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International Journal of Family & Community Medicine

Case Report

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Variant p190 of the *BCR-ABL1* gene in a pediatric patient with chronic myeloid leukemia

Abstract

Chronic myeloid leukemia is a clonal disease characterized by the overproduction of cells of the myeloid lineage, this entity affects mainly adults, describing a low frequency in the pediatric population. The development of the disease is due to the formation of the *BCR-ABL1* fusion gene, the 190 kDa product being an infrequent finding. We present the case of an 11-year-old patient whose disease started 2 months before diagnosis, characterized by weight loss. Physical examination revealed parenchymal pallor and splenomegaly with an analytical test showing leukocytosis with the presence of myeloid precursors, for which morphological, cytogenetic and molecular study of bone marrow was performed. It was established the diagnosis of CML in chronic phase with the unusual presence of the transcript p190. Therefore, initial treatment with imatinib was indicated, showing a suboptimal response, being replaced by dasatinib, once a major molecular response was documented, a transplant of hematopoietic stem cells from a related compatible donor was scheduled. Currently the patient is 17 years old and molecular tests show that he is free of the disease.

Keywords: chronic myeloid leukemia, hematopoietic stem cell transplantation, tyrosine kinase inhibitors, pediatrics, BCR-ABL1

Volume 3 Issue 5 - 2019

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Received: September 23, 2019 | **Published:** October 04, 2019

Abbreviations: CML, chronic myeloid leukemia; Hb, hemoglobin; Hct, hematocrit; MCV, median corpuscular volume; MCH, median corpuscular hemoglobin; MCHC, median corpuscular hemoglobin concentration; MMR, major molecular response; HSCT, allogeneic hematopoietic stem cell transplantation; WBC, white blood cell count

Introduction

Chronic myeloid leukemia (CML) is a disease that encompasses clonal over production of myeloid lineage cells, with predominance of neutrophilic precursors. There is an annual incidence of 1 in every million inhabitants, in younger than 15 years.[1] The condition arises from the translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)] which produces the fusion gene *BCR-ABL1*. From the different points of rupture, there may arise different transcripts, being the most common (99% of cases) the variant that codifies a 210 kDa protein (p210), with the extremely rare occurrence of p190 fusion protein.[2] Herein is the presentation of the diagnosis, treatment and 48 month follow-up, of an 11 year old girl affected by CML, characterized by presence of the unusual e1a2 transcript, which encodes the p190 protein.

Case report

11 year old girl with no previous known medical condition, presented with 2 month history of weight loss (~20%), not associated to hyporexia, and generalized pallor. At the local health facility, complete blood count revealed hyperleukocytosis of 512 x 10^9/L, neutrophils 77%, lymphocytes 12%, promyelocytes 2%, myelocytes 4%, metamyelocytes 5%, hemoglobin (Hb): 10.4 g/dL, hematocrit (Hct): 34,6%, median corpuscular volume (MCV): 106,6 fL, median corpuscular hemoglobin (MCH): 32 pg; median corpuscular hemoglobin concentration (MCHC): 30% and platelets: 377 x 10^9/L. She was referred to the University Hospital of Caracas where physical exam was consistent with hemodynamically stable, afebrile, cardiopulmonary uneventful, generalized pallor, splenomegaly (Boyd III), corroborated by ultrasound, no further pertinent findings. Wright-Giemsa colored peripheral smear showed erythroid lineage normocytic and normochromic. Increased number of leukocytes with neutrophil predominance and myeloid precursors (96%), basophils (1%) and myeloblasts (3%), consistent with the diagnosis of a myeloproliferative neoplasia. Bone marrow aspirate and biopsy were drawn for both morphology and cytogenetic assessment. Hypercellularity for age with myeloid hyperplasia. Myeloid/erythroid ratio 3:1 and presence of Philadelphia chromosome in 100% of metaphases evaluated.

