

Myeloid blast phase of chronic myelogenous leukemia, *BCR-ABL1*⁺, associated with a secondary translocation involving *MLL*: case report and review of the literature

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Abstract Although secondary cytogenetic aberrations are frequent in myeloid blast phase (MBP) of chronic myelogenous leukemia, *BCR-ABL1*⁺ (CML), balanced translocations of the type that are recurrent in de novo acute myeloid leukemia (AML) are unusual in the setting of CML-MBP, and rearrangement of *MLL* as a secondary event in CML-MBP is extremely rare. We present a case of CML-MBP in which a translocation involving *MLL* was acquired as a secondary abnormality and review the relevant literature. The clinical, morphologic, immunophenotypic, and genetic findings were reviewed. A search of the relevant literature was performed. We report a case of CML presenting in MBP, in which a balanced translocation involving *MLL* was identified as a secondary cytogenetic aberration. The specific translocation seen in this case, t(3;11)(q21;q23), which is rare in de novo AML, has not to our knowledge been reported in the context of CML-MBP. Upon the completion of induction therapy, and attainment of morphologic remission of the acute leukemia, the secondary *MLL* translocation became undetectable, though *BCR-ABL1* persisted. Although published examples are extremely rare, CML-MBP may be associated with secondary translocations involving *MLL*.

Keywords Myeloid blast phase · Chronic myelogenous leukemia · *MLL* gene

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Introduction

Chronic myelogenous leukemia, *BCR-ABL1*⁺, (CML) is a myeloproliferative neoplasm that arises from a pluripotent hematopoietic stem cell that is characterized by *BCR-ABL1* fusion [1]. The most common cytogenetic finding in CML, the Philadelphia (Ph) chromosome, results from a reciprocal translocation that juxtaposes the *ABL1* gene on chromosome 9 with the breakpoint cluster region (*BCR*) on chromosome 22, resulting in a *BCR-ABL1* fusion gene with enhanced *ABL1* kinase activity [2]. Variant translocations involving chromosomes 9 and 22 (and possibly additional chromosomes), or cryptic translocations of 9q34 and 22q11.2, are seen in 5–10 % of the patients with CML at diagnosis. The natural history of untreated *BCR-ABL1*⁺ CML is potentially triphasic, with initial presentation as an indolent chronic phase, followed by progression to a so-called accelerated phase, and terminating in a blast phase, at which point patients meet criteria for acute leukemia (which is more commonly of myeloid lineage, and termed myeloid blast phase or MBP).

Data from multiple studies indicate that progression of CML to accelerated and blast phases is accompanied by the acquisition of chromosomal alterations and mutations in addition to the initial *BCR-ABL1* [2]. At diagnosis, fewer than 5 % of the patients have chromosomal abnormalities in addition to the Ph chromosome, but as the disease progresses, the proportion of additional chromosomal abnormalities increases to 40–70 % [3]. The most frequent secondary abnormalities associated with disease progression in CML include trisomy 8, a second Ph chromosome, isochromosome 17q, and other alterations involving p53, trisomies of 19 or 21, and abnormalities of chromosome 7 [4]. By comparison, the balanced translocation characteristic of de novo

acute myeloid leukemia (AML) with recurrent genetic abnormalities [1] is uncommon in CML-MBP [5–7]. Translocations involving *MLL* on chromosome 11q23, which are most commonly associated with B lymphoblastic leukemia in infants, de novo AML, and therapy-related myeloid neoplasms are extremely rare as secondary genetic events in CML-MBP. We present here a case of CML-MBP in which a translocation involving *MLL* was acquired as a secondary genetic abnormality and review the literature regarding *MLL* rearrangements as secondary abnormalities in CML-MBP.

