



Philadelphia-positive atypical chronic myeloid leukemia, BCR/ABL negative: a case report

Germán Rivera Monroy^{a1}, Federica Riccio Cuomo^{b2}, Dunia Michelle Bustos Campa^{b3}, Jorge Luis López Marthen^{c4*}

^aUniversidad Anáhuac México, Campus Norte, Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud, Huixquilucan, México, México.

^bUniversidad Anáhuac Puebla, Escuela de Medicina, San Andrés Cholula, Puebla, México.

^cCentro Médico Nacional Manuel Ávila Camacho (IMSS), Puebla, México.

ID ORCID:

¹<https://orcid.org/0000-0003-0630-0867>, ²<https://orcid.org/0000-0002-0439-5893>, ³<https://orcid.org/0000-0003-4078-3321>,

⁴<https://orcid.org/0000-0002-4140-4306>.

<https://doi.org/10.36105/psrua.2022v2n3.05>

ABSTRACT

Atypical myeloid leukemia is a myeloproliferative neoplasm in which patients have a dysplastic increase in blood cells of the myeloid lineage as a result of hypercellular bone marrow. Our patient presented a positive Ph karyotype and a negative ABL/BCR transcript. Moreover, her age does not correspond to the mean of diagnosis. Her first treatment was hydroxyurea 1 g/kg for 60 days, which was not positive for the evolution of the disease and thus the elective treatment was changed to imatinib 400 mg/day. After two months, the treatment has produced a favorable response, which leads to think that the therapy with imatinib offers better clinical results than other conventional ones. This text presents the study carried out at the Manuel Ávila Camacho National Medical Center and compares it with the existing literature regarding diagnosis and treatment to assess similarities and highlight specific points that may help in future case management.

Key words: atypical CML; Ph positive; ABL/BCR negative; hydroxyurea; imatinib.

RESUMEN

La leucemia mieloide atípica es una neoplasia mieloproliferativa en la que los pacientes presentan un incremento displásico de células sanguíneas del linaje mieloide como resultado de una médula ósea hiperclular. Nuestra paciente presentó un cariotipo Ph positivo y un transcrito ABL/BCR negativo y se encuentra en una edad no correspondiente a la media de diagnóstico. Su primer tratamiento fue hidroxiurea 1 g/kg durante 60 días, el cual no resultó positivo para la evolución de la enfermedad. Por ello, el tratamiento electivo se cambió a imatinib 400 mg/día y, tras dos meses de tratamiento, tiene una respuesta favorable, lo cual inclina a pensar que el tratamiento ofrece mejores resultados clínicos que otras terapias convencionales. En este texto se busca presentar el estudio realizado en el Centro Médico Nacional Manuel Ávila Camacho y compararlo con la literatura existente respecto a diagnóstico y tratamiento para evaluar similitudes y destacar puntos específicos que puedan ayudar al manejo de casos futuros.

Palabras clave: LMC atípica; Ph positivo; ABL/BCR negativo; hidroxiurea; imatinib.

* *Corresponding author:* Jorge Luis López Marthen. Centro Médico Nacional Manuel Ávila Camacho (IMSS), Puebla. Address: Calle 2 Nte núm. 2004, Centro Histórico de Puebla, 72000 Puebla, Pue, México. Tel.: +52 22 2455 6760. Email: jorge84luis@gmail.com



INTRODUCTION

Chronic myeloid leukemia (CML) is a hematologic disease characterized as a myeloproliferative disorder that gives rise to an overproduction of cells of the myeloid lineage¹. It was first described in 1845, and ever since, multiple studies have led to a better understanding of its pathophysiology, genetics, treatment, and prognosis.² Genetically, it is characterized by presenting the Philadelphia chromosome, a consequence of a reciprocal translocation between the long arms of chromosomes 9 and 22. This produces the BCR/ABL transcript, a constitutively active abnormal tyrosine kinase that causes an abnormal proliferation of the entire hematopoietic line, preserving its differentiation. Atypical chronic myeloid leukemia (aCML) is a rare clonal hematopoietic stem cell disorder with the absence of a detectable BCR-ABL1 fusion or the Philadelphia (Ph) chromosome.^{1,3}

