CASE REPORT

Co-existence of AML1-ETO and BCR-ABL1 transcripts in a relapsed patient of acute myeloid leukemia with favorable risk group: A coincidence or clonal evolution?

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Abstract
Prognosis of acute myeloid leukemia relies heavily on the cytogenetic and molecular abnormalities. AML1-ETO fusion protein resulting from t(8;21), a recurring cytogenetic abnormality, is known to be associated with favorable prognosis. Additional molecular defects may, however, co-operate with the fusion proteins and alter the course of the disease. Among the additional cytogenetic defects, presence of Philadelphia (Ph) chromosome has rarely been documented in this subtype. Little is known about the consequences of its interactions with AML1-ETO, and its effect on morphological and clinical picture. Moreover, Ph+ clones or subclones may appear at any point during the disease course. We herein report one such unusual case of a 26-year-old female, who was diagnosed to have t(8;21) and managed accordingly. During disease relapse after 2.5 years, the bone marrow showed extensive eosinophilia and basophilia. Subsequent molecular testing showed the presence of BCR-ABL in addition to the AML1-ETO fusion product. © 2016 King Faisal Specialist Hospital & Research Centre. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction
Philadelphia (Ph) chromosome, along with the corresponding BCR-ABL fusion transcript, results from the reciprocal translocation of the BCR gene on chromosome 22 and the
ABL gene on chromosome 9 and is the hallmark of chronic myeloid leukemia (CML). Ph+ acute lymphoblastic leukemia (Ph+ ALL) is another well-established entity, which is known to be associated with poor prognosis. However, Ph positivity is rarely seen in acute myeloid leukemia (AML) and accounts for approximately 1% of all AML [1]. If present in AML, this mutation can interact with other Class I and II mutations, and further confer the leukemic cells with abnormal proliferative and antiapoptotic properties [1]. Translocation (8;21) [t(8;21) AML1-ETO] is one such Class II mutation, which is reportedly the most common recurrent cytogenetic abnormality in AML. It is found to be associated with other cytogenetic abnormalities such as del Y and del 9q(22) [2]. Although the co-existence of inv(16) and t(9;22) has been reported in both de novo AML and myeloid blast crisis in CML, concurrence of BCR-ABL1 and t(8;21) is extremely rare [1]. So far, its impact on morphology and clinical picture is not well-described in the literature. We document here an interesting case of AML1-ETO-positive AML where both BCR-ABL1 and AML1-ETO fusion transcripts were detected simultaneously at the time of relapse. The study was approved by the Institutional Review Board.

Case report

A 26-year-old female, diagnosed and treated as a case of AML, presented 2.5 years later with increasing leucocyte count. At the time of initial presentation in 2012, her conventional cytogenetic analysis had shown a normal female karyotype. However, molecular analysis revealed the presence of AML1-ETO fusion transcript. FLT3-ITD and nucleophosmin 1 (NPM 1) mutations were not detected. She had received the standard 3 + 7 induction treatment protocol for AML. The bone marrow of the patient showed morphological remission after completion of induction therapy. Following induction therapy she received four cycles of consolidation therapy with high-dose cytarabine. The consolidation phase was uneventful and the patient remained in remission until March 2015. In her present follow-up, the total leucocyte count was elevated and peripheral blood showed circulating blasts. A repeat bone marrow examination confirmed the presence of disease relapse. Differential count on aspiration smear showed approximately 30% blasts, 50% eosinophils including eosinophil and basophil (Eo-Baso) precursors, and 5% basophils (Figure 1), which were not present in the original marrow. Such extensive eosinophilia and basophilia prompted us to look for other additional molecular abnormalities like Ph chromosome. Nested polymerase chain reaction (PCR) as well as quantitative real-time PCR showed the presence of p210 fusion transcript. Patient was again given a similar 3 + 7 protocol of daunorubicin and cytarabine, respectively. Interestingly, she achieved morphological remission. Imatinib was not added to the treatment protocol because of low copy numbers of the clone. Further, she has been planned for allogenic bone marrow stem cell transplantation.