Peripheral blood sample was studied for molecular studies of the different transcripts of fusion gene BCR-ABL1 and to assess the immunophenotype of circulating leukocytes, which showed presence of transcript e1a2 of BCR-ABL1 gene and 91% of cells with granulocyte series immunophenotype compatibility. The diagnosis of chronic phase CML, was established. Cytorreductive measures were begun with administration of hydroxycarbamide 2 g/day and after achieving leukocytes <50 x 10^9/L, imatinib was prescribed (400 mg/day). Major molecular response (MMR) after one year of therapy, despite achieving hematologic and cytogenetic responses. She was treated with imatinib during 18 months, despite the suboptimal response (BCR-ABL1 0.27%). Allogeneic hematopoietic stem cell

transplantation (HSCT) was sought, as well as switching the Tyrosine Kinase Inhibitor (TKI) to dasatinib (100 mg/day), obtaining a MMR after 6 months of treatment. 36 months post-diagnosis an identical sibling allogeneic HSCT was performed (A*24, A*33, B*07, B*13, BW4, BW6, DRB1*08, DRB1*10), from her healthy brother, using myeloablative conditioning with busulfan and cyclophosphamide in the *Hospital de Clínicas de Caracas* (Figure 1). 49 days and 163 days after transplantation a bone marrow aspirate showed 100% chimerism, at the *loci CSF1PO, D13S317, D16S539, D18S51, D3S1358, D5S818, D7S820, D8S1179, FGA, Penta D, Penta E, THO1, TPOX* and *vWA*. Currently, the patient is 17 years old and the molecular evaluation of the BCR-ABL1 oncogene shows that she is free of disease (Figure 2).

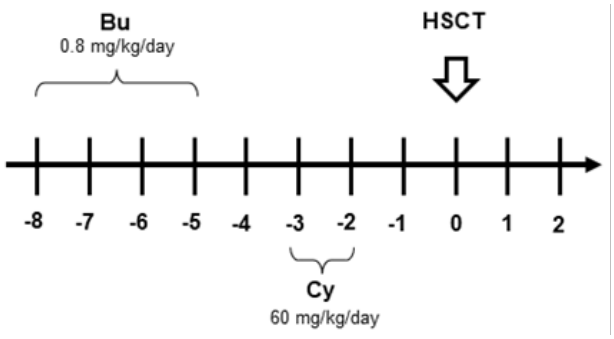

Figure 1 *Conditioning regimen*

Bu, busulfan; Cy, cyclophosphamide; HSCT, allogeneic hematopoietic stem cell transplantation

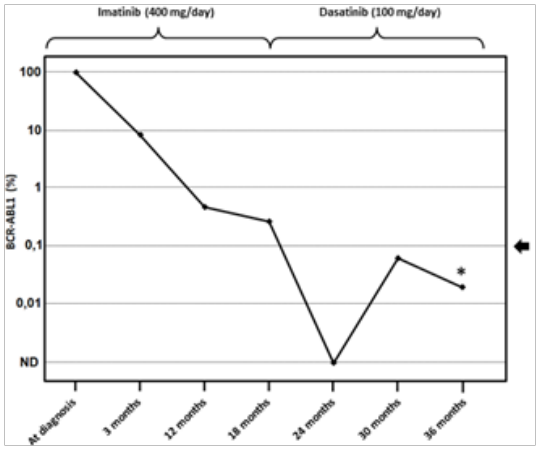

Figure 2 Outcome to treatment with tyrosine kinase inhibitors.

ND, Not detectable; *Hematopoietic stem cell transplantation; The arrow indicates the major molecular response.

Discussion

CML is a disease that is present mainly in the adult population. However, when it presents in childhood and adolescents it behaves aggressively, with most patients presenting advanced disease when diagnosed (accelerated phase or blastic crisis), splenomegaly and higher leukocytosis.[1] In most cases, initial are non-specific, being more frequently resembling anemia syndrome. In this case there was mild anemia (Hb=10.4 g/L), similar to cases 4, 7, 8 and 9, although there are also reports of moderate anemia (Case 6) and severe (Cases 2, 3, 5 and 10) (Table 1).[3–8] Regarding leukocytosis, the reviewed literature determined a mean leukocyte count 237±161 x 10^9/L, (Cases 1-10) being the highest value the case reported here (512 x 10^9/L). As Table 1 shows, splenomegaly has been reported in most published cases. With respect to presence of BCR-ABL1 transcripts, it has been shown their distribution throughout pediatric and adult patients are similar.[9] In the case described here, there was documentation of the unusual presence of e1a2 transcript which codifies the p190 variant, which goes against previous case reports (Table 1).