CML incidence varies depending on geographical areas, and it is estimated to affect about one in 100 000 people per year.³ Due to the low incidence of aCML compared to other hematologic disorders, it is hard to estimate a global report of aCML epidemics. Nevertheless, a study by Smith et al. (2015) using the SEER database 18, spanning from 1973 to 2011, reported a total of 114 cases with negative BCR/ABL CML and a final analysis of 82 cases of negative BCR/ABL CML.⁴ The mean age of the patients was 69 years, 57% were male, and 81%, Caucasian.⁴

Signs and symptoms of CML can be classified in three phases and, depending on the stage, patients may present fatigue, night sweats, malaise, weight loss, left upper quadrant pain, discomfort, satiety, and splenomegaly. Less commonly, they may refer priapism, retinal hemorrhages, thrombosis, bleeding, or hepatomegaly.¹ The clinical features of BCR/ABL-negative CML resemble those of BCR/ABL-positive and thus specific genetics studies must be done to identify BCR/ABL and other genetic abnormalities. The 2019 American Cancer Society guidelines suggest blood count with blood film differential, cytogenetics, and bone marrow aspirate with differential to include percentages of blasts, promyelocytes, myelocytes, eosinophils, and basophils. In addition, karyotyping by G-banding is recommended to identify chromosomal abnormalities other than t(9;22) while translocation and reverse transcriptase PCR for BCR-ABL1 mRNA transcripts help in CML diagnosis. However, health care systems and technology variations between countries might hinder the fulfillment of those recommendations.⁵

In the past, the treatment for CML consisted of chemotherapeutic agents such as busulfan and hydroxyurea, but they are not very effective in eliminating the malignant clones. Novel therapies targeting specific genetic characteristics of the disease, as tyrosine kinase inhibitors (TKIs) like imatinib, have

revolutionized CML therapy by improving clinical outcomes and patient prognosis.⁵ However, the use of TKIs in aCML has not been vastly studied and new outcomes are evaluated every year to adequate this therapy for aCML patients.^{5,6} In this work, we present the case of a 19-year-old female diagnosed with aCML and the early outcomes of her treatment with imatinib. We also show the challenges for the diagnosis and the expectations for her prognosis based on the current literature.

Case report

On June 23, 2021, a 19-year-old female patient attended our health center; she had no personal or family medical history relevant to the current pathology. Respecting the current ailment, the patient referred asthenia, adynamia, headache, and nausea for a month. Moreover, the patient informed she had suffered considerable weight loss (around 12 kg). The physical examination revealed pallor and splenomegaly of 4 cm (ULCB).

Hematic biometry was requested and the results are summarized in Table 1, showing compatibility with a myeloproliferative disorder. Due to the tests and abnormal laboratory results, a cytogenetic analysis was performed and revealed a 46, XX,t(9;22)(q34.1;q11.2) Philadelphia positive. A molecular biology analysis of negative p210 BCR/ABL fusion gene by RT-PCR was performed twice. The patient was diagnosed with aCML.

TABLE 1. Initial hematic biometry results (06/21/2021).

	Initial hematic biometry	Reference values
Total leukocytes	243 x 10 L	4-11 x 10 L
Hemoglobin	9 g/dL	13.0-16.0 g/dL
Hematocrit	25%	35.5-44.9%
Lymphocytes	13%	24-38%
Platelets	1.295 x 10 L	120-400 x 10 L

An initial treatment with hydroxyurea (1 g/kg/day) as single dose was established, with a monthly progress schedule checked by hematic biometry. The first month analysis reported total leukocytes of 243,000/mcL, hemoglobin of 9,3, blasts at 4%, and platelets at 1,295,000. There was no improvement on anemia since the normal range of hemoglobin normal is 9.7–9.3 g/dL (Table 1), that of thrombocytosis is 1.128,000–1,295,000 mcL, and leukocytes range from 204 to 243/mcL. In addition, no reduction in the spleen size was observed. Then, the treatment was changed to imatinib (400mg/day), with a monthly schedule for progress check-up by hematic biometry.

After two months of therapy with imatinib (monthly check-ups), the patient’s laboratory tests showed remarkable clinical changes in hematologic parameters. As shown in Figure 1, there was an improvement in hemoglobin, blasts, and platelets. After the first month (30 days), the results showed an increase in total leukocytes versus the last hydroxyurea report. However, the second measurement (60 days after beginning the treatment) showed a slight reduction in the total leukocyte count with respect to the previous report.

This report was written before the check-up in the third month.

