

LEUKEMIA IN ERYTHROID BLAST CRISIS AND AUTOIMMUNE HEMOLYTIC ANEMIA: A CASE REPORT

Yamilé Quintero Sierra ^{1*} <https://orcid.org/0000-0002-6872-4326>

Carlos Hernández Padrón ² <https://orcid.org/0000-0002-7625-1864>

Yusleidy Concepción Fernández ³ <https://orcid.org/0000-0003-1916-2336>

Adrián Romero González ⁴ <https://orcid.org/0000-0002-5029-9616>

^{1,2,3,4} *Institute de Hematología e Inmunología, La Habana, Cuba.*

ARTICLE INFO

ABSTRACT

Corresponding Author:

Yamilé Quintero Sierra ¹

¹*College of Information Technology
Institute de Hematolog Immunological, La
Habana, Cuba*

Orcid ID : <https://orcid.org/0000-0002-6872-4326>

Introduction: Chronic myeloid leukemia is a chronic myeloproliferative neoplasm characterized by the uncontrolled proliferation of myeloid precursors and autoimmune hemolytic anemia is an unregulated immune reaction towards the antigens themselves that are on the surface of the membrane of red blood cells. The combination of these diseases is extremely rare and even greater when chronic myeloid leukemia is in erythroid blast crisis.

Objective: To describe a case with the coexistence of chronic myeloid leukemia in erythroid blast crisis and autoimmune hemolytic anemia.

Clinical case: Patient with a history of chronic myeloid leukemia who presents an erythroid blast crisis and develops an autoimmune hemolytic anemia due to warm IgG antibodies. The treatment for both diseases will be administered. After a clinical improvement of the autoimmune hemolytic anemia, he maintained the erythroid blast crisis and was administered an intensive chemotherapy regimen where complications occurred and he died.

Conclusions:

The treatment with steroids in autoimmune hemolytic anemia in patients with chronic myeloid leukemia is effective when they are in the chronic phase of the disease, but little responsive when they are in blast crisis, as was the case we present, and the fatal outcome in the patient was multi factorial.

KEYWORDS :- Chronic myeloid leukemia; Autoimmune hemolytic anemia; Erythroid blast crisis; Chemotherapy

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic myeloproliferative neoplasia characterized by uncontrolled proliferation of myeloid precursors. Patients show a reciprocal translocation between chromosomes 9 and 22 t(9,22), and the Philadelphia chromosome is formed, which produces the BCR / ABL fusion gene with high tyrosine kinase activity. It occurs in any of its three phases: chronic, accelerated and blast crisis. ⁽¹⁾

The aberrant activation of kinases hinders different signaling pathways, and it leads to an increase in cell proliferation, arrest of cell maturation and differentiation processes and resistance to apoptosis, which can bring about different phases of transformation of the LMC. ⁽²⁾

Blast crises can be of lymphoid, myeloid, or hybrid lineage, but in about 70% of cases, the blast lineage is myeloid. The most common phenotypes correspond to the populations of granulocytes and monocytes, but it can be in any of its morphological variants and they manifest as secondary acute leukemia. ^(3,4) Erythroid blast crises are very rare, occurring in only 1% of cases. ⁽⁴⁾

Autoimmune hemolytic anemia (AIHA) is an unregulated immune reaction towards the patient's own antigens on the surface of the patient's red blood cell membrane, leading to extravascular hemolysis in warm AIHA mediated mainly by IgG and intravascular hemolysis in the IgM-mediated cold agglutinin disease. The diagnosis of AIHA is suggested by the evidence of hemolysis in the anemia study and confirmed by a positive direct antiglobulin test (DAT). ⁽⁵⁾

Treatment efforts are aimed at counteracting hemolysis or increasing red blood cell survival, in addition to treating and managing possible associated conditions. ⁽⁶⁾

The combination of CML or acute myeloid leukemia (AML) and AIHA, in contrast to lymphoproliferative syndromes as it is in the case of chronic lymphoid leukemia, is extremely unusual, as few case reports and series have been published in the medical literature that link these entities. There have been reports of rare cases of adult patients with AIHA associated with AML according to the morphological

Classification by the Franco-American-British (FAB) group AML-M0, AML-M2, ⁽⁷⁾ AML-M3 ⁽⁸⁾ and in 1963 it was reported a case of AIHA due to cold agglutinins that evolved into AML with a monocytic component but was not immunologically classified. ⁽⁹⁾ Few cases of AHAI and CML combination have also been reported. ⁽¹⁰⁾

We report a clinically relevant case due to the coexistence of severe AHAI due to warm IgG antibodies developed in the course of an erythroid AML (M6) secondary to the blast crisis of a CML in a patient diagnosed with this disease since 2018.

