



Atypical chronic myeloid leukemia BCR-ABL 1 negative: A case report and literature review

Jihane Belkhair^{a,*}, Abderahim Raissi^b, Hicham Elyahyaoui^a, Mustapha Ait Ameur^a, Mohamed Chakour^a

^a Department of Laboratory Hematology, Ibn Sina Military Hospital, Marrakech, Morocco

^b Department of Clinical Hematology, Ibn Sina Military Hospital, Marrakech, Morocco

ARTICLE INFO

Key Words:

Atypical chronic myeloid leukemia
World Health Organization
Myelodysplastic syndroms/myeloproliferative syndroms
BCR-ABL1
Philadelphia chromosome
Cytology
Karyotype
Molecular biology

ABSTRACT

Atypical chronic myeloid leukemia (aCML), *BCR-ABL1* negative is a rare myelodysplastic syndrome/myeloproliferative neoplasm for which no current standard of care exists. The blood smear of patients with aCML showed prominent immature granulocytosis, and granulocytic dysplasia. We admitted a 58-year-old man with splenomegaly, hyperleukocytosis, anemia, and thrombocytopenia; then cytology, cytogenetic and molecular biology analysis of bone marrow were performed and the diagnosis of aCML was made according to 2016 World Health Organization diagnostic criteria. The patient was initially treated by chemotherapy; the patient achieved an aggravation of anemia. This motivated the change of treatment.

1. Introduction

Atypical chronic myeloid leukemia (aCML) is a subtype of myelodysplastic syndroms/myeloproliferative syndroms diseases (MDS/MPN), the incidence rate about 1/100,000 or less [1]. Patients present in the 7th or 8th decade of life with leukocytosis, splenomegaly, frequent anemia and variable platelet counts. The aCML is defined largely by morphologic criteria by circulating myeloid precursors, obvious dysgranulopoiesis, cytogenetic and molecular studies are negative for Ph1 and BCR-ABL A fusion gene. Overall, aCML is generally associated staggeringly with poor prognosis: median survival less than 2 years, with 20–40% chance of evolving to acute myeloid leukemia [2]. The challenges of aCML relate to its heterogeneous clinical and genetic features, high rate of transformation to acute myeloid leukemia, and historically poor survival. In this report we summarize our experience with a patient diagnosed with aCML revealed by dermohypodermatitis.

2. Case report

We present a case about a man in 58 year-old, with a negative past medical history. In the last 2 months, the patient reported increasing fatigue, and describes inflammatory skin lesion on left temple. Physical examination revealed pallor and mild splenomegaly, without tumor

syndrom. Laboratory examinations showed hyperleukocytosis with Wight Blood Cell WBC $56.8 \times 10^9/L$ (reference range, $4-10 \times 10^9/L$), thrombocytopenia with Platelets $112 \times 10^9/L$ (reference range, $120-400 \times 10^9/L$), and hemoglobin of 93 g/L (reference range, 130–180 g/L). Manual differential count revealed 60% neutrophiles, 16% metamyelocytes, 8% myelocytes, 2% promyelocytes; 1% Blasts, 3% monocytes, 1% basophilic granulocytes, 2% Eosinophilic granulocytes, 7% lymphocytes, with dysgranulopoiesis showed abnormal nuclear segmentation: hypolobation nuclear, hypersegmentation nuclear, Pseudo Pelger-Huet and hypogranular granulocytes (Fig. 1). Then the Bone Marrow Aspirate (BMA) was performed: morphology of BMA showed a hypercellular marrow, with myeloid hyperplasia to 73%, including: myeloblasts 3%, promyelocytes 5%, myelocytes 12%, metamyelocytes 20%, neutrophilic granulocytes 28%, eosinophils 5%, basiphiles 0%, and 4% monocytes, with subtle dysgranulopoiesis (Fig. 2). Cytogenetic analysis revealed a normal karyotype: 46, XY. Molecular biology analysis of BCR/ABL fusion gene negative. The histopathological study of skin lesion from the left temple showed polymorphic dermohypodermatitis, with negative immunohistochemical complement: CD3 and CD 20. The patient was diagnosed with aCML and treated with hydroxurea (2 capsules of 500 mg/j \times 21 days). The evolution was marked by the fall of the white blood cells (57 G/L to 24 G/L), and the moderate reduction of the size of the spleen. However,

* Corresponding author.

E-mail addresses: belkhairjihane01@gmail.com, docjihanebel@gmail.com (J. Belkhair).

<https://doi.org/10.1016/j.lrr.2019.100172>

Received 11 December 2018; Received in revised form 25 April 2019; Accepted 25 May 2019

Available online 25 May 2019

2213-0489/ © 2019 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/>).

