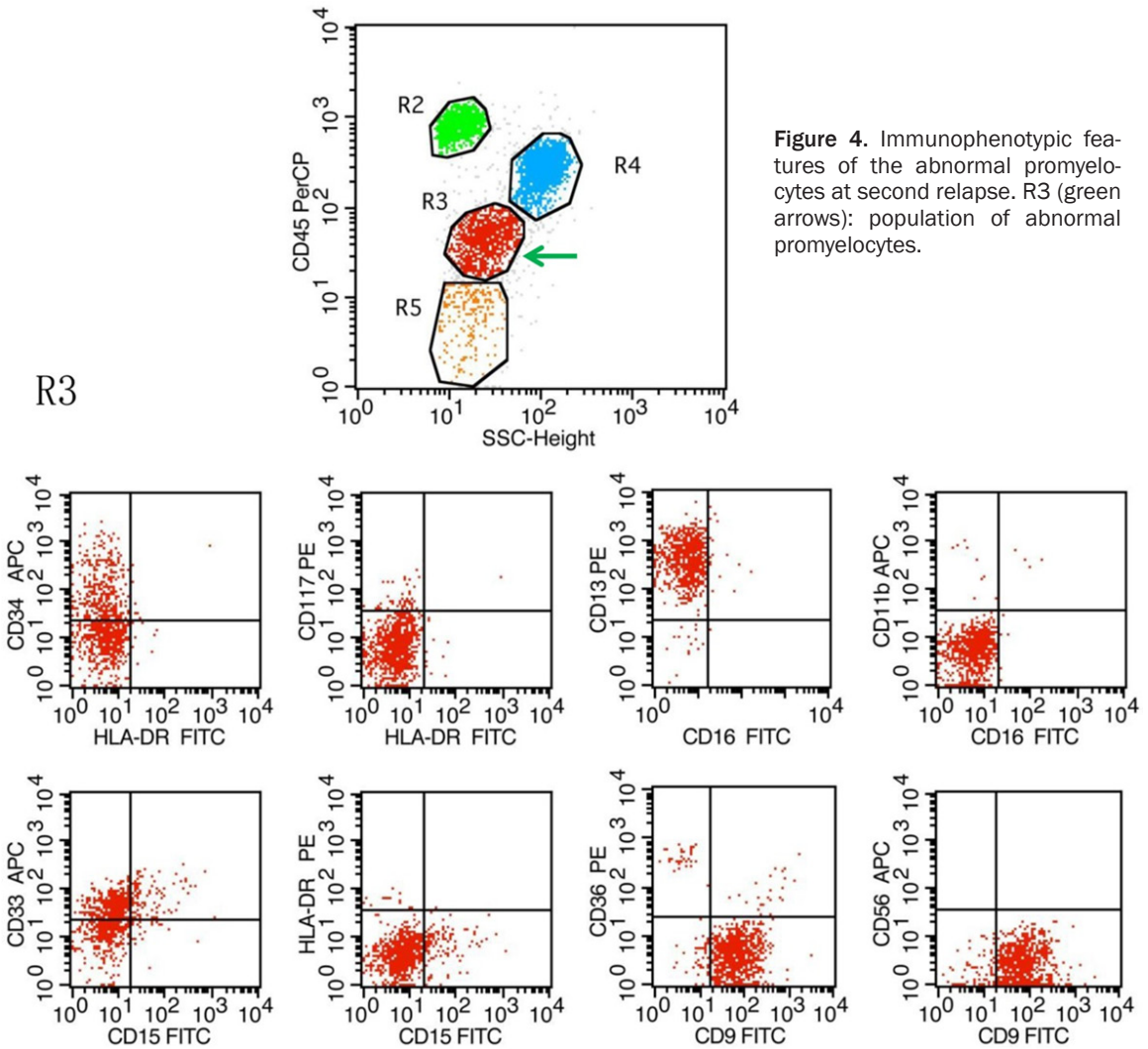

Figure 4. Immunophenotypic features of the abnormal promyelocytes at second relapse. R3 (green arrows): population of abnormal promyelocytes.

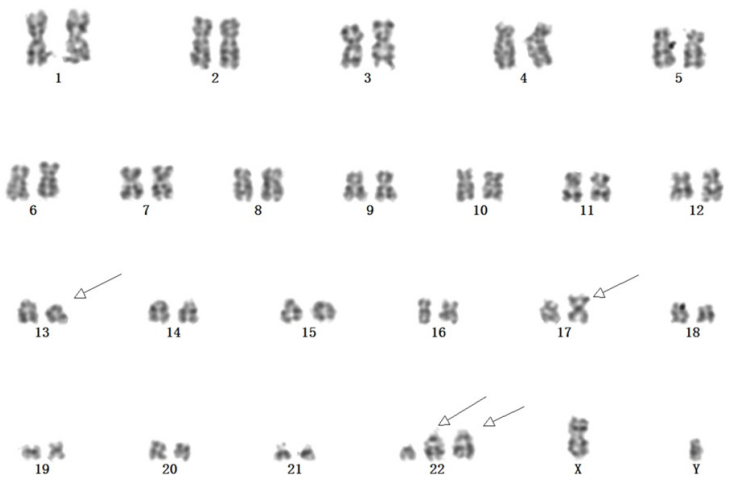

Figure 5. Partial karyograms of the patient at second relapse. Karyotype of G banding showing 47, add(X)(p22)Y,del(13)(q31),i(17)(q10),add(22)(q13)*2,+22. Arrows indicate structurally abnormal chromosomes.

