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Case Report
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Coexistence of Trisomy 8 and 13 in a Newly Diagnosed Patient with Diffuse Large B Cell Non-Hodgkin's Malignant Lymphoma and Acute Myeloblastic Leukemia Secondary to Primary Myelofibrosis

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Abstract

Background: Concomitant diagnosis of Non-Hodgkin lymphoma (NHL) and acute myeloid leukemia secondary chronic Myeloproliferative Neoplasms (MPNs) is rarely reported. Patients with MPNs may have a second neoplasm; the risk of lymphoid line neoplasms is 2.5 to 3.5 times. The explanation for this association is the genetic instability of hematopoietic progenitors in MPNs.

Case Report: Patient man 80 years old, Caucasian, known with much comorbidity, presents for physical asthenia, sweating, and right inguinal adenopathy with a diameter of 5 cm to 6 cm, partial mobility, and pain (appearing 1 month before the examination). The patient was diagnosed concomitantly with DLBCL and AML secondary to Primary Myelofibrosis (PMF) and presented a complex karyotype - trisomy 8 and 13 and triple-negative PMF status. The patient initially received 2 well-tolerated R mini CHOP series, this type of treatment was selected to treat DLBCL for one unfit patient for intensive chemotherapy due to his age and comorbidities. R mini CHOP administration was followed by severe aplasia that lasted approximately 2 weeks followed by severe thrombocytosis that reached 4000 x 10^9/L and thromboreductin recommendation was mandatory. The result of the treatment was a partial response but with severe adverse events neutropenia G4, due to the delay of the treatment the patient lost the response. It was mandatory to select another treatment line and the chosen was Venetoclax, it was selected for the simultaneous treatment of DLBCL and the underlying AML. It was obtained a significant reduction in the size of the inguinal lymph node block in 2 weeks of the treatment. Severe neutropenia was diagnosed and complicated with sepsis. The evolution is unfavorable with the installation of multiple organ dysfunctions.

Conclusion: The presence of a complex karyotype (trisomy 8, trisomy 13) in a patient with myeloid metaplasia with triple-negative PMF was associated with blast transformation and severe thrombocytosis. The patient was diagnosed concomitantly with DLBCL, making the therapeutic decision difficult. Venetoclax has been shown to be useful in the treatment of DLBCL but has been associated with severe neutropenia, which has led to infectious complications.

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Introduction

Large B cell non-Hodgkin's malignant lymphoma (DLBCL) represents 30% to 40% of the total number of patients diagnosed with Non-Hodgkin's Lymphoma (NHL). This type of NHL presents 2 molecular subtypes: Germinal center B-Cell like (GCB) and Activated B-Cell like (ABC) subtypes; however, 10% to 15% of cases are unclassifiable [1]. The diagnosis of NHL in rare cases may be

associated with chronic Myeloproliferative Neoplasms (MPNs) [2,3]. Sometimes the diagnosis of MPNs has been established in patients with NHL history during the remission period [4]. Patients with MPNs may have a second neoplasm, with a risk of 1.5 to 3 times for solid tumors (skin, lung, thyroid, kidney) and 2.5 to 3.5 times for lymphoid line neoplasms: Monoclonal gammopathy or chronic lymphoproliferative syndrome: B Chronic Lymphocytic Leukemia (B-CLL), NHL [5-7]. The higher incidence of the development of lymphoproliferation in patients with MPNs is higher in men and those with the JAK2V617F mutation, and the median duration for the identification of the second neoplasm is 68 months after the diagnosis of MPNs. The risk of lymphoproliferation is 3 times higher for NHL and up to 12 times for B Chronic Lymphocytic Leukemia (B-CLL). The explanation for this association is the genetic instability of hematopoietic progenitors in MPNs [2,5]. Some studies have shown that treatment with JAK inhibitors can be involved in increasing the risk of developing NHL, a hypothesis unconfirmed by other studies. However, not all studies have confirmed this hypothesis [8]. The concomitant presence of Acute Myeloblastic Leukemia (AML) and DLBCL is rarely reported in the literature. Cases of acute leukemia diagnosed after the diagnosis of DLBCL have been reported [9,10]. Acute myeloid leukemia discovered in DLBCL patients is often secondary to chemotherapy that includes alkylating agents (fludarabine, cyclophosphamide), especially if it also combines rituximab but is also due to immune dysfunction or infections [11-13]. The association at the time of diagnosis of AML and NHL was not reported. We will present the clinical case of a patient diagnosed concomitantly with DLBCL and AML secondary to Primary Myelofibrosis (PMF) who presented a complex karyotype - trisomy 8 and 13 and triple negative PMF status.