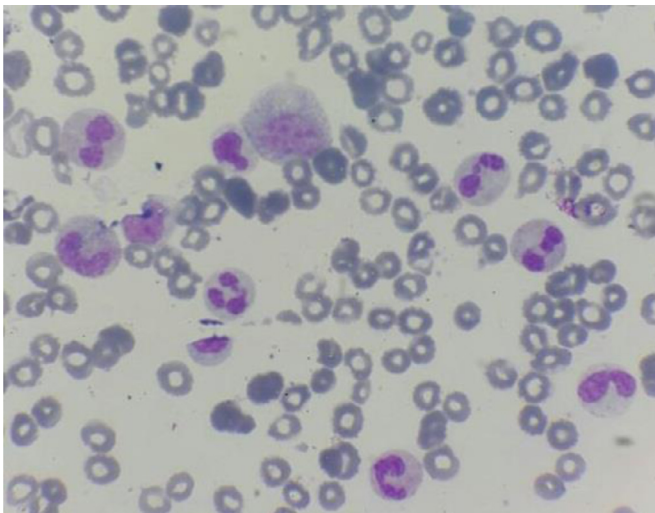


Fig. 1. Blood smear of the case report- dysgranulopoiesis: hypogranular granulocytes, hypoblobation nuclear, and Pseudo Pelger-Huet.

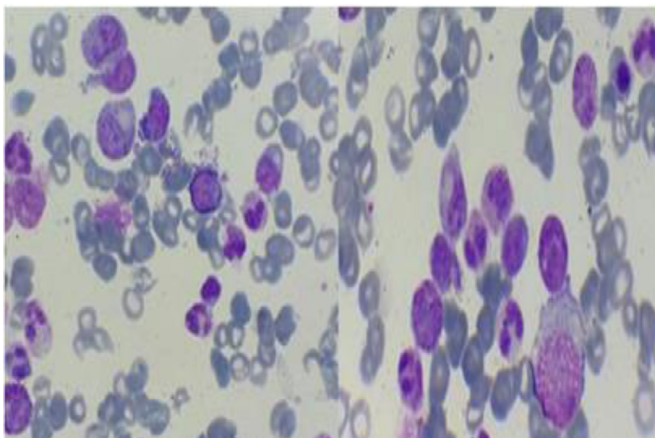


Fig. 2. Spinal smear of the case report.

there was an aggravation of anemia (from 9.5 g/dL to 8 g/dL) which motivated the change of treatment and the patient was put on azacytidine 75 mg/m²/j × 1 to 7 days; every 28 days. HLA typing is also underway to search for potential donors for hematopoietic stem cell transplantation (HSCT).

3. Discussion

Atypical chronic myeloid leukemia is a clonal hematopoietic disorder characterized by both dysplastic and proliferative features, including persistent granulocytosis with left shift, bone marrow hypercellularity with dysplastic hematopoiesis, and myeloid preponderance; aCML is a disorder of older adults with apparently no sex predominance [2]. The aCML is a rare myeloid neoplasm with an incidence of 1–2 cases for every 100 cases of Philadelphia-positive CML. Clinical manifestations, similar to those of myeloproliferative syndrome, are related to anemia, thrombocytopenia, and splenomegaly. The etiology and pathogenesis of aCML are not known. The 2016 WHO diagnostic criteria for aCML relies on: 1) Peripheral blood leukocytosis (WBC ≥ 13 × 10⁹/L) due to increased number of neutrophils and their precursors ≥ 10%, 2) Dysgranulopoiesis (abnormal chromatin clumping). 3) Basophils < 2% of leukocytes, No or minimal absolute basophilia 4) Monocytes < 10% of leukocytes, No or minimal absolute monocytosis 5) Hypercellular BM with granulocytic proliferation and granulocytic, dysplasia, with or without dysplasia in the erythroid and

megakaryocytic lineages 6) <20% blasts in the blood and BM; 7) No Philadelphia chromosome or BCR-ABL fusion gene. 8) No rearrangement of PDGFRA, PDGFRB, FGFR1 rearrangement or JAK2 [3]. This patient meets the aCML diagnostic criteria. He has mild splenomegaly and normal chromosomes, negative BCR-ABL fusion gene, peripheral blood monocytes <1.0 × 10⁹/L, myeloid precursor in the peripheral blood is 30%, with 60% neutrophils, therefore, it can be excluded the diagnosis of Chronic Myeloid Leukemia (CML), Chronic Myelomonocytic Leukemia (CMML) and chronic neutrophilic leukemia (CNL). So the diagnosis of aCML was correct.

