Coexistence of p210$^{\text{BCR-ABL}}$ and CBFβ-MYH11 fusion genes in myeloid leukemia: A report of 4 cases

YUAN-YUAN WANG[1*], WEN-JING DING[2*], FENG JIANG[3*], ZI-XING CHEN[1], JIAN-NONG CEN[1],
XIAO-FEI QI[1], JIAN-YING LIANG[1], DAN-DAN LIU[1], JIN-LAN PAN[1] and SU-NING CHEN[1]

[1]Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University,
Collaborative Innovation Center of Hematology, Soochow University, Key Laboratory of Thrombosis and Hemostasis of
Ministry of Health, Suzhou, Jiangsu 215006; [2]Central Hospital of Zibo, Zibo, Shandong 255036;
[3]The Second People's Hospital of Chizhou, Chizhou, Anhui 247100, P.R. China

Abstract. Numerous acquired molecular and cytogenetic abnormalities are strongly associated with hematological malignancies. The breakpoint cluster region-ABL proto-oncogene 1 (*BCR-ABL*) rearrangement leads to a p210 chimeric protein in typical chronic myeloid leukemia (CML), whereas 17-25% of patients with acute lymphocytic leukemia and 0.9-3% patients with *de novo* acute myeloid leukemia (AML) carry a p190$^{\text{BCR-ABL}}$ fusion protein. Cases of patients with AML/CML carrying two specific primary molecular changes, *BCR-ABL* and core binding factor-β-myosin heavy chain 11 (*CBFβ-MYH11*) fusion genes have been rarely reported. The present study aimed to understand the nature and mechanism of this particular type of leukemia through case reports and literature review. A total of four patients who were diagnosed as AML/CML with *BCR-ABL* and *CBFβ-MYH11* fusion genes in the First Affiliated Hospital of Soochow University (Suzhou, China) between January 2004 and December 2012 were examined. Morphological analysis of bone marrow cells, flow cytometry, quantitative polymerase chain reaction of *p210$^{BCR-ABL}$* and *CBFβ-MYH11* transcripts as well as cytogenetic and fluorescence *in situ* hybridization analyses were performed. A total of 4 patients who exhibited fusion of *p210$^{BCR-ABL}$* and *CBFβ-MYH11* were identified. A single patient (case 1) was first diagnosed CML-acute phase (AP), which progressed rapidly to CML-blast crisis (BC), and three patients (cases 2, 3 and 4) were diagnosed with AML with bone marrow eosinophilia at first presentation with no evidence of previous onset of CML. All cases achieved remission following conventional chemotherapy/hematological stem cell transplantation combined with the inhibitor of tyrosine kinase (TKI) maintenance therapy. The patients with CML carrying and expressing *BCR-ABL* and *CBFβ-MYH11* fusion genes appeared more likely to rapidly progress to AP or BC. Therefore, the product of the *CBFβ-MYH11* fusion gene may serve an important role in the transformation of CML. The co-expression of p210$^{\text{BCR-ABL}}$ and *CBFβ-MYH11* fusion genes in myeloid leukemia may be a molecular event occurring not only during the development of CML, but also in AML.

Introduction

Numerous acquired molecular abnormalities and cytogenetic abnormalities are strongly associated with hematological malignancies (1). Core binding factors (CBFs) are a family of heterodimeric transcriptional regulators containing CBFβ (2). The inversion of chromosome 16, fusion of *CBFβ* gene at 16q22 with the smooth muscle myosin heavy chain (*MYH11*) gene at 16p13 region, forms the *CBFβ-MYH11* fusion gene, inhibiting the differentiation of hematopoietic cells by altering transcriptional regulation (3,4). Inv(16)(p13q22) or t(16;16)(p13q22) is a recurrent genetic abnormality, which fuses the core binding factor-β (*CBFβ*) gene to the myosin heavy chain 11 (*MYH11*) gene. Inv(16)(p13q22) or t(16;16)(p13q22) has been recognized as a feature of acute myelomonocytic leukemia with abnormal eosinophils by the 2008 World Health Organization classification and was designated as M4EO in the French-America-British cooperative group classification (5). Patients with inv(16)(p13q22) or t(16;16)(p13q22) mutations have been identified to exhibit a more favorable clinical course, an improved response to chemotherapy/stem cell transplantation, and longer remission and survival in this AML subtype compared to those without inv(16)(p13q22) or t(16;16)(p13q22)(2). First described by Nowell and Hungerford as a minute chromosome in patients with granulocytic leukemia, the Philadelphia (Ph) chromosome is a result of