Case Presentation

Patient man 80 years old, Caucasian, known with ischemic heart disease, mitral and tricuspid insufficiency, hypertension, heart failure class III NYHA, morbid obesity, presents for physical asthenia, sweating. The clinical examination shows right inguinal adenopathy with a diameter of 5 cm to 6 cm, partial mobility, and pain (appearing 1 month before the examination). Laboratory investigation at the onset: WBC 3.14 × 10^9/L (N 4-11 × 10^9/L), Hb 10.6 g/dl (N 12.3 g/dl to 17 g/dl), Plt 1380 × 10^9/L (N 150-450 × 10^9/L); peripheral blood smear revealed 20% erythroblasts, 25% blasts, 43% lymphocytes, 30% monocytes, 26% neutrophils, macro platelets and giant platelets, normochromic red cells, frequent polychromatic cells, anisocytosis, ovalocytes and rare tear drop cells. Bone marrow aspiration revealed normal cellularity with 35% to 40% myeloblasts and very large groups of platelets. Abnormal biochemistry results were uric acid 8.6 mg/dl (N 3.4 mg/dl to 7 mg/dl), LDH 502 IU/L (N 135 IU/L to 225 IU/L), and CRP 39.72 mg/L (N 0 mg/L to 5 mg/L); the rest of the hematologic, coagulation and biochemistry parameters were normal. It should be noted that the platelet count in January 2021 was 461 × 1000/μL, and the rest of the hematological parameters were normal. Lymph node biopsy was performed, and the histopathological result identified diffuse malignant lymphoid tumor proliferation with medium/large polymorphic cells, rounded, incised, lobed nuclei, hardly visible nucleoli, and weak basophilic cytoplasm. Immunohistochemistry showed that lymphoid tumor proliferation was B large cell positive diffuse for CD20+ and BCL2, with phenotype CD10 negative, BCL6 positive, and MUM1 positive. The proliferation index Ki67 was 85%, with aberrant expression of CD5 and negative for Cyclin D1, CD3 CD30, and CD23, establishing the diagnosis of DLBCL NOS with a non-germinal center phenotype/non-GCB (Figure 1). The PET-CT evaluation revealed a hyper captive voluminous area (SUVmax 16.13) corresponding to a tumor mass of 9.68/8.55 cm located inter gastrosplenic and hypercapture along the great gastric curvature up to the antrum, without clear differentiation between these hyper fixations. Multiple hyper fixed areas located right laterocervical (SUVmax 9.39 and dimensions 2/1.85 cm), mediastinal (SUVmax 7.33), intra-abdominal (celiac area SUVmax 7.34, dimensions 2.62/2.35 cm, hilum splenic with confluent appearance and SUV max 5.23, paraaortic and right paravertebral), right internal and external iliac (SUVmax 17.11 and dimensions 3.3/2.38 cm), left obturator (SUVmax 5.82), right inguinofemoral with confluent aspect (SUVmax 26.08, diameter 9.97/10.29 cm) in correspondence with lymph node formations. Diffuse and inhomogeneous hyper tracking of the radiotracer at the bone marrow level of the scanned bone segments suggestive of the presence of MPNs (Figure 2). Upper

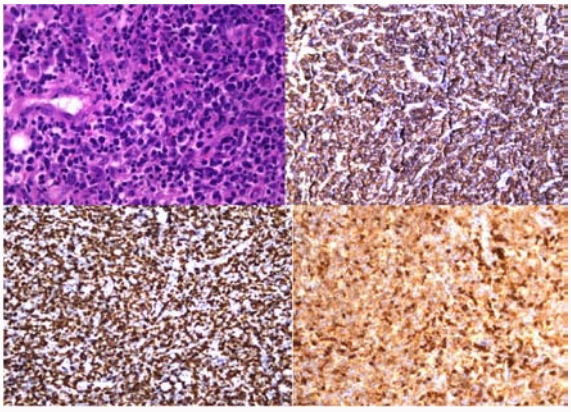

Figure 1: Lymph node biopsy - a) diffuse malignant lymphoid proliferation with large-sized cells (HE stain, ob20x). b) Proliferation is indicated by large B-cells diffusely positive for CD20 (IHC stain for CD20 Ab, ob 20x); c) the tumor presents a very high (85%) Ki67 proliferation index (IHC stain for Ki67 Ab, ob 20x); d) malignant proliferation of large B-cells presents aberrant expression of CD5 (IHC stain for CD5 Ab, ob 20x).

