A Novel Jumping Translocation of 12q21 in a Patient with Chronic Idiopathic Myelofibrosis

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Jumping translocation (JT) has been defined as the translocation involving one donor chromosome and multiple recipient chromosomes in different cell lines in the same patient. This is rarely observed in various hematologic malignancies. Chronic idiopathic myelofibrosis (CIMF) is considered to be a clonal hematopoietic stem cell disorder, and clonal cytogenetic abnormalities have been reported to occur in about 30～60% of patients. We report here on a case of CIMF with JT involving 12q21; t(5;12)(q13;q21) and t(12;12)(p13;q21) as the sole aberration. A pathogenetic relation between CIMF and the 12q rearrangement has been suggested in the literature, but neither the JT in CIMF nor the JT of 12q21 has been reported on. This is the first report of JT involving 12q21 in a patient with CIMF (ED note: nice writing). ***(Korean J Hematol 2006;41:99-104.)***

Key Words: Jumping translocation, Chronic idiopathic myelofibrosis, 12q rearrangement

INTRODUCTION

Jumping translocation (JT) refers to the translocation of one donor chromosome segment onto multiple recipient chromosomes in different cell lines in an individual, and leads to a mosaic karyotype. It was rarely observed as constitutional abnormalities but had been reported in various hematologic malignant disorders including acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), blastic phase of chronic myeloid leukemia (CML), lymphoma and multiple myeloma (MM). JT as the sole aberration was extremely rare, and previously reported cases were secondary changes with co-existing specific translocation mostly. The most commonly involved donor segment was long arm of chromosome 1 (1q), and the majority of cases were resulting in a partial trisomy or tetrasomy of 1q by unbalanced translocations.[1-3] We report here a case of chronic idiopathic myelofibrosis (CIMF) with JT of 12q21; t(5;12)(q13;q21) and t(12;12)(p13;q21) as the sole aberration. To our knowledge, this is the first report of JT in CIMF and involving 12q21.

CASE REPORT

An 81-years-old male was admitted for the evaluation of the cause of hemoptysis. He had suffered from a dyspnea for a week at admission. In terms of his medical history, he had been diagnosed with essential thrombocythemia (ET) 13 years previously

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(in January 1993), and had been treated with hydroxyurea for 7 years (from January 1993 to February 2000). A complete blood cell count revealed hemoglobin 8.4g/dL, platelets 489×10^9/L, white blood cells (WBCs) 8.14×10^9/L with segmented neutrophils 61%, band form neutrophils 5%, metamyelocytes 3%, myelocytes 9%, lymphocytes 17%, monocytes 2%, eosinophils 1%, blasts 2%, and nucleated red blood cells 4/100 WBCs. Peripheral blood films showed leukoerythroblastosis with marked poikilocytosis of red blood cells, particularly dacryocytes (Fig. 1). The bone marrow was not aspirable. A bone marrow biopsy showed severe myelofibrosis with reticulin grade 4 and marked increase of bizarre, atypical megakaryocytes (Fig. 2). These findings were more consistent with a diagnosis of CIMF rather than ET, according to the World Health Organization (WHO) classification. The spleen was palpable on physical examination and splenomegaly was noted by CT scan. A chest X-ray showed pleural effusion on the left side. Cytogenetic analysis was performed using 24-hour unstimulated cultures with a peripheral blood specimen. Karyotypes were described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. A clone was defined as at least two cells with the same additional numerical and/or structural abnormality or three cells with a loss of the same chromosome. Apparently balanced translocations between 5q and 12q were examined in 7 metaphases, and between 12p and 12q were examined in 3 metaphases. His karyotype was 46,XY,t(5;12)(q13;q21)[7]/46,XY,t(12;12)(p13;q21)[3]/46,XY[10] (Fig. 3). The karyotype obtained in January of 2001 had proved normal. He received thoracentesis for pleural effusion and supportive care without cytotoxic therapy. Up to the time of writing, there has been no clinical of hematologic evidence of blastic transformation.