Case report

A 25-year-old man with no previous medical history presented to our hospital with a 3-day history of headache, cough, post-tussive emesis, chest pain worsening with deep breaths, and leg pain. He denied any dizziness, blurry vision, or weight loss. At presentation, he was found to be tachycardic and hypertensive, with a normal mental status. Computed tomography angiography done in the emergency department to exclude acute pulmonary embolism was negative but showed diffuse multifocal pulmonary nodular opacities, suspicious for pneumonia. During his initial evaluation in the emergency department, his white blood cell (WBC) count was noted to be markedly elevated (629,000/uL). He was also anemic (hemoglobin 9.1 g/dL) and thrombocytopenic (platelet count 47,000/uL).

Review of a peripheral blood smear revealed anemia, thrombocytopenia, and marked leukocytosis with a preponderance of blasts. The blasts were medium to large in size, with ovoid or irregular nuclei and finely dispersed chromatin. One or more distinct nucleoli were noted, in addition to moderate amounts of agranular basophilic cytoplasm (Fig. 1). Because of the patient's marked leukocytosis, emergent leukopheresis was performed. 8-color flow cytometric immunophenotyping was performed on peripheral blood. Of the WBCs, 85 % were blasts, positive for HLA-DR, CD123, and the myeloid antigens, CD13, CD33, CD64, and CD117. The progenitor cell antigen (CD34), myeloperoxidase, and other antigens associated with myelomonocytic maturation, TdT, and all B-lineage and T-lineage antigens tested were negative (Table 1, Fig. 2). On the basis of the morphologic and flow cytometric findings in the peripheral blood, a diagnosis of AML was established. After hydration and initial treatment with hydroxyurea and allopurinol, the patient underwent induction chemotherapy with cytarabine, daunorubicin, and etoposide, to which bortezomib was added.

Cytogenetic studies performed on peripheral blood revealed two cell populations: a stemline with a variant t(9;22)(q34;q11.2) was present in all 20 metaphases, while a second abnormality, t(3;11)(q21;q23), was present in 15/20

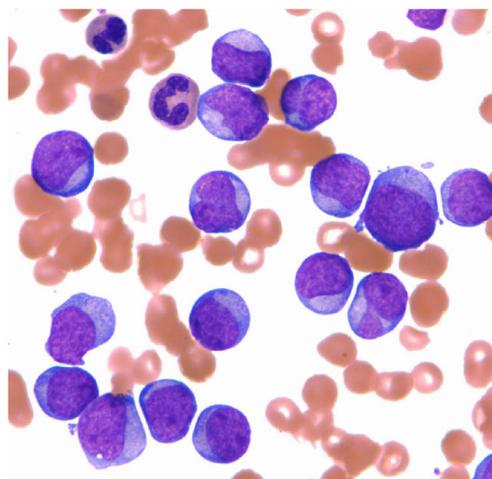


Fig. 1 Bone marrow aspirate smear illustrating cytomorphology of the blasts. The blasts are medium to large in size, with ovoid or irregular nuclei, finely dispersed chromatin, one or more distinct nucleoli, and moderate amounts of agranular basophilic cytoplasm. (Wright stain, $\times 1000$)