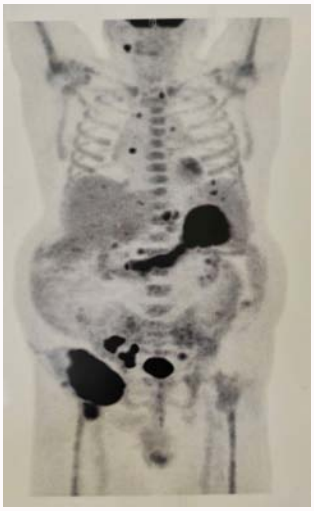

Figure 2: Intense uptake at the level of an inter gastrosplenic tumor mass (SUVmax =16.13) goes further along the large curvature of the stomach and multiple uptaken lymph nodes situated above and under the diaphragm, isolated or organized as confluated masses, with more expressive masses located at the right inguinofemoral region. (SUVmax =26,08). There was also diffuser and inhomogeneous uptake at the level of the medulla throughout all scanned bones, suggesting MPNs.

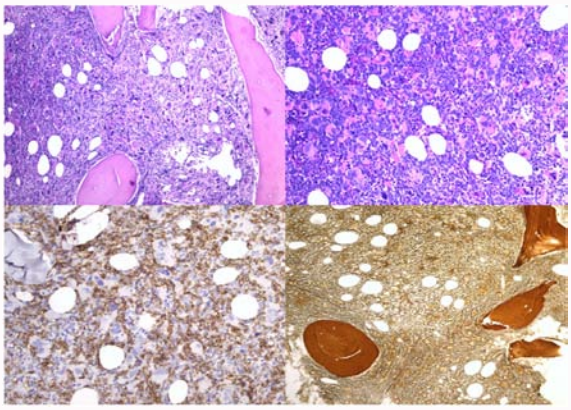

Figure 3: Bone marrow trephine biopsy: a) Hypercellular marrow with granulocyte and megakaryocyte proliferation; areas with dense clusters of atypical megakaryocytes (HE stain, ob 20x); b) Inegal distribution of blasts - areas with clusters of blastic cells (HE stain, ob 20x); c) Blasts are positive for CD34; the percent of CD34 positive blasts is up to 20% of the bine marrow nucleated cells (IHC stain for CD34 Ab, ob 20x); d) Grad 2 fibrosis (reticulin stain, ob 10x).

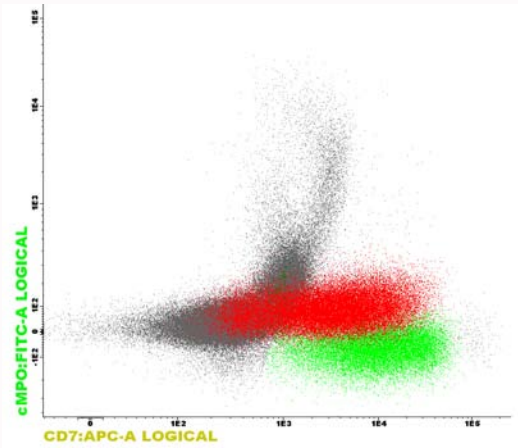

Figure 4: CD7-green - lymphocytes, purple - neutrophils, red - blasts, Burghundy - erythroid precursors. The blast population (red) is positive for CD7, internal positive lymphocyte standard (green) and internal negative erythroid series (cherry).

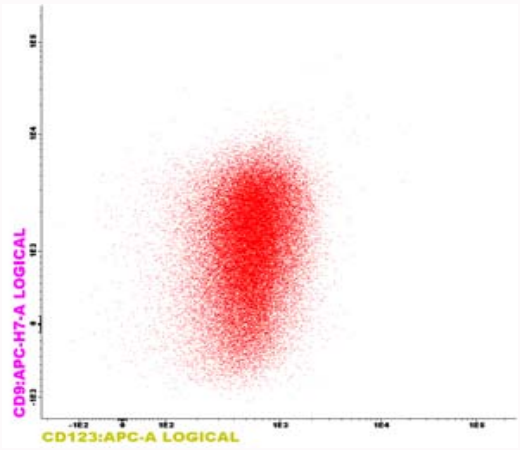

Figure 5: CD9 CD123 - green - lymphocytes, purple - neutrophils, red - blasts, Burghundy - erythroid precursors, blast population (red) is positive for CD123 and estrogen positive (+/-) for CD9, it is also observed the erythroid precursor positive for CD9, the granulocytic series expresses CD123 (pozitiv) si CD9 (heterogen +/-) aberrantly.

