A Case of Acute Promyelocytic Leukemia with PML/RARA Translocation Showing Familial t(9;15)(q34;q22)

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We report the unusual case of an APL patient with a familial t(9;15)(q34;q22) and acquired t(15;17)(q22;q21). This is unique in that the patient had a constitutional abnormality with the same breakpoints as those observed in the tumor clone from the APL. It is unclear if the breakpoint, 15q22, in the constitutional aberration influenced the induction of the *PML/RARA* translocation in the APL. If a specific translocation in a patient with leukemia does not go away with clinical improvement, a congenital or familial chromosomal abnormality should be considered. Additional patients with similar findings are needed to understand the pathogenesis of these events. ***(Korean J Hematol 2007;42:428-432.)***

Key Words: Acute promyelocytic leukemia, Chromosomal translocation, t(9;15), t(15;17), Constitutional chromosomal abnormality

INTRODUCTION

Acute promyelocytic leukemia (APL) is genetically well characterized by a gene fusion transcript involving the gene for the retinoic acid receptor alpha (*RARA*) of chromosome 17 and the *PML* of chromosome 15. The product of the fusion genes, *PML/RARA*, maintains the ligand-binding domains of *RARA* and blocks the transcription of the genes required for myeloid cell differentiation resulting promyelocytic leukemogenesis.[1)]

Although most APL cases present with classic t(15;17) and some cases with either simple or complex variants of this translocation, involving chromosomes 15, 17 and one or more other chromosomes, such as t(15;20;17)(q22;p13pq21), t(6;15;17)(q25;q22;q21), t(2;15;17)(q21;q22;q21), t(1;15;17)(q36;q22;q21.1),[2-5)] t(17;20)(q21;q12), t(3;17)(q26.3;q12) and t(5;17)(q35; q21),[1,6,7)] familial or constitutional chromosomal abnormalities associated with hematological malignancies are rare.[8)]

However, variable constitutional chromosomal abnormalities have been steadily presented with a possible to definite association.[9)] The most frequent abnormality is a constitutional trisomy 8 mosaicism, which is found in 15～20% hematological dysplasias and neoplasias. The inversion of chromosomes 8 and trisomy 21 are known to be strongly associated with an increased risk of hematological malignancy.[10,11)] There is also a report of constitutional 21 trisomy in APL.[12)]

Generally, most trisomies or structural rearrangements those are often observed in cancers

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are acquired abnormalities associated with the disease process. However, some specific breakpoints of constitutional translocations observed in some hematological malignancies suggest that the constitutional translocation itself plays a major role in the malignancy process.[13] However, in our literature review, there were no other constitutional abnormalities that can provide more clues to understanding the process of leukemogenesis in APL.

We report an unusual case of APL with the classical *PML/RARA* translocation in a patient with constitutional t(9;15)(q34;q22). It is unclear if the breakpoint, 15q22, in the constitutional aberration of this patient might have influenced the induction of *PML/RARA* translocation in APL. This is a unique case with a constitutional abnormality with the same breakpoint as those observed in the tumor clone in APL.

CASE REPORT

A 25-year-old woman was admitted for an evaluation of persistent gum bleeding and epistaxis. She showed menorrhagia, arthralgia, and myalgia, and bruised easily. The hematologic tests showed the following: hemoglobin 9.8g/dL, platelet 6×10^9/L and a white blood cell count of 18.15×10^9 with 53% blast cells, 6% promyelocytes, 1% myelocytes, and 6% band neutrophils. The FDP and D-dimer were increased by up to 58ug/mL and 15.95ug/mL. The bone marrow biopsy showed a packed marrow with immature cells and in aspirate, the cytoplasms of cells were filled with coarse azurophilic granules without prominent Auer rod (Fig. 1). Immunophenotyping revealed CD13+ (91.2%), CD33+ (96.9%), MPO+ (85.6%), HLA DR− (4.54%). A diagnosis of acute promyelocytic leukemia (APL M3) with DIC was made. The patient was treated with Idarubicin and ATRA for induction therapy. After complete remission had been achieved, consolidation therapy was performed 3 times, and she has remained in complete remission since.