Correspondence to: Professor Zi-Xing Chen, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Hematology, Soochow University, Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, 188 Shizi Street, Suzhou, Jiangsu 215006, P.R. China
E-mail: szchenzx@263.net

*Contributed equally

reciprocal translocation involving the long arms of chromosomes 9 and 22 (6,7). This translocation results in the formation of a hybrid breakpoint cluster region-ABL proto-oncogene 1 (*BCR-ABL*) gene, which codes for a protein with enhanced tyrosine kinase activity (8). It has been demonstrated that the *BCR-ABL* fusion gene is the hallmark of typical chronic myeloid leukemia (CML). Cases of CML were additionally classified as chronic phase (CP), accelerated phase (AP) or blast crisis (BC) according to criteria of WHO classification (9). The *BCR-ABL* rearrangement leads to a p210 chimeric protein in typical CML, whereas 17-25% of patients with acute lymphocytic leukemia and 0.9-3% patients with *de novo* acute myeloid leukemia (AML) possess a p190[BCR-ABL] fusion protein (1,10). The present study aimed to understand the nature and mechanism of this particular type of leukemia through case reports and literature review. A total of 4 patients who were diagnosed as AML/CML with *BCR-ABL* and *CBFβ-MYH11* fusion genes at the First Affiliated Hospital of Soochow University between January 2004 and December 2012 were examined, with a detectable protein product of p210[BCR-ABL], were included in the present study. The cases described in the present report may assist in understanding the entity and mechanism of this particular type of leukemia.

Case report

The clinical files of the First Affiliated Hospital of Soochow University were examined for patients who were diagnosed with acute/chronic leukemia with *BCR-ABL* and/or *CBFβ-MYH11* fusion genes during January 2004 to December 2012. A total of four patients were identified with the *CBFβ-MYH11* fusion gene concomitant with *BCR-ABL* expression. The patient samples were taken at different time points: Case 1 was taken in June 2010, case 2 in August 2010, case 3 in September 2011 and case 4 in September 2010. Bone marrow (BM) aspirates were collected into syringes containing media supplemented with heparin. Therefore, the present report summarizes the clinical and laboratory features of four patients with the coexistence of *BCR-ABL* and *CBFβ-MYH11* fusion genes, including three males and one female with a median age of 29 years (range, 18-40; Tables I and II). All patients exhibited constitutional symptoms, including progressive fatigue, localized or diffuse pain and low-grade fever. Physical examination revealed splenomegaly in cases 1 and 4 and scattered petechiae and ecchymosis on the trunk and lower extremities in cases 3 and 4. The peripheral blood count revealed anemia and thrombocytopenia in three cases. Morphology and cytochemical studies were performed on cells from the bone marrow aspirate smears stained with Wright's stain (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) for 15 min and myeloperoxidase respectively. For myeloperoxidase staining, slides had 10-15 drops 0.3% benzidine ethanol solution added to them, after 1 min, 10-15 drops of H_2O_2 solution were added for 5 min. Slides were rinsed and Wright's stain was added for 30 min, followed by another rinse (benzidine ethanol solutionand H_2O_2 solutionwere purchased from Shanghai Sun Biotech Co., Ltd., Shanghai, China). Images were captured using an optical microscope (OLYMPUS CX-31; Olympus Corporation, Tokyo, Japan) at magnifications, x100 and x1,000. Based on the morphology of the BM cells (Fig. 1), three cases were diagnosed with AML-M4 subtype with an