PRESENTATION OF THE CASE

Patient MRP, female, white, urban origin, 55 years old, overweight, with a family history of a mother with CML since 2013; and personal medical history of Bronchial Asthma since childhood and CML since July 2018 where it was necessary to transfuse her with 500ml of erythrocyte concentrate on debut and she was on treatment with Imatinib Glivec, (Novartis Pharma AG, Basel, Switzerland) 400mg / day.

During the first year of diagnosis of CML, the patient presented a favorable evolution, reaching in July 2019 hematological and greater cytogenetic remission, as well as negative qualitative BCR / ABL gene rearrangement studies. She continued with the same treatment behavior and in September of that same year she went to the emergency department consultation due to shortness of breath on exertion, easy fatigue, severe mucous skin paleness and bone pain for more than 15 days.

The patient had a good general condition despite being symptomatic. The physical examination revealed hypocoloured mucous membranes with slight icterus, the presence of hematomas and edema in the lower limbs that reached up to the middle third of both legs with easy godet, sinus tachycardia, and hepatomegaly at 2 cm below the right costal margin, of firm consistency and not painful. Due to all this situation, it was decided to hospitalize her for a comprehensive health assessment.

In the complementary tests performed, severe anemia was observed with hemoglobin of 69 g/L, hematocrit 0.20, existence of reticulocytosis with a reticulocyte count of 4.0%, normal leukocytes in number but with the presence of 6% myeloblasts, 7 % myelocytes, 21% metamyelocytes, 8% fallen, 47% neutrophils, 2% eosinophils, 3% monocytes and 36% lymphocytes; and severe thrombocytopenia where the platelet count was $42.0 \times 10^9/L$.

In the peripheral blood smear, marked hypochromia, anisocytosis, poikilocytosis, normoblasts, basophilic stippling, cabot rings, and polychromatophilia were observed.

The elevated erythrocyte sedimentation rate was 95 mm / h. Serum enzymes were determined, such as: very high lactate dehydrogenase levels (1024 IU/L), leukocyte alkaline phosphatase elevated at 190 IU, and normal muramidase. Liver enzymes such as puruvic, oxaloacetic and glutamic transaminase within normal limits; the determinations of creatinine, uric acid and urea in normal values.

Immunohematological studies are performed where negative group and factor B with negative cceeKell phenotype, positive DAT studies with IgG specificity and positive indirect agglutination test (IAT) with anti Fyb specificity are obtained. It was concluded as the presence of AIHA by warm antibodies and with alloimmunization by previous transfusions received by the patient.

Abdominal ultrasonography showed a homogeneous liver with increased echogenicity, without focal lesion but exceeding the rib margin by 3 cm, cholecystectomized; and the rest of the abdominal organs without alterations.

The chest X-ray did not show pleuropulmonary alterations or the cardiac silhouette.

The echocardiogram showed anleft ventricular ejection fraction 63.0%, fraction of left ventricular shortening 34.0%. No effusion or pericardial fibrosis that concluded a structurally healthy heart.

The bone marrow biopsy reported the positivity of myeloperoxidase and glycoporhin A using immunohistochemistry (Figure 1).

The bone marrow aspirate showed hyper cellularity, infiltrated by two populations of cells, the first in 60% by immature cells with very basophilic cytoplasm that correspond to proerythroblasts with the presence of cytoplasmic mamelons, and the second in 30% by immature cells with granulations in the cytoplasm, lax chromatin, presence of nucleoli in number from 1 to 2 of myeloid appearance; the megakaryopoietic system was depressed, and the erythropoietic and granulopoietic system was hyperplastic, the latter showing cells of intermediate maturation and signs of dysgranulopoiesis. The morphological appearance according to the FAB classification corresponds to the M6 variant, and with the patient's history of CML it was concluded as CML in erythroid blast crisis. (Figure 2 A/B)