The cytogenetic result of her first BM cytogenetic study was 46,XX,t(9;15)(q34;q22), t(15;17)(q22;q21) (Fig. 2). Each allele of chromosome 15 translocated with each chromosome 9 and 17. In FISH study, 99% cells showed fusion signals of *PML/RARA* (LIS PML/RARA dual color translocation probe; 15q22 LSI PML spectrumOrange/ 17q21.1 LSI RARA spectrumGreen) (Fig. 3). A *PML/RARA* rearrangement was found using reverse transcriptase nested PCR.

After achieving complete remission, t(15;17)(q22;q21) was no longer found in the karyotype and FISH studies (Fig. 4). However, the t(9;15)(q34;q22) still remained after consolidation chemotherapy. Considering the possibility of a constitutional chromosomal abnormality of t(9;15)(q34;q22), her healthy family's karyotypes were examined. Her mother and two elder sisters were

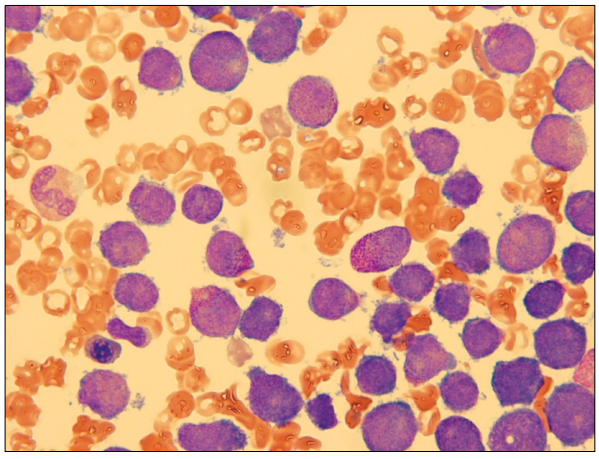

Fig. 1. The blasts are filled with coarse azurophilic granules without prominent Auer rods.

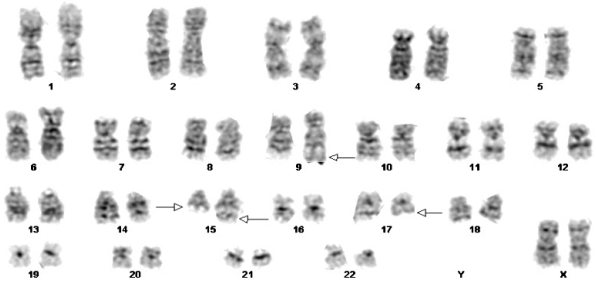

Fig. 2. G-banded karyotype of bone marrow cells showing 46,XX,t(9;15)(q34;q22),t(15;17)(q22;q21).

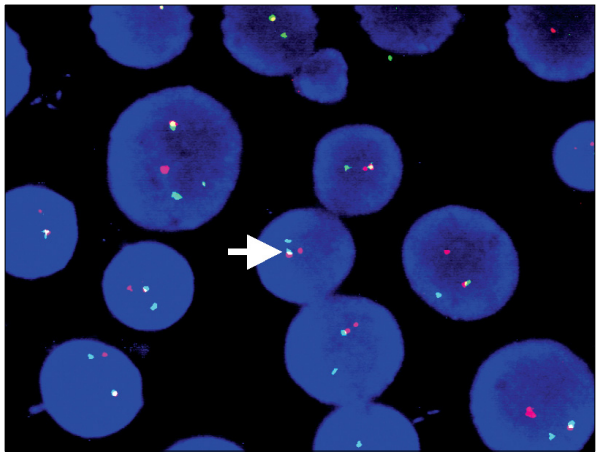

Fig. 3. In FISH study, 99% cells show fusion signals (white arrow) of *PML/RARA* (LIS PML/RARA dual color translocation probe;15q22 LSI PML spectrumOrange/17q21.1 LSI RARA spectrumGreen).