digestive endoscopy does not show any pathology. Osteomedullary biopsy (trephine biopsy) performed for staging and diagnosis of DLBCL but also for differential diagnosis of thrombocytosis) indicates the presence of medullary hypercellularity (85%) by diffuse blast infiltration (approximately 50%) with medium cell, vesicular, rounded nucleus, hardly visible nucleoli, normoblastic maturation with rare macro/megaloblastoid elements, very common megakaryocytes, very polymorphic, some with nucleocytoplasmic atypia grouped compactly perivascular and peritrabecular. Silver impregnation Gomori MF2 focal (>30%). This result is suggestive of acute transformation (AML) of Primary Myelofibrosis (PMF) (Figure 3). Molecular testing of BCR/ABL, JAK2 V617F, CALR and Mpl was negative. ASXL1 and TET2 mutation was not performed. Immunophenotype evaluation of bone marrow by flow cytometry indicated 30% myeloid blasts CD34+, CD117+, HLA-DR+, CD3-, CD7+, CD19-, CD33+, CD36-, CD13+, CD300e-, CD35-, CD14+/-, CD16-, CD64-, CD11b-, CD10-, CD15-, CD56-, CD9+/-, CD123+/-, CD105-, CD71+/- suggestive for myeloblast without maturation with aberrant co expression of CD7, CD9, CD13 (AML M1 FAB) (Figure 4, 5). Cytogenetic examination of bone marrow aspirate revealed the presence of trisomy 8 and 13. FISH examination did not reveal IGH-BCL2 rearrangement (t (14; 18) (q32, q21) or BCL 6 (3q27). Additionally, MYC rearrangements (8q24) and FGFR1 (8p11) were not revealed. Deletions of the DLEU (13q14), TP53 (17p13) or KMT2A rearrangement (11q23) genes were not detected. The diagnosis was DLBCL stage III in a patient with blastic phase PMF (AML M1 FAB post PMF) associated with trisomy 8 and 13. The patient initially received 2 well-tolerated R mini CHOP series; this type of treatment was selected to treat DLBCL for one unfit patient for intensive chemotherapy due his age and comorbidities. R mini CHOP administration was followed by severe aplasia that lasted approximately 2 weeks followed by severe thrombocytosis that reached 4000 × 10^9/L. For this reason, it was decided to administer anagrelid (Thromboreductin) under which the platelet count returned to normal. The result after administration of the 2 R mini CHOP applications was partially response with a slight reduction of the right inguinal lymph node block. The decision was made to stop the administration of R mini CHOP (due to severe neutropenia as an adverse event and loss of response by increasing the size of the lymphadenopathy) and to start taking venetoclax. It was selected for the simultaneous treatment of DLBCL and the underlying AML. The evaluation made 2 weeks after the onset of venetoclax indicated a significant reduction in the size of the inguinal lymph node block as well as the presence of severe leucopenia associated with moderate anemia. During pancytopenia, the patient presents with sepsis with a respiratory starting point. CT evaluation shows right lobe pneumonia associated with small bilateral pleural effusion and minimal pericardial effusion. All microbiologic cultures (blood, sputum) were negative, but the patient was positive for SARS-CoV-2, and the rest of the serology tests, CMV, and EBV were negative. At admission, the WBC count was 0.56 × 10^9/L, Hb 6.5 g/dl, Plt 781 × 10^9/L, IL-6 84 pg/ml, CRP 136.57 mg/L, procalcitonin1 ng/mL (N<sau= 0.05 ng/ml), and D dimers 1.43 µg/ml FEU (N 0-0.5 µg/ml FEU). The evolution is unfavorable with the installation of multiple organ dysfunctions (aggravation of renal failure, the installation of severe ventilatory dysfunction and toxic septic shock). As a peculiarity of evolution, it is worth mentioning the deterioration of cardiac function with the effect of myocardial contractility, the appearance of pulmonary hypertension and valvular-mitral and tricuspid insufficiencies that

contributed to the existing complications (ventilatory dysfunction and pleural and pericardial effusions). Additionally, the presence of severe thrombocytosis over 3000-4000 × 10^9/L required the administration of anagrelide to prevent thrombotic complications.