The conventional cytogenetic study reported 20 metaphases with chromosomal formula: $46,xx,t(9,22)$, and was performed by fluorescence in situ hybridization (FISH) technique: nucish 9q34 (ABLx3), 22q11.2 (BCRx3) (170/200) with BCR / ABL probe, where an atypical positive pattern was obtained in which a third chromosome $t(9; 22; v)$ is involved in the translocation. The molecular study by the polymerase chain reaction technique was again positive for the rearrangement of the MBCR / ABL gene. (Figure 2 C)

The flow cytometry study determined the existence of two populations of cells, the first 28.50% with expression of CD13 +, CD45 +, CD33, CD71 + and CD235a + antigens and negative for CD15, DR, CD4, CD41, CD117, CD34 antigens. CD38 and the second population with 49.14% with expression of CD13 +, CD45 +, CD15 +, CD4 +, DR +, CD33 +, CD117 +, CD38 +, CD34 +, CD71 + and CD235a +, the CD14 and CD41 antigens were negative. It was concluded as a bilinear blast crisis: erythroid and granulocytic. (Figure 3)

The coexistence of the onset of AIHA due to warm antibodies and AML secondary to erythroleukemic blast crisis was considered and treatment of AIHA was started with prednisone at immunosuppressive doses of 1.5 mg / kg of body weight, and patient surveillance In relation to hemodynamics to avoid the use of erythrocyte concentrate

transfusions, the search for the most compatible blood cells with the patient was also started by immunohematology in case of the need to transfuse her, the dose of ITK of the Imatinib type was increased, to 800 mg daily orally.

During the first 30 days of steroid treatment, hemoglobin levels rose to 90 g/L, without requiring transfusion, but the patient maintained thrombocytopenia and began with leukopenia in addition to maintaining the existence of myeloblasts with leukemic hiatus in peripheral blood, reason for which the case is discussed collectively and in the month of November it is decided to carry out an intensive chemotherapy scheme for secondary AML with an intensive "7 + 3" scheme using the combination of arabinoside cytosine at 100mg/m² in continuous infusion for 7 days and daunorubicin at 60mg / m² the first 3 days intravenously to last 1 hour; the same dose of 800mg daily by oral route of Imatinib was maintained; and the dose of prednisone was decreased to 1mg/kg/day.

On the tenth day of rest from chemotherapy, hemoglobin figures were found to be greatly decreased by 45 g/L, which led to the use of intravenous immunoglobulin at immunosuppressive doses of 1g/kg for two days, and it was necessary to administer 150 ml of erythrocyte concentrate that is most compatible for the patient, which tolerated without complications and improved her hemodynamics, as well as apheresis platelet concentrate was used as prophylaxis to prevent bleeding at any level, but despite these measures, on the twelfth day of aplasia post-chemotherapy begins with upper digestive bleeding with the presence of abundant melena in number and quantity, with a very torpid evolution of the patient leading to hypovolemic shock, which despite using a concentrate of erythrocytes compatible with it, a cardiorespiratory arrest occurs suddenly that despite resuscitation measures, it was not possible to reverse it and the patient died.

DISCUSSION

AIHA is a rare cause of anemia in CML, but when it does occur, it develops after the diagnosis of CML in the chronic phase that generally responds to steroids. In a study carried

out by Mohamed A Yassin et al ⁽¹¹⁾ in 54 patients with CML developed AIHA between the years 1952 to 2018, all were in the chronic phase of the disease except for three patients; one in accelerated phase and two in blast crisis.

The transformation of CML into AML is more frequent in granulocytic variants, although in some cases erythroid blast crisis has also been described, ⁽¹²⁾ but this transformation is an aggressive type of leukemia due to the frequent association with chromosomal alterations involving chromosomes 5 and 7 and the appearance of multidrug resistance genes. ⁽¹³⁾

Electron microscopy techniques make the classification of leukemias more objective and accurate. In the case of erythroid blast cells, it has allowed their precise identification, by discovering the existence of ferritin particles as free molecules in the cytoplasm, forming aggregates, or surrounded by cytoplasmic membrane, which are associated with the absorption of the molecules of ferritin (rphocytosis) and are characteristic of erythroblasts, even in their earliest forms. ⁽¹⁴⁾ These cells are highly undifferentiated, without heterochromatin; abundant ribosomes, endothelial reticulum and mitochondria are discovered in its cytoplasm; there is a very active Golgi complex and lipid vacuoles and glycogen aggregates are sometimes very apparent. ^(3,4,14)

