An interesting case of chronic myeloid leukemia (CML) with T315I mutation raising suspicion of de novo AML, a diagnostic conundrum.

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April 12, 2021

Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative disorder due to translocation between chromosomes (9, 22), known as the "Philadelphia chromosome." In 2016, the World health organization (WHO) introduced a new clinical entity of de novo acute myeloid leukemia (AML). Both diseases share some commonalities, therefore, create a challenge to diagnose.

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Introduction:

CML is a myeloproliferative neoplasm characterized by a translocation between chromosomes (9, 22), resulting in a BCR-ABL fusion gene with tyrosine kinase activity. The CML-BP can transform into acute lymphoblastic leukemia (ALL) as well as acute myeloblastic leukemia [1]. In 2016, WHO has included AML with BCR/ABL+ gene as a separate provisional entity in its latest classification of myeloid neoplasms [1,2]. We report a case of CML-BP in a middle aged gentleman that posed a challenge to diagnose and differentiate it from de novo AML due to lack of a definite clinical criteria in such clinical scenarios [2].

Keywords: Chronic Myeloid leukemia, de Novo AML,*BCR-ABL* + AML, Philadelphia chromosome, T315I.

Clinical key message:

The differentiation of CML-BP from de novo AML is crucial in the management of the patient. Therefore, a cautious diagnostic approach involving hematologists and hemato-histopathologist is required where there is a diagnostic dilemma.

Case presentation:

A 33-year-old healthy, non-smoker Bangladeshi gentleman presented with fatigue, subjective fever, bruises, and gum bleeding from 7 days without any significant weight loss or swellings on the body. He had no significant past medical history or any co-morbid illness.

Physical examination was remarkable for conjunctival pallor and few scattered patches of ecchymosis all over the body, with the largest measuring 3x2 cm over the abdomen. There were petechiae on the tongue and palpable spleen below the left costal margin. The rest of the systemic examination was normal. Initial blood investigations are shown in table:1.

Peripheral smear showed many circulating blasts cells (40%), few promonocytes, shift to left, and basophilia. Bone marrow aspirate showed many blasts (24%) with increased basophils, dwarf megakaryocytes, and significant dysgranulopoiesis, as shown in Figures 1, 2, and 3.

Flow cytometry on Bone Marrow aspirate showed a blast population with monocytic immunophenotype. FISH study revealed BCR/ABL-1 fusion gene in 95% of the cells. Karyotype analysis revealed, 46,XY,t(9;22;17)(q34;q11;q23)[2]/46,idem,t(3;21)(q26.2;q22)[28]/47,idem, t(3;21)(q26.2;q22),+8[25].

Overall findings were consistent with Acute Myeloid Leukemia with monocytic differentiation with features favoring evolvement on top of CML (blast phase), but another differential diagnosis of de novo AML with BCR/ABL-1 could not be excluded entirely during diagnostic workup. It was suggested initially to commence the patient on chemotherapy as per de novo AML protocol. However, after a thorough discussion with hemato-histopathologists and senior hematologists in a multi-disciplinary team (MDT) meeting, he was commenced earlier on TKI (Tyrosine kinase inhibitor therapy) as the majority of cells were suggestive of CML with BCR ABL fusion gene. Cytoreduction therapy with hydroxyurea and Dasatnib was started. He had a suboptimal response with an increase in blast cells after 3 weeks of therapy. It raised a concern about his diagnosis and reconsideration of de novo AML. Therefore, another MDT was held to review the patient clinical presentation and diagnostic workup. It concluded in favor of CML with evolution into acute myeloblastic phase with monocytic differentiation. As he was resistant to TKI therapy, mutation analysis for the T315I gene was sent to rationalize blast cells' increase after Dasatinib therapy. Mutational analysis for the T315I gene turned out to be positive. Therefore, he was started on Ponatinib, a recommended TKI therapy for CML patients with a positive T315I gene. The drug was made available on special arrangements by a local hospital charity's help due to its unavailability in the country. There was a good response with a decrease in WBCs, basophil cells, and blast cells in one week, as shown in Figures: 4.5 and 6, respectively. Further donor search was also initiated for hematopoietic stem cell transplant (HSCT), and he remained stable throughout his hospital course.

Discussion:

CML is a form of myeloproliferative neoplasm (MPN) characterized by a balanced chromosomal translocation t(9; 22) (q34; q11.2), also known as the Philadelphia chromosome [1]. The resultant gene, BCR/ABL (breakpoint cluster region/Abelson gene, has tyrosine kinase activity that leads to abnormal growth of the cells [2,3]. CML accounts for about 15% of newly diagnosed cases of leukemia in adults [3].