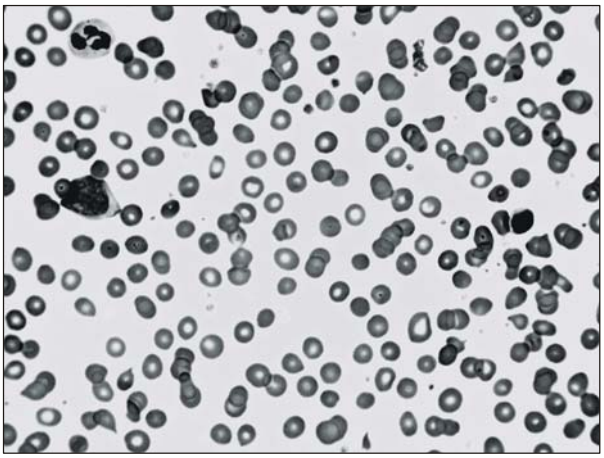

Fig. 1. Peripheral blood smear showed leukoerythroblastosis with dacryocytosis. (Wright stain, ×400)

DISCUSSION

CIMF is a chronic myeloproliferative disorder

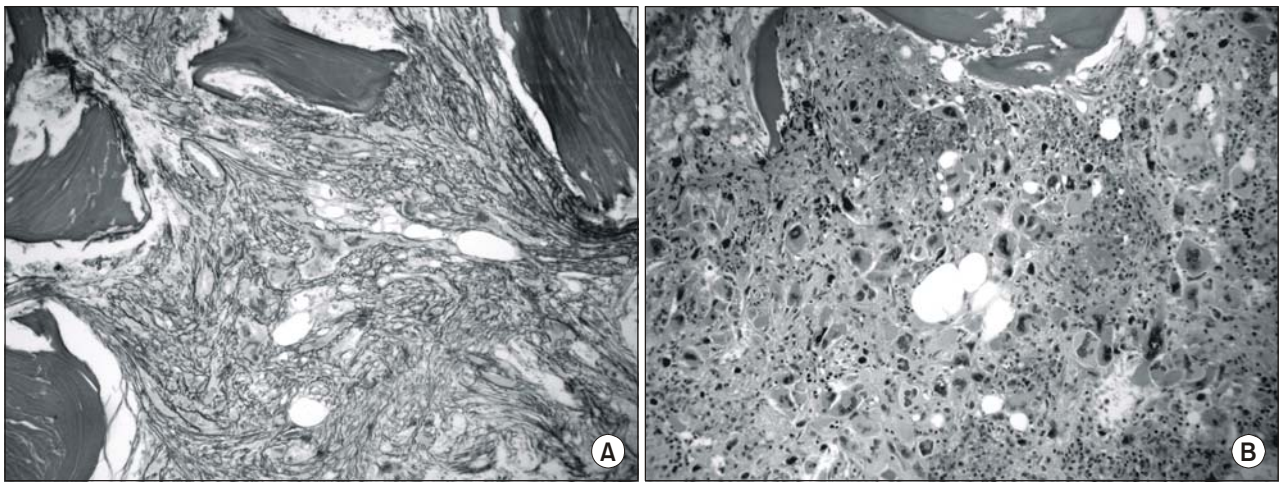

Fig. 2. Bone marrow biopsy showed severe myelofibrosis (A) and marked increase of atypical megakaryocytes (B).

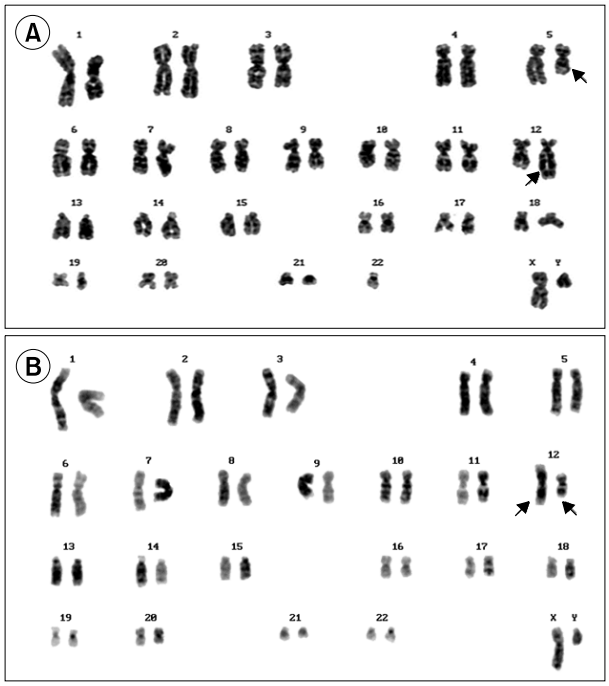

Fig. 3. The representative karyotypes showed 45,XY,t(5;12)(q13;q21),-22 (A, monosomy 22 was not clonal abnormality) and 46,XY,t(12;12)(p13;q21) (B).