This variant has been associated with monocytosis,[10] but there are also reports on pediatric patients with monocytosis and variant p210.[3] However, this case has no monocytosis, which concurs with the description by Carvalho et al.[11] who reported a 62-year-old woman with p190 variant and no monocytosis.[11] It has been shown that the presence of certain specific BCR-ABL1 transcripts determine clinical response. Suttorp et al.[12] documented in pediatric patients with CML and e14a2 (b3a2) transcript have a faster response to Imatinib in comparison to those who present with e13a2 (b2a2) variant.[12] However, due to the rarity of patients with e1a2 transcript there is no documented association between response to imatinib which may explain the suboptimal response of the present case. On the other hand, prognostic classification systems used in adult patients lack any value in pediatric patients. Thus, the value of clinical features such as splenomegaly and white blood cell count (WBC) at diagnosis is inversely proportional to early response (3 months) to imatinib, in adults, Millot et al.[13] showed statistically significant differences (p=0.02) between average WBC in those patients with BCR-ABL1/ABL >10% (378 x 10^9/L) and ≤10% (252 x 10^9/L), having the former less chance of acquiring a MMR by 12 months of therapy and less progression free survival.[13]

Despite the presented case showing evidence of BCR-ABL1/ABL at 8.4% at 3 months from diagnosis, the patient did not achieve MMR by 12 months of imatinib (BCR-ABL1/ABL=0.48%), revealing the importance or other factors associated with response to therapy. This suboptimal response may be explained by both clinical features such as WBC count (512 x 10^9/L) and splenomegaly (Boyd III) at diagnosis. Since our patient did not acquire a MMR after 18 months of therapy with imatinib, and because of predisposing high risk factors for disease progression, there was the decision to switch therapy to dasatinib at a dose of 100 mg/day, achieving a MMR by 6 months thereafter. Although at the time of patient identification dasatinib was approved only for adults with CML, this drug could be considered as a therapeutic option in pediatric patients with failure to respond or suboptimal response to imatinib.[14] Nevertheless, dasatinib was recently approved as a front-line treatment in pediatric patients with CML.[15] On the other hand, although in CML in chronic phase the hematopoietic stem cell transplantation is not a formal indication due to the excellent response of TKI from different generations, this can be considered as a curative option in children. This offers additional benefits because it eliminates the need for chronic treatment, as has been described in the present case.

Citation: Carina A, Carlos FA, Siu P, et al. Variant p190 of the *BCR-ABL1* gene in a pediatric patient with chronic myeloid leukemia. *Int J Fam Commun Med.* 2019;3(5):196–198. DOI: 10.15406/ijfcm.2019.03.00157

Table 1 Characteristics of pediatric patients with chronic myeloid leukemia

Case	Age (Years)	WBC (x10⁹/L)	Hb (g/dL)	N (%)	M (%)	B (%)	MP (%)	Blasts (%)	Platelets (x 10⁹/L)	SM	Ph chr	Transcript	Ref.
1	11	512	10.4	40	0	1	56	3	377	+	+	e1a2 (p190)	Present case
2	1,6	40	7.4	41	12	3	5	1	111	+	+	b2a2 (p210)	3
3	0,8	38	5.9	43	16	2	5	2	47	+	+	b3a2 (p210)	3
4	11	246	10.7	47	3	5	34	1	885	+	+	NR	4
5	11	221	7.42	54	2	1	38	1	915	+	+	NR	5
6	3	265	8.4	60	0	6	27	4	1063	+	+	b3a2 (p210)	6
7	7	99,7	11.9	ND	ND	ND	ND	ND	350	+	+	b3a2 (p210)	7
8	5	155	10.8	ND	ND	ND	ND	ND	559	-	+	b2a2 (p210)	7
9	16	424	10.1	45	1	5	16	1	348	+	+	ND	8
10	12	366	5.2	35	1	3	55	2	193	+	ND	p210	8

WBC, white blood cells; Hb, hemoglobin; N, neutrophils; M, monocytes; B, basophils; MP, myeloid precursors; SM, splenomegaly; Ph chr, philadelphia chromosome; ND, not described

Conclusion

The low frequency of CML in the pediatric population creates the need to describe the cases diagnosed in this group, standing out Latin America due to the ethnic features; this report constitutes the first pediatric case described in Venezuela. Currently, the patient is the disease-free thanks to the treatment protocol used.

Acknowledgments

None.

Funding details

None.

Conflicts of interest

The author declares there is no conflict of interest.

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