DISCUSSION

An initial CML diagnosis can represent a severe challenge due to several factors, such as epidemiological differences between countries and regions, lack of laboratory and genetics diagnosis equipment, the inexperience of clinicians, and even the ignorance of the pathology itself.⁷ CML is a myeloproliferative neoplasm commonly, characterized by a triphasic natural history: an indolent chronic phase, followed by an accelerated phase, and finally, an aggressive blast phase. Depending on the phase, signs and symptoms might be confused with other diseases by the time patients see a clinician.^{7,8} Likewise, it must be noted that our patient’s age is outside the diagnostic mean (between the sixth and seventh decade of life) in addition to the incompatibility with the epidemiological male predominance.

The initial blood studies suggested a hematological disorder with abnormal cell proliferation. Nevertheless, the literature reports several differential diagnoses (chronic myelomonocytic leukemia, chronic neutrophilic leukemia, and essential thrombocythemia, among others) that must be excluded

before a final diagnosis is established. Simple differences in hematological biometry can lead clinicians to suspect a specific blood disorder.⁷ The characteristic blood count features of CML are absolute leukocytosis (median of 100,000/ μ L), a normal or elevated platelet count, and thrombocytopenia suggesting an alternative diagnosis or an advanced stage of the disease.^{1,8}

Once the suspected CML has been established, additional tests are necessary to identify specific genetic and morphologic characteristics. If it is intended to differentiate CML from aCML, the initial tests should focus on excluding the BCR-ABL1 fusion. Cytogenetics, FISH, and PCR can help to distinguish other aCML common genetic alterations, like PDGFRA, PDGFRB, and FGFR1, among others.^{7,9} In our diagnostic approach, we performed a cytogenetic analysis that revealed a 46, XX,t(9;22)(q34.1;q11.2) karyotype, and the result confirmed the existence of Philadelphia. A molecular biology analysis of BCR/ABL by RT-PCR was performed twice with a negative result for the p210 gene fusion. Despite the current American Cancer Society guidelines recommending karyotyping by G band as well as other blood parameters, the lack of technology resources and professionally trained physicians made it impossible to follow those recommendations. The sum of the results of all the studies performed led us to the diagnosis of aCML. We consider it important to highlight that if the diagnosis of aCML or other myeloproliferative disorders is unclear, recent guideline updates suggest implementing mutation sequencing, targeting JAK2, CALR, MPL, TET2, and SRSF2 among others, to reach the correct diagnosis.⁵

As stated before, the treatment for CML used to consist of hydroxyurea in combination with low doses of cytarabine or interferon. Still, the literature has reported that this therapy has poor results in increasing life expectancy and reducing

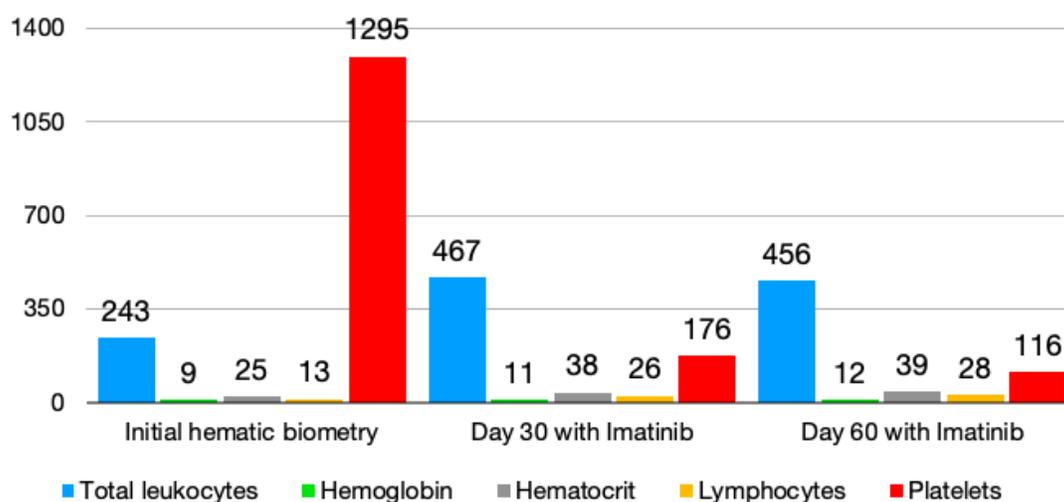


FIGURE 1. Hematic biometry (total leukocytes, hemoglobin, blasts, and platelets). Results after treatment with Hydroxyurea and first and second month after treatment with Imatinib.



laboratory parameters worsening after 8–10 months of treatment.⁷ Over the last 20 years, novel therapies, specifically TKIs, have shown promising results in treating this disease as well as other neoplastic pathologies. Focusing on aCML, several studies (most of them case reports) have shown that treatment with imatinib has succeeded in improving laboratory parameters like total leukocytes, blasts, hemoglobin, myeloid-lymphocytic rate, and symptomatology.¹⁰ Although life expectancy has not been specified in the literature, we suggest some causes might be the absence of follow-up and reports of results after several years and death of patients due to other causes, just to mention a few examples.