abnormal eosinophil component (M4EO; cases 2, 3 and 4), and case 1 was diagnosed with CML-BC. As summarized in Table I, the percentage of blasts in bone marrow samples was 10-49%, and the eosinophil counts ranged from 4-14%. Immunophenotyping, the blasts of all patients were positive for cluster of differentiation (CD)13, CD33, CD117, CD34 and negative for B and T cell markers. The multiplex polymerase chain reaction (PCR) detected *BCR-ABL* and *CBFβ-MYH11* transcripts in all 4 cases. Bone marrow mononuclear cells (BMNCs) were separated from bone marrow of patients by Ficoll-Hypaque (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Total RNA was extracted from BMNCs using TRIzol® (Invitrogen; Thermo Fisher Scientific, Inc.). The RNA was pretreated with DNase and used for cDNA synthesis with random hexamers (Invitrogen; Thermo Fisher Scientific, Inc.). The primers were synthesized to order by Sangon Biotech Co., Ltd. (Shanghai, China) with the following sequences: *BCL-ABL* F, 5'-AGCATTCCGCTGACCATCA-3'; *BCL-ABL* R, 5'-ACTCAGACCCTGAGGCTCAAAG-3'; *BCL-ABL* P, 5'-6-carboxyfluorescein (6-FAM)-AAGCCC TTCAGCGGCCAGTAGCAT-carboxytetramethylrhodamine (TAMRA)-3'. CBFβ/MYH11 F, 5'-CATTAGCACAACAGG CCTTTGA-3'; CBFβ/MYH11 R, 5'-AGGGCCCGCTTGGA CTT-3; *CBFβ/MYH11* P, 5'-6-FAM-TCGCGTGTCCTTCTC CGAGCCT-TAMRA-3'. The quantitative (q)PCR conditions were as follows: 2 min at 50°C for denaturation, 10 min at 95°C, 15 sec at 95°C and 60 sec at 60°C, followed by 40 cycles of amplification. The relative quantification of *CBFβ-MYH11* and *BCR-ABL* fusion genes was performed by the $2^{-\Delta\Delta Cq}$ method (11). The reverse transcription (RT)-qPCR results demonstrated that the copy numbers of *CBFβ-MYH11* and *BCR-ABL* fusion genes were >5,000 copies/10^4 ABL copies in three patients (cases 2, 3 and 4). By contrast, in case 1 only the *BCR-ABL* transcript was detected at similar levels (>5,000 copies/10^4 ABL copies). Cytogenetic analysis was performed on of the BM cells after 24 h culturing by the RBG (R-band by Brdu using Giemsa) technique (12). At least 10 metaphases were examined for each case. Karyotypes were described according to the standard 2009 International System for Human Cytogenetic Nomenclature criteria (13,14).

Fluorescence *in situ* hybridization (FISH) analysis was performed on interphase nuclei and metaphases of the BM cells to confirm the presence of the *BCR-ABL* and *CBFβ-MYH11*-fused genes. The *BCR-ABL* dual-color, double fusion translocation probes and the *CBFβ* dual color break-apart rearrangement probes were used in the FISH analysis according to the manufacturer's protocol (Beijing GP Medical Technologies, Ltd., Beijing, China). Bone marrow cells were cultured in RPMI-1640 medium (Hyclone; GE Healthcare Life Sciences, Logan, UT, USA) supplemented with 10% bovine fetal serum (Bovogen Biologicals, Keilor East, VIC, Australia). The specimens were placed on the slide, precipitated in ethanol, then ageing in 2X 0.3 M trisodium citrate, (SSC; pH 7.0) for 30 min at 37°C. Samples were then dehydrated using increasing gradients (70, 85 and 100%) of ethanol at room temperature for 2 min, and then dried at room temperature. A total of 5 μg probes were mixed with the denatured control probe, denatured for 5 min at 75°C, then hybridized overnight at 37°C. Slides were then washed in 0.4X SSC at 72°C for 2 min and rinsed in 2X SSC at room temperature

Table I. Summary of clinical features and morphology data of bone marrow samples.

Case no.	Sex	Age, years	Symptoms	Signs	Peripheral blood			Bone marrow, %		Initial diagnosis	Outcome
					WBC, x10⁹/l	PLT, x10⁹/l	HB, g/l	Blast	Eosinophils		
1	M	40	Body pain	Splenomegaly	191.8	389.0	119.0	10.0	5.5	CML-BC	Succumbed to disease
2	M	36	NA	Splenomegaly	50.6	50.0	60.0	49.0	NA	AML-M4EO	Succumbed to disease
3	F	18	Fever	Petechiae, ecchymosis	72.2	22.0	61.0	46.0	4.0	AML-M4EO	Succumbed to disease
4	M	31	Fatigue	Splenomegaly, petechiae, ecchymosis	67.5	21.0	99.0	43.0	14.0	AML-M4EO	Alive

NA, not available; M, male; F, female; WBC, white blood cell count; PLT, platelet count; HB, hemoglobin; AML-M4EO, AML with bone marrow eosinophilia; CML-BC; chronic myeloid leukemia-blast crisis.