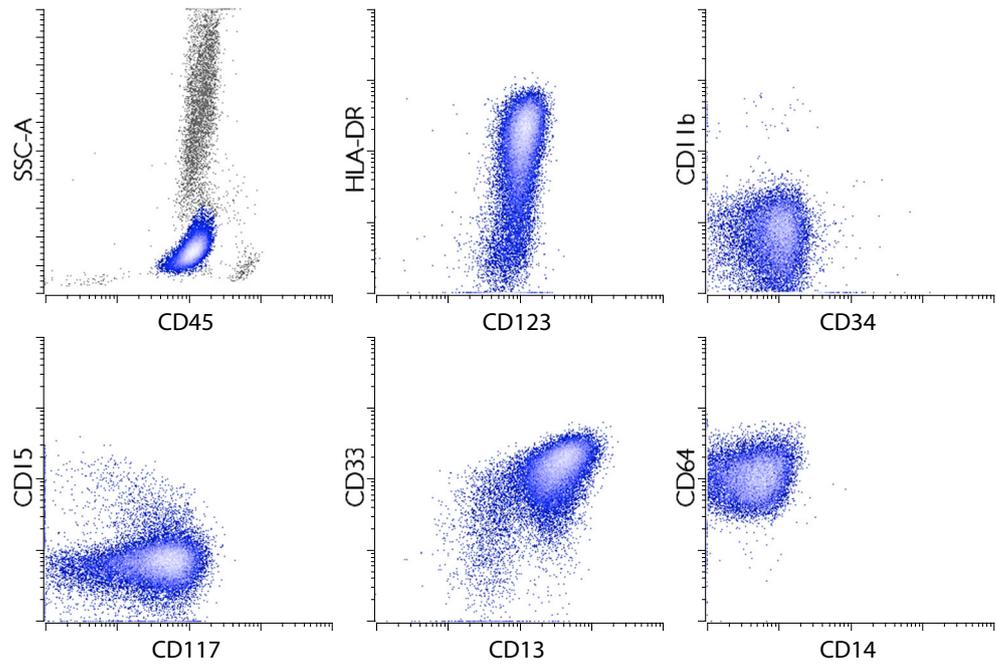
metaphases. Fluorescence in situ hybridization (FISH) studies confirmed *BCR-ABL1* fusion with a variant signal pattern in 90 % of nuclei scored and demonstrated *MLL* rearrangement in 86 % of nuclei scored. By quantitative RT-PCR, two fusion transcripts were identified (b3a2 and b2a2) that are transcribed from the major breakpoint cluster region (M-bcr) and translated into the p210 fusion protein typical of CML.

Evaluation of the bone marrow after induction therapy revealed a hypocellular marrow with fewer than 5 % blasts (Fig. 3). In addition, there were numerous small, monolobated (“dwarf”) megakaryocytes and many sea-blue histiocytes (Fig. 4), both of which are common in the bone marrow at diagnosis in patients with CML [1]. Cytogenetic studies showed the same variant t(9;22) seen at diagnosis in 4/20 metaphases. However, none of the metaphases contained the t(3;11), which had also been seen at diagnosis in 15/20 metaphases. FISH studies confirmed both the variant t(9;22) and the absence of *MLL* rearrangement. The patient was discharged to home on dasatinib and was being evaluated for a possible stem-cell transplant from a matched sibling but was re-admitted 6 months later with altered mental status and multiple hyperdense annular masses throughout supratentorial

Table 1 Summary of blast immunophenotype

Myeloid	B-lineage	T-lineage	Other
CD13+	TdT-	cCD3-	HLA-DR+
CD33+	CD19-	CD2-	CD34-
CD64+	CD79a-	CD4-	
CD117+	CD22-	CD8-	
MPO-		CD5-	
		CD7-	

Fig. 2 Peripheral blood flow cytometric immunophenotyping data. Gated blasts are indicated in blue



cortex, which were associated with prominent edema. Microscopic review of the cerebrospinal fluid revealed pleocytosis, with a predominance of blasts cytologically similar to those seen at diagnosis. Flow cytometric analysis of the CSF confirmed a predominance of myeloblasts, whose composite immunophenotype resembled that seen at diagnosis. The patient’s status declined rapidly, and he expired within days of his presentation with CNS relapse.

Discussion

We describe a patient who presented clinically with CML-MBP, in whom a balanced translocation involving *MLL* was

acquired as a secondary cytogenetic abnormality. Although a presumptive diagnosis of AML was made initially on the basis

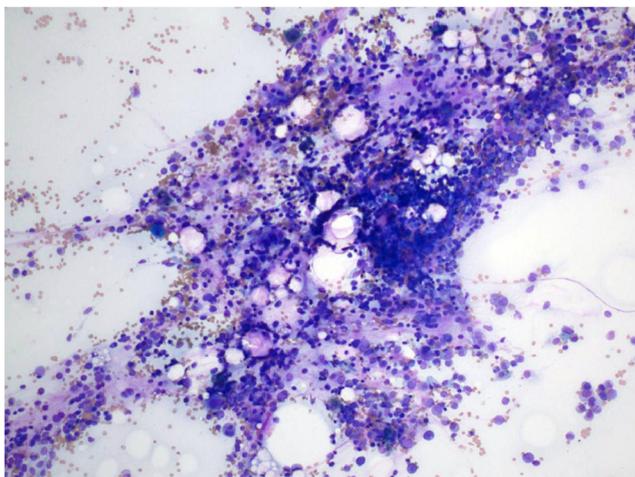


Fig. 3 Bone marrow aspirate smear after induction therapy. The marrow is hypocellular, with fewer than 5 % blasts. (Wright stain, ×200)