No specific chromosomal changes correlations with disease features were found in aCML patients. The most common karyotypic changes reported in aCML include trisomy 8 and del (20q), abnormalities involving other chromosomes such as 12, 13, 14, 17, 19 and 21 have also been described [4]. The etiology and pathogenesis of aCML are not known, many gene mutations have been found in aCML, such as, NRAS/KRAS (33% patients), TET2 (33% patients) CBL (10% patients), E2H2 (13% patients) and SETBP1 (25% patients) and so on [5]. In this case, the patient has normal chromosome. The syndrome of abnormal chromatin clumping, which has long been recognized as representing a hematologic neoplasm with both myelodysplastic and myeloproliferative features is, in most cases, simply a morphologic variant of aCML; the risk of leukemic transformation is approximately 30% [6]. The majority of patients die of BM failure.

Atypical CML patients showed poor prognosis when treated with conventional chemotherapy, the median survival is only 24 to 25 months [7]. A retrospective study in MD Anderson Cancer Center found that: Age (> 65 years), anemia (hemoglobin < 10 g/dL), white blood cell count (WBC > 50 × 10⁹/L) are three independent factors in aCML [7]. Treatment options such as AML induction type chemotherapy followed by an allogeneic stem cell transplantation are an option for only a minority of patients, but are the only modality that offers a cure. Koldehoff et al. [8] confirmed that allogeneic hematopoietic stem cell transplantation (HSCT) evaluated the outcome of aCML. Our candidate have included Hydroxyurea, that is converted to a free radical at the active site of the M2 protein subunit of ribonucleotide reductase, inactivating the enzyme, and DNA synthesis is selectively inhibited, producing cell death in S phase and synchronization of the fraction of cells that survive [9]. Our patient has an aggravation of anemia which the change of treatment was motivated. 5-Azacytidine, in particular, has been shown to be effective in all subtypes of MDS to prolong the time to disease progression and is the only drug in this group that has been licensed by the US Food and Drug Administration (FDA) for all subtypes of MDS [10].

4. Conclusion

In conclusion, aCML is difficult to distinguish from other subtypes of MPS (CML, CNL and CMML), which is easy to misdiagnosis clinically. The presence of a granulocytic proliferation associated with marked dysgranulopoiesis and the absence of BCR-ABL1 translocation are the defining features of aCML. The success of azacytidine in improving overall survival of high-risk patients with MDS makes it worth studying in aCML cases. The only known curative therapy involves stem cell transplantation for aCML, but that carries high risks of toxicity and morbidity.

CRedit authorship contribution statement

Jihane Belkhair: Validation, Writing - original draft, Supervision.
Abderahim Raissi: Validation, Writing - original draft, Supervision.
Hicham Elyahyaoui: Validation, Writing - original draft, Supervision.
Mustapha Ait Ameur: Validation, Writing - original draft, Supervision.
Mohamed Chakour: Validation, Writing - original draft, Supervision.

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgment

We thank Dr A. Raissi for her cooperation to drafting the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.100172.

References

- [1] M. Cazzola, L. Malcovati, R. Invernizzi, Myelodysplastic/myeloproliferative neoplasms. *hematology*, Am. Soc. Hematol. Educ. Program 2011 (1) (2011) 264–272.
- [2] N. Faramarz, Atlas of Hematopathology Morphology, Immunophenotype, Cytogenetics, and Molecular Approaches, first ed., Academic presse, Cambridge, Massachusetts, 2013.
- [3] D.A. Arber, A. Orazi, R. Hasserjian, The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood J.* 127 (20) (2016) 2391–2405.
- [4] A. Efferi, G. Gilliland, Classification of chronic myeloid disorders: from Dameshek towards a semi-molecular system, *Best Pract. Res. Clin. Haematol.* 19 (3) (2006) 365–385.
- [5] R. Piazza, S. Valletta, N. Winkelmann, S. Redaelli, R. Spinelli, et al., Recurrent SETBP1 mutations in atypical chronic myeloid leukemia, *Nat. Genet.* 45 (1) (2013) 18–24.
- [6] M. Czader, A. Orazi, *Blood and Bone Marrow Pathology*, second ed., Churchill Livingstone, London, 2011.
- [7] F. Onida, G. Ball, H.M. Kantarjian, T.L. Smith, A. Glassman, et al., Characteristics and outcome of patients with Philadelphia chromosome negative, bcr/abl negative chronic myelogenous leukemia, *Cancer* 95 (October, 8) (2002) 1673–1684.
- [8] M. Koldehoff, D.W. Beelen, R. Trenschele, N.K. Steckel, R. Peceny, et al., Outcome of hematopoietic stem cell transplantation in patients with atypical chronic myeloid leukemia, *Bone Marrow Transpl.* 34 (December, 12) (2004) 1047–1050.
- [9] J.W. Yarbrow, Mechanism of action of hydroxyurea, *Semin. Oncol* 19 (June, 3 Suppl 9) (1992) 1 - .
- [10] E. Kaminskas, A.T. Farrell, Y.C. Wang, R. Sridhara, R. Pazdur, FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension, *Oncologist* 10 (March, 3) (2005) 176–182.