Discussion

AML with t(8;21)(q22;q22)/RUNX1-RUNX1T1 (AML1-ETO) belongs to the subgroup of AMLs with recurrent cytogenetic abnormalities and is found in about 7% of de novo adult AMLs [3]. However, the core binding factor (CBF)-related fusion proteins and inv(16) alone are incapable of promoting leukemic transformation. Certain secondary alterations cooperate with CBF fusion proteins in leukemogenesis, which encode protein effectors controlling cell proliferation and confer survival advantage to the malignant cells (Class I mutations) [4]. These Class I mutations commonly include mutations in the FLT3, RAS, KIT, and JAK2 genes. Almost 90% of AML with t(8;21) harbor additional secondary chromosome aberrations/mutations including FLT3, KIT, and RAS [5]. Although CBF-related AML confers favorable prognosis [2], a significant proportion of patients with CBF-AML still relapse at different points of time, indicating the need to identify other mutations that may be interplaying in such patients. Ph+ AML, by contrast, constitutes <1% of newly diagnosed AML cases and is considered to have an adverse prognosis [6–8]. BCR-ABL1 mutation behaves as a Class I...

Figure 1 Photomicrographs. (A) May-Grünwald–Giemsa-stained bone marrow aspiration smear showing the presence of numerous eosinophils and basophils in adjacent to blasts (arrows); (B) agarose gel electrophoresis showing polymerase chain reaction (PCR) products of second-round nested PCR: p210 (b2a2) fusion product in Lane 2; AML1-ETO fusion product in Lane 3; positive control for t(8;21) in Lane 4; negative and positive controls of p190 product in Lanes 1 and 5, respectively; 50-bp ladder in Lane 6. Note. PC = positive control.
mutation, as it confers the cells abnormal proliferative capacity. However, co-occurrence of the BCR-ABL1 fusion transcript along with other recurring cytogenetic abnormalities in AML is extremely rare [1,6,9–11] and even rarer is the acquisition of this mutation during relapse of CBF-AML [1].

In a retrospective study of >1000 AML cases, Bacher et al. [1] reported only five cases with recurrent cytogenetic abnormality co-existing with Ph+ subclones. These recurrent abnormalities included two cases of t(8;21)/RUNX1-RUNX1T1; one patient each with inv(16)/CBFB-MYH11, NPM 1 mutation, and secondary AML following myelodysplastic syndrome (MDS) with 5q deletion. These patients developed Ph chromosome at different periods [1]. Similarly, Soupir et al. [12] reported only four cases of secondary AML, all of whom developed t(9;22) following treatment for pre-existing AML or MDS over the study period of 8 years. Chen et al. [13] reported Ph positivity in one of their AML patients at the time of relapse and proposed that the Ph chromosome was a secondary aberration, which possibly had a role in clonal evolution and disease progression. Although many studies have reported the presence of t(9;22)/BCR-ABL1 at the time of initial diagnosis in cases of different subtypes of AML [7,8,10–12], its concurrence in relapsed AML patients with favorable cytogenetics group, that is, t(8;21)/inv(16), is rare. Our patient did not have any of the other established risk factors associated with relapse in AML patients such as older age, adverse cytogenetics or FLT3 mutation, or shorter duration of first remission (CR1) [14]; yet, she relapsed. Although it may be difficult to conclude whether these subclones were present at diagnosis or developed during relapse, the authors believe that these Ph+ clones evolved during relapse, because the patient had achieved remission initially.

In comparison with ALL, status of BCR/ABL1 at the time of diagnosis or relapse in AML patients is a gray zone of this malignancy. Whether it is a co-incidental finding or has implications on the overall clinical picture is not yet validated. The role of incorporating imatinib in treatment is also not well-known in such patients. Different authors had published their experiences with imatinib and the median response duration ranges from 2.5 months to 15 months [14]. A larger number of patients and in vitro studies need to be taken up to ascertain whether this mutation is just a component of the genetic instability or actually confers a higher proliferative potential to the leukemic cells.

Conflicts of interest
The authors declare that they have no conflict of interest.

References