One of the great advances is the possibility of defining the immunophenotype of leukemic cells by means of monoclonal antibodies, with the use of the flow cytometry technique. The most common markers include: hemoglobin, erythroid cell products, glycophorin A, spectrin, CD36, molecules related to the erythrocyte membrane structure such as aldehyde dehydrogenase, carbonic anhydrase, and molecules related to erythroid metabolic pathways such as caderin-e, markers related to adhesion, transferrin receptor 1 (CD71) and ferritin H, markers related to iron metabolism. ⁽¹⁵⁾

In conclusion, treatment with steroids in AIHA in patients with CML is effective when they are in the chronic phase of the disease but little responsive when they are in blast crisis, as was the case we present, and the fatal outcome in the

patient was fundamentally multifactorial because there were complications such as: digestive bleeding and the impossibility of transfusing her without this constituting another factor of increase in hemolysis in the patient. The combination of severe hypoxia, low hemoglobin levels, post chemotherapy aplasia with haemostasis disorders, and increased acute blood loss lead to cardiovascular dysfunction and death.

BIBLIOGRAPHIC REFERENCES

1. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. *Am J Hematol.* 2018; 91(2): 252–65.
2. Kang ZJ, Liu YF, Xu LZ, Long ZJ, Huang D, Yang Y et al. The Philadelphia chromosome in leukemogenesis. *Chin J Cancer* 2016; 35(48):1-15.
3. Nagales-Nagamos R, Gentile T, Vajpayee N. Erythroid blast crisis in chronic myelogenous leukemia: Case report and review of literature. *Leukemia Res Rep.*2016; 5:18-22.
4. Domínguez Domínguez G, Marsán Suárez V, Hernández Padrón C, Lam Díaz RM, Quintero Sierra Y, Olivera Morán O. Caracterización inmunofenotípica de pacientes con leucemia mieloide crónica en crisis blástica. *Rev Cubana Hematol Inmunol Hemoter.*2017;33(4). Disponible en: <http://www.revhematlogia.sld.cu/index.php/hih/article/view/>
5. Kalfa TA. Warm antibody autoimmune hemolytic anemia. *Hematol Am SocHematolEduc Program.* 2016; 2016(1):690–7.
6. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. *Blood.* 2017; 129(22):2971–9.
7. Tamura H, Ogata K, Yokose N, et al. Autoimmune hemolytic anemia in patients with de novo acute myelocytic leukemia. *Ann Hematol* 1996;72:45-47. DOI: 10.1007/BF00663016. [PubMed]
8. Jacob J.S, Suman F.R, Scott J.X, Latha MS Co existence of acute promyelocytic leukemia and autoimmune haemolytic anaemia in a girl – A diagnostic and therapeutic challenge. *Int J Pediatr Res.*2016;3(8):640-643.doi:10.17511/ijpr.2016.8.15.
9. Ben-Ishay D, Freund M, Groen JJ. A case of autoimmune hemolytic anemia with circulating cold agglutinins presenting for many years as "hypersplenism" and terminating in leukemia. *Blood.* 1963 Jul 1;22(1):100-8.
10. Arbaje YM, Beltran G. Chronic myelogenous leukemia complicated by autoimmune hemolytic anemia. *The American journal of medicine.* 1990 Feb 28; 88(2):197-9. [PubMed].
11. Mohamed A Yassin, TahseenHamamyh; Autoimmune Hemolytic Anemia in Chronic Myeloid Leukemia from Busulfan to the Era of Tyrosine Kinase Inhibitors. *Blood* 2019; 134 (Supplement_1): 5917. doi: <https://doi.org/10.1182/blood-2019-121433>.
12. Ekbloom M, Borgström G, Von Willebrand E, Gahmberg CG, Vuopio P, Anderson LC. Erythroidblast crisis in chronicmyelogenousleukemia. *Blood* 1983; 62:591-6.
13. Wang SA, Medeiros LJ, and Khoury JD. Pure erythroid leukemia. *Am J Hematol.* 2017;92:292–296. <https://doi.org/10.1002/ajh.24626>.
14. O' Malley FM, Garson OM, McGrath K, Elliot PJ, Whiteside MG. Erythroblastic transformation of chronic granulocytic leukemia: a clinical and cytogenetic case study. *Am J Hematol* 1983; 14:371-6.
15. Dong HY, Wilkes S, Yang H. CD71 is selectively and ubiquitously expressed at high levels in erythroid precursors of all maturation stages: a comparative immunochemical study with glycophorin A and hemoglobin A. *Am J SurgPathol.* 2011;35:723–732.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR INFORMATION

