Myeloid and lymphoid synchronous neoplasm with t(8;13) (p12;q12) - FGFR1 in a positive SARS-CoV-2 patient: Case report

Abstract

33 year-old male with a myelo-lymphoid neoplasm presentation at the debut. He went to Hospital because of fever and throat pain, with SARS-CoV2 infection at the same time. Initial blood tests showed hyperleukocytosis (49,320 x 10^3/L) and high cell count of neutrophils (39,440 x 10^3/L). Peripheral blood studies were suggestive of myeloproliferative Syndrome, and SARS-CoV-2 test was positive.

Flow citometry (FCM) studies showed lymphocytes with pathological immunophenotype (CD3-) indicative of lymphoid component. Genetic studies showed 8p11/FGFR1 traslocation with caryotype: 46,XY,t(8;13)(p11.2;q12) [22]/46,XY[3]. Myeloid genetical studies were negative, but TCR was positive.

We concluded he presented lymphoid / myeloid complex neoplasm with significant tumor burden at debut, which is characteristic of this traslocation. Bone marrow and peripheral blood studies were compatible with myeloproliferative Neoplasm, even though genetic studies guide to lymphoid disease. Both ganglio biopsy and FCM of bone marrow diagnosed a T-lymphoma.

B symptoms (asthma and weight loss) and palpable lymphadenopaties also indicate T component. This complex hematological neoplasm was aggravate by SARS-CoV-2 infection. It was decided to treat the haematological disease once the infection was solved. Patient received standard doses according to usual protocol for T acute lymphoblastic leukemia (T-ALL) in Spain, in an allogenic stem cell trasplant (ASCT) candidate. Also SARS-CoV-2 infection was treated and solved. Now patient is responding to treatment, showing antibodies to the virus. With control-test negatives until today doing every two weeks, recommended by Infectious disease department of our center.

Grow factor receptor (FGFR) is a non-exclusive molecule of human being. Four different types of FGFR are known in our environment. FGFR trosin kinase activity has a N-terminal sequence codified by FIM gene, which joins the kinase domain. This covalent bond is responsible for oncogenic potential of this hematopoietic cells. The gen receptor plays an important role in Haematoipoiesis. Its hyperactivity leads to abnormalities in signal pathways, resulting with cellular mutations or Hematological neoplasms.

Abnormalities in this factor are also responsible for genetic diseases such as Pfeifer or Kallman syndrome (FGFR3). Also tumors (FGFR1- lymphoblastic lymphomas) or genetic traslocations related to Hematological malignancies are described. They are usually associated to chromosome eight traslocation (8;13), as a result of gene fusion ZMYM2(ZNF198)-FGFR1. Few cases are registered about 8p11/FGFR1 traslocation-related neoplasms at literature. Mixed myelo-lymphoid neoplasms are usually related to this traslocation. This neoplasms associated with FGFR1 mutation frequently get the origin in Stem cell, resulting in a wide and heterogeneous clinical presentation.

Keywords: FGFR1, lymphoid, synchronous, SARS-CoV2, myeloproliferative, leukemia

Background

Few cases are described about 8p11/FGFR1 traslocation-related neoplasms. They are commonly associated to chromosome eight (8;13), as a result of gene fusion ZMYM2(ZNF198)-FGFR1. At least 3 different traslocations 11 and 12 region of chromosome 8 are known4,5 t(6;8)(q27;p11), t(8;9)(p11;q33) y t(8;13)(p12;q12).

Lymphoblastic lymphoma is the most common presentation way. It can evolve in a metachronous way, as myeloid neoplasm, or as a synchronous debut. WHO 2016 describes this entities like “Myeloids and lymphoid neoplasms with eosinophilia and PDGFRα, PDGFRβ, FGFR1 mutations” .6 Debut such as lymphoblastic leukemia B is very uncommon. Only seven cases are reported.

Case report

An 33 year-old male referred to our Hospital because of throat pain, fever and anoma. He has no personal history, married, one 3-year-old healthy son and two healthy brothers with no treatment at home and no other chronic diseases. SARS-CoV2 test was done because of clinical symptoms, with positive result. He also explained weight loss about 5 kg during last month, also asthena and night sweating.

After isolation because of infection, the physical examination was remarkable cervical symmetrical lymphadenopathies, painless, fickle, 1-2 cm size. Splenomegaly was unpalpable. Respiratory noises were normal, also cardiac auscultation.

