Short communication

Two distinct clonal populations in acute promyelocytic leukemia, one involving chromosome 17 and the other involving an isochromosome 17

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Abstract

Acute promyelocytic leukemia (APL) is characterized by a t(15;17)(q22;q21) rearrangement. Additional chromosomal rearrangements have been reported in 25–40% of APL patients. The most common abnormality involving chromosome 17 is ider(17). Here we report the case of a patient with APL with isochromosome 17q combined with ider(17), confirmed by fluorescence in situ hybridization. Cytogenetic data strongly suggest that the involvement of chromosomes 15 and 17 in translocation occurs after formation of the isochromosome 17. The case reported here presents the novel finding of two separate clonal events apparently occurring at the same time in an APL patient. © 2010 Elsevier Inc. All rights reserved.

1. Introduction

Acute promyelocytic leukemia (APL) according to the World Health Organization (WHO) classification, and the M3 subtype according to the French–American–British (FAB) classification, is a well-defined subtype of acute myeloid leukemia (AML). It is characterized by the morphology of leukemic cells, the presence of the t(15;17) rearrangement, and specific coagulopathy [1,2]. Chromosomal rearrangements in addition to t(15;17) have been reported in 25–40% of APL patients, with a large predominance of trisomy 8. Other abnormalities are far less frequent, and they usually involve chromosomes 17, 9, and 7—particularly as ider(17), del(9q), and del(7q) abnormalities [3]. The significance of additional chromosomal abnormalities is uncertain. Even though the number of published cases is small, ider(17) in APL patients might be related to a poor prognosis. We know of no previous publication of APL with an isochromosome 17q that is not ider(17). We report here on a novel case of APL with isochromosome 17q combined with ider(17).

2. Case report

A 69-year-old woman was referred to our hospital because of easy bruising for 1 month and pancytopenia. The laboratory test results were as follows: hemoglobin 8.0 g/dL, hematocrit 22.2%, white blood cell count 0.48 \times 10^9/L, and platelet count 7 \times 10^9/L. A few leukemic cells were found (1%) on the peripheral blood smear. The prothrombin and activated partial thromboplastin times were within normal ranges, but fibrinogen degradation products and D-dimer were increased (33.15 \mu g/mL and 13.43 \mu g/mL fibrinogen equivalent units, respectively). Bone marrow aspirate and biopsy were performed. Morphologic examination of the bone marrow revealed 100% cellularity. Most of the nucleated elements were abnormal promyelocytes with numerous granules, and some of them had Auer rods. Occasionally faggot cells were found (Fig. 1). Immunophenotyping using monoclonal antibodies (BD Biosciences, San Jose, CA) indicated CD13, CD33, and cytoplasmic MPO positivity, and CD34, CD10, CD19, CD20, CD5, CD7, CD41, CD14, CD3, cytoplasmic CD3, and CD22 negativity.

Classical cytogenetic analysis performed on the bone marrow aspirate showed 13 metaphase cells with 46,XX,t(15;17)(q22;q21),i(17)(q10), 2 metaphase cells with 46,XX,der(15)t(15;17),ider(17)(q10)t(15;17)(q22;q21), and...
5 normal cells (Fig. 2). We performed fluorescence in situ hybridization (FISH) using a Vysis LSI PML/RARA dual-color, dual-fusion translocation probe (Abbott Molecular, Des Plaines, IL). In the 13 metaphase cells, we detected one PML/RARA fusion on der(15)t(15;17) and one RARA/PML fusion on der(17)t(15;17); the isochromosome 17 had two RARA signals on both arms (2F1O2 G, where F is fusion, O is orange [PML], and G is green [RARA]). The other two abnormal metaphase cells revealed one PML/RARA fusion signal on der(15)t(15;17) and two RARA/PML fusions on ider(17)(q10)t(15;17) (3F1O1 G) (Fig. 3).