(CMPD) characterized by the proliferation of mainly megakaryocytic and granulocytic elements in the bone marrow, and is associated with the reactive deposition of bone marrow connective tissue and extramedullary hematopoiesis. Chromosome abnormalities are considered clonal markers of hematologic malignancies and nonrandom cytogenetic abnormalities have been found in CIMF. The proportion of cases with abnormal karyotypes in CIMF varies from 30% to 60% with widely differing frequencies of specific abnormalities. The most common recurring abnormalities are del(13q), del(20q) and partial trisomy 1q. These three cytogenetic findings are observed in nearly two-thirds of patients with chromosome abnormalities.[4] However, no single consistent abnormality, such as Philadelphia translocation in chronic myeloid leukemia has been identified, even though recent studies have proposed that the abnormal activation of tyrosine kinase-dependent signal translocation pathways is associated with the development of CMPD. In these studies, it was found that a single point mutation in JAK2 was identified in 50% of patients with CIMF, which suggested that this had a potential role in MPD.[5] However, the pathogenesis of about 50% of CIMF patients has not been established.

Balanced translocations in myelofibrosis are very rare events, though several isolated case reports have been published.[6-14] Nevertheless, these limited reports suggest that the involvement of chromosome 12 might be of pathogenetic relevance, and this conclusion was recently strengthened by a study that documented structural abnormalities in the long arm of chromosome 12 (12q) in seven of 205 cases of CIMF.[7] Furthermore, chromosome 12 seems to be commonly implicated in structural balanced translocation, whereas deletion and inversion are less common. 12q rearrangements were reported to be the most common translocation-type karyotypic abnormalities in CIMF, but no single specific translocation partner was identified.[7,8] To our knowledge, balanced translocations involving 12q in myelofibrosis have been reported in 17 patients, including the present case (Table 1). It is of note that translocation-type abnormalities in myelofibrosis showed clustering breakpoints on chromosome 12q: 12q21 in 6/17 cases, 12q23 in 2/17 cases, 12q24 in 6/17 cases and 12q12～q13 in 2/17 cases, which suggest that two different “hot-spots” on 12q21 and 12q24 may be related to the etiology of myelofibrosis. Moreover, these should help in the identification of the genetic basis of this disease. It is still unknown which genes are involved, and further studies at the molecular level are currently ongoing. Andrieux et al[15] showed that some patients with 12q anomalies exhibit high-mobility group protein A2 (HMGA2) overexpression in myeloid progenitors. The HMGA2 gene is known to be on 12q and to play a major role in fetal growth and development, whereas its expression in adult tissues is restricted to lung, kidney and synovia. They assumed that HMGA2 reactivation might contribute to the pathogenesis of myelofibrosis.

JT had initially been defined as nonreciprocal translocation involving a same donor chromosome segment onto two or more recipient chromosomes

Table 1. Clinical and cytogenetic findings of the reported cases of myelofibrosis with balanced 12q rearrangement