Blood test showed leukocytosis (49,320 x 10^3 /µL, normal values 3,91-8,77x10^3 /µL), with myelemia (39,440 x 10^3 /µL, normal values 1,8-8,1x10^3 /µL). Eosinophil (2080 x 10^3 /µL) and basophil cell count (1,600x10^3 /µL, normal values 0-0,5x10^3 /µL) were also elevated. Other laboratory findings were normal, but LDH 577 U/L (Normal values 200-380 U/L). At peripheral blood examination appeared 2 atypical cells, compatible with blasts from chronic myeloproliferative neoplasm (CMN). Epstein Barr Virus was negative, and the other laboratory findings were normal.

Image test described an extense cervical, torathic and abdominal lymphadenopaties probably related to Lymphoproliferative Syndrome. Also splenomegaly of 15 cm was observed.

Bone marrow aspirate revealed abnormal promyelocytes count (7-8%), and 3% of myeloid blasts. It was hypercellular. Bone marrow biopsy and peripheral blood suggest lymphoid disease. FCM revealed 3% of T-lymphocytes with pathological phenotype: CD3- CD4+ CD10+.
Biopsy of lymphadenopathy was done too, which describes 3% of T-lymphocytes. Its phenotype was pathological by FCM: CD3−, CD5−, CD4+, CD8−, CD10−, CD11a−, CD19+ and CD20−. All these results, with clinical presentation were suggestive for Lymphoblastic lymphoma.

Genetical studies showed on caryotype t(8;13) traslocation (Complete caryotype: 46,XY,t(8;13)(p11.2;q12)[2]/46,XY[3] on small arm of chromosome 8, and FGFR1 rearrangement. CARL, BCR/ABL, JAK2, MPL were negative, all of them indicative for myeloid disease. ETV6, RUNX1, RARA, Inv.3 ASXL1 were all negative too. However, TCR mutation was present.

With all this information, we concluded we were facing a complex Myeloid (by bone marrow) and a lymphoproliferative (clinical symptoms, biopsy of ganglio, FCM both ganglio and bone marrow) synchronous neoplasm. This t (8;13) (p11.2;q12) traslocation usually includes both myelo and lymphoid neoplasm component.

Patient was treated of SARS-CoV-2 infection with Hydroxicloroquine 200mg/12h + Aztymricine 500mg 1/24h, also Clindamicine 600mg 1/8h because of throat pain. Once infection was solved the standard high-risk Chemotherapy outline for T-ALL in Spain was started: Vincristine (VCIR): 1,5 mg/m2 (highest dose 2 mg) i.v. days 1, 8, 15 and 22 + Daunorubicine (DNR): 45 mg/m2 i.v. days 1 to 3 + Peg-Asparraginase: 1500 U/m2, i.v., days 16 and 29 + Prednisone 15 mg/m2 days 22 to 28 and 30 mg/m2 days 15 to 21.

After first cycle of treatment: Clinical symptoms disappeared, also lymphadenopathies. Blood cells count turned into normal values. Bone marrow studies showed by FCM, positive measurable residual disease (MRD). FCM showed 0.0012% of abnormal T lymphocytes with same phenotype, with 0.0045% achieved sensibility. Morphological response was complete.

Genetical studies described persistence FGFR1 rearrangement in a 72% of total cellularity, also t(8;13) in 3 metaphase cells. Patient’s brothers were tested looking for a compatible donor to develop bone marrow Alogenic stem cell transplant. None of them were compatible for our patient. Our goal nowadays is to achieve complete response looking for a compatible unrelated-donor for ASCT.

Discussion

Few cases are described about 8p11/FGFR1 traslocation-related neoplasms. This is the second case in our center with FGFR1 rearrangement myeloid also lymphoid component. Synchronic behaviour was observed since the beginning. They are commonly associated to chromosome 8 traslocation (t8;13), as a result of gene behaviour was observed since the begining. They are commonly rearrangement myeloid also lymphoid component. Synchronic neoplasms. This is the second case in our center with FGFR1 looking for a compatible unrelated-donor for ASCT.

For our patient. Our goal nowadays is to achieve complete response was complete.

Based on experience, we ask ourselves: Wich treatment is the most effective? In this case and with the complexity of diagnosis, it was decided to choose a treatment directed to his worst prognosis based disease: Leukemia/ T-lymphoma. FGFR1 gen, merged to ZMYM2 can developed an oncogenic role which affects chromosome eight, inducing t(8;13) traslocation. There are very few cases registered at literature because of low prevalence. We did not found any case SARS-CoV2 positive at the debut on literature.10-12 We test patient every two weeks COVID-19 test agreed with Infectious disease Department, all of them negative until today. We ask ourselves some questions for which we still have no answer: How the COVID-19 virus affects to the evolution of these patients? Is it necessary to treat infection before neoplasm? Can we treat both pathologies at the same time?

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Conflicts of interest
The author declares no conflicts of interest.

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