The patient refused chemotherapy, so she was treated with oral all-trans retinoic acid (ATRA) at a dose of 45 mg/m² per day without chemotherapy. On day 21 of ATRA treatment, she recovered. Blood examination revealed a white blood cell count of 4.18 × 10⁹/L, neutrophils, 2% eosinophils, 2% metamyelocytes, 2% myelocytes, 71% neutrophils, 2% metamyelocytes, 2% myelocytes, 71% lymphocytes, 2% eosinophils), and she was discharged. The patient continued taking ATRA, and 11 months after diagnosis, she was continuing on ATRA at the same dose and was receiving conservative management. Three months later, she visited emergency room and died, her death due to hemorrhagic complications.

3. Discussion

Isochromosome 17q is a structural abnormality that results from loss of the short arm and duplication of the long arm of chromosome 17, resulting in a single copy of 17p and three copies of 17q. Isochromosome 17q, which is the most common isochromosome in hematologic malignancies, has been reported in lymphomas and in acute and chronic myeloid and lymphoid leukemias. Isochromosome 17q is also a common karyotype abnormality in solid tumors, most notably in medulloblastoma [4]. For myeloid disorders, isochromosome 17q is the most frequent genetic abnormality observed during disease progression of chronic myeloid leukemia (CML). In a CML-blastic crisis, isochromosome 17q is the third most common secondary chromosomal aberration, seen in ~20% of cases of blastic crisis [5]. In myelodysplastic syndrome (MDS), isochromosome 17q has been reported in 0.4–1.57% of all cases, and it has been associated with characteristics that range over MDS and chronic myeloproliferative disorders such as hypercellular bone marrow, eosinophilia, basophilia, increased micromegakaryocytes, severe dysgranulopoiesis, pseudo-Pelger-Huët anomaly, dysmegakaryocytopoiesis, and short survival. Isochromosome 17q in MDS may be associated with a poor prognosis [6–10].

Seven cases of APL with isochromosome 17q have been reported previously [11–15]. For all of those cases, we ascertained that the abnormality i(17)(q10) was ider(17)(q10)t(15;17), not a true i(17)(q10), because the long arm of chromosome 17 with t(15;17) was not easily differentiated from that without t(15;17). A few were defined as i(17)(q10) that contained cryptic t(15;17) [16–18]. Although cryptic t(15;17) cannot be identified by conventional cytogenetics, those cases do not represent true i(17)(q10), because they reveal PML/RARA fusions on 15q or i(17)(q10) with FISH or reverse transcriptase PCR analysis.

The present case, therefore, represents a novel case of APL with a true i(17)(q10) combined with ider(17)(q10)t(15;17). Usually, hematologic malignancies are clonal disorders arising from a single mutated cell. Gain of secondary genetic abnormality can occur as a subclone in addition to the main-line. The presence of two or more clonally distinct populations occurring in AML has rarely been reported. In the present case, cytogenetic data strongly suggested two separate clonal evolution events: After formation of isochromosome 17, the involvement of the chromosome 15 and 17 in translocation seems to occur. In other words, two clonal pathways took place: one involving chromosome 15 and 17, and the other involving chromosome 15 and the isochromosome 17.
A correlation between isochromosome 17 and a mechanism of disease progression has not yet been established. Loss of a copy of the TP53 tumor suppressor gene on chromosome 17p is an important mechanism associated with tumorigenesis. Some investigators have insisted that, because of reduction of the total p53 level, the integration of genetic repair and apoptosis may be interfered with, and that this can contribute to disease progression [19]. Others insist that one TP53 allele is normal, and thus any direct link of TP53 inactivation and progression is unclear [20].

In the present case, notably, no metaphase cells were detected with simultaneous i(17)(q10) and ider(17)(q10)t(15;17). One normal TP53 was always preserved. The other mechanism associated with isochromosome is that the oncogenes THRA and ERBB2 on chromosome 17q are duplicated and their protein products are amplified [21]. Because the patient refused intensive chemotherapy, we could not monitor the status of the abnormal clones, nor estimate the definite effect of isochromosome 17q reduction of the total p53 level, the integration of genetic evolution of chronic myeloid leukemia. Acta Haematol 2002;107:76–94.


References