for 2 min, then in 70% ethanol for 2 min. Finally, slides were counterstained with 1 mg/ml 10 μl DAPI for 15 min. Slides were then screened using an fluorescence microscope DMRB (OLYMPUS BX-51; Olympus Corporation, Tokyo, Japan) at magnification, x1,000. A minimum of 500 interphase cells were observed. Images were captured and analyzed using the VideoTesT (VT-FISH2.1, Nature Gene Corporation, Medford, NJ, USA). FISH analysis also demonstrated the rearrangement of *CBFβ-MYH11* and *BCR-ABL* fusion signals in all cases, and the percentage of the two fusion genes was >45% (Fig. 2). Cytogenetic analysis of all patients revealed inv(16)(p13q22) or t(16;16)(p13q22) and Philadelphia chromosome (Fig. 3). In addition, expression of trisomy 8 was detected in case 1, and the loss of Y chromosome was detected in case 2. Based on physical examinations, hematological data, BM morphology and cytogenetic and molecular analyses, a single patient (case 1) was first diagnosed with CML-acute phase (AP), which rapidly progressed to CML-BC, and three patients (cases 2, 3 and 4) were diagnosed with AML-M4EO at first presentation with no evidence of previous onset of CML. Patients were treated with various therapeutics, including idarubicin (cases 1-4), cytarabine (cases 1-4), daunorubicin (cases 2 and 3) and tyrosine kinase inhibitors (TKI; cases 1 and 4). A total of three patients achieved complete remission following first round of chemotherapy (cases 1, 3 and 4). Case 2 succumbed to respiratory failure following a pulmonary infection. Following the fourth round of chemotherapy, case 3 abandoned treatment. A total of two patients received unrelated donor peripheral hematopoietic stem cell and autologous peripheral hematopoietic stem cell (case 4) transplantations. Case 1 succumbed to Graft vs. host disease (GVHD), and case 4 was in good condition for 24 months following transplantation. The abnormal eosinophils observed in case 1 and case 2 presented as excessive eosinophils in BM samples. In all cases, the blasts were of myeloid lineage and there was evidence of monocytic differentiation, as demonstrated by immunophenotypic analysis, in cases 3 and 4. Peripheral blood monocytosis was exhibited in all cases. Patient data and protocol were approved by the Ethics Committee at the First Affiliated Hospital of Soochow University. Informed written consent was obtained from each patient.

Discussion

The present report describes four patients with *CBFβ-MYH11* and *BCR-ABL* fusion genes. The inv(16) genetic abnormality was detected in case 1 at the time of blastic transformation. Although case 2 was diagnosed with AML-M4EO based on the BM cell morphology, the patient (case 2) should have been diagnosed CML-BP for the following reasons: i) The patient displayed clinical characteristic of CML, including leukocytosis and massive splenomegaly; ii) the Ph chromosome, which typically occur in CML-BC, was detected in case 2; the rearrangement of *CBFβ* in addition to *BCR-ABL* had been detected by FISH in the BM samples of case 3 and 4. Additionally, karyotype analysis of the BM samples from case 4 at diagnosis also confirmed that the chromosome translocation inv(16) coexisted with the Ph chromosome, suggesting that the translocation of inv(16) occured following the Ph chromosome translocation, therefore this case should have been diagnosed as *de novo* Ph(+) AML-M4EO.

Table II. Summary of the molecular and cytogenetic findings.

Case no.	Multiplex PCR	qPCR (copies/10^4 ABL copies)	FISH (%)	Cytogenetic data
1	*p210^{BCR-ABL}* *CBFβ-MYH11*	BCR-ABL (9958)	BCR-ABL(94) CBFβ-MYH11 (47)	46,X,der(Y),t(Y;1) (q12;q23), t(9;22)(q34;q11),t(9;11)(p22,q23)[4]/ 47,idem,+18[3]/ 51, idem,+4,+8,+12, +21,+mar?der(16) inv(16) (p13;q22)[4]/46,XY[2]
2	*p210^{BCR-ABL}* *CBFβ-MYH11*	BCR-ABL(8158) CBFβ-MYH11(5610)	BCR-ABL(92) CBFβ-MYH11(95)	45,X,-Y,t(9;22)t(16;16)(p13;q22)[1]/ 46,idem,+ph[9]
3	*p210^{BCR-ABL}* *CBFβ-MYH11*	BCR-ABL(9496) CBFβ-MYH11 (12602)	BCR-ABL(85) CBFβ-MYH11(91)	46,XX,t(9;22)(q34;q11) inv(16)(p13;q22)[9]/ 46,XX[2]
4	*p210^{BCR-ABL}* *CBFβ-MYH11*	BCR-ABL(5399) CBFβ-MYH11(10473)	BCR-ABL(46) CBFβ-MYH11(89)	48,XY,der(8)t(8;10)(p23;q25), der(10),t(8;10),t(10;16)(p13;q22), der(16),inv(16)(p13;q22)t(10;16)[4]/ 46,XY,idem,t(9;22)(q34;q11)