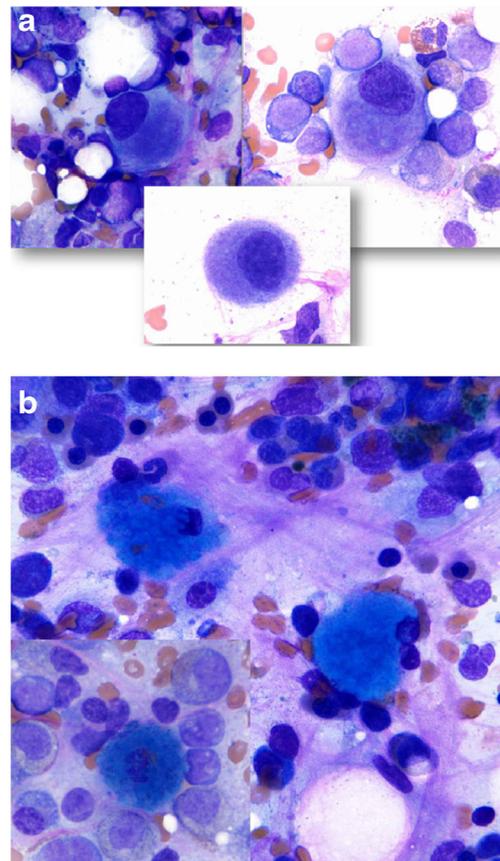


Fig. 4 Bone marrow aspirate smear after induction therapy showing monolobated (“dwarf”) megakaryocytes (a), and sea-blue histiocytes (b) (both Wright stain, ×1000)

of the peripheral blood morphologic and flow cytometric findings without cytogenetic studies, several lines of evidence support a diagnosis of CML-BP rather than de novo Ph + AML [8]. First, whereas the variant t(9;22) was present in 20/20 metaphases at diagnosis, t(3;11) was only present in a subset (15/20) of metaphases, indicating its acquisition as a secondary cytogenetic abnormality. Second, after induction therapy, at which time blasts represented fewer than 5 % of the marrow cellularity, morphologic examination of the marrow revealed changes typical of chronic-phase CML, including dwarf megakaryocytes and sea-blue histiocytes. Finally, morphologic clearance of the blasts coincided with eradication of the secondary t(3;11) but not the variant t(9;22). Taken together, the findings are consistent with progression of a clinically inapparent chronic-phase CML to MBP associated with acquisition of a secondary t(3;11).

Clonal evolution of CML is common as the disease progresses to accelerated and blast phases. The most frequent abnormalities described in CML progression are trisomy 8, a second Ph chromosome, isochromosome 17q, and other p53 alterations, trisomies of 19 and 21, and abnormalities of chromosome 7 [4, 9, 10]. The frequency of additional cytogenetic abnormalities increases to 40–70 % as the disease progresses from CML-CP to CML-BP [3]. Interestingly, in a recent large series of patients with CML [9], the presence at diagnosis of a second Ph chromosome, trisomy 8, isochromosome 17q, or trisomy 19 (which together were only identified in 1.4 % of cases) was the only secondary cytogenetic aberrations associated with longer time to complete cytogenetic remission and shorter progression-free and overall survival, suggesting that these are the secondary genetic events signaling progression to accelerated and blast phases.