Despite the reported success of imatinib usage in aCML patients, some reports suggest that specific BCR-ABL and other genetic mutations may produce resistant clones against imatinib.¹¹ For example, studies correlate the expression of the Ikaros variant Ik6 with high BCR-ABL1 mRNA levels and imatinib resistance in Ph+ cases.¹² Furthermore, a report from 2011 strongly suggested the existence of another oncogene present in CML and aCML that might be responsible for imatinib resistance by activating the PI3K/AKT1/mTOR pathway.¹³ Nevertheless, further research must be done before establishing a direct relation between genetic aberrations and imatinib resistance.

Due to the availability of medications and the costs policy for initial therapies in oncology at our health center, our patient started treatment with hydroxyurea (1 g/kg/day) for two months. After two check-ups, the treatment showed no favorable results, so it was changed to imatinib 400 mg/day (being this the standardized initial dose recommended), providing a favorable clinical response so far.⁵ Further molecular tests must be performed to identify a possible molecular improvement. The total leukocytes increased in the first measurement of this treatment, which can be explained by the null response of the patient to the two-month treatment with Hydroxyurea. Furthermore, the second measurement after imatinib treatment showed a decrease in this parameter. We expect this decrease to continue and our patient to present better hematic parameters and clinical response.

The reported side effects related to imatinib treatment include developing nonspecific clinical symptoms, such as the appearance of diarrhea, muscle aches, and fatigue. According to laboratory findings, persistent leukopenia and thrombocytopenia might also be present. In these cases, it is recommended to readjust the dosage of imatinib and evaluate a possible treatment resistance. Moreover, cases of genetic alterations as trisomies and tetrasomies have been reported after the abandonment of treatment due to non-compliance with cycles adapted to the needs of the patients.^{14,15}

Some of the adverse prognostic factors have been reported in patients with a leukocyte count greater than $50 \times 10^9/L$,

hemoglobin lower than 10mg/dL, the presence of blasts examined by peripheral blood smear, and some genetic mutations like trisomy 8 clones. Nevertheless, no reports confirm that these abnormalities directly affect patient prognosis.¹² According to the Sokal index, our patient has an intermediate risk of 0.85. Using this therapy for three months, we expect a positive hematological response, along with a normalization of the abnormalities in the hematic cytometry and the disappearance of the splenomegaly.

It would be premature to discuss the prognosis of our patient; sometimes genotypic diagnosis is usually omitted since the karyotype of patients with CML is obviated. Obtaining the karyotype of each patient is essential to proceed to an accurate diagnosis and personalized treatment. In the literature reviews consulted, leukocytosis, blasts in peripheral blood, anemia, splenomegaly, and the atypical age of the patient remain negative factors in the prognosis of this disease, while the mean survival reported does not usually exceed 25 months.¹ For these reasons, the most pertinent route is to wait for the response to the treatment with constant clinical and molecular monitoring to evaluate the response to the treatment and its follow-up over the months. It is planned to perform a third RT-PCR after the third month of treatment to find possible genetic alterations in our patient.

CONCLUSION

Due to the complexity of its diagnosis and high mortality rate, aCML is an important hematological disease. As seen in the ongoing treatment of our patient and confirmed data of the existing literature, hydroxyurea is not an efficient treatment for this pathology. Still, the treatment with imatinib has shown promising results, improving the patient's symptomatology and laboratory measurements, which correlates with previous reports of TKI usage in aCML patients. Our case faced technological and clinical limitations for the initial diagnosis. Regarding the follow-up of the patient's condition, molecular tests were performed to identify molecular improvement, molecular aberrations, or side effects likely related to the treatment. More research of common treatments for CML applied to aCML patients must be done to identify possible side effects and prognosis. We aim to contribute to this purpose by reporting significant outcomes of this patient as the treatment with imatinib goes on.