No. case	Age/Sex	Cytogenetic abnormalities	Disease progress	Reference No.
1	68/F	46,XX,t(12;17)(q23;q21)[17]/47, XX,del(1)(p13),+ del(1)(p13),+ del(1)(q12),-13, der(15)t(13;15)(q12;q26)[2]/46,XX[1]	ND	6
2	43/M	t(4;12)(q33;q21)	Stable MF over 148 Months	7
3	75/M	t(5;12)(p14;q21)	Stable MF over 17 Months	
4	67/F	t(1;12)(q22;q24)	Died due to progress to AML	
5	57/M	t(12;17)(q24;q11)	Died due to progress to AML	
6	65/F	Inv(12)(p12q24)	Died due to unrelated malignancy (ovarian ca)	
7	58/M	t(7;12)(p11;q24)	Died	
8	44/F	t(1;12)(p21;q12)	Stable MF over 7 Months	
9	69/M	46,XY,t(4;12)(q31;q21)[22]	MF evolved from MDS	8
10	76/F	46,XX,t(1;12)(p31;q21)[10]	ND	9
11	78/F	46,XX,t(12;12)(q?;q?),del(13)(q12q14)[10]	ND	
12	65/M	46,XY,t(4;12)(q26;q15),t(5;12)(q13;q24),del(7)(q22)	Progress to AML	10
13	64/M	46,XY,t(8;12)(p23;q21)[42%]/47,XY,+8[12%]/ 46,XY[40%]	ND	11
14	ND/M	46,XY,t(6;12)(q23;q13)[21]	ND	12
15	75/M	45,XY,der(2)t(2;6;15),der(6)t(2;6;15),-15[7]/ 46,XY,del(7)(p15),t(19;22)(p13;q13),-20[5]/ 46,XY,+8[4]/46,XY,t(12;17)(q23;q22)[2]/46,XY[2]	Stable MF over 88 Months	13
16	ND	t(7;12)(q22;q24.1)	ND	14
17	81/M	46,XY,t(5;12)(q13;q21)[7]/46,XY, t(12;12)(p13;q21)[3]/46,XY[10]	Stable MF over 159 Months	Present case

Abbreviations: M, male; F, female; MF, myelofibrosis; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ND, not described.

in different cell lines, but the concept of JT is now being extended that the same donor segment is translocated onto different chromosome recipients in the different cell lines reciprocally or in the same cell lines.[1)] Acquired JTs are rare chromosomal aberration and mainly observed in hematologic neoplasms including different type of leukemia, lymphoma and multiple myeloma. The long arm of chromosome 1 (1q) is the most common donor chromosome in acquired JTs regardless of their hematologic diagnosis.[1-3)] But neither the JT in CIMF nor the JT of 12q21 has been reported, this is the first report of JT involving 12q21 in a patient with CIMF. JT had not been consistently associated with a specific type of malignancy and appeared in the course of clonal karyotypic evolution with coexisting specific rearrangement, thus it seemed to be related to tumor progression rather than tumorigenesis. To our knowledge, only three previously reported cases had JT as the sole chromosomal aberration, each of them was ALL, AML and follicular lymphoma.[2)] This is another case of JT as the sole

chromosome aberration, but it seemed to represent disease progression rather than pathogenesis because it developed 13 years later from initial diagnosis. It is generally agreed that JT is associated with a poor prognosis. The etiology and the biologic mechanism of this type of aberration are still not clearly known. Pericentromeric heterochromatic decondensation and telomeric shortening are most widely accepted. Therefore the largest, heterochromatin region on 1q appears to be the simple explanation to its most frequent involvement as the donor chromosome. Almost all of the telomeric regions can be involved as the recipients.[1-3] But in this case, the breakpoint of donor segment is not in heterochromatin region, so another mechanism is suspicious.

We report here a first case of CIMF with JT involving 12q21. A literature review revealed that structural abnormalities of the long arm of chromosome 12 seem to have a pathogenetic relevance in CIMF, but the prognostic implication of this novel jumping translocation of 12q is unclear due to the lack of report. However, evolution to more complex karyotypic abnormalities and the developments of new karyotypic abnormalities may be a sign of clinical progression, and thus careful observation is needed.

요 약

도약 전위는 동일한 환자에서 하나의 제공 부위 염색체 분절이 각기 다른 클론의 여러 받는 부위 염색체에 전위되는 것으로 정의하며, 다양한 혈액 종양에서 드물게 보고되었다. 만성특발성골수섬유증은 클론성 조혈모세포 질환으로 여겨지며, 약 30～60%의 환자에서 클론성 염색체 이상이 관찰된다. 우리는 12q21을 제공 부위로 하는 도약 전위인 t(5;12)(q13;q21)과 t(12;12)(p13;q21)을 가진 만성특발성골수섬유증 환자 1예를 보고하고자 한다. 문헌고찰에 따르면, 다양한 염색체와 12q간의 재배열이 만성특발성골수섬유증과 병인론적 연관관계가 있는 것으로 보고되고 있지만 도약 전위를 가진 만성특발성골수섬유증이나 12q21의 도약 전위는 보고된 바가 없다. 이 증례는 만성특발성골수섬유증 환자에서 12q21의 도약 변위를 보인 첫번째 증례이다.

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