qPCR, quantitative polymerase chain reaction, CBFβ-MYH11, core binding factor-β-myosin heavy chain 11; BCR-ABL, breakpoint cluster region-ABL proto-oncogene 1.
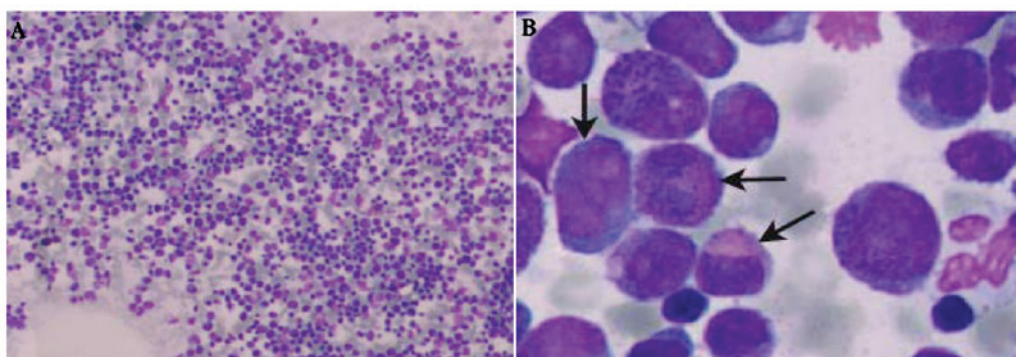

Figure 1. Bone marrow smear with hypercellular, dysplastic monocytes and eosinophils. (A) Wright's staining, magnification, x100. (B) Wright's staining, magnification. Arrows indicate monocytes. Magnification, x1,000.

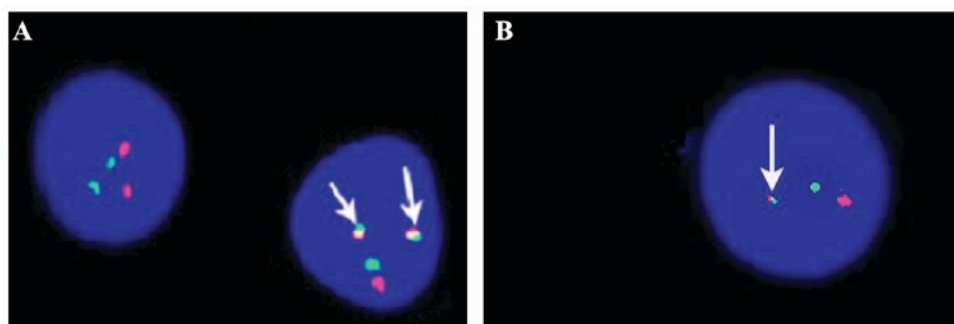
Figure 2. Fluorescence *in situ* hybridization. (A) LSI *BCR-ABL* dual-colordouble fusion translocation probes demonstrating a fused red-green (*BCR-ABL*) signal (yellow). (B) LSI core binding factor-β dual color break-apart rearrangement probe revealed the presence of inv(16). BCR-ABL, breakpoint cluster region-ABL proto-oncogene 1. Magnification, x1,000.