Yamile Quintero Sierra, MD. Specialist in Hematology. MSc. Infectious diseases (corresponding author), Auxiliary Professor and Investigator. Adults service, Institute of Hematology and Immunology. La Habana, Cuba. CP 10400. Email: yquinteros@infomed.sld.cu

Carlos Hernández Padrón, MD. Specialist in Hematology. PhD. Senior Investigator, Head of the adults service, Institute of Hematology and Immunology. La Habana, Cuba. CP 10400. Email: chdezp@infomed.sld.cu

Dr. Yusleidy Concepción Fernández, MD. Specialist in Hematology. Aggregate Investigator.

Assistant Professor. Adults service, Institute of Hematology and Immunology. La Habana, Cuba. CP 10400. Email: yconcepcionf@infomed.sld.cu

Dr. Adrián Romero González, MD. Specialist in Hematology. Auxiliary Professor and Investigator. Adults service, Institute of Hematology and Immunology. La Habana, Cuba. CP 10400. Email: aromerog@infomed.sld.cu

AUTHORS' CONTRIBUTIONS

Dra. Yamilé Quintero Sierra: Participated in the diagnosis and treatment of the case, compiled the entire bibliography used, and selected the relevant articles for the review. She made important contributions to the conception of the article, the writing of the draft, the critical review of its content and the final approval of the version to be published. Dr. Carlos Hernández Padrón: Participated in the contributed with his experience in reporting cases with atypical patterns in oncohematology, and participated in the

critical review of its content and the final approval of the version to be published.

Dra. Yusleidy Concepción Fernández: Participated in the critical review of its content and the final approval of the version to be published.

Dr. Adrián Romero González: Participated in the critical review of its content and the final approval of the version to be published.

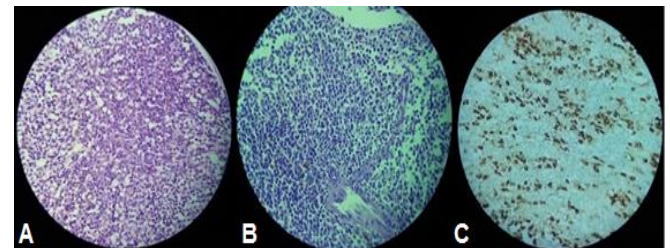


Figure 1. Bone marrow biopsy images. (A) Hematoxylin and eosin [H&E] staining. (B) May-Grünwald-Giemsa [MGG] staining. (C) Myeloperoxidase (MPO) staining by immunohistochemistry.

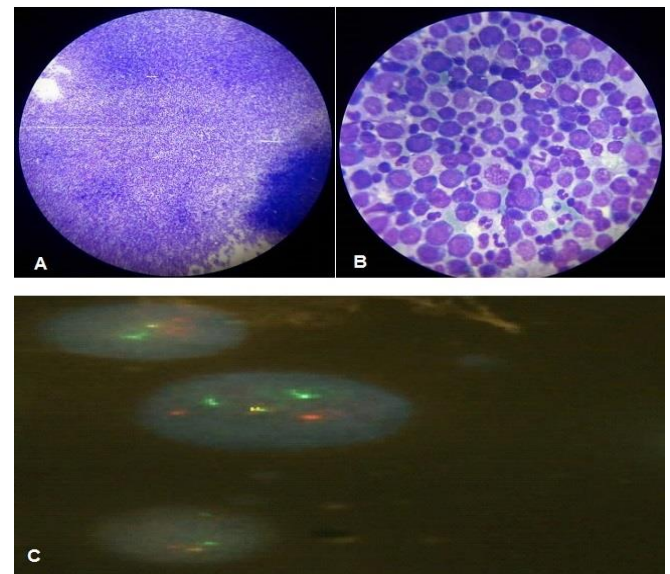


Figure 2. (A) Bone marrow aspirate showing hypercellularity with the lower magnification lens. (B) Higher magnification lens showing both myeloblast and proerythroblast cell populations. (C) FISH in interface for BCR / ABL rearrangement. Atypical positive pattern with 1 yellow (Ph), 2 red (ABL) and 2 green (BCR) signals (1A 2R 2V). Translocation variant t(9; 22; v).