Discussion

The patient was diagnosed with AML M1 FAB (with abnormal expression of CD7) secondary to PMF. This expression is associated with a reserved prognosis [14,15]. Two genetic aberrations are associated – trisomy 8 and 13. Trisomy 8 is one of the most common cytogenetic mutations found in AML (10% to 15%) but also in other neoplasms - Myelodysplastic Syndromes (MDS) (15% to 20%), MPNs, Acute Lymphoblastic Leukemia (ALL) (5%), solid tumors (colon, breast), rarely in B-CLL or NHL [16-18]. The prognosis of AML 8+ patients is reserved; patients with NHL have not been reported [17]. Trisomy 13 has been described in AML M0 and M1 FAB, especially in men over 70 years of age (0.7%), MDS, PMF, and atypical chronic granulocytic leukemia (atypical CML).The prognosis of AML 13+ patients is unfavorable, with a median survival of 0.5 to 14.7 months [19]. At the same time, the patient was diagnosed with DLBCL NOS (not otherwise specified) with a non Germinal Center B cell (GCB) phenotype and aberrant expression of CD5. CD5 expression in DLBCL is more frequently associated with advanced disease or the presence of extra ganglionic determinations. The clinical evolution of such a patient is unfavorable [20,21]. The concomitant diagnosis of AML and NHL is rare. Cases of AML have been reported in patients with untreated B-CLL, and this association gives a reserved prognosis [22]. In the case of the presented patient, there was no treatment prior to the diagnosis of NHL and transformed MPNs. Although the diagnosis of AML secondary to PMF was made concomitantly with that of NHL-DLBCL, it should be noted that this patient had elevated platelet counts at least 6 months prior to diagnosis, and the patient was not investigated. The patient did not have any dynamics of morphology in the past or the result of a previous peripheral blood smear or spleen and liver size. This patient has two trisomy 8 and 13 genetic mutations that give a reserved prognosis. Trisomy 8 has been found, in a few cases, in patients with T cell NHL or B cell NHL (B-CLL, DLBCL, follicular or mantle cell NHL) [23-26]. It has also been identified in patients diagnosed with MDS or MPNs. The unique presence of trisomy 8+ in MDS patients indicates the presence of an intermediate prognosis. However, the association with other anomalies determines the inclusion of the patient in the category of unfavorable prognosis [26]. In our patient, trisomy 8 was associated with trisomy 13, a less common cytogenetic abnormality. Baer reported the presence of trisomy 13 in patients, especially in elderly men, with AML with undifferentiated or biphenotypic type and the prognosis of these patients were reserved [27]. Trisomy 13 was also identified in patients with PMF, and the evolution of these patients was rapid with blastic transformation [28,29]. The presence of the complex karyotype represented by trisomy 8, 13 and deletions del (20q), del (13q) or chromosome 1 abnormalities is associated with the blastic transformation of PMF and decreased patient survival. The patient presented associated trisomy 8 and 13, explaining the rapid unfavorable evolution. In addition, it is associated with the triple-negative status of PMF, and this status is associated with an increased risk of blast transformation and unfavorable prognosis [30,31]. Mention should also be made of the need to differentiate primary triple myelofibrosis from secondary myelofibrosis secondary to DLBCL or AML. PET-CT examinations as well as bone marrow HP and IHC examination are important in the differential diagnosis of secondary myelofibrosis due AML evolution [32]. Both ex-HP IHC and ex-PET-CT performed in our patient confirm the diagnosis of the blastic phase of PMF. In addition, the patient was diagnosed with aggressive NHL a recent clinical manifestation. A variety of lymphoproliferative neoplasms may be associated with secondary myelofibrosis (B-CLL, HL or NHL, HCL, multiple myeloma) [33] and secondary fibrosis. The pathogenetic mechanism involved in the onset of secondary myelofibrosis could be the release of IL-1 by neoplastic cells that stimulate fibroblast growth by inducing secondary fibrosis. Another explanation could be the separate proliferation of two clones that are due to molecular and chromosomal abnormalities of the multipotent hematopoietic cell, thus causing bilinear clonal proliferation [33].

Conclusion

The presence of a complex karyotype (trisomy 8, trisomy 13) in a patient with myeloid metaplasia with triple-negative PMF was associated with blast transformation and severe thrombocytosis. The patient was diagnosed concomitantly with DLBCL, making the therapeutic decision difficult. Venetoclax has been shown to be useful in the treatment of DLBCL but has been associated with severe neutropenia, which has led to infectious complications.

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