The morphological features of CML-BC with inv(16) in the present study closely resembled those of AML-M4EO, as described in the WHO classification (15). To the best of our knowledge, the coexistence of the *BCR-ABL* and *CBFβ-MYH11* fusion genes are very rare in CML and *de novo* AML, with only 34 cases having been identified at present (Tables III and IV) (1,16-34), including the cases described in the present study. Extramedullary disease occurs in a wide age
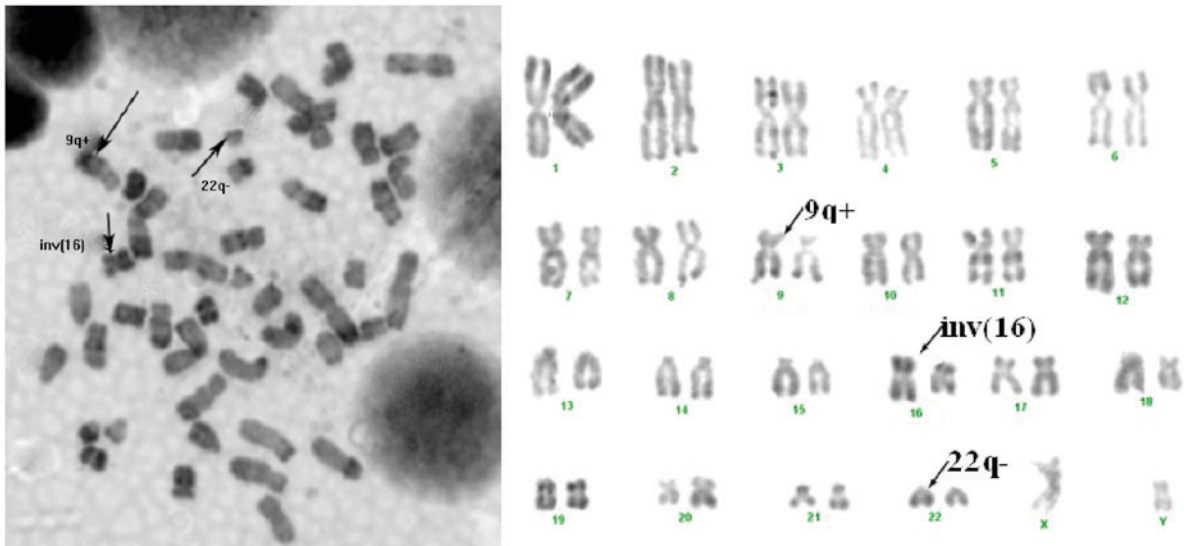
Figure 3. Karyotype of case 4 with the coexistence of t(9;22) and pericentric inv(16) at metaphase.

spectrum, ranging from 9 to 78 years (17). *CBFβ-MYH11* and *BCR-ABL* affects males and females, with an increased risk in males (17). It is suggested that males may be more likely to exhibit the simultaneous expression of *CBFβ-MYH11* and *BCR-ABL* compared with females.

It is well-known that the patients with CML-BC exhibit a poor clinical outcome. By contrast, patients with Ph(+) AML with *CBFβ-MYH11*(+) exhibit a relatively favorable prognosis, similar to AML with *CBFβ-MYH11*(+) alone (16,17). Notably, the outcomes of the patients of the present study were consistent with these data. As initially diagnosed with CML-AP, case 1 was first treated with imatinib (400 mg/day orally), but was shortly changed to chemotherapy with cytarabine (100 mg/m^2/day, days 1-7, intravenous drip) and idarubicin (8 mg/m^2/day, days 1-3, intravenous drip) for 2 cycles, in combination with imatinib as the patient rapidly progressed to CML-BC. Although bone marrow and blood remission was achieved, the patient quickly relapsed and the treatment course was complicated by the lung infection. The patient underwent unrelated donor-allogeneic hematopoietic stem cell transplantation in November 2011. However, 15 months following transplantation, the patient succumbed to serious GVHD. Following the standard dose of induced chemotherapy, case 3 and 4 attained complete remission. Subsequently, case 3 received autologous-peripheral blood stem cell transplantation in June 2011 and remained in complete remission for 32 months following diagnosis.

Based on the data of the patient with CML in the present study, and previous studies (35), it is suggested that patients with CML carrying and expressing the *BCR-ABL* and *CBFβ-MYH11* fusion genes appear more likely to rapidly progress to AP or BC compared with patients with CML without the co-existence of these two genes. The product of the *CBFβ-MYH11* fusion gene may have served an important role in the transformation of CML, and the monocytes and eosinophils may be derived from common leukemic progenitors affected by the product of the *CBFβ-MYH11*.

p210$^{BCR-ABL}$ is the hallmark of CML, as identified in case 1 and case 2. However, it has also been previously demonstrated that an additional rearrangement to the classical p190$^{BCR-ABL}$ may be identified in AML (36). It appears that t(9;22)(q34;q11) with a p210$^{BCR-ABL}$ rearrangement may be a molecular event occurring not only during the development of CML, but also in AML following the Ph chromosomal anomaly. From the results of the previously described patients and the patients with AML with p210$^{BCR-ABL}$ in the present study, the TKI imatinib used in maintenance therapy was able to diminish the detectable levels of *BCR-ABL* transcripts, suggesting that in such cases, imatinib may be an effective treatment.