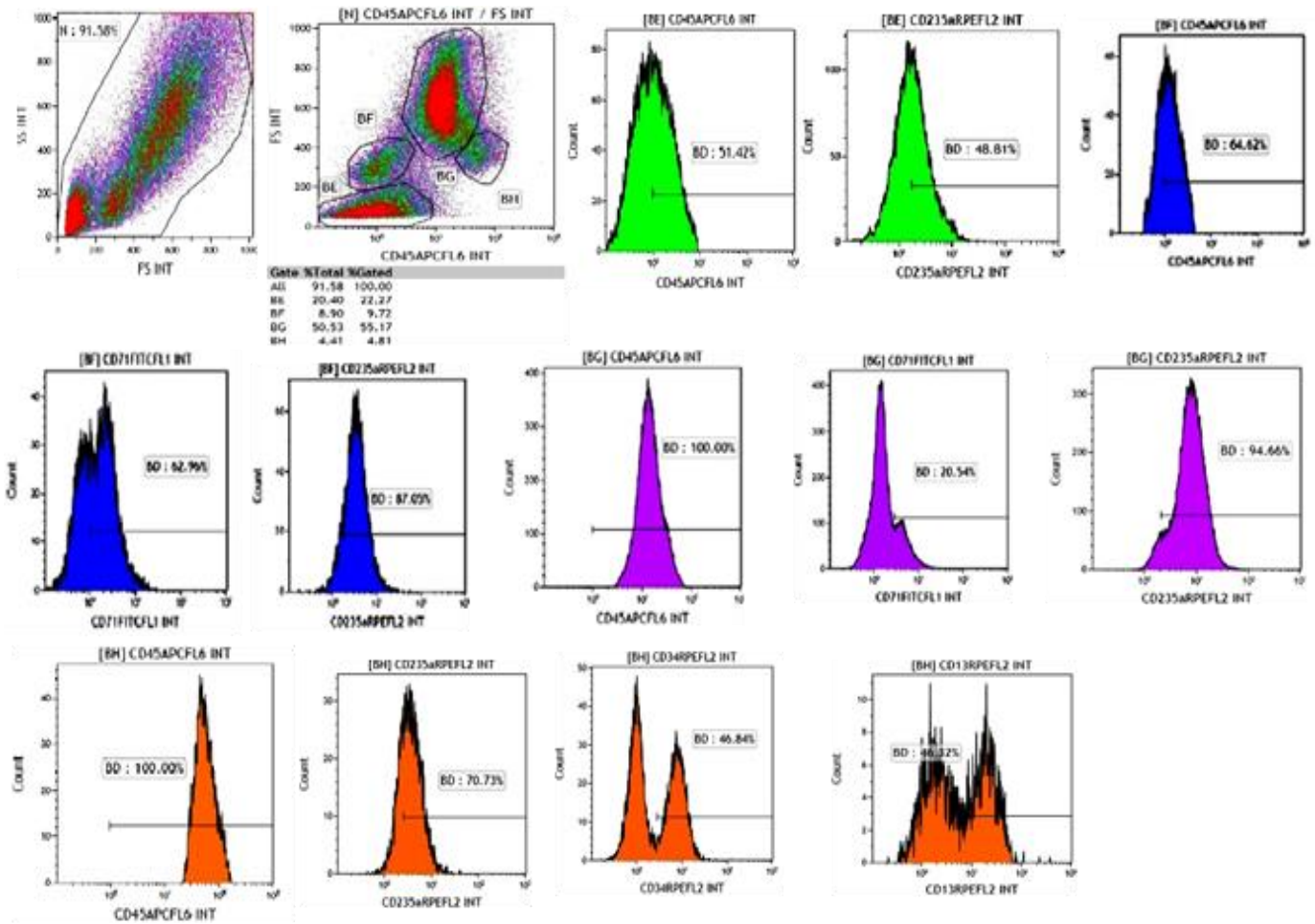


Figure 3. Sequence of analysis of the immunophenotype by flow cytometry. Dot plots pertain to total cells counted and the use of CD45/side scatter (SS) to separate the different cell populations. The histograms correspond to the expression of the CD45 + / CD235a + / CD71 + / CD34 + / CD13 + antigens, expressed in them.