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613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Concurrent BCR::-ABL1 and CBFB Rearrangement in De Novo Acute Myeloid Leukemia

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Introduction

Acute myeloid leukemia (AML) is known for its genetic heterogeneity. Several recurrent genetic variants have been characterized including AML-defining chromosomal rearrangements involving the core binding factor (CBF), such as inv(16)/t(16;16)/*CBFB*:: *MYH11*. [1] Less common is a subset of AML characterized by the Philadelphia chromosome (Ph+), generating a BCR::ABL1 fusion protein. [2] The Ph+ AML subtype is associated with poor prognosis and treatment resistance. [3,4] Co-occurrence of *CBFB* rearrangement and *BCR::ABL1* fusion is rare, representing a subgroup with unique clinical and molecular features. To date, there have been less than 30 cases reported in the literature. [5-8]

Case Description

A 62-year-old male presented to hospital with headaches, visual changes, weakness, and a nodular rash on his back, with leukocytosis, thrombocytopenia, and 42.5% circulating blasts. A bone marrow (BM) aspirate and biopsy was diagnostic of AML with 56% myeloblasts. RT-PCR was positive for an e19a2 *BCR::ABL1* fusion transcript coding for p230 kDa fusion protein (p230) and *CBFB*: :*MYH11* fusion gene transcript. Cytogenetics identified a complex karyotype with an inv(16) and a Ph chromosome (46,XY,t(1;14)(p32;q24),t(9;22)(q34;q11.2),inv(16)(p13.1q22)[10]), consistent with concurrent *BCR::ABL1* and *CBFB::MYH11* rearrangements within the same clonal population of cells.

Treatment consisted of hydroxyurea for cytoreduction, 7+3 induction, one cycle of low dose cytarabine consolidation, and oral azacytidine maintenance, in combination with dasatinib. He did not receive Gemtuzumab ozogamicin (GO) given patient preference and comorbidities. Post-induction course was complicated by febrile neutropenia due to *Enterococcus Faceium* bacteremia, pre-renal acute kidney injury, and dasatinib-related complications including rash and transaminitis. These issues resolved by holding dasatinib for 15 days. Complete morphologic remission (CR) was obtained by Day 33 post-induction and no fusion gene transcripts were detectable by nested RT-PCR from BM aspirate on day 49 post-induction, nor day 76 post-consolidation The patient was ineligible for an allogeneic stem cell transplant given his poor performance status. At present, the patient remains alive and well, continuing on maintenance with oral azacytidine and dasatinib.

Discussion

We present the only case, to our knowledge, of a concurrent *BCR::ABL1* p230 isoform and *CBFB::MYH11* with *de novo* AML. Based on our literature search, 26 cases have been reported. *BCR::ABL1 and CBFB::MYHII* rearrangements in *de novo* AML potentially confers an intermediate to favorable prognosis with outcomes comparable to those of CBF-AML. Studies suggest that this entity may be more akin to AML with inv(16) rather than CML-BP with inv(16), thereby retaining favorable prognosis. [5,9-11]

There are no formal guidelines for management of *de novo* AML with concurrent *BCR::ABL1* and *CBFB* rearrangements. Traditional chemotherapy treatment strategies for Ph+ AML are often ineffective in these cases. The presence of *BCR::ABL1* fusion transcript raises the possibility of utilizing TKIs targeting the BCR::ABL1 kinase domain. In our case, the patient achieved rapid CR with induction chemotherapy and dasatinib, but experienced multiple complications, precluding further intensive chemotherapy and allogeneic stem cell transplantation. This case raises a number of questions, including the optimal timing, combination, and duration of TKI therapy in the context of dual rearrangement *de novo* AML. This patient subgroup may

benefit from intensive chemotherapy regimens and TKIs. Prospective monitoring of these cases is warranted to assess outcomes in comparison to Ph+ AML without coinciding *CBFB* rearrangement. This case report underscores the importance of comprehensive genetic profiling in Ph+ AML to determine the genetic landscape and individualize therapeutic strategies.

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