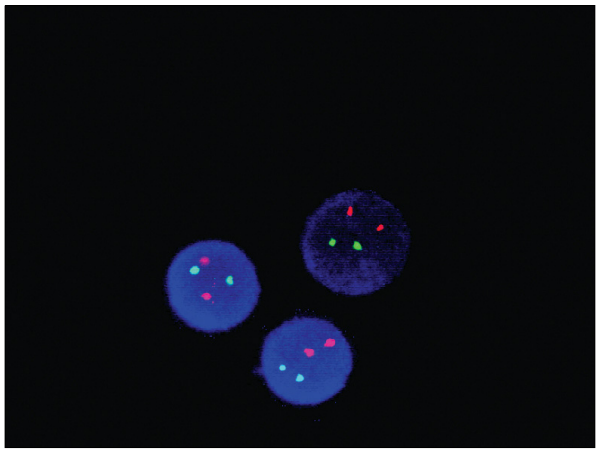

Fig. 4. After treatment, follow up FISH studies show no fusion signal of *PML/RARA* (LIS PML/RARA dual color translocation probe;15q22 LSI PML spectrumOrange/17q21.1 LSI RARA spectrumGreen).

included for the cytogenetic analysis of peripheral blood. Her father was deceased. In addition, her peripheral blood was evaluated for the karyotype.

The cytogenetic analysis showed t(9;15)(q34;q22) in all three families' and her peripheral blood, which confirming that t(9;15)(q34;q22) was a constitutional and familial rearrangement (Fig. 5). Metaphase FISH study of the patient's peripheral blood with LIS PML/RARA dual color translocation probe showed that the two Orange PML

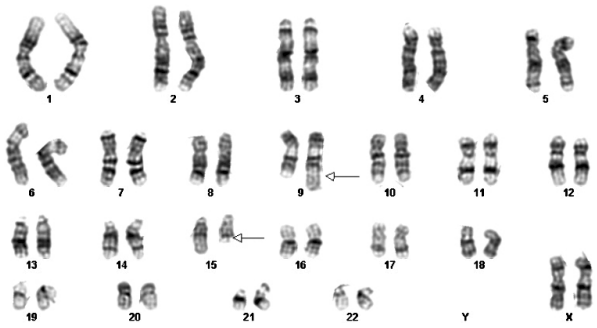

Fig. 5. G- banded karyotype of the patient's mother's peripheral blood showing t(9;15)(q34;q22).

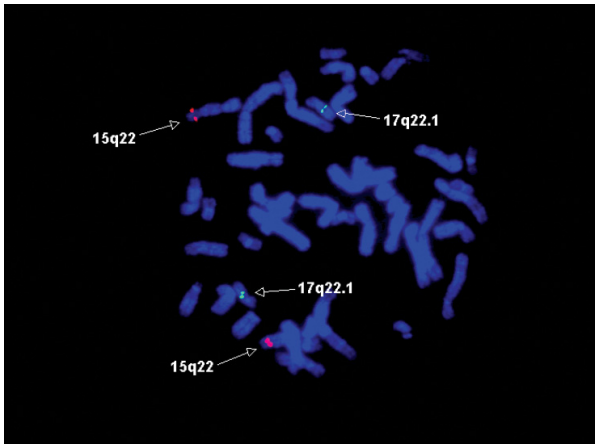

Fig. 6. Metaphase FISH study of the patient's peripheral blood shows a PML probes hybridize with q34 of chromosome 9 (LIS PML/RARA dual color translocation probe; 15q22 LSI PML spectrumOrange/17q21.1 LSI RARA spectrumGreen).

probes hybridize with each different chromosome locus; q22 of a normal allele of chromosome 15 and q34 of chromosome 9 (LIS PML/RARA dual color translocation probe; 15q22 LSI PML spectrumOrange/17q21.1 LSI RARA spectrumGreen) (Fig. 6).