As these patients are so rare, an appropriate diagnosis and the standard treatment for them are currently not available. As the leukemic cell populations in the majority of patients are composed of diverse clones with heterogeneous phenotypes, the possibility that the *p210$^{BCR-ABL}$* rearrangement and *CBFβ-MYH11* may reside in different subclones in these patients cannot be excluded. These different subclones would subsequently evolve during the clinical course, depending on their response to treatment. Therefore, more careful karyotyping and FISH analysis are required to dissect the sequential molecular events occurring in a singular clone or in various subclones in these patients, in order to more precisely define this subtype of leukemia.

In conclusion, the present report demonstrated that t(9;22)(q34;q11) with a *p210$^{BCR-ABL}$* rearrangement may be a molecular event occurring not only during the development of CML but also in AML following a primary specific chromosomal anomaly. Co-expression of *p210$^{BCR-ABL}$* and *CBFβ-MYH11* fusion genes may be a molecular event in various types of myeloid leukemia. The patients with CML carrying and expressing *BCR-ABL* and *CBFβ-MYH11* fusion genes appear more likely to progress rapidly to AP or BC compared with patients with CML without the co-existence of these two genes; The product of the *CBFβ-MYH11* fusion gene may serve an important role in the transformation of CML.

Acknowledgements

Table III. Summary of identified patients with acute myeloid leukemia with *BCR-ABL* and core binding factor-β-myosin heavy chain 11.

Author, year	Age	Sex	Blasts, % (bone marrow)	*BCR-ABL* status	Cytogenetic findings	Clinical outcome, time from diagnosis (months)	(Refs.)
Preudhomme *et al*, 1992	64	M	32	p190	46,XY,inv(16)(p13q22),t(9;22)(q34;q11)[30]	Alive, 12	(18)
Siddiqui *et al*, 2002	23	M	21	ND	46,XY,t(9;22)(q34;q11.2)inv(16)(p13q22)	Alive, 36	(19)
Li and Hayhoe, 1988	39	M	>30	ND	46,XY(9%)/47,XY,-18,+22,inv(16)(p13q22),del(20)(p12p13) del(20)(q12q13),t(9;22)(q34;q11),der(16)t(16;?18) (q24;q21),+mar(91%)	Alive, 38	(20)
Wu *et al*, 2006	44	M	44.5	p190	46,XY,t(9;22)(q34.1;q11.2)inv(16)(p13.1q22)	Succumbed to disease	(16)
Miura *et al*, 1994	40	M	36	M-bcr(-)	46,XY,inv(16)(p13q22)[17]/46,XY,idem,t(9;22)(q34;q11)[3]	Alive, 27	(21)
Secker-Walker *et al*, 1992	9	F	ND	p190	46,XX,inv(16)(p13q22)[21]/46,XX,t(9;22)(q34;q11)inv(16) (p13q22)[8]/ 46,XX[10]	Molecular remission, 1 month	(22)
Svaldi *et al*, 2001	40	F	NA	p190	46,XX,inv(16)(p13q22)[4]/46,idem(9;22)[18]	NA	(23)
Tirado *et al*, 2010	13	M	92	ND	46,XY,inv(16)(p13.1q22)[2]/46,idem,del(7) (q22q32)[16]/46,idem,t(9;22;19)	Alive, 10	(24)
Cividin *et al*, 2004	38	F	41	p190	46,XX[22]/46,XX,inv(16)(p13q22)[1]/46,XX,idem,t(9;22) (q34;q11)[25]/ 46,XX,t(2;9;22)(q32;q34;q11),inv(16)(p13q22)[23]	Alive, 12	(1)
Roth *et al*, 2011	30	F	9	p190	46,XX,t(9;22;17;19)(q34;q11.2;q25;p13.1),inv(16)(p13q22)[19]	Alive, 80	(25)
Roth *et al*, 2011	35	M	48	p190	46,XY,der(16)inv(16)(p13q22)del(16)(p11.2p13.1)[2]/ 46,XY,idem,t(9;22)(q34;q11.2)[18]	Alive, 17	(25)
Bustamante *et al*, 2012	49	M	10-15	p190	46,XX,inv(16)(p13.1q22)[5]/46,idem,t(9;22)(q34;q11.2)	NA	(26)

Breakpoint cluster region-ABL proto-oncogene 1; M, male; F, female; ND, not done; NA, not available.