In rare instances, chromosomal translocation characteristic of de novo AML with recurrent genetic abnormalities may be seen in CML-MBP. Examples of inv(16)(p13q22), t(15;17)(q22;q12), and t(8;21)(q22,q22) have all been reported as secondary abnormalities in CML-MBP [5–7]. In these cases, the clinical and/or morphologic findings at the time of CML-MBP resembled those seen in the corresponding de novo AML. For example, in a series of five cases of CML-MBP with inv(16), peripheral blood monocytosis and abnormal bone marrow eosinophils were identified in all cases [5], and in a report of two cases of CML-MBP with t(15;17), both patients had evidence of disseminated intravascular coagulation at the time of diagnosis [6].

Translocations involving *MLL* as a secondary alteration in CML-MBP are likewise extremely rare. Chromosome 11q23 breakpoints are characterized by a marked heterogeneity, as more than 80 chromosomal loci have been reported as partner sites in reciprocal translocations [11]. Accordingly, acute leukemias involving *MLL* may demonstrate a variety of immunophenotypes, including lymphoid and myeloid/monocytic differentiation, as well as mixed phenotype acute

Table 2 Summary of reported cases of CML with *MLL* gene rearrangement

Reference	Patient age (years) at the time of CML diagnosis and gender	Original diagnosis of diagnosis	Diagnosis at the time of MLL rearrangement	Specific translocation involving <i>MLL</i> gene	Blast phenotype	Time to BP from the original diagnosis	Survival (months from BP diagnosis)
Dastugue et al., 1991 [13]	50, M	CML-CP	CML-AP (19 % blasts)	t(9;11)(p22;q23)	MPO negative (was called undifferentiated blasts)	56 months	Died before complete BP
Sessarego et al., 1991 [14]	M	CML-CP	CML-BP	inv(11)(p11q23)	Myeloid BP	2 months after BMT	Died 5 months after BMT
Li et al., 1993 [15]	29, M	CML-CP	CML-BP	t(11;9)(q22;q23;p22;q34;q11)	Myeloid BP (FAB-M1)	84 months	Died 4 months after BP diagnosis
Nishii et al., 2001 [16]	40, F	CML-BP	CML-BP	t(11;17)(q23;q21)	Described as mixed lineage	BP at diagnosis	Died 9 months later from BMT complications
Suzuki et al., 2004 [17]	32, M	CML-CP	CML-BP	t(11;19)(q23;p13.3)	Myeloid BP	15 months	5 months

leukemias [1]. Among de novo AML with *MLL* rearrangement, t(9;11) is the most common translocation and is usually associated with monocytic features. Rearrangements of the *MLL* gene result in a variety of chimeric oncoproteins. In contrast, the t(3;11)(q21;q23) seen in the current case is rare in de novo AML [12], and to the best of our knowledge, has not been reported in CML-BP.

In a review of the literature, we identified five additional cases of CML-BP in which *MLL* rearrangement was a secondary cytogenetic abnormality (Table 2). Of the six cases reported (including the case reported here), there were five men and one woman, whose ages ranged from 25 to 50 years. In four of the five cases reported previously, patients presented clinically with chronic-phase CML, and a translocation involving *MLL* was only detected at the time of progression to blast phase, while in one case, the patient presented in accelerated phase with 19 % blasts, at which time *MLL* rearrangement was detected by karyotype in a minor clone (10 out of 50 cells). In most of the cases reported previously, the blasts were myeloid; in one case, they were considered to be undifferentiated on the basis of their lack of myeloperoxidase. Although the blasts were characterized as mixed phenotype in one reported case [16], by current WHO criteria, the antigen expression profile would be considered to represent a myeloid leukemia with aberrant expression of CD7 and dim CD19 [16].

Although published examples are extremely rare (Table 2), *MLL* rearrangement as a secondary event in CML-BP appears to be associated with a poor survival. Of five previously reported patients, four died within 5 months of blast crisis, and one died from complications of bone marrow transplant 9 months after the diagnosis of blast crisis. Our patient also died after an interval of 6 months.

Conflict of interest The authors declare that they have no competing interests.

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