DISCUSSION

The identification of constitutional chromosome anomalies is important in some specific malignancies including neurofibromatosis, retinoblastoma and Wilm's tumor because they may help to determine the location of the DNA sequences involved in the genetic predisposition.[14-17]

Variable constitutional chromosomal abnormalities have been reported with a possible to definite association with hematologic malignancies, including trisomy 8, trisomy 21.[10-12] In addition to these aneuploidy or large defects in chromosomes, constitutional structural rearrangements also have been reported, suggesting the association with hematologic malignancies. One of the cases was a case with constitutional and familial inv(8), three of the five carriers have a diagnosed clinical disease: ANLL-M7, ITP and breast carcinoma. In the case of acute nonlymphocytic leukemia with a constitutional inv(4)(p16q26) coding murine leukemia viral (v-raf) oncogene, pseudogene 1 and IL-2 gene, the author said activation of the genes could have played a role in the pathogenesis of the patient's leukemia.[18] Mozziconacci et al. presented 4 cases of constitutional balanced pericentric inversion of chromosome X, 2 and 5 with or without acquired chromosomal aberration in myeloid malignancies, suggesting influence of the constitutional pericentric inversion to hematologic malignancies.[19]

In particular, constitutional translocations with the break points that harbor the genes in charge of a specific type of leukemia also have been reported in several patients with hematological malignancies as in this presented case. In the case of Ganly et al. of myelodysplastic syndrome and transforming to acute myelocytic leukemia with constitutional t(5;7)(q11;p15), the disruption of bands 5q11 or 7p15, which are frequently observed in MDS, AML as acquired translocations.[20] Becher et al. and Qian et al. reported cases of CML with constitutional Robertsonian tranlocation attended by Philadelphia chromosome.[21,22] Constitutional t(5;11)(p15.3;q23) attended by acute lymphoblastic leukemia and t(8;21) with acute nonlymphocytic leukemia in a Down syndrome were also reported.[23] As a chromosomal fragile site, constitutional chromosomal aberrations harboring the genes involved pathogenesis in hematologic malignancies would provide more information to discover their unknown pathogenesis.

In this case, the break point 15q22 of constitutional t(9;15)(q34;q22) was located proximally from the general breakpoint of 15q22 in APL in metaphase FISH study, which were observed as same breakpoint in G-banding. To our knowledge, this is the first case of constitutional t(9;15)(q34;q22) attended by APL. There are just two constitutional t(9;15) cases associated with Prader-Willi syndrome and unknown psychomotor retardation syndromes.[24,25] Those were not a sole aberration and the break points were different from our case, as the former was 45,XY,-9,-15,+der(9),t(9;15)(9pter->9q34::15q11->15qter) and the later was 46,XY,-9,-15,+i(9P),t(9;15)(q11;p12). The carrier family members showed normal appearance and mental status.

This case showed a clinical response and there was no difference in the clinical progress and outcome with cases of APL with the typical t(15;17). Although, the role of the constitutional t(9;15)(q34;q22) and the association with PML/RARA translocation in this case are unclear, the patient was found to have an unusual breakpoint that harbored the PML gene.

요 약

급성전골수성백혈병의 특징적인 t(15;17)(q22;q21)에 동반되어 나타난 선천성 t(9;15)(q34;q22) 최초의 1예를 보고하는 바이다. 이 환자에서 보여진 선천성 t(9;15)(q34;q22)에서의 breakpoint 15q22가 PML/RARA를 유도하였는지는 알 수 없지만, 질병에 특이적인 전좌에 동반된 다른 전좌들이 치료에 반응하지 않는 경우 선천성 및 가족성 염색체 이상의 가능성을 고려하여야 하며, 질병에 특이적인 전좌와 동일한 breakpoint를 공유하는 선천적 염색체 이상에 대한 보고들은 질병의 병인을 이해하는 데 도움이 될 것으로 생각한다.

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