DECLARATION OF COMPETING INTEREST

The authors declare no competing financial interests.





REFERENCES

1. Lasho T. *Atypical CML- the role of morphology and precision genomics*. Best Pract Res Clin Haematol. 2020;33(2):101133
<https://doi.org/10.1016/j.beha.2019.101133>
2. Minciacchi VR, Kumar R, Krause DS. *Chronic Myeloid Leukemia: A Model Disease of the Past, Present and Future*. Cells, 2021; 10(1), 117.
<https://doi.org/10.3390/cells10010117>
3. Belkhair J, Raissi A, Elyahyaoui H, Ameer MA, Chakour M. *Atypical chronic myeloid leukemia BCR-ABL 1 negative: A case report and literature review*. Leuk Res Rep. 2019 25(12)100172.
<https://doi.org/10.1016/j.lrr.2019.100172>
4. Onida F, Ball G, Kantarjian HM, Smith TL, Glassman A. *Characteristics and outcome of patients with Philadelphia chromosome negative, bcr/abl negative chronic myelogenous leukemia*. Cancer. 2002;95(8):1673–1684.
<https://doi.org/10.1002/cncr.10832>
5. Jabbour E, Kantarjian H. *Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring*. Am J Hematol. 2020;95(6), 691–709.
<https://doi.org/10.1002/ajh.25792>
6. Zhou T, Medeiros LJ, Hu S. *Chronic Myeloid Leukemia: Beyond BCR-ABL1*. Curr Hematol Malig Rep. 2018;13(6), 435–445.
<https://doi.org/10.1007/s11899-018-0474-6>
7. Giri S, Pathak R, Martin MG, Bhatt VR. *Characteristics and survival of BCR/ABL negative chronic myeloid leukemia: a retrospective analysis of the Surveillance, Epidemiology and End Results database*. Ther Adv Hematol. 2015;6(6):308–12.
<https://doi.org/10.1177/2040620715607416>
8. Sampaio MM, Santos M, Marques HS, Gonçalves V, Araújo G, Lopes LW, Apolonio JS, et al. *Chronic myeloid leukemia- from the Philadelphia chromosome to specific target drugs: A literature review*. World J Clin Oncol. 2021;12(2), 69–94.
<https://doi.org/10.5306/wjco.v12.i2.69>
9. Sadigh S, Hasserjian RP, Hobbs G. *Distinguishing atypical chronic myeloid leukemia from other Philadelphia-negative chronic myeloproliferative neoplasms*. Curr Opin Hematol. 2020;27(2), 122–127.
<https://doi.org/10.1097/MOH.0000000000000565>
10. Ali MA. *Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors: An Evolving Paradigm of Molecularly Targeted Therapy*. Mol Diagn Ther. 2016;20(4), 315–333.
<https://doi.org/10.1007/s40291-016-0208-1>
11. Narasimha M, Khamkar V, Tilwani S, et al. *Atypical activation of signaling downstream of inactivated Bcr-Abl mediates chemoresistance in chronic myeloid leukemia*. J. Cell Commun. Signal. (2021).
<https://doi.org/10.1007/s12079-021-00647-x>
12. Iacobucci I, Lonetti A, Messa F, Cilloni D, Arruga F, Ottaviani E, et al. *Expression of spliced oncogenic Ikaros isoforms in Philadelphia-positive acute lymphoblastic leukemia patients treated with tyrosine kinase inhibitors: implications for a new mechanism of resistance*. Blood rev. 2009;112:3847–3855.
<https://doi.org/10.1182/blood-2007-09-112631>
13. Schwartz LC, Mascarenhas J. *Current and evolving understanding of atypical chronic myeloid leukemia*. Blood rev. 2019;33, 74–81.
<https://doi.org/10.1016/j.blre.2018.07.004>
14. Quentmeier H, Eberth S, Romani J, Zaborski M, & Drexler HG. (2011). *BCR-ABL1-independent PI3Kinase activation causing imatinib-resistance*. J hematology, 4, 6.
<https://doi.org/10.1186/1756-8722-4-6>
15. Issa GC, Kantarjian HM, Gonzalez GN, Borthakur G, Tang G, Wierda W, Sasaki K, et al. *Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment*. Blood rev. 2017;130(19), 2084–2091.
<https://doi.org/10.1182/blood-2017-07-792143>