17 at centromeric region. It is also found that PML/RARA is necessary but not sufficient for the development of APL in transgenic mouse; however, a coexpression of its reciprocal form, RARA/PML, can increase the incidence of this disease (55%-60%) [17]. Consistently, Grimwade et al found that in each of the cases with cryptic PML/RARA rearrangements, PML/RARA transcripts were detected in the absence of RARA/PML [18]. Consequently, patients with cryptic t(15;17) on i(17q) may have a different pathogenesis in contrast to the classic APL cases. However, it is also

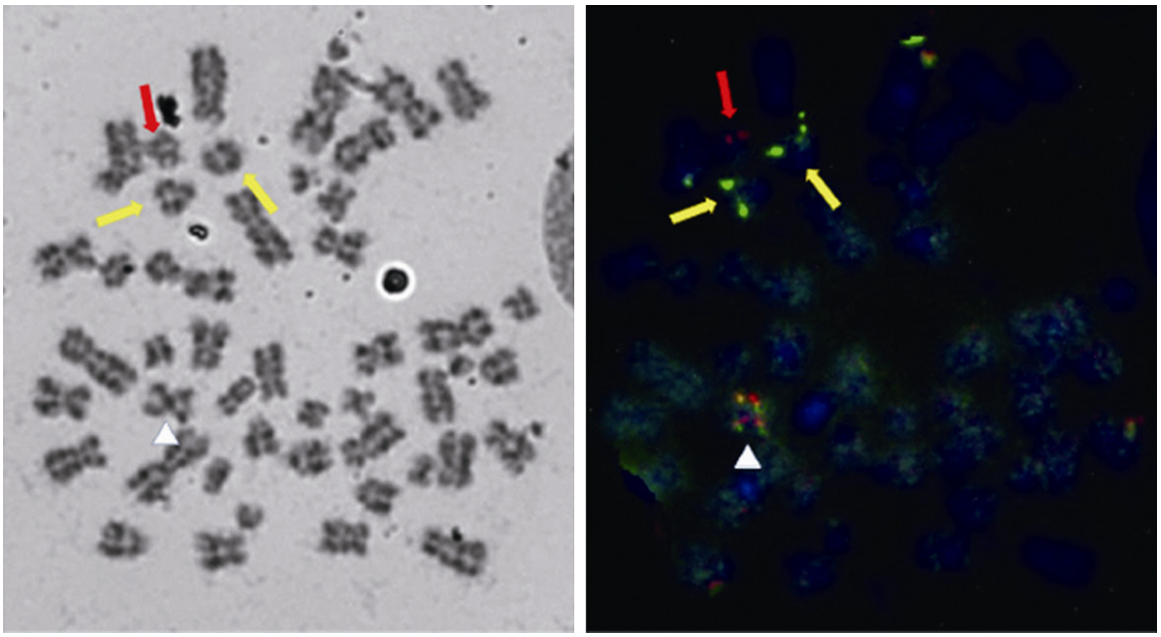

Figure 6. The FISH analysis at second relapse. The metaphase FISH on bone marrow cytogenetic specimens detected 2 green PML signal on both normal chromosome 15 (yellow arrows), 1 red RAR signal on the normal chromosome 17 (red arrow) and 2 red/green fusion signals on both the long arms of isochromosome 17 (white triangle symbol). The FISH results confirmed the cryptic insertion of PML on chromosome 15 to isochromosome 17 in this case.

Table 1. Reported cases of APL with Cryptic t(15;17) on Isochromosme 17 at presentation

Age	Gender	Karyotype	Complete Remission Duration	References
51 y	Female	46,XX,i(17)(q10)[20]	24 months	[16]
13 y	Female	46,XX,i(17)(q10)[18]/46,XX[2]	15 months in CR1, 48 months in CR2	[2]
42 y	Female	446,XX,del(7)(q31q33),i(17)(q10)[14]/46,XX[6]	> 23 months	[2]

CR1 = First complete remission; CR2 = Second complete remission.

believed that no difference exists between the immunophenotyping of classic and cryptic translocation cases [2]. Therefore, studies on cryptic t(15;17) translocation pathogenesis and its effect on disease progression are needed.

In this case, we used both traditional chemotherapy and ATO. However, it didn't give rise to a better prognosis for him compared to other similar cases reported. It is reported that relapsed or refractory APL patients had better outcomes by auto-HSCT than by allogeneic hematopoietic stem cell transplantation (allo-HSCT) or chemotherapy only [19, 20]. As a result, early auto-HSCT may be the choice of APL patients with cryptic t(15;17) on isochromosome 17, given the high relapse rate of them. However, prospective randomized control trials are required for more evidences.

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Disclosure of conflict of interest

None.

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