AML with BCR/ABL+ had been included as a separate provisional entity in 2016 by WHO classification of myeloid neoplasms [1]. AML with BCR/ABL+ is considered to carry a worse prognosis, and hence its management approach is different from CML-BP [4]. There are overlapping clinical features between *BCR-ABL* + AML and myeloid CML blast crisis; moreover, there are no definite clinical criteria established yet to distinguish among these entities [4,5]. The involvement of molecular markers such as IKZF1, CDKN2A, and antigen receptor gene deletions in IGH or TRG2 can distinguish between de novo *BCR-ABL* + AML from myeloid blast crisis of CML [1,2]. Certain other reported clinical features in the literature can also guide in this diagnostic dilemma, as mentioned in the table: 2; however, they may not be seen in every case [5,6].

Our patient presented with clinical features of splenomegaly, peripheral circulating basophils more than 2% with blast cells, and hypercellular bone marrow supporting CML-BP diagnosis [6]. He had mixed cellular phenotypic variation of CML-BP and AML with monocytic differentiation on bone marrow examination, which created another differential diagnosis of de novo AML on the table. Later after discussing the case in an MDT of hemato-histopathologist and reviewing the patient's clinical file supplemented with cytogenetics and molecular analysis, he was labeled as a case of CML-BP and treated accordingly with TKI therapy, i.e.,

dasatinib but did not respond adequately. Later T315I mutation analysis came positive, and he received the recommended treatment with ponatinib therapy with optimal response [3].

The reason to differentiate de novo AML is based upon its difference in genetic and molecular nature that poses high-risk other than BCR/ABL+ gene only, treatment modality, and response from CML [1,2,3,4]. Studies have also revealed that de novo AML with BCR/ABL has more prevalence of fusion protein 190 and NPM1 mutation in contrast to Ph+ CML and also possess different treatment and prognostic value than CML with BCR/ABL-1 in blast phase [7]. After a thorough literature search, we managed to execute a table to guide the CML-BP and de novo gene AML, table:2.

Although the myeloid blast phase is quite common, the monocytic blast phase of CML associated with T315I is the first case reported in our National Center for Cancer care and research institute (NCCCR) in Qatar.

Conclusion:

We aim to highlight a diagnostic approach towards a new clinical entity of de Novo AML with BCR/ABL fusion gene described by WHO in 2016 from CML with BCR/ABL gene which can be challenging in some clinical scenarios. And we also emphasize the need for T315I mutation analysis study in TKI resistant cases of CML to deliver optimum patient care.

Conflict of interest statement:

All authors of this manuscript has not conflict of interest to disclose.

Acknowledgement:

I would like to thank Dr. Abdel-Naser Elzouki senior consultant internal medicine department and Dr. Dabia Al-Mohanadi program director of internal medicine department at Hamad Medical Corporation for always supporting young researchers. The Open Access funding provided by the Qatar National Library.

References:

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391–405.

2. Nacheva EP, Grace CD, Brazma D, Gancheva K, Howard-Reeves J, Rai L, et al. Does BCR/ABL1 positive Acute Myeloid Leukaemia Exist? Br J Haematol. 2013;161(4):541–50.

3. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol. 2018;93(3):442–59.

4. Neuendorff NR, Hemmati P, Arnold R, Ihlow J, Dörken B, Müller-Tidow C, et al. BCR-ABL+ acute myeloid leukemia: are we always dealing with a high-risk disease? Blood Adv. 2018 Jun 18;2(12):1409–11.

5. Pastoret C, Houot R. "Chronic myelogenous leukemia in primary blast crisis" rather than "de novo BCR-ABL1-positive acute myeloid leukemia." Clin Case Rep. 2017 Apr 4;5(6):757–60.

6. Shao X, Chen D, Xu P, Peng M, Guan C, Xie P, et al. Primary Philadelphia chromosome positive acute myeloid leukemia: A case report. Medicine (Baltimore). 2018 Nov;97(44):e12949.

7. Reboursiere E, Chantepie S, Gac A-C, Reman O. Rare but authentic Philadelphia-positive acute myeloblastic leukemia: Two case reports and a literature review of characteristics, treatment and outcome. Hematol Oncol Stem Cell Ther. 2015 Mar 1;8(1):28–33.

8. Ashar KM, Vaghasiya V, Patel SC. Megakaryocytic blast crisis in chronic myeloid leukemia: A primary presentation. Indian J Pathol Microbiol. 2017 Jul 1;60(3):445.

Figures/ Legends:

Figure: 1: showing circulating blast cells.

Figure: 2: Circulating Basophil cells.

Figure: 3: dwarf megakaryocytes and significant dysgranulopoiesis.

Figure: 4: Trend of blast cells after Panotinib treatment.

Figure: 5: Trend of WBCs after Panotinib treatment.

Figure: 6: Trend of Basophils cells after Panotinib treatment.

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