Table IV. Summary of identified patients with chronic myeloid leukemia with *BCR-ABL* and core binding factor-β-myosin heavy chain 11.

Author, year	Age	Sex	Blasts, % (bone marrow)	BCR-ABL status	Cytogenetic findings	Clinical outcome, time from diagnosis	(Refs.)
Wu et al, 2006	33	M	27	p210	46,XY,t(9;22)(q34.1;q11.2)[18]/46,XY,idem,inv(16)(p13.1q22)[2]	Succumbed following allo-BMT	(16)
Wu et al, 2006	41	M	63	p210	46,XY,t(9;22)(q34.1;q11.2),inv(16)(p13.1q22)[20]	Alive, 4 years	(16)
Wu et al, 2006	62	F	52	p210	46,XX,t(9;22)(q34.1;q11.2,inv(16)(p13.1q22)[20]	Succumbed to disease, 24 months	(16)
Wu et al, 2006	21	M	2	p210	46,XY,t(9;22)(q34.1;q11.2)[17]/46,idem,inv(16)(p11.2q22)[3]	Alive, 6 years	(16)
Wu et al, 2006	44	M	10	p210	46,XY,t(9;22)(q34.1;q11.2)[90%]46,XY,inv(16)(p13q22),t(9;22)(q34.1;q11.2)[1] 46,XY,t(6;16)(q22;q22),t(9;22)(q34.1;q11.2)[1]	Succumbed to disease, 24 months	(16)
Merzianu et al, 2005	43	F	30	p210	46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[20]	Succumbed to disease, 3 months	(27)
Merzianu et al, 2005	61	F	20	p210	46,XX,t(9;22)(q34;q11.2)[3]/46,XX,t(9;22)(q34; q11.2),inv(16)(p13q22)[7]/ 47,XX,+8,t(9;22)(q34; q11.2)[2]/47,XX,+8,t(9;22)(q34;q11.2),inv(16)(p13q22)[4]/ 46,X,add(X)(p22.3),t(9;22)(q34;q11.2),del(12)(p11.2),inv(16)(p13q22)[1]/ 47,XX,t(9;22)(q34;q11.2),inv(16)(p13q22),+der(2)t(9;22)[1]/46,XX[2]	Succumbed to disease, 7 months	(27)
Merzianu et al, 2005	47	M	40	p210	46,XY,t(9;22)(q34;q11),inv(16)(p13q22)[25]	Succumbed to disease, 1 month	(27)
Merzianu et al, 2005	36	F	70	p2102	46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[20]	Succumbed to disease, 1 month	(27)
Merzianu et al, 2005	48	M	20	p210	46,XY,t(9;22)(q34;q11.2),inv(16)(p13q22)[6]/46,XY[14]	Alive, 7 months	(27)
Tsuboi et al, 2002	44	M	59	p210	47,XY,t(9;22)(q34;q11)inv(16)(p13q22),+der(22)t(9;22)/48,idem,+8	Succumbed to disease, 3 months	(28)
Myint et al, 1997	29	M	90	p210	46,XX,t(9;22)inv(16)(p13;q22)	Succumbed to disease, 0 months	(29)
Evers et al, 1992	39	M	25	p210	46,XX,-2,-9,-12,-21,+der(9)t(9;?;22),+der(12)t(12;?2)(q24?p22),inv(16)	Succumbed to disease, 10 months	(30)
Asou et al, 1992	51	M	10	p210	46,XY,t(9;22)(q34;q11),inv(16)(p13q22)	Succumbed to disease, 3 months	(31)
Enright et al, 1992	78	M	19	p210	46,XY,t(9;22)(q34;q11.2),inv(16)(p13q22)	Succumbed to disease, 3 months	(32)
Heim et al, 1992	21	M	70	p210	45,X,-Y,t(9;22)(q34.1;q11.2),inv(16)(p13.1q22)	Alive, 30 months	(33)
Colovic et al, 1998	58	M	18	p210	46,XY,t(9;22)(q34.1;q11.2),inv(16)(p13.1q22)	Alive, 10.5 years	(34)
Ninomiya et al, 2011	63	M	31	p190	46,XX,t(9;22)(q34;q11.2),inv(16)(p13.1q22)	Succumbed to disease, 7 months following BMT	(17)

BCR-ABL, breakpoint cluster region-ABL proto-oncogene 1; M, male; F, female; BMT, bone marrow transplantation.

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